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Evaluation et prise en charge de l'insuffisance tricuspide

Julien Dreyfus

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Thèse de Doctorat
de l'Université Paris-Est

présentée à l'Ecole Doctorale Sciences de la Vie et de la Santé

par

Julien DREYFUS

pour obtenir le grade de Docteur de l'Université Paris-Est

Evaluation et prise en charge de l'insuffisance tricuspide

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Résumé

Titre: Evaluation et prise en charge de l'insuffisance tricuspide

L'insuffisance tricuspide (IT) est actuellement considérée comme un problème de santé publique. Malgré la prévalence de l'IT et sa gravité, la grande majorité des patients est traitée uniquement médicalement par diurétiques et un traitement curatif chirurgical n'est que rarement proposé, y compris chez des patients hospitalisés pour insuffisance cardiaque avec IT significative, car la chirurgie isolée de la valve tricuspide (VT) est associée à une mortalité post-opératoire élevée. Nous avons montré que le devenir post-opératoire du patient était prédit par sa présentation pré-opératoire et développé, à partir d'un registre multicentrique Français, le TRI-SCORE, premier score de risque spécifique pour prédire à l'échelon individuel le risque de mortalité post-opératoire après chirurgie isolée de la VT, que ce soit sur VT native ou pour chirurgie redux, indépendamment du mécanisme de l'IT. Nos résultats suggèrent d'intervenir plus précocement dans l'évolution de la maladie chez les patients atteints d'IT sévère isolée, avant l'apparition de conséquences avancées/irréversibles de l'IT qui grèvent le pronostic. Moins invasif que le traitement chirurgical, le traitement percutané de l'IT, qui peut être une réparation ou un remplacement valvulaire, est actuellement en plein développement, avec des premiers résultats encourageants, et pourrait permettre d'augmenter le nombre de patients traités. De nombreuses études, dont certaines randomisées, sont actuellement en cours pour évaluer le bénéfice des traitements percutanés de l'IT en comparaison au traitement médical et permettront d'aider à mieux définir le meilleur moment et le type de procédure le plus adapté à chaque patient.

Mots-clés : insuffisance tricuspide, chirurgie, pronostic, TRI-SCORE

Abstract in English

Title: Assessment and management of tricuspid regurgitation

Tricuspid regurgitation (TR) should be considered as a public health problem. Despite the high TR prevalence and its adverse consequences on outcomes, the vast majority of patients remain under conservative management (diuretics) and a curative intervention is rarely performed, including in patients admitted for heart failure presenting with significant TR, because isolated tricuspid valve (TV) surgery is associated with high in-hospital mortality. We have shown that this high morbidity and mortality is hiding important disparities and that postoperative outcome is predicted by the clinical presentation. We have developed, from a French multicenter cohort, the TRI-SCORE, the first specific risk score to predict in-hospital mortality risk after isolated TV surgery at the individual level, both for native TV or for redo surgery, regardless of TR mechanism. Our results suggest intervening earlier in the course of the disease in patients with severe isolated TR, before the onset of advanced/irreversible consequences of TR that markedly negatively impact the prognosis. Transcatheter interventions, a less invasive alternative to surgery, are showing promising preliminary results and could increase the number of patients curatively treated. Ongoing observational and randomized controlled studies are currently evaluating the benefit of transcatheter therapies compared to conservative / medical management and will help to better define the candidates, timing and the most appropriate type of intervention.

Keywords: tricuspid regurgitation, surgery, prognosis, TRI-SCORE

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Liste des publications

I. Articles originaux

A. Premier ou dernier auteur

- **Dreyfus J**, Durand-Viel G, Raffoul R, Alkhoder S, Hvass U, Radu C, Al-Attar N, Ghodbhane W, Attias D, Nataf P, Vahanian A, Messika-Zeitoun D. Comparison of 2-Dimensional, 3-Dimensional, and Surgical Measurements of the Tricuspid Annulus Size: Clinical Implications. *Circ Cardiovasc Imaging*. 2015.
- **Dreyfus J**, Ghalem N, Garbarz E, Cimadevilla C, Nataf P, Vahanian A, Caranhac G, Messika-Zeitoun D. Timing of Referral of Patients With Severe Isolated Tricuspid Valve Regurgitation to Surgeons (from a French Nationwide Database). *Am J Cardiol*. 2018.
- **Dreyfus J**, Flagiello M, Bazire B, Eggenpieler F, Viau F, Riant E, Mbaki Y, Bohbot Y, Eyharts D, Senage T, Dubrulle H, Nicol M, Doguet F, Nguyen V, Coisne A, Le Tourneau T, Lavie-Badie Y, Tribouilloy C, Donal E, Tomasi J, Habib G, Selton-Suty C, Raffoul R, Iung B, Obadia JF, Messika-Zeitoun D. Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes. *Eur Heart J*. 2020.
- **Dreyfus J**, Audureau E, Bohbot Y, Coisne A, Lavie-Badie Y, Bouchery M, Flagiello M, Bazire B, Eggenpieler F, Viau F, Riant E, Mbaki Y, Eyharts D, Senage T, Modine T, Nicol M, Doguet F, Nguyen V, Le Tourneau T, Tribouilloy C, Donal E, Tomasi J, Habib G, Selton-Suty C, Raffoul R, Iung B, Obadia JF, Messika-Zeitoun D. TRI-SCORE: A New Risk Score for In-Hospital Mortality Prediction after Isolated Tricuspid Valve Surgery. *Eur Heart J*. 2021.
- **Dreyfus J**, Bohbot Y, Coisne A, Lavie-Badie Y, Flagiello M, Bazire B, Eggenpieler F, Viau F, Riant E, Mbaki Y, Eyharts D, Senage T, Modine T, Nicol M, Doguet F, Nguyen V, Le Tourneau T, Tribouilloy C, Donal E, Tomasi J, Habib G, Selton-Suty C, Radu C, Lim

P, Raffoul R, Iung B, Obadia JF, Audureau E, Messika-Zeitoun D. Predictive Value of the TRI-SCORE for in-hospital mortality after redo isolated tricuspid valve surgery. *Heart*. 2023.

- Teiger E, Nejjari M, Lim P, Ruf T, Blanke P, Schäfer U, Treede H, Gallet R, **Dreyfus J**. First-in-human implantation of the Topaz transcatheter tricuspid valve replacement system. *Eurointervention*. 2022.
- **Dreyfus J**, Komar M, Attias D, De Bonis M, Ruschitzka F, Popescu BA, Laroche C, Tribouilloy C, Bogachev Prokophiev A, Mizariene V, Bax JJ, Maggioni AP, Vahanian A, Iung B, on behalf of the EORP VHD II Registry Investigators Group. Tricuspid regurgitation: frequency, management and outcome among patients with severe left-sided valvular heart disease in Europe. Insights from the ESC-EORP Valvular Heart Disease II survey. *Soumis*.

B. Autres

- Messika-Zeitoun D, Candolfi P, **Dreyfus J**, Burwash IG, Iung B, Philippon JF, Toussaint JM, Verta P, Feldman TE, Obadia JF, Vahanian A, Mesana T, Enriquez-Sarano M. Management and Outcome of Patients Admitted with Tricuspid Regurgitation in France. *Can J Cardiol*. 2020.
- Guérin A, Vabret E, **Dreyfus J**, Lavie-Badie Y, Sportouch C, Eicher JC, Maréchaux S, Le Tourneau T, Donal E. “Cardiac remodelling in secondary tricuspid regurgitation: Should we look beyond the tricuspid annulus diameter? *Arch Cardiovasc Dis*. 2021.
- Donal E, Leurent G, Ganivet A, Lurz P, Coisne A, Laffitte S, Leroux L, Karam N, Biere L, Rouleau F, Sportouch C, **Dreyfus J**, Nejjari M, Josselin JM, Anselmi A, Galli E, Bajoux E, Guerin P, Obadia JF, Trochu JN, Oger E. Multicentric randomized evaluation of a tricuspid valve percutaneous repair system (clip for the tricuspid valve) in the treatment of severe

secondary tricuspid regurgitation Tri. Fr Design paper. *Eur Heart J Cardiovasc Imaging*. 2021.

- Chen E, L'Official G, Guérin A, **Dreyfus J**, Lavie-Badie Y, Sportouch C, Eicher JC, Maréchaux S, Le Tourneau T, Oger E, Donal E. Natural history of functional tricuspid regurgitation: impact of cardiac output. *Eur Heart J Cardiovasc Imaging*. 2021.
- Vely M, L'official G, Galli E, Kosmala W, Guerin A, Chen E, Sportouch C, **Dreyfus J**, Oger E, Donal E. Functional tricuspid regurgitation: A clustering analysis and prognostic validation of three echocardiographic phenotypes in an external cohort. *Int J Cardiol*. 2022.
- Bohbot Y, Tordjman L, **Dreyfus J**, Le Tourneau T, Lavie-Badie Y, Selton-Suty C, Elegamandji B, Enriquez-Sarano M, Coisne A, Donal E, Tribouilloy C. Comparison of effective regurgitant orifice area by the PISA method and tricuspid coaptation gap measurement to identify very severe tricuspid regurgitation and stratify mortality risk. *Soumis*.
- Lim P, Sharifi J, Aouate D, Wolter C, Landon V, De Pommereau A, Ennezat PV, Teiger E, Folliguet T, **Dreyfus J**, Gallet R, Huguet R. Repetitive Use of Levosimendan in Severe Functional Tricuspid Regurgitation. *Soumis*.

II. Revues ou éditoriaux

- Guérin A, **Dreyfus J**, Le Tourneau T, Sportouch C, Lairez O, Eicher JC, Flécher E, Réant P, Donal E. Secondary tricuspid regurgitation: Do we understand what we would like to treat? *Arch Cardiovasc Dis*. 2019.
- **Dreyfus J**, Obadia JF, Messika-Zeitoun D. Tricuspid regurgitation: Light at the end of the tunnel? *Arch Cardiovasc Dis*. 2022.
- **Dreyfus J**, Dreyfus GD, Taramasso M. Tricuspid valve replacement: The old and the new. *Prog Cardiovasc Dis*. 2022.

- Messika-Zeitoun D, Burwash IG, **Dreyfus J**. Tricuspid Transcatheter Edge-to-Edge Valve Repair: Sooner Rather Than Later. *JACC Cardiovasc Interv.* 2022.
- **Dreyfus J**, Messika-Zeitoun D. Cardiac implantable electronic devices: Leads can lead to tricuspid regurgitation and death! *Int J Cardiol.* 2023.

Liste des abréviations

AT : Anneau Tricuspide

AUC : Aire sous la Courbe

A4C : incidence Apicale 4 Cavités en Echocardiographie Trans-Thoracique Bidimensionnelle

DFG : Débit de Filtration Glomérulaire

ETT : Echocardiographie Trans-Thoracique

ETT-2D : Echocardiographie Trans-Thoracique Bidimensionnelle

ETO : Echocardiographie TransOesophagienne

ETO-3D : Echocardiographie TransOesophagienne Tri-dimensionnelle

FA : Fibrillation Atriale

FEVG : Fraction d'Ejection du Ventricule Gauche

HTAP : HyperTension Artérielle Pulmonaire

IC : Insuffisance Cardiaque

IM : Insuffisance Mitrale

IT : Insuffisance Tricuspide

NYHA : New York Heart Association

OD : Oreillette Droite

OR : Odd Ratio

PAPS : Pression Artérielle Pulmonaire Systolique

PISA : Proximal Isovelocity Surface Area

PMSI : Programme de Médicalisation des Systèmes d'Information

RVT : Remplacement Valvulaire Tricuspide

SOR : Surface de l'Orifice Régurgitant

STS : Société des Chirugiens Thoraciques

TAPSE : Excursion Systolique du Plan de l'Anneau Tricuspide

VD : Ventricule Droit

VG : Ventricule Gauche

VT : Valve Tricuspide

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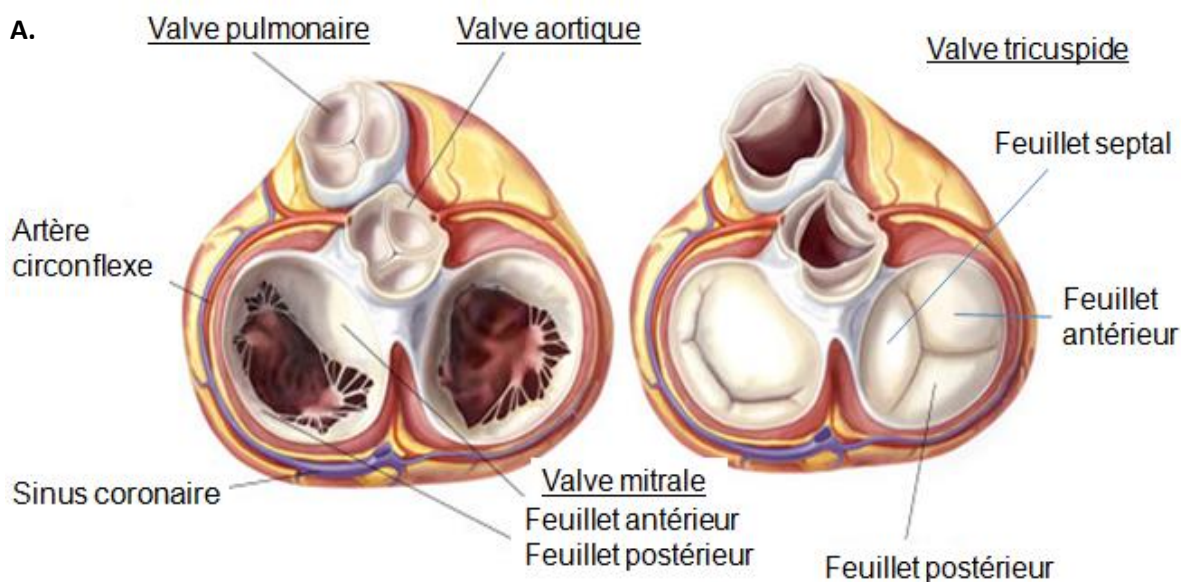
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Introduction sur l'insuffisance tricuspide

La valve tricuspide (VT) a été négligée pendant des décennies et considérée comme « la valve oubliée »¹. Actuellement, l'insuffisance tricuspide (IT) fait l'objet d'un regain d'intérêt du fait de sa prévalence, de sa gravité et du développement de traitements curatifs, notamment percutanés².

Anatomie de la valve tricuspide

La VT est située entre l'oreillette droite (OD) et le ventricule droit (VD) et est la plus large et la plus apicale des 4 valves cardiaques avec un orifice normal entre 7 et 9 cm². Il s'agit d'une structure complexe composée de l'anneau, des feuillets, des cordages et des muscles papillaires³ (Figure 1).



B.

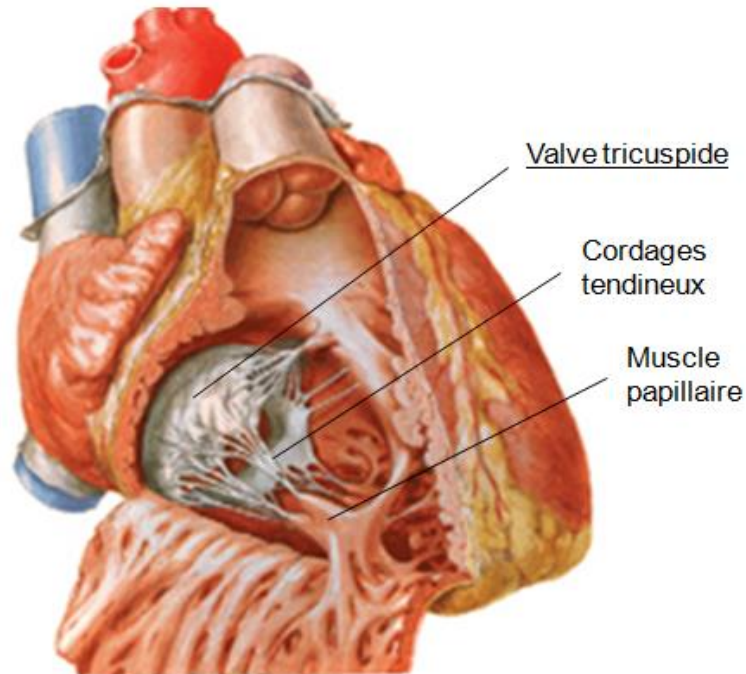


Figure 1. Anatomie de la valve tricuspide

A. Illustration extraite et adaptée de « www.mitralvalverepair.org/...anatomy.jpg »

B. Illustration extraite et adaptée de « The Netter collection »

Comme son nom l'indique, la VT est le plus souvent composée de 3 feuillets valvulaires de taille inégale (antérieur, postérieur et septal). Le feuillet antérieur est le plus grand, à la partie supérieure et externe de la VT, à proximité de la valve aortique. Le feuillet septal est le plus médial, localisé au niveau du septum inter-atrial, à la partie médiale de la VT, en regard de la valve mitrale. Le feuillet postérieur est situé au niveau inférieur de la VT, à proximité du foie. La commissure entre les feuillets antérieur et septal est proche du nœud auriculo-ventriculaire et du faisceau de His. La commissure entre les feuillets septal et postérieur est proche de l'entrée du sinus coronaire dans l'OD. Il existe de très nombreuses variations anatomiques pour les feuillets de la VT (Figure 2), en général avec des festons surnuméraires.

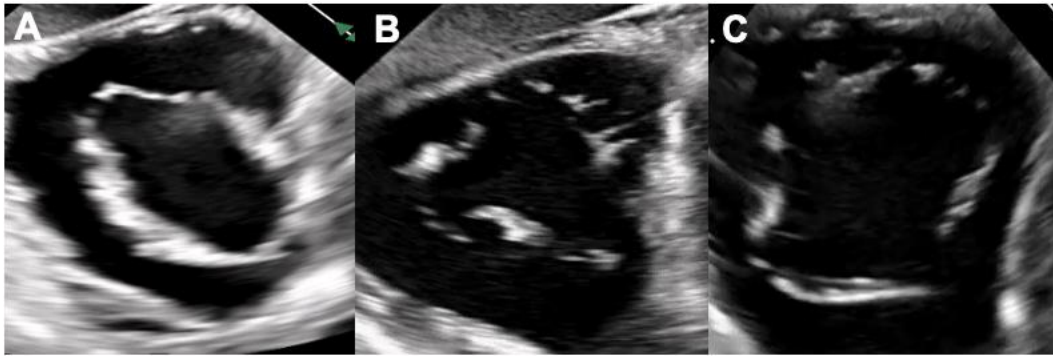


Figure 2. Exemples de variantes anatomiques du nombre de feuillets de la valve tricuspide visualisées en échocardiographie trans-oesophagienne dans l'incidence transgastrique vers 40°

- A. 2 feuillets
- B. 3 feuillets (forme anatomique la plus fréquente)
- C. 4 feuillets

Ainsi, une forme anatomique avec 3 feuillets n'est présente que chez un peu plus de la moitié des individus alors qu'environ un tiers des individus ont 2 festons au niveau du feuillet postérieur. Une nomenclature des feuillets de la VT a été récemment proposée à partir d'analyses en échocardiographie trans-oesophagienne (ETO)⁴ (Figure 3).

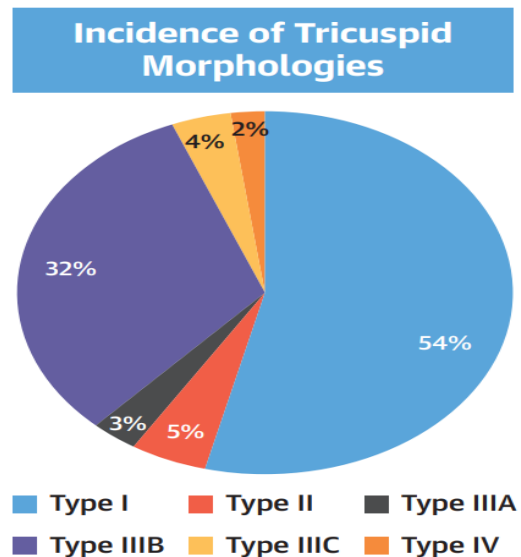
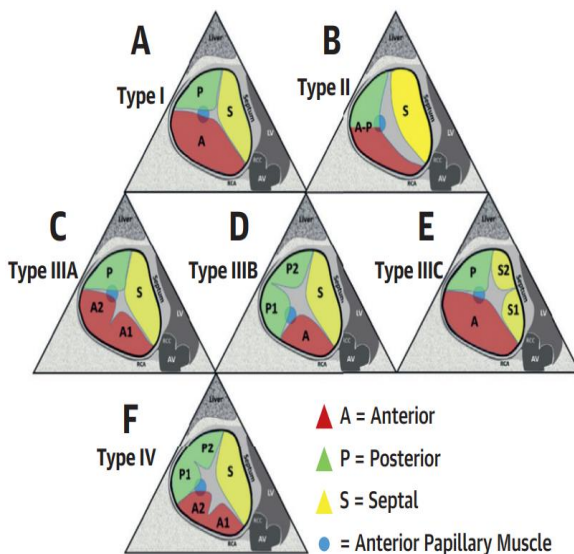


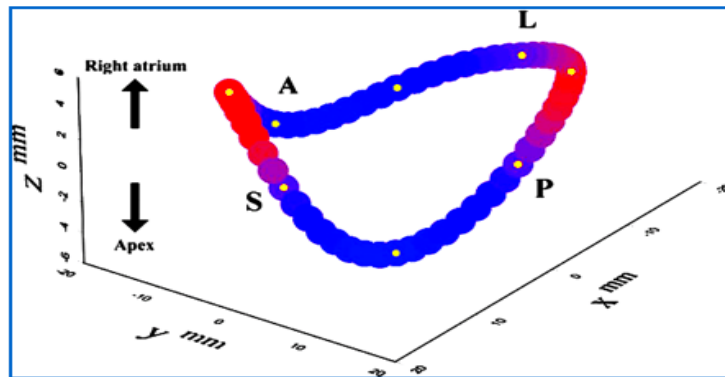
Figure 3. Proposition de nomenclature des feuillets de la valve tricuspide, d'après Hahn et al⁴

A : feuillet antérieur, P : feuillet postérieur, S : feuillet septal

Les incidences échocardiographiques pour l'analyse de la VT, notamment des feuillets valvulaires, sont présentées en Annexe (Figure S1).

Chez le sujet sain, l'anneau tricuspide (AT) est une structure tri-dimensionnelle complexe, ovalaire, non plane, en « selle de cheval ». Il présente 2 sommets, antéro-septal et postéro-latéral, et 1 nadir, postéro-septal (Figure 4A). Il se contacte normalement de 25% en systole. Quand l'AT se dilate, il a tendance à s'aplanir et à se circulariser^{5,6} (Figure 4B). La dilatation de l'AT se produit au niveau de sa paroi libre, c'est-à-dire au niveau des feuillets antérieur et postérieur, le feuillet septal étant contraint par le septum inter-atrial et la valve mitrale⁷ (Figure 4C).

A.



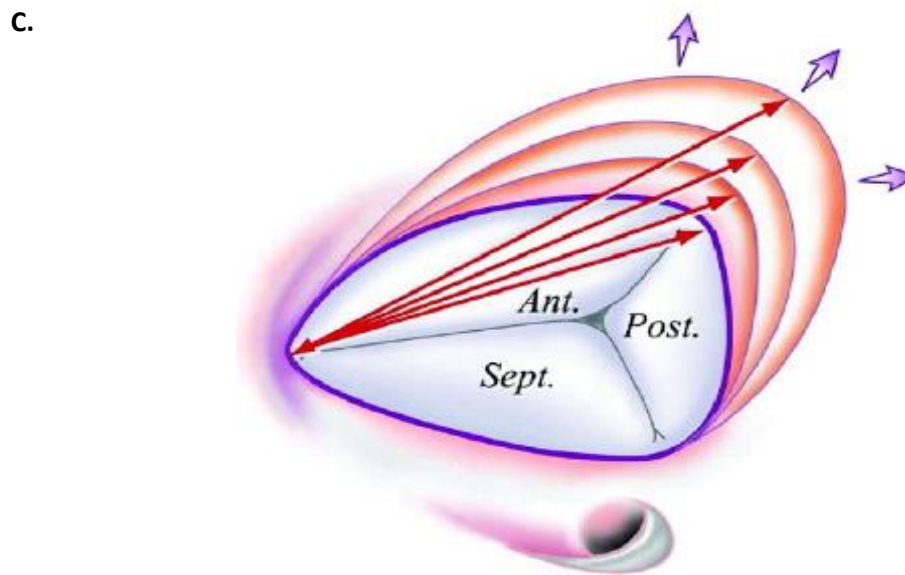
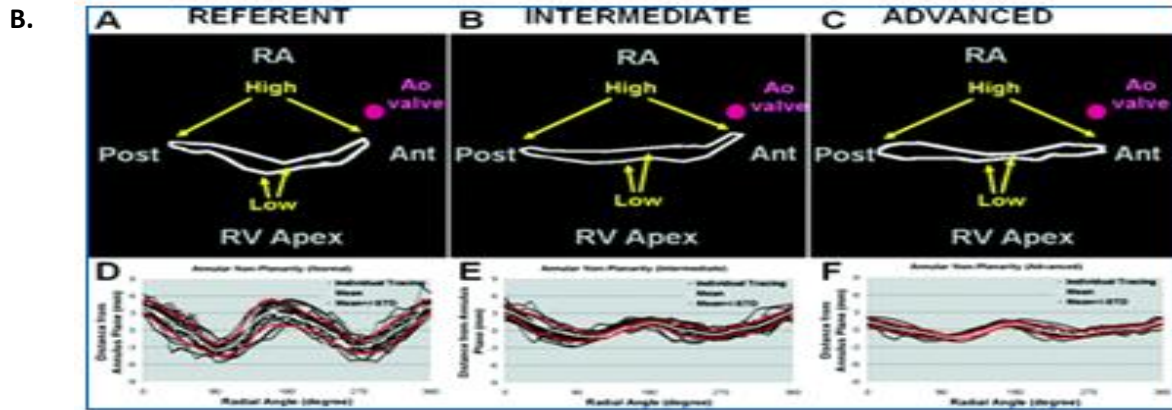


Figure 4. Morphologie de l'anneau tricuspide

- A. Aspect normal en selle de cheval, d'après Fukuda et al⁵
 A : antérieur, L : latéral, P : postérieur, S : septal
- B. Tendance à s'aplanir et à se circulariser lorsqu'il se dilate, d'après Ton-Nu TT et al⁶
 RA : oreillette droite, RV : ventricule droit
- C. Dilatation au niveau de sa paroi libre, c'est-à-dire au niveau des feuillets antérieur et postérieur, d'après Dreyfus GD et al⁷
 Ant : feuillet antérieur, Post : feuillet postérieur, Sept : feuillet septal

Le nombre de muscles papillaires est variable (2 ou 3 le plus souvent, antérieur, postérieur et souvent septal). Le plus souvent, le muscle papillaire antérieur donne des cordages aux feuillets valvulaires antérieur et postérieur, le muscle papillaire postérieur aux feuillets valvulaires postérieur et septal, et le muscle papillaire septal aux feuillets valvulaires septal et antérieur, mais il existe d'importantes variations inter-individuelles.

Le bon fonctionnement de la VT dépend de l'intégrité et de la coordination de l'ensemble de ces composants⁸, permettant une bonne coaptation des feuillets valvulaires, et donc l'absence de fuite tricuspide⁹.

Prévalence de l'insuffisance tricuspide

L'IT significative (moyenne/sévère) est fréquente puisqu'elle affecte 0,55% de la population générale (soit plus de 1,6 million de personnes aux USA)¹⁰, avec une prévalence qui augmente avec l'âge (jusqu'à 4% après 75 ans). Sa prévalence, similaire à celle de la sténose aortique ou de la régurgitation mitrale, est plus élevée chez les femmes que chez les hommes quel que soit l'âge¹¹ et va continuer à augmenter avec le vieillissement de la population (Figure 5).

A. Estimated structural heart disease opportunity:

United States

| | Patient population |
|-------------------------|---------------------------|
| Mitral regurgitation | |
| Moderate to severe | 2,300,000 ^{2,3} |
| Severe | 220,000 ^{2,3} |
| Aortic stenosis | |
| All grades | 749,000 ^{2,4} |
| Severe | 125,000 ^{†2,4,5} |
| Tricuspid regurgitation | |
| Moderate to severe | 1,600,000 ^{‡2,3} |

B. The Prevalence of All-Cause TR in the Community by Age and Sex and Adjusted for the Age and Sex Distribution of the U.S. White Population

| | | All-Cause TR Greater or Equal to Moderate | | | | | | |
|---------|-----------------|---|------------------|------------------|------------------|------------------|----------------------|--------------------------|
| | | Age Group, yrs | | | | | | |
| | Number of Cases | 18-44 (n = 51) | 45-54 (n = 36) | 55-64 (n = 58) | 65-74 (n = 128) | 75+ (n = 408) | Linear Trend p Value | Age Adjusted U.S. Burden |
| Female | 426 | 0.04 (0.02-0.07) | 0.06 (0.02-0.13) | 0.36 (0.24-0.53) | 1.23 (0.94-1.58) | 4.40 (3.89-4.96) | 0.0001 | 0.59 (0.52-0.67) |
| Male | 255 | 0.05 (0.03-0.08) | 0.16 (0.10-0.26) | 0.30 (0.19-0.47) | 0.93 (0.67-1.27) | 3.16 (2.58-3.84) | 0.0001 | 0.47 (0.39-0.55) |
| Overall | 681 | 0.05 (0.03-0.07) | 0.11 (0.07-0.16) | 0.33 (0.24-0.44) | 1.09 (0.89-1.33) | 3.96 (3.56-4.39) | 0.0001 | 0.55 (0.50-0.60) |

C.

Prevalence of TR and Combined Prevalence of All Left Valvular Heart by Age

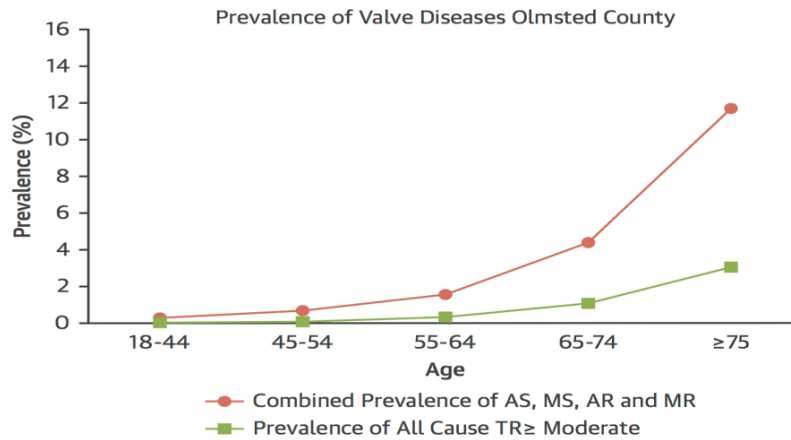


Figure 5. Prévalence de l'insuffisance tricuspide significative (moyenne/sévère)

- A. Estimation de la prévalence aux Etats-Unis d'Amérique, comparativement à l'estimation de la prévalence de la sténose aortique et de l'insuffisance mitrale, d'après Stuge et al¹⁰
- B. Prévalence en fonction de l'âge, globale et selon le sexe, dans le comté d'Olmsted, d'après Topilsky et al¹¹
- C. Prévalence en fonction de l'âge dans le comté d'Olmsted, comparativement à la prévalence de l'ensemble des valvulopathies du cœur gauche, d'après Topilsky et al¹¹

Mécanismes et étiologies de l'insuffisance tricuspide

L'IT peut être « primaire » / « organique » ou « secondaire » / « fonctionnelle »¹² (Figures 6 et 7).

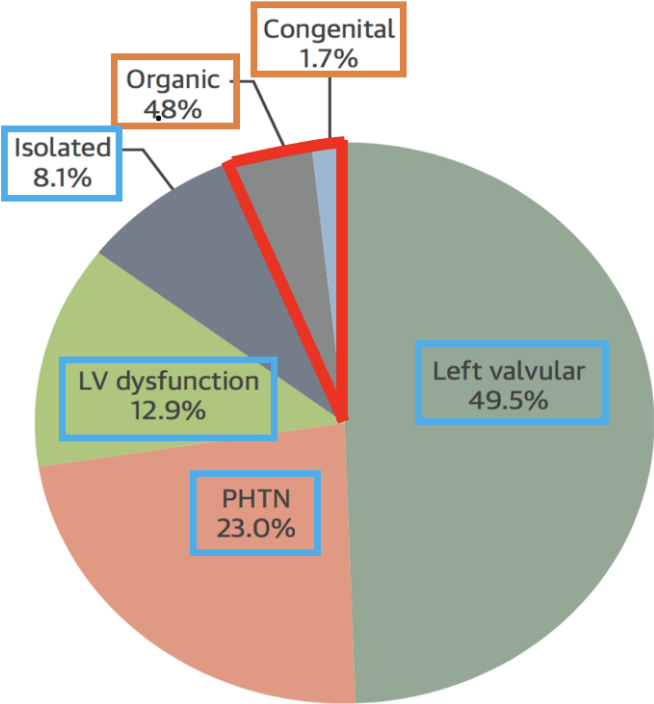


Figure 6. Prévalence de l'insuffisance tricuspide en fonction de l'étiologie, d'après Topilsky et al¹¹

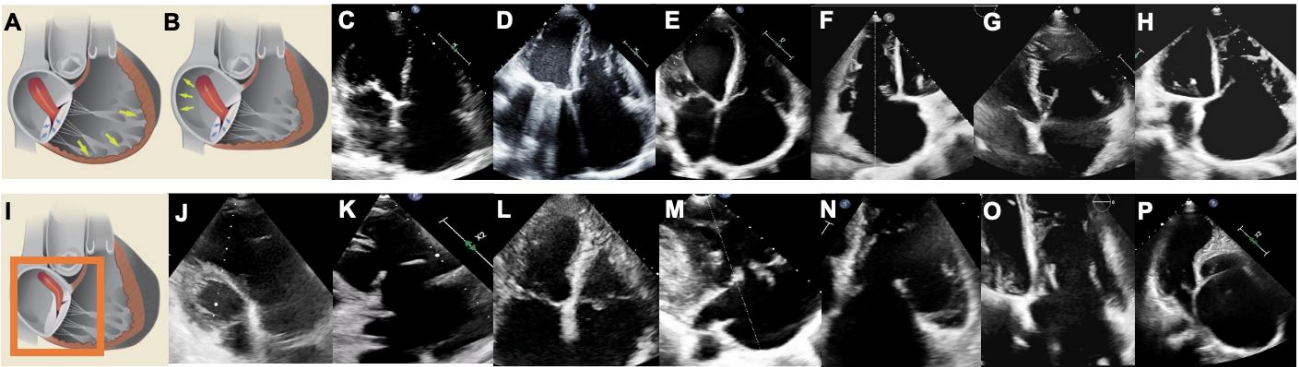


Figure 7. Illustration des différentes étiologies d'insuffisance tricuspide en échocardiographie trans-thoracique, d'après Prihadi et al¹²

IT fonctionnelles ou secondaires par dilatation ventriculaire (A) et/ou atriale (B) favorisées par une valvulopathie mitrale (C, D), une dysfonction ventriculaire gauche (E), une dysfonction ventriculaire droite (F), une hypertension artérielle pulmonaire (G), ou une fibrillation atriale (H)

IT organiques ou primaires liées à une atteinte intrinsèque de la valve (I), en rapport avec une maladie d'Ebstein (J), ou des anomalies acquises de la valve, telles qu'une atteinte rhumatismale (K), dystrophique (L), une endocardite infectieuse (M), une atteinte médicamenteuse ou carcinoïde (N), la gêne induite par une sonde de pacemaker ou de défibrillateur (O) ou une fibrose endomyocardique (P)

Plus de 90% des IT significatives sont « secondaires » ou « fonctionnelles », c'est-à-dire sans atteinte intrinsèque de la valve, en rapport avec une dilatation de l'AT et/ou un tenting des feuillets suite au remodelage de l'OD et/ou du VD, lui-même induit par une surcharge en pression et/ou en volume favorisée par une pathologie du cœur gauche (valvulopathie aortique ou mitrale, et/ou dysfonction ventriculaire gauche), une hypertension artérielle pulmonaire (HTAP), une dysfonction VD ou une fibrillation atriale (FA)^{1,13,14} (Figure 8 et Annexe – Revue 1).

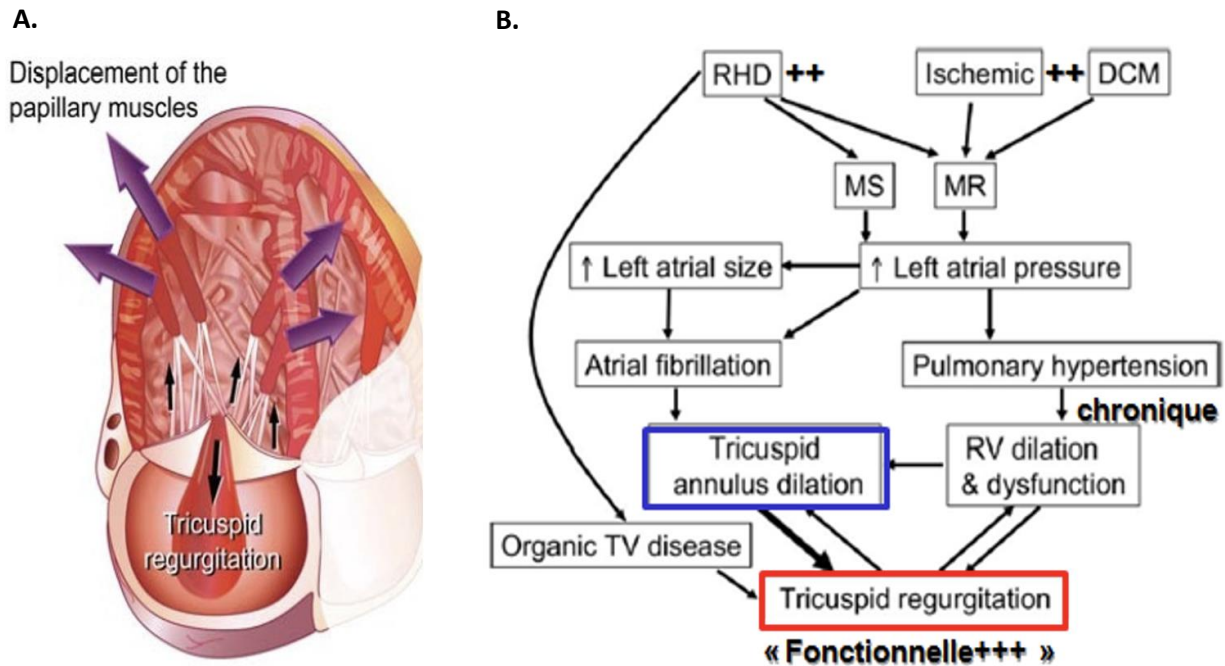


Figure 8. Mécanismes physiopathologiques de l'insuffisance tricuspide fonctionnelle

- A. Remodelage du ventricule droit avec dilatation et déplacement des piliers responsables d'un tenting des feuillets de la valve tricuspide induisant une insuffisance tricuspide fonctionnelle, d'après Mascherbauer et al¹
- B. Cascade physiopathologique de l'insuffisance tricuspide fonctionnelle, d'après Shiran et al¹³

DCM: cardiomyopathie dilatée, MR: insuffisance mitrale, MS: stenose mitrale, RHD: atteinte valvulaire rhumatismale, TV : valve tricuspide, VD : ventricule droit

L'atteinte valvulaire du cœur gauche (aortique ou mitrale) est la cause la plus fréquente de l'IT puisqu'elle représente environ 50% des cas¹¹. La FA permanente, responsable d'une dilatation de l'OD et de l'AT, est également une cause fréquente d'IT secondaire. Une classification récente propose de diviser les IT « secondaires » en « atriales » ou « ventriculaires » selon le mécanisme principal responsable de la fuite, l'IT « atriale » étant surtout induite par la dilatation de l'AT et

l'IT « ventriculaire » par le remodelage VD avec dilatation VD et déplacement des piliers responsables d'un tenting des feuillets valvulaires¹⁵ (Figure 9).

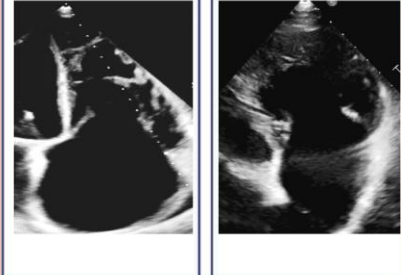

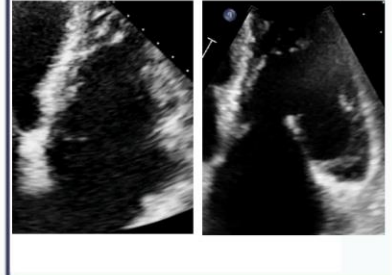
| Parameter | FUNCTIONAL/SECONDARY | | CIED-RELATED | ORGANIC/PRIMARY | |
|---------------------|---|-----------------|---|---|-----------------|
| | ATRIAL | VENTRICULAR | | | |
| |  | |  |  | |
| | Atrial FTR | Ventricular FTR | CIED-Related | Primary TR | |
| | | | | Prolapse (I) | RHD (IIIA) |
| Leaflet Tethering | - | +++ | ++ | - | - |
| Leaflet Restriction | - | Systole | Systole/Diastole | - | Diastole |
| RA/TA Dilatation | +++ | ++ | +/- | ++ | ++ |
| RV Dilatation | +/- | +++ | +/- | +/- | +/- |
| RV Dysfunction | +/- | +++ | +/- | +/- | +/- |

Figure 9. Classification des mécanismes d'insuffisance tricuspide, d'après Praz et al¹⁵

CIED : pacemaker ou défibrillateur implantable, FTR : insuffisance tricuspide fonctionnelle, RA : oreillette droite, RV : ventricule droit, TA : anneau tricuspide, TR : insuffisance tricuspide

A l'inverse, les IT « primaires » ou « organiques » sont assez rares, conséquences d'une lésion initiale de la VT qui affecte les feuillets et/ou l'appareil sous-valvulaire, dont les causes sont très variables, comme les atteintes congénitales, telles que la maladie d'Ebstein, ou les anomalies acquises de la VT, telles que l'atteinte myxomateuse, l'endocardite infectieuse (notamment chez les toxicomanes), le syndrome carcinoïde, l'atteinte rhumatismale, la radiothérapie, le traumatisme

thoracique, la fibrose endomyocardique ou les causes iatrogènes (médicamenteuse, radiothérapie, sonde de pacemaker ou défibrillateur...)¹¹.

Une classification récente propose de considérer les IT chez les patients ayant des sondes de pacemaker ou défibrillateur comme une entité à part¹⁵, sachant qu'il est parfois difficile de dire si l'IT est induite par la sonde (« organique ») ou si elle est simplement associée (« fonctionnelle »), et qu'il s'agit d'une situation de plus en plus fréquente avec un nombre croissant d'implantation de sondes de pacemaker ou défibrillateur¹⁶,¹⁷ (Annexe – Editorial 1).

Diagnostic, grade de sévérité et retentissement

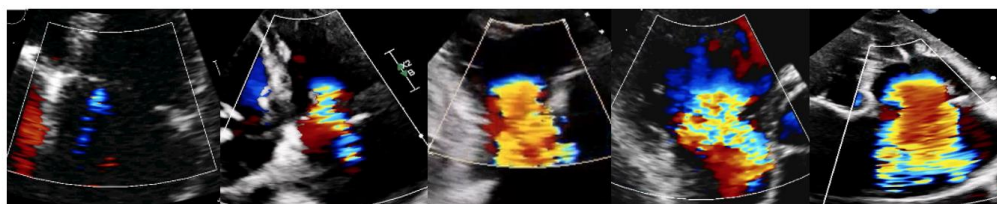
Le diagnostic est souvent évoqué tardivement devant un tableau d'insuffisance cardiaque droite, le tableau clinique étant jusque-là pauvre, le patient étant soit asymptomatique, soit avec des symptômes peu spécifiques comme de l'asthénie.

L'échocardiographie transthoracique (ETT) est l'examen de première intention et l'examen clé pour caractériser une IT. Elle permet de préciser le mécanisme et d'évaluer la sévérité de l'IT et son retentissement sur le VD (Figures 10). L'analyse ETT du degré de sévérité de l'IT, qui est complexe, doit être multiparamétrique :

- Paramètres qualitatifs : morphologie de la VT, jet couleur du flux d'IT, signal du jet d'IT en Doppler continu
- Paramètres semi-quantitatifs : rayon de Proximal Isovelocity Surface Area (PISA), largeur de la vena contracta (biplan), flux antérograde tricuspide, reflux dans les veines sus-hépatiques
- Paramètres quantitatifs : surface de l'orifice régurgitant (SOR), volume régurgitant, fraction de régurgitation
- Retentissement : dimension de la veine cave inférieure, taille et fonction de l'OD et du VD
- D'autres paramètres tels que la surface de l'orifice régurgitant 3D sont conceptuellement intéressants mais non encore disponibles en routine

La classification des grades de sévérité de l'IT est débattue. Les recommandations suggèrent d'utiliser 3 grades de sévérité (minime, modérée à moyenne, sévère) et d'ajouter 2 grades (massif et torrentiel) lorsqu'un traitement percutané est envisagé^{18,19}. De façon schématique, les critères suivants plaident pour une IT sévère : volumineux défaut de coaptation, flux laminaire (aspect triangulaire, pic <2m/s), largeur de la vena contracta ≥ 7 mm, rayon de PISA >9mm, surface de l'orifice régurgitant ≥ 40 mm², volume de l'orifice régurgitant ≥ 45 ml, onde E antérograde >1cm/s, reflux dans les veines sus-hépatique, dilatation de la veine cave inférieure. A noter que le degré de sévérité de l'IT varie de façon significative avec la volémie.

A.



| Grade de sévérité de l'IT | Minime | Modérée à moyenne | Sévère | Massive | Torrentielle |
|---|-----------------------------------|--------------------------------|--|---------|--------------|
| Paramètres qualitatifs | | | | | |
| - Morphologie de la valve tricuspide | Normale | Anomalie modérée des feuillets | Lésions valvulaires sévères/flail/large défaut de coaptation/tening majeur | | |
| - Jet d'IT en Doppler couleur ^a | Petit, étroit, central | Modéré central | Central large | | |
| - Flux à travers la zone de convergence | Non visible, transitoire ou petit | Modéré en taille et en durée | Large pendant toute la systole | | |
| - Flux d'IT en Doppler continu | Léger, parabolique | Dense, parabolique | Dense, triangulaire avec pic précoce (pic <2m/s) | | |
| Paramètres semi-quantitatifs | | | | | |
| - Rayon de PISA (mm) ^b | ≤ 5 | 6-9 | >9 | | |
| - Largeur de la vena contracta (mm) ^c | <3 | 3-6 | 7-13 | 14-20 | ≥ 21 |
| - Flux tricuspide antérograde | Onde A dominante | Variable | Onde E dominante (≥ 1 m/s) | | |
| - Flux veineux sus-hépatique ^d | Dominance systolique | Diminution du flux systolique | Inversion du flux systolique | | |
| Paramètres quantitatifs | | | | | |
| - Surface de l'orifice régurgitant (mm ²) | <20 | 20-39 | 40-59 | 60-79 | ≥ 80 |
| - Volume régurgitant (ml) | <30 | 30-44 | 45-59 | 60-74 | ≥ 75 |
| - Fraction de régurgitation (%) | <15 | 15-49 | ≥ 50 | | |
| Retentissement^e | | | | | |
| - Veine cave inférieure, | Normaux | Normaux ou peu dilatés | Dilatés | | |
| - Oreillette droite, | | | | | |
| - Ventricule droit | | | | | |

^aLimite de Nyquist vers 50-60cm/s ; ^bLimite de Nyquist vers 30cm/s ; ^cSi vena contracta biplan, IT considérée sévère quand >9 mm ; ^den l'absence d'autre raison (fibrillation atriale, élévation des pressions dans l'oreillette droite) ; ^een l'absence d'autre raison.

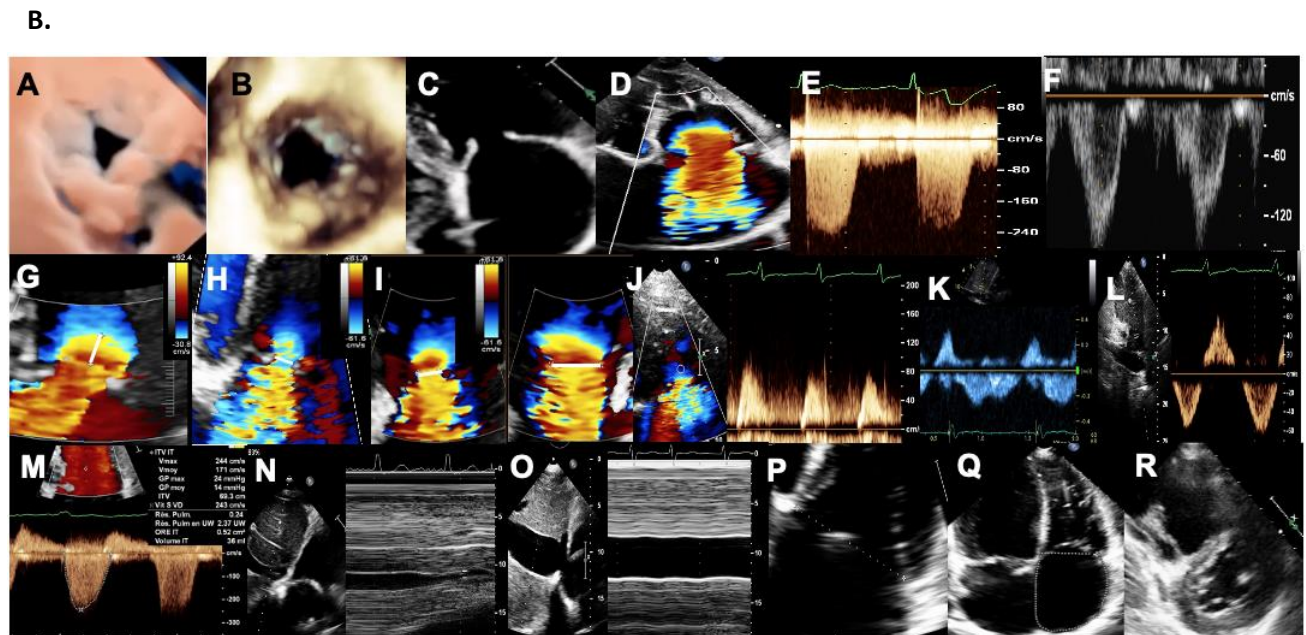


Figure 10. Grades de sévérité de l'insuffisance tricuspide en échocardiographie transthoracique

- A. Classification des différents grades et paramètres à analyser, d'après Lancellotti et al¹⁸
- B. Illustration des paramètres à analyser en échocardiographie transthoracique : analyse morphologique et taille du défaut de coaptation en 3D (A, B) ou en 2D (C), jet d'IT en Doppler couleur (D), flux d'IT en Doppler continu normal (E) ou laminaire (F), rayon de PISA en Doppler continu après réglage de la limite de Nyquist vers 30cm/s (G), largeur de la vena contacta dans 1 plan (H) ou dans 2 plans orthogonaux (I), flux antérograde tricuspide en Doppler continu (J), flux veineux sus-hépatique en Doppler pulsé normal (K) ou avec reflux systolique (L), surface de l'orifice régurgitant, volume régurgitant et fraction de régurgitation à partir du Doppler continu du flux d'IT (M), dimensions de la veine cave inférieure en 2D et en TM normale (N) et dilatée (O), dimensions de l'anneau tricuspide (P), de l'oreillette droite (Q) et du ventricule droit (R)

IT : insuffisance tricuspide

L'IRM cardiaque peut être intéressante pour l'analyse de la sévérité de l'IT en cas de doute en échocardiographie (calcul du volume régurgitant en faisant la différence entre le volume d'éjection systolique du VD obtenu par la planimétrie du VD en diastole et en systole dans une pile

de coupes dynamiques petit-axe et le volume antérograde à travers la valve pulmonaire obtenu avec les vitesses en contraste de phase), et surtout pour l'analyse de la taille et de la fonction des cavités droites, notamment du VD (Figure 11).

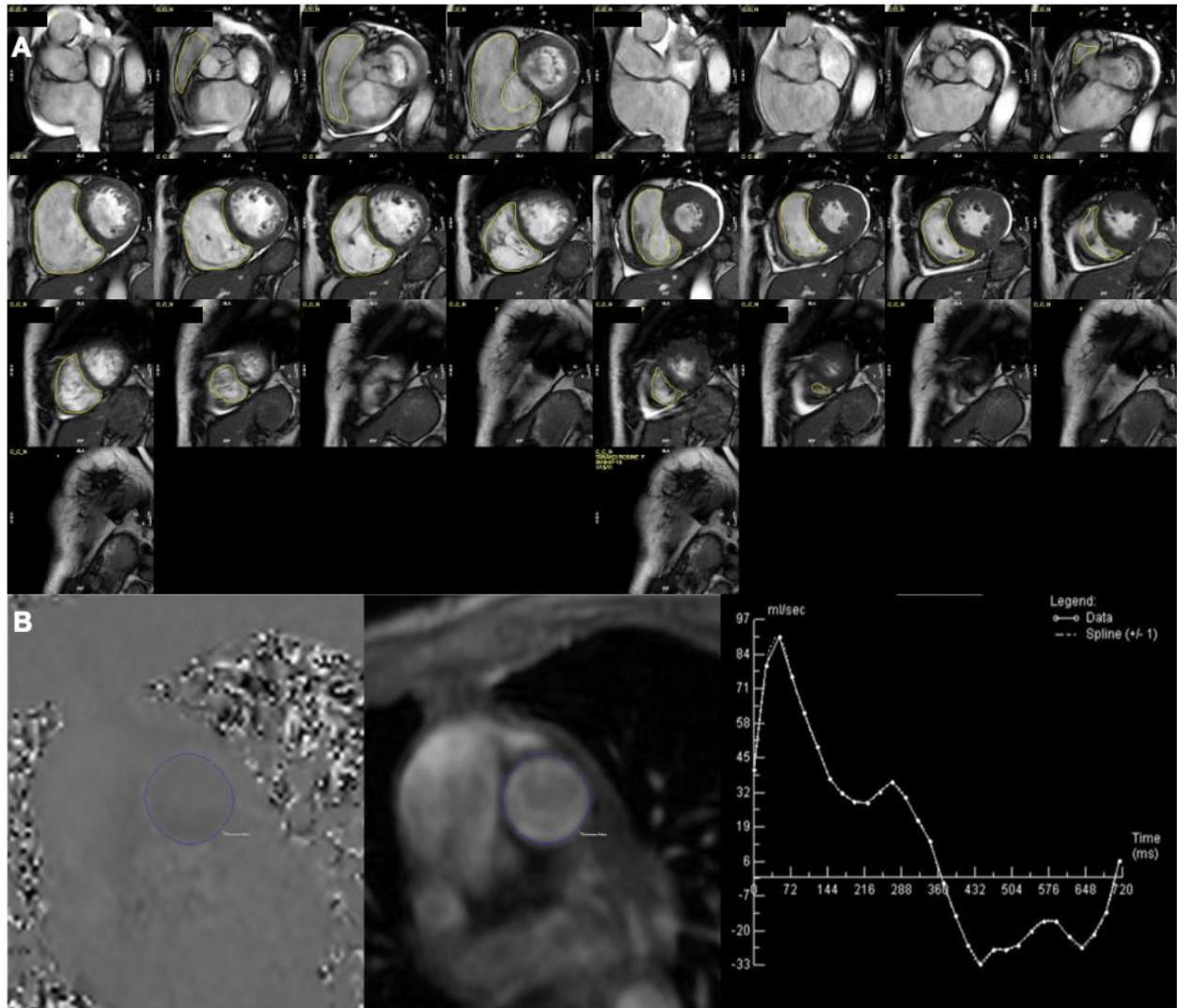


Figure 11. Apport de l'IRM cardiaque en présence d'une insuffisance tricuspide

- A. Pile de coupes dynamiques petit-axe permettant le calcul des volumes et de la fonction du ventricule droit, ainsi que du volume d'éjection systolique
- B. Analyse des vitesses en contraste de phase dans le tronc de l'artère pulmonaire permettant le quantifier le flux antérograde à travers la valve pulmonaire (le volume régurgitant

tricuspid correspond à la différence entre le volume d'éjection systolique du ventricule droit et le volume antérograde à travers la valve pulmonaire)

Histoire naturelle

Quel que soit son mécanisme, l'IT va aggraver le remodelage du VD et de l'OD, qui va accentuer la dilatation de l'AT et le tenting des feuillets, ce qui va encore aggraver l'IT, engendrant un cercle vicieux. Plusieurs classifications de l'histoire naturelle de l'IT en différentes étapes ont été proposées, basées sur le degré de sévérité de la fuite, les symptômes, le traitement, la taille de l'AT, le degré de tenting des feuillets, le défaut de coaptation valvulaire, le remodelage et la fonction systolique VD²⁰⁻²⁵ (Figure 12 et Annexe – Article 10).






| Central Role of TR in RV REMODELING | | Stage 1 | Stage 2 | Stage 3 | Stage 4 | Stage 5 |
|--|--|--|--|--|--|--|
| |  |  |  |  |  | |
| ABNORMAL COAPTATION Resulting in TRICUSPID REGURGITATION | Symptoms | None | None* | None-vague* | Current or previous episodes of RHF | Overt RHF and/or end-organ damage due to chronic RV volume overload# |
| Progressive ANNULAR DILATATION with ADAPTIVE RV REMODELING to accommodate volume load | TR grade | Less than moderate | >Moderate | Severe | Severe | Torrential |
| | Annular remodeling | Normal | Normal or mildly remodeled | Present | Moderate-severe | Severe |
| | Leaflet coaptation | Normal | Mildly abnormal | Abnormal | Coaptation gap | Large coaptation gap |
| MALADAPTIVE RV REMODELING with RV DYSFUNCTION (RV-PA uncoupling) | Tethering | None | None or mildly abnormal (<8 mm) | Abnormal (usually <8 mm) | Significantly abnormal with varying degree of tethering | Significantly abnormal (usually >8 mm) |
| | RV function and remodeling | Normal | Normal function Absent or mild remodeling | Mild RV dysfunction and/or remodeling | >Moderate dysfunction and remodeling | Severe RV dysfunction and remodeling |

Figure 12. Histoire naturelle de l'insuffisance tricuspid, d'après Taramasso et al²⁰

RHF : insuffisance cardiaque droite, RV : ventricule droit

Valeur pronostique

L'IT a longtemps été considérée bénigne. Il est désormais clairement établi que l'IT est associée à un mauvais pronostic, avec une morbi-mortalité qui augmente avec le degré de sévérité de la fuite^{26,27} (Figure 13A), quel que soit le mécanisme ou l'étiologie de l'IT^{11,28} (Annexe – Article 11).

L'IT est associée à une augmentation des symptômes (asthénie, anorexie, signes d'insuffisance cardiaque (IC) droite avec ascite, foie cardiaque, œdème des membres inférieurs par augmentation des pressions dans l'OD), et à une baisse des capacités fonctionnelles à l'effort par diminution du débit cardiaque²⁹.

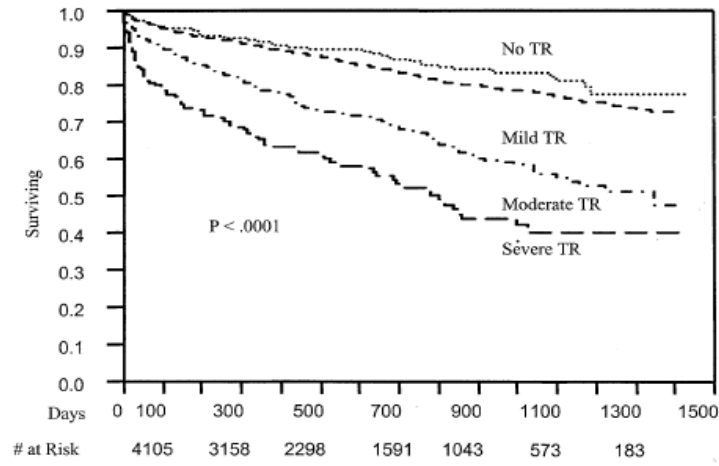
L'IT est un facteur pronostic indépendant de mortalité et de morbidité, comme montré dans une série de patients avec IT organique isolée sévère par flail (capotage avec rupture de cordage) d'étiologie en majorité traumatique. Longtemps asymptomatique, l'IT est associée à une augmentation tardive mais significative de la morbi-mortalité³⁰.

Une méta-analyse sur plus de 32 000 patients retrouve un risque de mortalité 2 fois plus élevé chez les patients ayant une IT moyenne/sévère que chez les patients ayant une IT absente ou minime, quelles que soient les pressions artérielles pulmonaires et les fonctions systoliques des ventricules gauche et droit³¹.

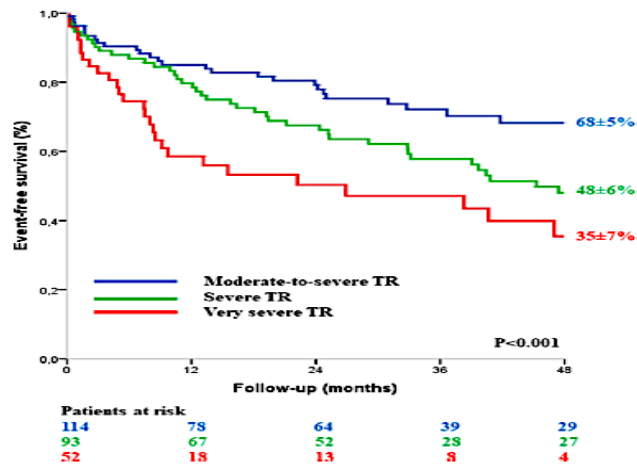
La corrélation entre le degré de sévérité de l'IT et l'altération du pronostic est également vraie chez les patients ayant une IT « plus sévère que sévère » (massive ou torrentielle)^{32,33} (Figure 13B).

Toutes les études retrouvent cette corrélation, que ce soit en population générale ou dans des sous-groupes spécifiques comme les patients ayant une insuffisance cardiaque (IC) à fonction systolique ventriculaire gauche altérée³⁴ (Figure 13C), une insuffisance mitrale (IM) dégénérative quel que soit le traitement médical, chirurgical³⁵ ou percutané³⁶, ou après remplacement valvulaire aortique chirurgical³⁷ ou percutané³⁸.

A.



B.



C.

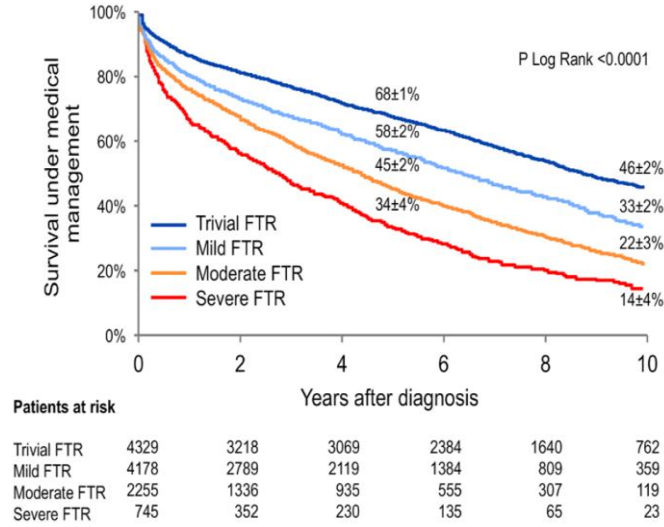


Figure 13. Courbes de survie en fonction du degré de sévérité de l'insuffisance tricuspide

- A. En population générale, en 4 grades, d'après Nath et al²⁶
- B. En ajoutant le grade « very severe », qui regroupe les IT massives et torrentielles, d'après Peugnet et al³²
- C. Dans la sous-population de patients ayant une insuffisance cardiaque à fonction systolique ventriculaire gauche altérée, d'après Benfari et al³⁴

FTR : insuffisance tricuspide fonctionnelle, TR : insuffisance tricuspide

Prise en charge

La très grande majorité des patients est actuellement traitée uniquement de façon médicale par diurétiques. Cela permet de réduire la volémie et ainsi le degré de sévérité de la fuite. Pour autant, il s'agit d'un traitement uniquement symptomatique qui ne permet pas de corriger le mécanisme de la fuite.

Le seul traitement curatif de l'IT est un traitement interventionnel, qui consiste soit à réparer soit à remplacer la VT, que ce soit de façon chirurgicale ou percutanée.

Les recommandations Européennes et Américaines pour la prise en charge de l'IT et les indications de traitement interventionnel sont présentées dans les Figures 14 et 15^{39,40}.

A. Traitement chirurgical

A.1. Indications chirurgicales

Il est important de distinguer 2 situations cliniques. Dans la première situation, le patient est adressé pour la prise en charge chirurgicale d'une valvulopathie sévère du cœur gauche et se pose la question d'un geste concomitant sur la VT. Dans la deuxième situation, le patient présente une IT sévère isolée, c'est-à-dire sans valvulopathie significative du cœur gauche.

A.1.1. Chirurgie de la valve tricuspide au moment d'une chirurgie valvulaire du cœur gauche

Dans cette situation, le patient est adressé au chirurgien pour une chirurgie valvulaire du cœur gauche, aortique ou mitrale.

Un geste sur la valve tricuspide sera proposé dans le même temps opératoire en cas d'IT sévère quel qu'en soit le mécanisme (classe I), ou en cas d'IT organique moyenne (classe IIaC), ou lorsque l'AT est dilaté (≥ 40 mm ou 21 mm/m² en ETT bidimensionnelle) quel que soit le degré d'IT (classe IIaB) pour les Européens³⁹ et les Américains⁴⁰. Les Américains ajoutent l'antécédent d'IC droite même en l'absence d'IT significative (classe IIaB)⁴⁰.

Les principaux facteurs prédictifs d'apparition d'une IT sévère à distance d'une chirurgie valvulaire du cœur gauche sont l'âge, le sexe féminin, la FA, l'HTAP, l'étiologie rhumatismale de l'atteinte valvulaire mitrale et la dilatation des cavités droites⁴¹⁻⁴³. La présence d'une dilatation de l'AT est un marqueur plus précoce d'atteinte de la VT que l'IT significative et traduit déjà un stade avancé dans la cascade physiopathologique complexe qui aboutit à l'IT fonctionnelle^{7,13,44,45}.

La réalisation d'une annuloplastie tricuspide (geste le plus souvent réalisé) au moment d'une chirurgie valvulaire du cœur gauche est un geste simple et rapide qui n'est pas associé à une

augmentation de la mortalité ou de la morbidité en dehors d'un surrisque de pacemaker (risque multiplié par 2 ou 3)⁴⁶⁻⁴⁸. La réalisation d'un geste sur la VT au moment d'une chirurgie valvulaire du cœur gauche permet de prévenir l'aggravation de l'IT dans les années qui suivent l'intervention^{7,48-50}.

A.1.2. Chirurgie de la valve tricuspide pour insuffisance tricuspide isolée

Dans la deuxième situation, le patient présente une IT isolée. Une chirurgie isolée de la VT est indiquée chez les patients ayant une IT sévère isolée primaire sans dysfonction VD sévère (classe I pour les Européens³⁹ et classe IIa pour les Américains⁴⁰) et peut être envisagée chez les patients ayant une IT primaire sévère asymptomatique ou peu symptomatique avec dilatation progressive du VD ou dégradation de la fonction systolique du VD (classe IIa pour les Européens³⁹ et classe IIb pour les Américains⁴⁰). Une chirurgie isolée de la VT peut également être proposée aux patients ayant une IT sévère isolée secondaire en rapport avec une dilatation de l'AT qui sont symptomatiques malgré le traitement médical optimal (classe IIa pour les Européens³⁹ et les Américains⁴⁰) ou qui sont asymptomatiques mais avec dilatation du VD sans HTAP ni dysfonction ventriculaire gauche (VG) ou VD sévère (classe IIa pour les Européens³⁹).

A.

| Recommendations on primary tricuspid regurgitation | | |
|--|-----|---|
| Surgery is recommended in patients with severe primary tricuspid regurgitation undergoing left-sided valve surgery. | I | C |
| Surgery is recommended in symptomatic patients with isolated severe primary tricuspid regurgitation without severe RV dysfunction. | I | C |
| Surgery should be considered in patients with moderate primary tricuspid regurgitation undergoing left-sided valve surgery. | IIa | C |
| Surgery should be considered in asymptomatic or mildly symptomatic patients with isolated severe primary tricuspid regurgitation and RV dilatation who are appropriate for surgery. | IIa | C |
| Recommendations on secondary tricuspid regurgitation | | |
| Surgery is recommended in patients with severe secondary tricuspid regurgitation undergoing left-sided valve surgery. ⁴²³⁻⁴²⁷ | I | B |
| Surgery should be considered in patients with mild or moderate secondary tricuspid regurgitation with a dilated annulus (≥ 40 mm or > 21 mm/m ² by 2D echocardiography) undergoing left-sided valve surgery. ^{423,425-427} | IIa | B |
| Surgery should be considered in patients with severe secondary tricuspid regurgitation (with or without previous left-sided surgery) who are symptomatic or have RV dilatation, in the absence of severe RV or LV dysfunction and severe pulmonary vascular disease/hypertension. ^{418,433 e} | IIa | B |
| Transcatheter treatment of symptomatic secondary severe tricuspid regurgitation may be considered in inoperable patients at a Heart Valve Centre with expertise in the treatment of tricuspid valve disease. ^f | IIb | C |

B.

| COR | LOE | Recommendations |
|-----|------|--|
| 1 | B-NR | 1. In patients with severe TR (Stages C and D) undergoing left-sided valve surgery, tricuspid valve surgery is recommended. ¹⁻⁸ |
| 2a | B-NR | 2. In patients with progressive TR (Stage B) undergoing left-sided valve surgery, tricuspid valve surgery can be beneficial in the context of either 1) tricuspid annular dilation (tricuspid annulus end diastolic diameter > 4.0 cm) or 2) prior signs and symptoms of right-sided HF. ³⁻¹⁰ |
| 2a | B-NR | 3. In patients with signs and symptoms of right-sided HF and severe primary TR (Stage D), isolated tricuspid valve surgery can be beneficial to reduce symptoms and recurrent hospitalizations. ¹¹⁻¹⁴ |
| 2a | B-NR | 4. In patients with signs and symptoms of right-sided HF and severe isolated secondary TR attributable to annular dilation (in the absence of pulmonary hypertension or left-sided disease) who are poorly responsive to medical therapy (Stage D), isolated tricuspid valve surgery can be beneficial to reduce symptoms and recurrent hospitalizations. ^{11,12,15-19} |
| 2b | C-LD | 5. In asymptomatic patients with severe primary TR (Stage C) and progressive RV dilation or systolic dysfunction, isolated tricuspid valve surgery may be considered. ^{12,20} |
| 2b | B-NR | 6. In patients with signs and symptoms of right-sided HF and severe TR (Stage D) who have undergone previous left-sided valve surgery, reoperation with isolated tricuspid valve surgery may be considered in the absence of severe pulmonary hypertension or severe RV systolic dysfunction. ^{1,2,11,18} |

Figure 14. Indications de traitement curatif en cas d'insuffisance tricuspide

A. Selon les recommandations de la Société Européenne de Cardiologie et la Société Européenne de Chirurgie Cardio-Thoracique, d'après Vahanian et al³⁹

B. Selon les recommandations Américaines, d'après Otto et al⁴⁰

COR: classe de recommandation, LOE : niveau d'évidence, LV : ventricule gauche, RV : ventricule droit, TR : insuffisance tricuspide

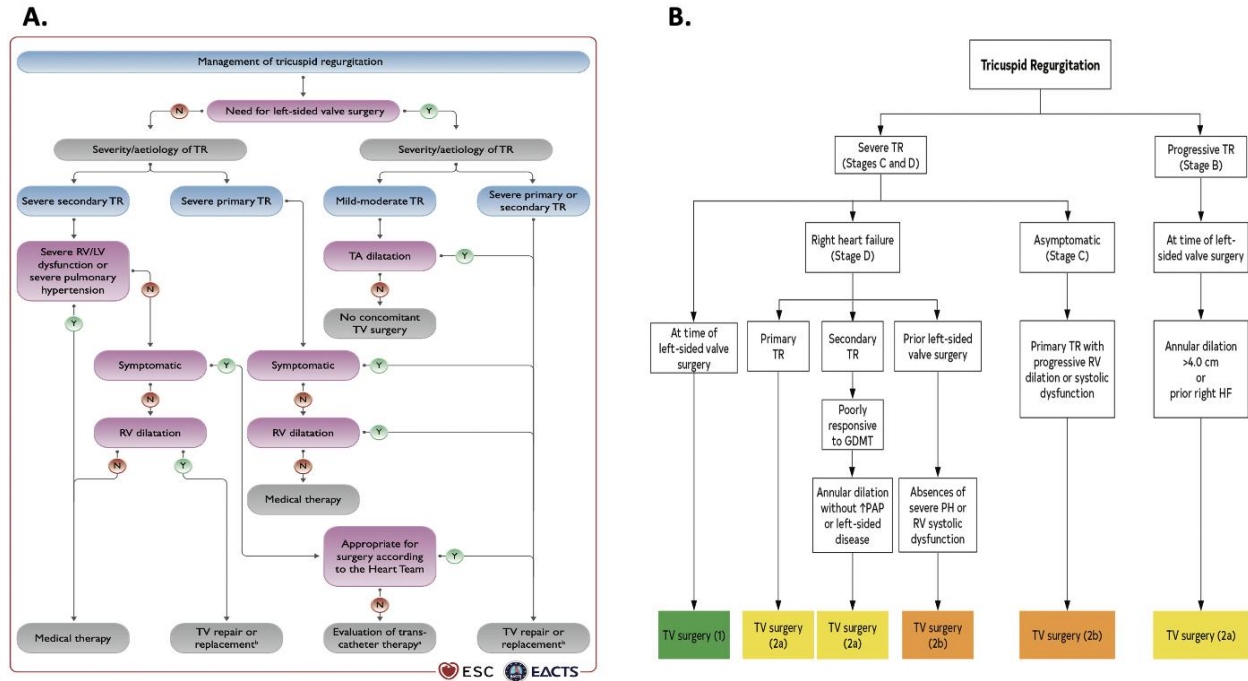


Figure 15. Prise en charge de l'insuffisance tricuspide

A. Selon les recommandations de la Société Européenne de Cardiologie et la Société Européenne de Chirurgie Cardio-Thoracique, d'après Vahanian et al³⁹

B. Selon les recommandations Américaines, d'après Otto et al⁴⁰

LV : ventricule gauche, RV : ventricule droit, TR : insuffisance tricuspide, TV : valve tricuspide

A.2. Type de geste chirurgical

Le geste chirurgical peut être une réparation ou un remplacement valvulaire.

Les recommandations indiquent que, si possible, un geste conservateur par réparation valvulaire doit toujours être privilégié, en préférant l'implantation d'un anneau prothétique (par opposition aux autres techniques type De Vega ou bicuspidisation, qui sont associées à de moins bons résultats)^{39,51}. Il s'agit le plus souvent d'une annuloplastie tricuspide avec mise en place d'un anneau prothétique rigide tridimensionnel ouvert qui tente de reproduire et de maintenir la morphologie normale de l'AT avec pour objectif de corriger/limiter la dilatation de l'AT. L'anneau chirurgical est ouvert à proximité de la commissure antéro-septale, zone où passe le tissu de conduction, afin de diminuer le risque de trouble de conduction induit par ce geste chirurgical (Figure 16).

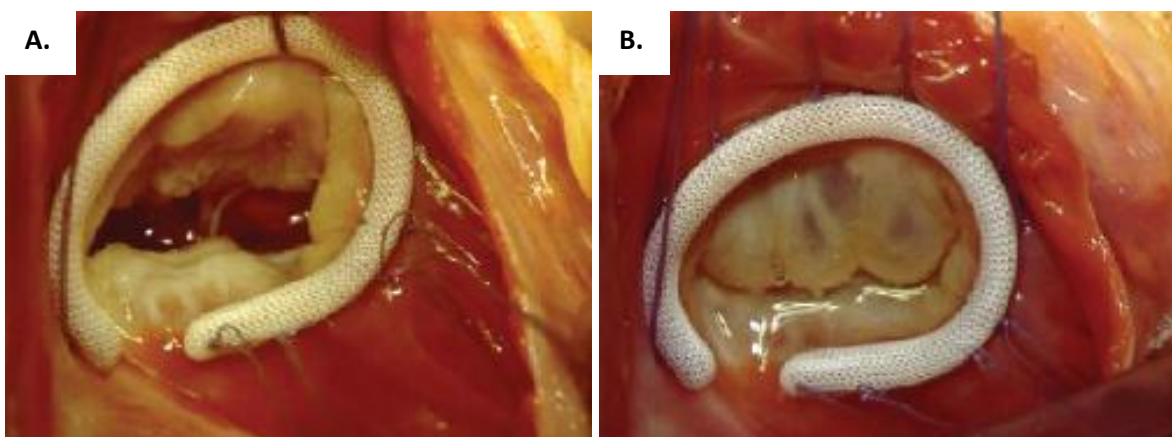


Figure 16. Annuloplastie tricuspide chirurgicale avec anneau ouvert MC3 (Carpentier-Edwards)

A. Valve tricuspide en position ouverte

B. Valve tricuspide en position fermée

Une chirurgie conservatrice par annuloplastie est le plus souvent réalisée en cas d'IT fonctionnelle et peut également être proposée pour certaines formes d'IT organiques lorsqu'elles

sont d'origine dystrophique, traumatique ou post-endocarditique, avec utilisation de néocordages. La présence d'un tenting important (hauteur de coaptation >8-10mm, surface de tenting >16mm² et volume de tenting >2.3ml en ETT dans l'incidence apicale 4 cavités)⁵² (Figure 17) est associée à un risque important d'IT résiduelle significative après annuloplastie tricuspide chirurgicale et doit orienter vers la réalisation d'un remplacement valvulaire tricuspide (RVT).

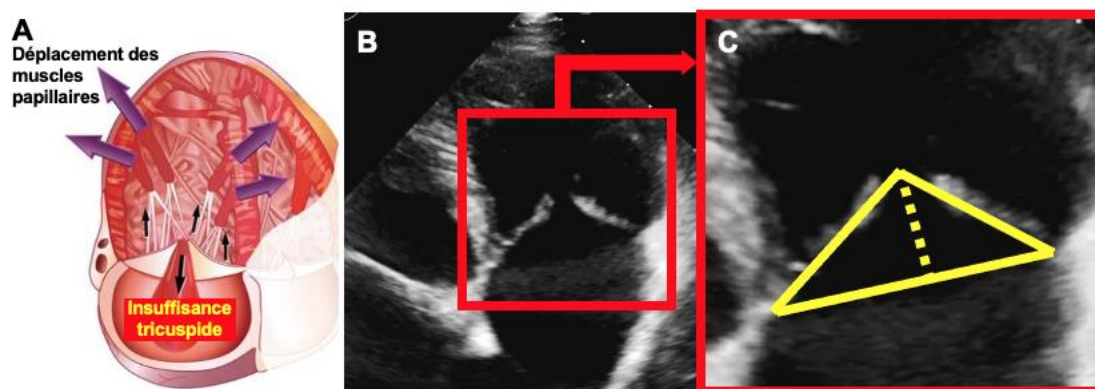


Figure 17. Insuffisance tricuspide avec tenting des feuillets de la valve tricuspide

- A. Schéma montrant le remodelage du ventricule droit avec déplacement des muscles papillaires responsable d'un tenting des feuillets de la valve tricuspide induisant la fuite tricuspide fonctionnelle, d'après Mascherbauer et al¹
- B. Tenting important visualisé en échocardiographie transthoracique dans l'incidence apicale 4 cavités
- C. Mesure du tenting (hauteur en pointillés jaunes et surface entre les traits jaunes) après zoom (cadre rouge) de l'incidence apicale 4 cavités

Lorsqu'une chirurgie conservatrice n'est pas réalisable, soit sur valve native (tenting important des feuillets valvulaires, délabrement valvulaire non réparable), soit sur dysfonction de plastie ou de prothèse valvulaire, un RVT est effectué, le plus souvent par bioprothèse et plus rarement par prothèse mécanique (Figure 18 et Annexe – Revue 2).

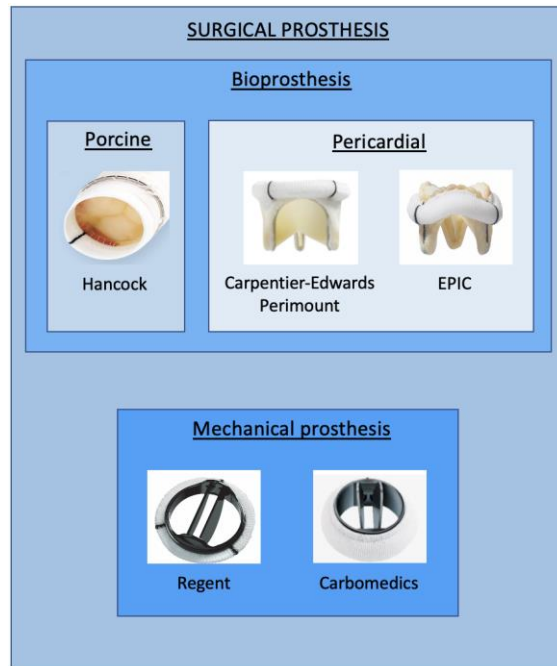


Figure 18. Différents types de prothèses valvulaire tricuspides chirurgicales, biologiques et mécaniques, d'après Dreyfus et al⁵³

(Abbott (Regent, Epic), Edwards-Lifesciences (Carpentier-Edwards Perimount), Medtronic (Hancock))

A noter que l'implantation d'un RVT est associée à un risque élevé de nécessité d'un pacemaker dans les suites (environ 30%, risque 2 à 3 fois plus élevé qu'après une annuloplastie tricuspide)⁵⁴.

B. Traitement percutané

Le traitement percutané de l'IT est actuellement en plein essor, avec la perspective d'offrir une stratégie de correction efficace de l'IT au prix d'une intervention moins invasive que le traitement chirurgical. De nombreux dispositifs de réparation ou de remplacement valvulaire tricuspide percutané sont actuellement approuvés ou en cours d'évaluation clinique (Figure 19).

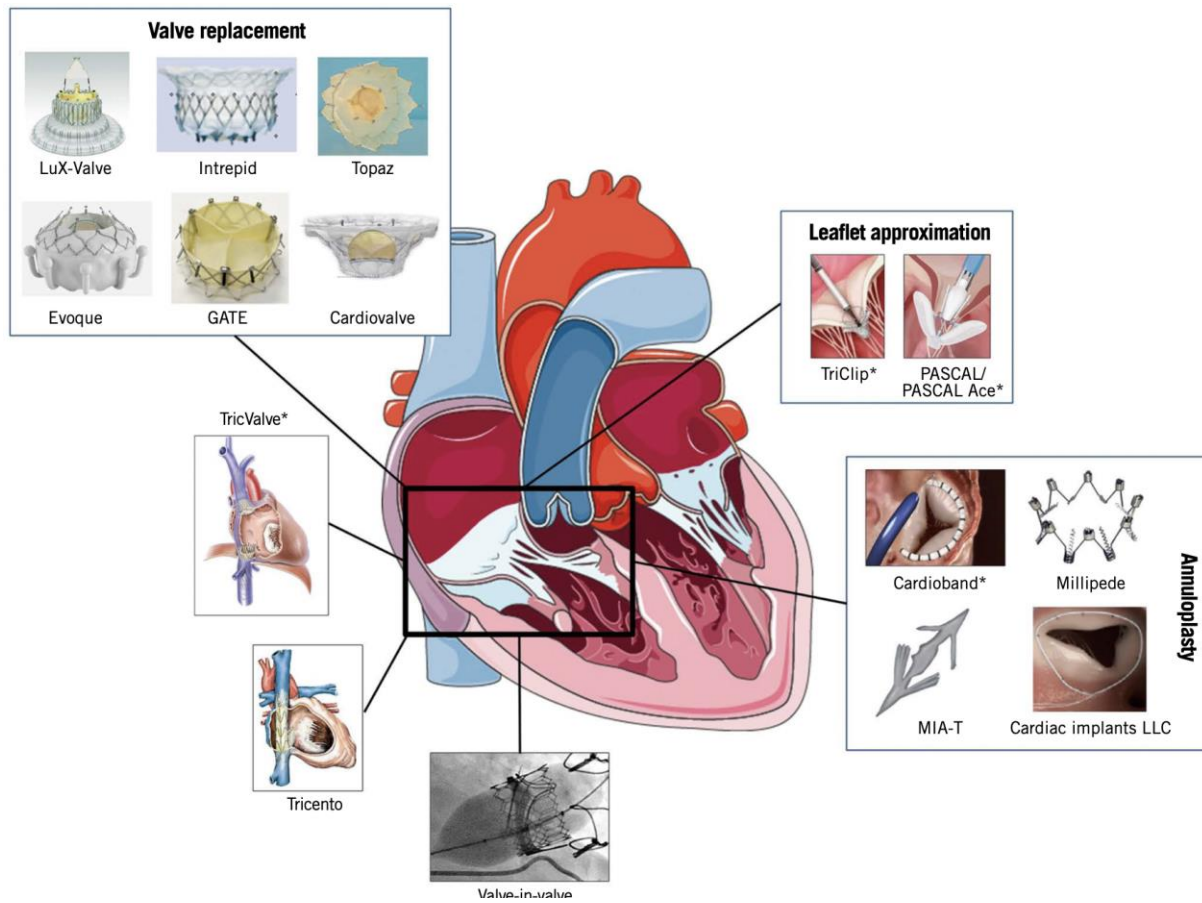


Figure 19. Systèmes de réparation ou de remplacement valvulaire tricuspide percutané approuvés ou en cours d'évaluation clinique, d'après Praz et al¹⁵

Le traitement par réparation percutanée bord-à-bord des feuillets de la VT (TriClip® ou PASCAL®) basée sur le concept d'Alfieri et par analogie au MitraClip® est la technique actuellement la plus utilisée à travers le monde (Figure 20).

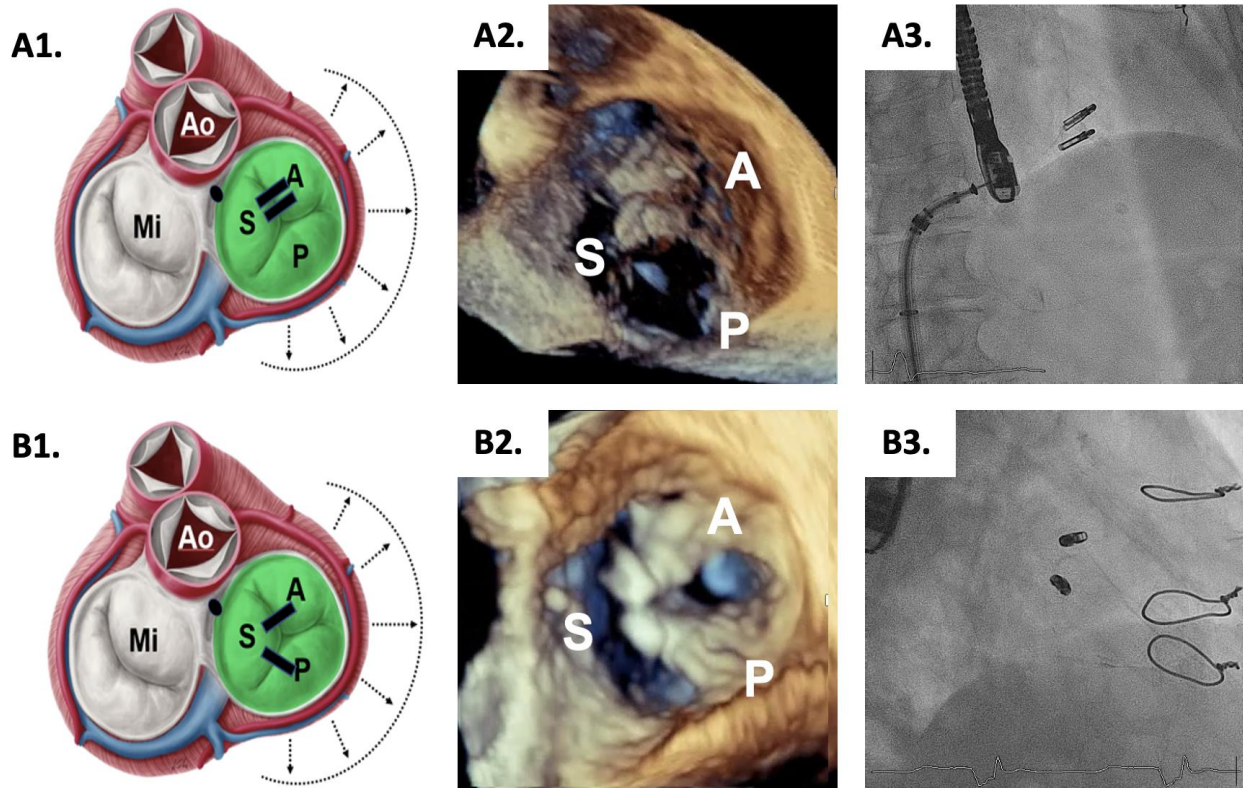


Figure 20. Exemples de réparation percutanée bord-à-bord des feuillets de la valve tricuspide par la technique de TriClip®

Stratégies à 2 clips :

- A. 2 clips implantés entre les feuillets antérieur et septal
- B. 1 clip implanté entre le feuillet antérieur et le feuillet septal, et 1 deuxième clip implanté entre le feuillet postérieur et le feuillet septal

A1. et B1. sont des schémas anatomiques illustrant la stratégie thérapeutique

A2. et B2. montrent le résultat final en échocardiographie trans-oesophagienne tri-dimensionnelle

A3. et B3. montrent le résultat final en fluoroscopie

A : feuillet antérieur de la valve tricuspide, Ao : valve aortique, Mi : valve mitrale, P : feuillet postérieur de la valve tricuspide, S : feuillet septal de la valve tricuspide

Pour les patients qui ne sont pas éligibles à une réparation valvulaire percutanée, un remplacement valvulaire tricuspide percutané peut être envisagé, avec des systèmes en cours d'évaluation dans des études cliniques. Les résultats des premières études publiées semblent prometteurs^{55,56} et le traitement percutané est proposé dans les dernières recommandations Européennes comme une alternative possible à la chirurgie chez les patients ayant une IT fonctionnelle sévère symptomatique jugés inopérables dans un centre expert pour le traitement percutané de l'IT (classe IIb)³⁹.

La faisabilité de ces interventions dépend de considérations anatomiques et de la qualité de l'imagerie. L'ETO est l'examen clé dans la sélection des patients en vue d'une réparation ou d'une remplacement valvulaire tricuspide percutané, ainsi que pour le guidage péri-procédural, avec les incidences oesophagiennes et transgastriques. En cas d'échogénicité insuffisante en ETO, l'échocardiographie intra-cardiaque peut être utile pour guider les procédures interventionnelles (Annexe - Figure S2).

Objectifs du travail

1. Comment mesurer l'anneau tricuspide

Article 1. Comparaison entre les mesures de l'anneau tricuspide en échocardiographie bidimensionnelle et tri-dimensionnelle et en chirurgie – implications cliniques

- Evaluer la faisabilité et la reproductibilité des différentes incidences en échocardiographie transthoracique bidimensionnelle
- Comparer les mesures de l'AT obtenues en échocardiographie transthoracique bidimensionnelle, en échocardiographie trans-oesophagienne tri-dimensionnelle et en chirurgie
- Définir des seuils pathologiques qui pourraient être utilisés en routine pour guider les indications de geste concomitant sur la VT au moment d'une chirurgie valvulaire du cœur gauche

2. Histoire naturelle de l'insuffisance tricuspide fonctionnelle

Article 2. Remodelage cardiaque dans l'insuffisance tricuspide secondaire : devrait-on regarder au-delà de l'anneau tricuspide ?

- Caractériser les déterminants échocardiographiques de la sévérité d'une IT fonctionnelle isolée

3. Prise en charge médicale, chirurgicale et percutanée de l'insuffisance tricuspide

Article 3 : Insuffisance tricuspide : fréquence, prise en charge et pronostic parmi les patients ayant une valvulopathie sévère du cœur gauche en Europe

- Evaluer la fréquence et le grade de sévérité de l'IT chez les patients ayant une valvulopathie sévère du cœur gauche, dans l'ensemble et en fonction de chaque valvulopathie
- Analyser la présentation des patients en fonction du grade d'IT
- Analyser la survie globale et cardiovasculaire à 6 mois selon le grade d'IT chez les patients ayant une valvulopathie sévère du cœur gauche, dans l'ensemble et en fonction de chaque valvulopathie
- Analyser les taux d'intervention sur la VT au moment d'une intervention valvulaire du cœur gauche, dans l'ensemble et en fonction de chaque valvulopathie

- Evaluer la concordance entre les recommandations et les pratiques pour la réalisation d'un geste concomitant sur la VT au moment d'une chirurgie valvulaire du coeur gauche pour les patients ayant une indication de classe I (IT sévère)

Article 4 : Prise en charge et pronostic des patients hospitalisés pour insuffisance tricuspide en France

- Evaluer la présentation, la prise en charge et le devenir des patients hospitalisés pour IT à l'échelon national

Article 5 : Moment de la prise en charge chirurgicale des patients avec insuffisance tricuspide sévère isolée à l'échelon national

- Evaluer le devenir immédiat des patients après chirurgie isolée de la VT et les déterminants des complications hospitalières

Article 6 : Chirurgie valvulaire tricuspide isolée : impact de l'étiologie et de la présentation clinique sur le pronostic

- Evaluer les déterminants du pronostic intra-hospitalier et à moyen terme après chirurgie isolée de la valve tricuspide en fonction du mécanisme et de l'étiologie de l'insuffisance tricuspide, et plus spécifiquement l'impact de la présentation pré-opératoire

Article 7 : TRI-SCORE : un nouveau score de risque pour prédire la mortalité hospitalière après chirurgie valvulaire tricuspide isolée

- Développer un score de risque spécifiquement dédié à la prédiction à l'échelon individuel du risque de mortalité post-opératoire intra-hospitalière après chirurgie isolée de la valve tricuspide

Article 8 : Fiabilité du TRI-SCORE pour prédire la mortalité hospitalière après chirurgie redux isolée de la valve tricuspide

- Evaluer la fiabilité du TRI-SCORE pour prédire la mortalité hospitalière après chirurgie isolée redux de la VT

- Comparer la valeur prédictive du TRI-SCORE aux autres scores de risque chirurgicaux

Article 9: Première implantation chez l'homme d'un système de remplacement valvulaire tricuspide percutané avec la prothèse TOPAZ

- Réaliser les premières implantations chez l'homme de la prothèse Topaz, nouveau système de remplacement valvulaire tricuspide percutané par voie transfémorale

Comment mesurer l'anneau tricuspide

Article 1

Comparison of 2-Dimensional, 3-Dimensional, and Surgical Measurements of the Tricuspid Annulus Size. Clinical Implications

**Dreyfus J, Durand-Viel G, Raffoul R, Alkhoder S, Hvass U,
Radu C, Al-Attar N, Ghodbhane W, Attias D, Nataf P, Vahanian
A, Messika-Zeitoun D**

Circ Cardiovasc Imaging. 2015 Jul;8(7):e003241

Article 1. Comparaison entre les mesures de l'anneau tricuspide en échocardiographie bidimensionnelle et tri-dimensionnelle et en chirurgie.

Implications cliniques

Depuis 2007, les recommandations Européennes suggèrent de réaliser un geste chirurgical sur la VT au moment d'une chirurgie valvulaire du cœur gauche (le plus souvent mitrale), soit en cas d'IT sévère quel que soit le mécanisme de l'IT (classe I), soit lorsque l'AT est dilaté quel que soit le degré d'IT (classe IIa)^{39,57}. Le seuil retenu dans les recommandations pour considérer l'AT comme dilaté était un diamètre >40mm ou > 21mm/m² en échocardiographie transthoracique mais la façon de mesurer l'AT n'était pas clairement définie et les seuils retenus étaient basés sur une extrapolation de mesures chirurgicales⁷.

Les objectifs de cette étude étaient :

- Evaluer la faisabilité et la reproductibilité des différentes incidences en échocardiographie transthoracique bidimensionnelle (ETT-2D)
- Comparer les mesures de l'AT obtenues en ETT-2D, en échocardiographie transoesophagienne tri-dimensionnelle (ETO-3D) et en chirurgie
- Définir des seuils pathologiques qui pourraient être utilisés en routine pour guider les indications de geste concomitant sur la VT au moment d'une chirurgie valvulaire du cœur gauche

Dans une première population prospective, la mesure de l'AT a été réalisée en ETT-2D chez 282 patients dans 4 incidences différentes (parasternale grand axe, parasternale petit axe, apicale 4 cavités (A4C) et sous-costale) parmi lesquels 183 patients ont également eu une mesure du grand axe de l'AT en ETO-3D et 120 patients une mesure *chirurgicale de l'AT* (Figure 21).

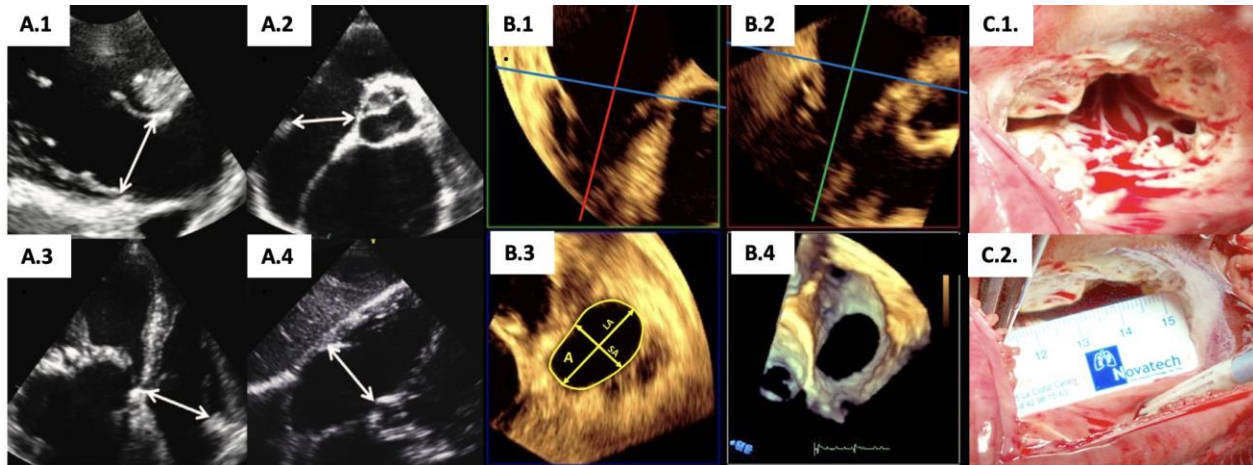


Figure 21. Mesure du diamètre de l'anneau tricuspide

- A. En échocardiographie transthoracique bidimensionnelle, dans les incidences A.1. parasternale grand axe, A.2. parasternale petit axe, A.3. apicale 4 cavités, A.4. sous-costale
- B. En échocardiographie trans-oesophagienne tri-dimensionnelle B.1 et B.2. reconstructions multiplanaires permettant d'obtenir B.3. la planimétrie de l'anneau tricuspide à partir de B.4. un volume tri-dimensionnel de la valve tricuspide
- C. Vue chirurgicale après atriotomie droite C.1. vue chirurgicale de la valve tricuspide, C.2. mesure chirurgicale de l'anneau tricuspide à l'aide d'une règle

Les flèches correspondent aux mesures des diamètres de l'anneau tricuspide

A : surface de l'anneau tricuspide, LA : grand axe de l'anneau tricuspide, SA : petit axe de l'anneau tricuspide

Bien que statistiquement significatives, les différences de mesures de l'AT entre les 4 incidences en ETT étaient faibles (respectivement 3.85 ± 0.58 , 3.87 ± 0.61 , 4.02 ± 0.69 et 3.92 ± 0.65 cm; $P < 0.0001$) et l'incidence A4C était celle qui était la plus faisable (respectivement 76%, 65%, 92% et 73%, $P < 0.0001$) et la plus reproductible.

Le diamètre de l'AT était plus petit dans l'incidence A4C en ETT-2D comparativement au grand axe de l'AT en ETO-3D (3.90 ± 0.63 versus 4.33 ± 0.62 cm; $P < 0.0001$) mais la corrélation était excellente ($r=0.84$; $P < 0.0001$) avec une sous-estimation systématique d'environ 4 mm (Figure 22).

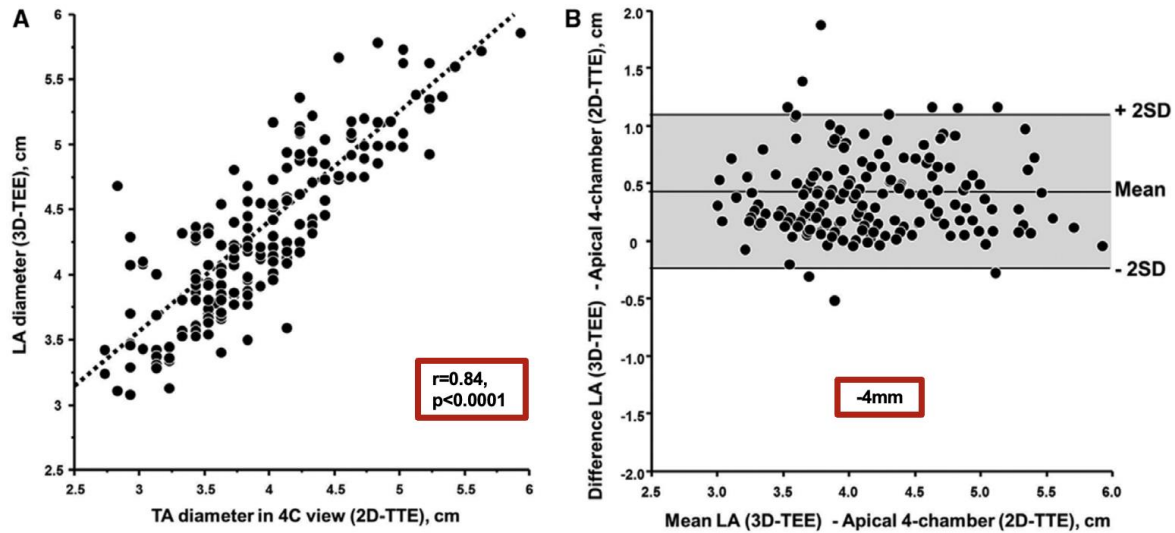


Figure 22. Comparaison entre les mesures du diamètre de l’anneau tricuspide dans l’incidence apicale 4 cavités en échocardiographie transthoracique bi-dimensionnelle et du grand axe de l’anneau tricuspide en échocardiographie trans-oesophagienne tri-dimensionnelle

A. Corrélation entre les mesures

B. Concordance entre les deux méthodes selon l’analyse de Bland et Altman

La ligne du milieu représente la moyenne et les lignes du dessus et du dessous délimitent l’intervalle de confiance à + ou – deux déviations-standard

LA : grand axe de l’anneau tricuspide en échocardiographie trans-oesophagienne tri-dimensionnelle, TA : diamètre de l’anneau tricuspide, TEE : échocardiographie trans-oesophagienne, TTE : échocardiographie transthoracique

Le diamètre de l’AT était plus petit dans l’incidence A4C en ETT-2D comparativement au diamètre mesuré chirurgicalement avec une corrélation modeste (4.11 ± 0.61 versus 4.37 ± 0.75 cm; $P < 0.0001$; $r = 0.57$; $P < 0.0001$) sachant que les mesures chirurgicales étaient peu reproductibles.

L’analyse tri-dimensionnelle de l’AT en ETO a permis de comprendre sa morphologie et son orientation. Ainsi, la morphologie de l’AT était le plus souvent ovalaire (indice d’excentricité moyen à 1.35), mais extrêmement variable d’un individu à l’autre, avec des formes allant de circulaire (indice d’excentricité à 1) à très allongées (indice d’excentricité > 2). L’orientation de l’AT était également très variable d’un individu à l’autre, de 5° à 175° en considérant l’angle entre

le grand axe de l'AT et un axe vertical passant par le septum-inter-atrial avec la valve aortique en haut à 0°, avec une distribution bi-modale. Les 2 orientations les plus fréquemment retrouvées étaient aux alentours de 40° et 140° (Figure 23).

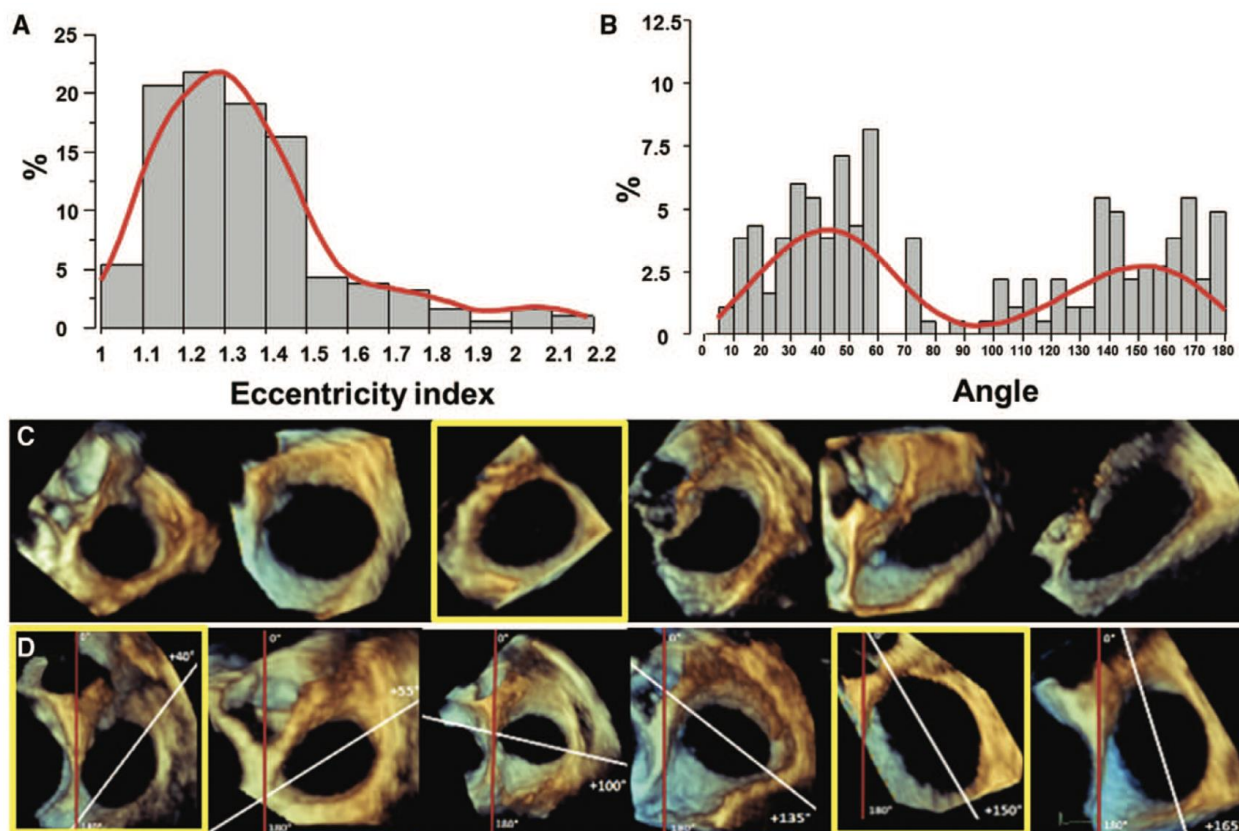


Figure 23. Morphologie et orientation de l'anneau tricuspide en échocardiographie trans-oesophagienne tri-dimensionnelle

- A. Distribution de l'indice d'excentricité de l'anneau tricuspide
- B. Distribution de l'orientation de l'anneau tricuspide
- C. Exemples de morphologie de l'anneau tricuspide, de circulaire à allongée, la forme la plus fréquente étant dans l'encadré jaune
- D. Exemples d'orientation de l'anneau tricuspide, les 2 orientations les plus fréquentes étant dans les encadrés jaunes

Dans une deuxième population prospective de 66 volontaires sains, la mesure du diamètre de l'AT a été réalisée dans l'incidence A4C, permettant de définir une valeur normale de 3.24 ± 0.46

cm ou 1.85 ± 0.23 cm/m², et des seuils pathologiques (valeur normale + 2 déviations standard) de 4.2 cm ou 2.3 cm/m².

Cette étude a donc montré que la mesure du diamètre maximal de l'AT en ETT dans l'incidence A4C était réalisable chez près de 95% des patients et reproductible, et bien que sous-estimant de façon systématique la mesure du grand axe de l'AT (d'environ 4 mm) comparativement à l'ETO-3D, offrait un bon reflet du degré de dilatation de l'AT. Les seuils obtenus à partir de sujets sains étaient relativement proches de ceux proposés dans les recommandations et actuellement utilisés en pratique^{39,40}.

Comparison of 2-Dimensional, 3-Dimensional, and Surgical Measurements of the Tricuspid Annulus Size Clinical Implications

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Background—Associated tricuspid annuloplasty is recommended during left-heart valve surgery when the tricuspid annulus (TA) is dilated but methodology for the measurement of TA size and thresholds for TA enlargement are not clearly defined.

Methods and Results—Measurement of the TA diameter (TAD) was prospectively performed using 2-dimensional transthoracic echocardiography (2D-TTE) in 282 patients in 4 different views (parasternal long axis, parasternal short axis, apical 4-chamber [A4C], and subcostal). TAD was also measured using 3D-transesophageal echocardiography in 183 patients (long axis), peroperatively in 120 patients who underwent a tricuspid valve surgery and using TTE (A4C) in 66 healthy volunteers. TAD was significantly different between the 4 2D-TTE views (3.85 ± 0.58 , 3.87 ± 0.61 , 4.02 ± 0.69 , and 3.92 ± 0.65 cm, respectively; $P<0.0001$) but differences were small and the A4C was the most feasible (76%, 65%, 92%, and 73%, respectively; $P<0.0001$) and offered the highest reproducibility. TAD measured in A4C view was smaller than when measured by 3D-transesophageal echocardiography (3.90 ± 0.63 versus 4.33 ± 0.62 cm; $P<0.0001$) but correlation was excellent ($r=0.84$; $P<0.0001$) with a systematic 4-mm underestimation. In contrast, 2D-TTE measurements were significantly smaller and only modestly correlated to surgical measurements (4.11 ± 0.61 versus 4.37 ± 0.75 cm; $P<0.0001$; $r=0.57$; $P<0.0001$) which were poorly reproducible. In healthy volunteers, we suggested 42 mm or 23 mm/m² as pathological values for the TAD in A4C.

Conclusions—Measurements of the TAD using 2D-TTE in A4C were highly feasible and reproducible and despite being systematically smaller than 3D measurements, accurately reflected the degree of TA enlargement as assessed using 3D transesophageal echocardiography. We proposed the thresholds that may be used in future prospective studies to demonstrate whether a preventive strategy would improve the outcome. (*Circ Cardiovasc Imaging*. 2015;8:e003241. DOI: 10.1161/CIRCIMAGING.114.003241.)

Key Words: aortic valve ■ echocardiography, three-dimensional ■ general surgery ■ mitral valve ■ tricuspid valve

Moderate or severe functional tricuspid regurgitation (TR) is commonly observed in patients with mitral valve disease and warrants concomitant or combined, at the same time, surgical correction.^{1,2} It is indeed well established that severe TR portends an adverse prognosis with an increase in mortality and morbidity³ and that TR only decreases temporarily and often worsens after the successful correction of the left-sided disease.⁴ Furthermore, short series have shown a 10% to 15% surgical mortality rate of isolated tricuspid valve surgery in highly selected patients.⁵⁻⁷ In contrast, tricuspid surgery eliminates TR and improves right ventricular function and this effect is durable over time.⁸

Clinical Perspective on p XXX

However, moderate or severe late TR often develops despite successful mitral valve correction and absence of TR

at the time of the index surgery.⁹⁻¹³ It has been suggested that tricuspid annulus (TA) enlargement may be a more sensitive criteria that may lead to the consideration of combined tricuspid surgery. Both the European Society of Cardiology and the recently published American College of Cardiology/American Heart Association guidelines recommend performing combined tricuspid surgery when the TA is enlarged even in the absence of significant TR (class IIa recommendation with a level C of evidence for the European Society of Cardiology and B for the American College of Cardiology/American Heart Association guidelines).^{1,2}

However, several issues remain to date unsolved. First, the incidence in which TA measurement should be performed (two-dimensional [2D] transthoracic echocardiography (TTE) in the apical 4-chamber [A4C] view in the European Society of Cardiology guidelines) relies on limited evidence. Second,

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the 3D shape of the TA is complex and whether currently performed 2D measurements accurately reflect the degree of TA enlargement has not been demonstrated. The 3D echocardiography now offers an accurate and real-time assessment of the size and shape of the TA¹⁴⁻¹⁶ to which both 2D and surgical measurements can be compared but such comparisons are seldom performed. Finally, recommended thresholds are not firmly established although they were evaluated in a few outcome studies.^{13,17,18} Thresholds of ≥ 40 mm or 21 mm/m² of body surface are proposed both in the European Society of Cardiology and in the American College of Cardiology/American Heart Association but it has also been suggested using direct surgical measurement but with a completely different threshold (70 mm) and the limitation of an obviously invasive method of measurement.⁹

Thus, the aims of the present study were (1) to evaluate the feasibility and the reproducibility of the different 2D-TTE views for TA measurements, (2) to compare TA measurements performed using 2D echocardiography, real-time 3D echocardiography and surgery, and finally (3) to provide TA thresholds that can be used in clinical practice to guide indications for the performance of associated tricuspid valve surgery.

Methods

Population

Patients

In this first subset, we prospectively enrolled 282 patients referred to our echocardiography laboratory between January 2010 and November 2013 who underwent a transthoracic and a transesophageal echocardiography (TEE) the same day performed by the last author. When available, the 3D-TEE probe was used (n=194). TTE and TEE were all clinically indicated. Patients with poor 2D-TTE image quality were excluded, whereas those in atrial fibrillation were not. In 120 patients who underwent combined tricuspid valve surgery within 15 days, TA size was measured peroperatively. Surgical decisions were made by the physician in charge of the patients. All TTE and TEE

were clinically indicated. The study was approved by our local ethical committee and informed consent was obtained from the patients.

Healthy Volunteers

In this second subset, we prospectively measured the TA size using 2D-TTE in 66 healthy volunteers. Healthy volunteers were mainly nurses, medical students, or physicians with no medical history, taking no medication and with no modifiable cardiovascular risk factors enrolled in an ongoing prospective study (GENERAC, clinical trial gov number NCT00647088). None of them had any echocardiographic abnormality including tricuspid valve or right-sided chambers abnormalities and thus could be surely considered as having normal tricuspid valve geometry.

Two-Dimensional Transthoracic Echocardiography

Two-dimensional-TTE was performed using a commercially available ultrasound system (S5-1 probe, IE33, Philips, Andover, MA or M4S probe, Vivid 7, General Electric, Fairfield, CT). TA diameter (TAD) was measured in 4 echocardiographic views: the parasternal long axis (LA) view of the right ventricle inflow (PS_{RVI}), parasternal short-axis view (PS_{SA}) at the level of the aortic valve, A4C, and the subcostal view (SC). Images were acquired in each view using the zoom mode focused on the tricuspid valve. Measurements of the TAD were performed offline by the first author at the time of the maximum TV diastolic opening between the 2 hinge points at the junction between the valvular leaflets and the TA (Figure 1). Three to 5 cycles were analyzed in each view and averaged. TR degree was semiquantitatively graded with color Doppler in 4 grades (absent, mild, moderate, and severe).¹⁹ Left ventricular systolic ejection fraction and systolic pulmonary artery pressure were measured as recommended.²⁰ Right ventricular dilatation was semiquantitatively assessed visually and graded as none, moderate, or severe.

Real-Time 3D-TEE

Three-dimensional-TEE was performed after topicalization using Xylocaine 2% and intravenous injection of midazolam using a commercially available matrix array transducer (X7-2t, Philips). Volumes were obtained using the zoom mode (1 beat) focused on the tricuspid valve in real-time 3D-TEE and digitally stored. The view was optimized for depth and gain setting before 3D acquisition and particular attention was given to including the entire TA in the sector boundaries.

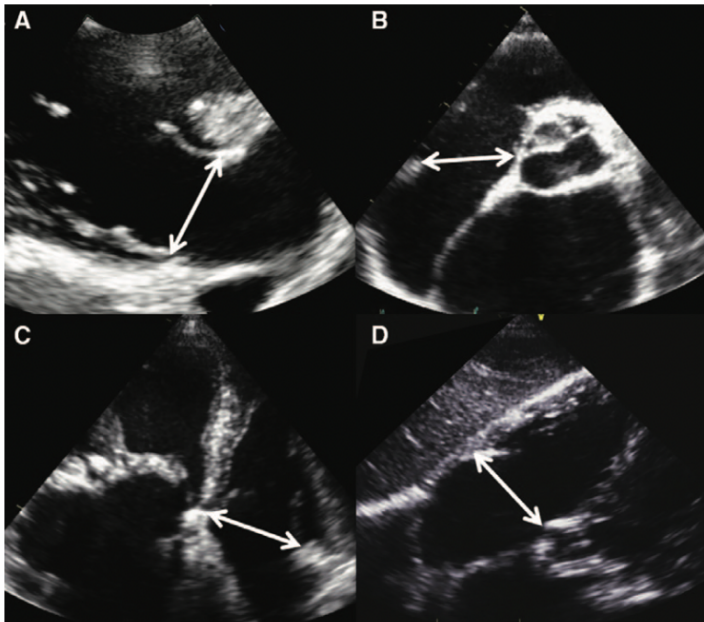


Figure 1. Measurements of the tricuspid annulus diameter using 2-dimensional transthoracic echocardiography. Measurements were performed in 4 views: (A) left parasternal long-axis view of the right ventricular inflow, (B) left parasternal short-axis view at the level of the aortic valve, (C) apical 4-chamber view, and (D) subcostal view.

Measurements of the TA were performed offline on a workstation using QLab7 software (Philips) by the first author in a random order and blinded to any clinical or echocardiographic information. Measurements were performed at the time of maximum diastolic leaflet opening. The plane of the TA was obtained by cutting the TA at its junction with the valvular leaflets in the different axes. From this plane, we measured the LA as the largest TAD, the short axis (SA), as the diameter perpendicular to the LA and the TA area (Figure 2). Measurements were performed in 3 to 5 cycles and averaged. TA eccentricity index (EI) was calculated as the LA/SA ratio. TA orientation (Figure 3) was evaluated by the angle between the LA and the vertical axis at the level of the interatrial septum in the surgical view (aortic valve on top, mitral valve on the left, and tricuspid valve on the right).

Surgical Measurements

TAD was measured in the operating room in unloaded conditions using a supple ruler as the maximal diameter from the interatrial septum to the opposite side in a so-called neutral position. A second measurement of the TA was also performed after slight traction was applied by the surgeon on the tricuspid valve (stretched measurement). Peroperative measurements were performed blinded of echocardiographic measurements.

Statistics

Quantitative variables were expressed as mean±SD. Comparison of the feasibility of the different TTE views was performed using the Cochran Q test and the McNemar test for pairwise comparisons to determine the most feasible view. A repeated measure ANOVA was performed to compare TA measurements performed in each TTE view and paired *t* tests and Pearson correlations for comparison between 2D-TTE, 3D-TEE, and surgery. Agreement between methods of TA measurements was assessed as described by Bland–Altman.²¹ Reproducibility of TA measurements, calculated as the absolute difference±SD, was evaluated for both 2D-TTE and 3D-TEE in 30 randomly selected patients a few weeks after the initial measurement for intraobserver variability (first author) and by a second observer (second author) for interobserver variability. Comparison of the differences between measurements (intra- and interobserver variability) was evaluated using a repeated measure

ANOVA and paired *t* test for pairwise comparisons. Intraclass correlations within each of the 4 views were also calculated. Pathological thresholds for TAD enlargement were defined as mean+2 SD of normal values obtained in the healthy volunteer subset. Time needed for 3D-TEE TA measurements was also evaluated in 30 patients. All tests were 2-sided. Statistical significance was defined with $P<0.05$. Statistics were performed using JMP software and MedCalc.

Results

Population

We prospectively enrolled 282 patients. Mean age was 60±16 years, 158 patients (56%) were women, 191 (68%) were in New York Heart Association functional class 3 or 4, 127 (45%) were in atrial fibrillation, and 180 (64%) had a rheumatic valve disease. The main reason for echocardiography was MV disease (90 mitral stenosis [32%] and 89 mitral insufficiency [32%]). Moderate or severe TR was present in 118 patients (42%) and mean systolic pulmonary artery pressure was 49±15 mmHg. Left ventricular ejection fraction was normal (≥60%) in 212 patients (75%). Right ventricular size was normal in 91 patients (33%), moderately enlarged in 118 (42%), and severely enlarged in 73 patients (26%).

Two-Dimensional TTE Measurements

Feasibility of TAD measurements in the 4 2D-TTE views was evaluated in the first 100 patients. Measurements were considered feasible in 1 view if image quality allowed clear measurement of the TAD. Feasibility of TAD measurements was significantly different between the 4 views (PS_{RVI} : 76%, PS_{SA} : 65%, A4C: 92%, and SC: 73%, respectively; $P<0.0001$) with the A4C view being the most feasible (P versus the 3 other views all <0.001).

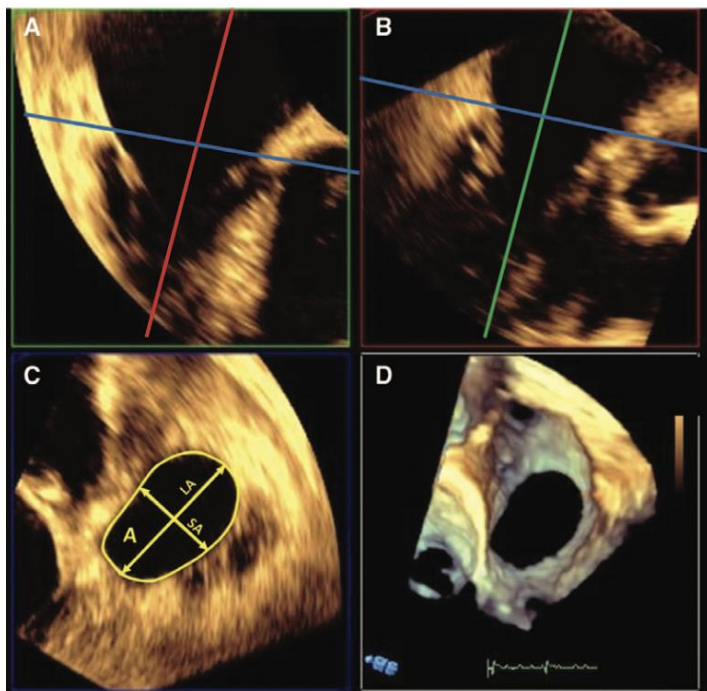


Figure 2. Measurements of the tricuspid annulus using 3-dimensional transesophageal echocardiography. The 3-dimensional volume (D) was sliced and oriented (A and B) to obtain a planimetry of the tricuspid annulus (C) and to measure the long axis (LA) diameter, the short-axis diameter (SA), and the tricuspid annulus area (A). The tricuspid annulus eccentricity index was defined as the ratio LA/SA.

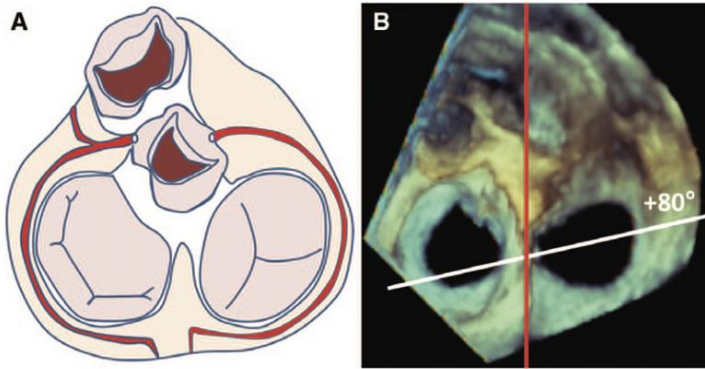


Figure 3. Tricuspid annulus orientation (3-dimensional transesophageal echocardiography). In the surgical view (A), the tricuspid orientation was evaluated by the angle between the long-axis (white line) and the vertical axis at the level of the interatrial septum (red line), with the aortic valve on the top (0°; B).

Comparison of TAD measurement was performed in 138 patients in whom the 4 TTE views were all feasible. There was a wide range of TAD from 2.5 to 5.9 cm. Correlations between views were excellent (from 0.69 to 0.85). TAD measurements were significantly different between views even if differences were minimal (PS_{RVI}: 3.85±0.58 cm, PS_{SA}: 3.87±0.61 cm, A4C: 4.02±0.69 cm, and SC: 3.92±0.65 cm; $P<0.0001$).

Intraobserver variability of TAD measurements between the 4 views was of borderline statistical significance (PS_{RVI}: -0.03±0.21 cm, PS_{SA}: -0.02±0.22 cm, A4C: -0.04±0.14 cm, and SC: 0.06±0.25 cm; $P=0.07$), whereas interobserver variability was significantly different (PS_{RVI}: 0.07±0.25 cm, PS_{SA}: 0.11±0.28 cm, A4C: -0.05±0.22 cm, and SC: 0.12±0.31 cm; $P=0.007$) and A4C achieved the highest reproducibility (all $P<0.05$). For intraobserver and for interobserver, intraclass correlations (95% confidence interval [CI]) for each of the 4 views were PS_{RVI}: 0.94 (0.90–0.96) and 0.91 (0.85–0.95), PS_{SA}: 0.92 (0.86–0.95) and 0.86 (0.77–0.92), A4C: 0.98 (0.97–0.99) and 0.96 (0.92–0.98), and SC: 0.93 (0.88–0.96) and 0.89 (0.80–0.94), respectively.

Thus, as the A4C offered the highest feasibility and reproducibility, A4C measurements were compared with 3D-TEE and surgical measurements.

Comparison With 3D-TEE Measurements

Evaluation of the TV using 3D-TEE was performed in 194 patients with feasible measurements of the TAD using TTE in the A4C view. Eleven patients (6%) were excluded because of poor image quality mostly related to an excess of gain (9 patients) or a truncated annulus (2 patients) thus leaving 183 patients who had both measurements of TA size using 2D-TTE in the A4C view and 3D-TEE.

TAD measured in A4C view correlated well with LA measured using 3D-TEE ($r=0.84$; $P<0.0001$) but was significantly smaller (3.90±0.63 and 4.33±0.62 cm; $P<0.0001$; Figure 4A and 4B). Correlation with the TA area was also excellent ($r=0.84$; $P<0.0001$). Thus, measurement of the TAD using 2D-TTE in the A4C view accurately reflected the degree of TA enlargement even if it did not measure its maximal diameter.

Intra- and interobserver variability of 3D measurements was good for diameters (0.02±0.15 and 0.09±0.19 cm for the

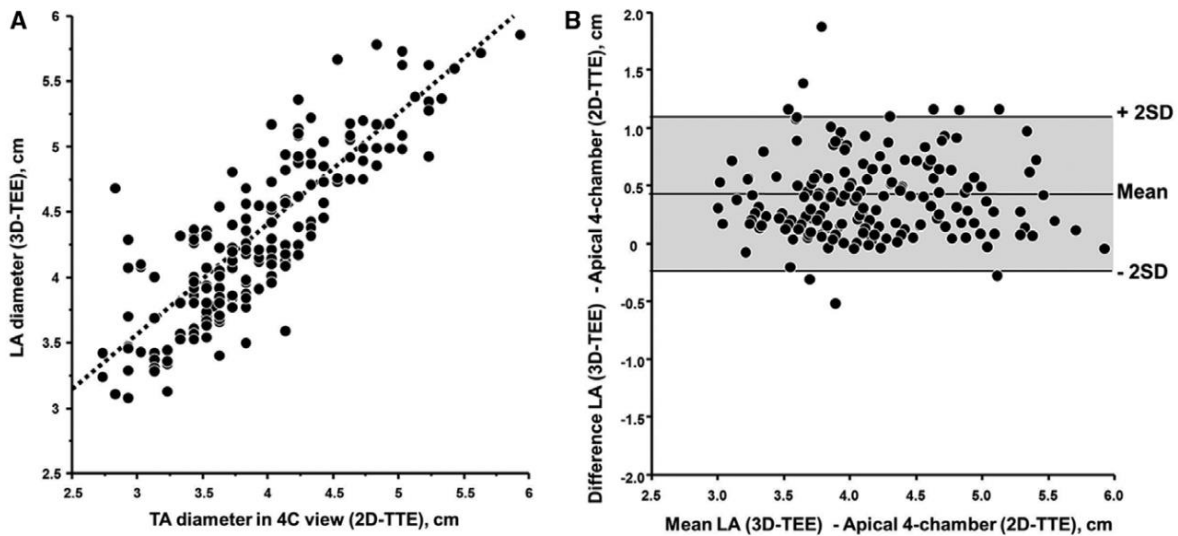


Figure 4. Comparison between 2-dimensional transthoracic echocardiography (2D-TTE) and 3D-transesophageal echocardiography (TEE) measurements of the tricuspid annulus (TA) diameter. **A**, Correlation between measurements of the TA diameter performed using 2D-TTE (apical 4-chamber [4C] view) and using the 3D-TEE (long axis [LA] diameter). **B**, Quality control plots using Altman and Bland analysis for the 2 methods. The middle line represents the mean and the upper and lower lines + or - SD.

LA and 0.02 ± 0.19 and 0.05 ± 0.22 cm for the SA, respectively) and area (0.09 ± 0.40 and 0.19 ± 0.52 cm², respectively). The mean time required for 3D measurements of TA size was 3 ± 1 minutes.

Impact of 3D Shape and Orientation of the TA on TTE Measurement

Shape

TA shape was generally oval (mean EI= 1.35 ± 0.22) but was markedly different among individuals from circular (EI=1) to severely oval (EI=2.15; median=1.31; 95% CI [1.07–2.04]; Figure 5A). TA dilatation seemed to occur homogeneously in all directions of the right ventricle free wall as suggested by the good correlation between TA area and both the LA ($r=0.89$; $P<0.0001$) and the SA ($r=0.88$; $P<0.0001$). Larger TA tended to be more circular with an inverse although modest correlation between TA area and EI ($r=-0.21$; $P<0.0001$). Accuracy of 2D-TTE measurements when compared with that of 3D-TEE was not influenced by the EI. When the population was dichotomized according to the median EI value (EI <1.31 or EI ≥ 1.31), excellent correlations between 2D-TTE and 3D-TEE measurements were observed in both subsets ($r=0.87$; $P<0.0001$ and $r=0.83$; $P<0.0001$, respectively) with a similar 4-mm systematic underestimation as shown by the Bland and Altman plots using 2D-TTE (Figure 6A–6D).

Orientation

Mean angle between the LA and the vertical axis at the level of the interatrial septum in the surgical view was $87^\circ \pm 57^\circ$ (median, 70; 95% CI [10–175]) but different orientations were observed among individuals from 5° to 175° with a bimodal distribution (Figure 5B). The 2 most frequent orientations were around 40° and 140° (LA directed toward the anterior and lateral side or toward the posterior and lateral side of the TA). TA orientation also did not affect the accuracy of TTE measurements as attested by the excellent correlations between TAD measurements performed using 2D-TTE in the A4C view and the LA measured using 3D-TEE in the subset of patients above or below the median angle value ($r=0.81$; $P<0.0001$ and $r=0.87$; $P<0.0001$, respectively) and a similar 4-mm systematic underestimation as shown by the Bland and Altman plots (Figure 6E–6H).

Comparison With Surgical Measurements

Surgical measurements of the TA were performed in 120 patients in the neutral position. TAD measurements obtained using 2D-TTE in the A4C view were significantly smaller but were only moderately correlated to surgical measurements (4.11 ± 0.61 versus 4.37 ± 0.75 cm; $P<0.0001$; $r=0.57$; $P<0.0001$). More importantly, a large SD of the difference was observed, twice the SD of the difference between 2D-TTE A4C and 3D-TEE LA measurements (0.64 versus 0.35 cm; Figure 7). In the 39 patients in whom 2D-TTE, 3D-TEE, and

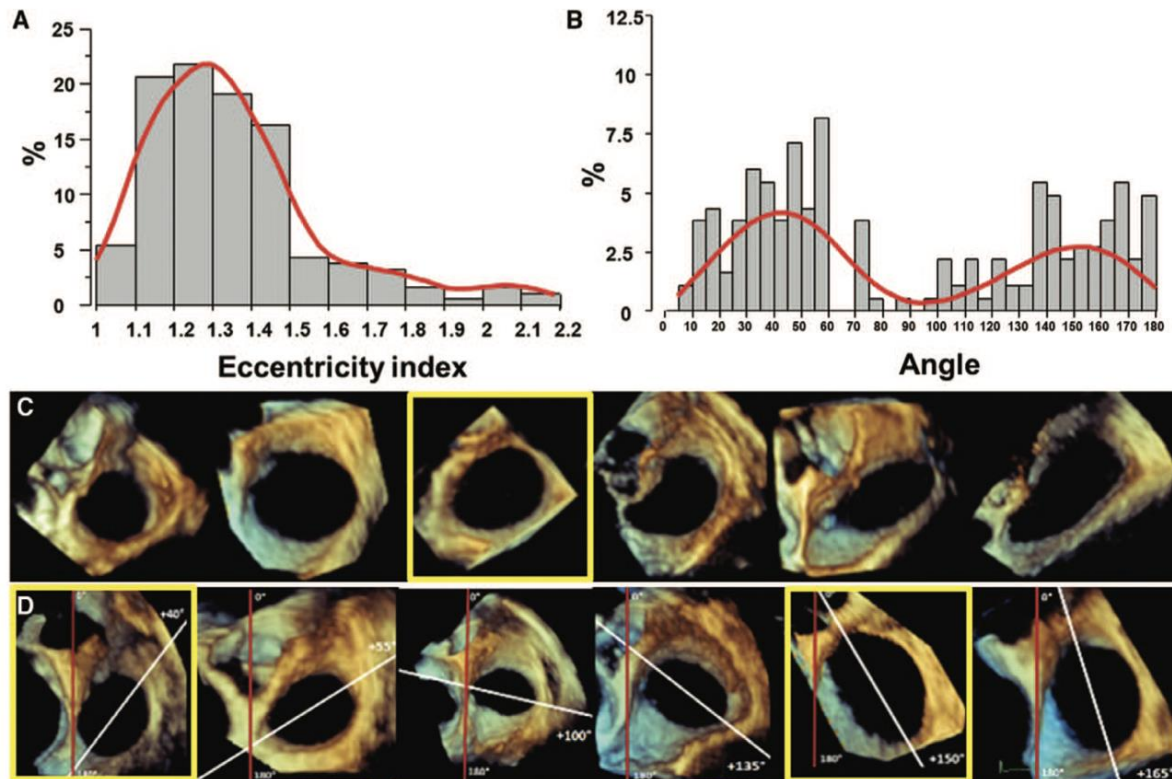


Figure 5. Tricuspid annulus shape and orientation. Distribution (A) of the eccentricity index and (B) of the orientation of the tricuspid annulus. C, Examples of shapes of the tricuspid annulus from circular to oval, with the most frequent morphology in the yellow box. D, Examples of orientations of the tricuspid annulus, with the 2 most frequent orientations in the yellow boxes.

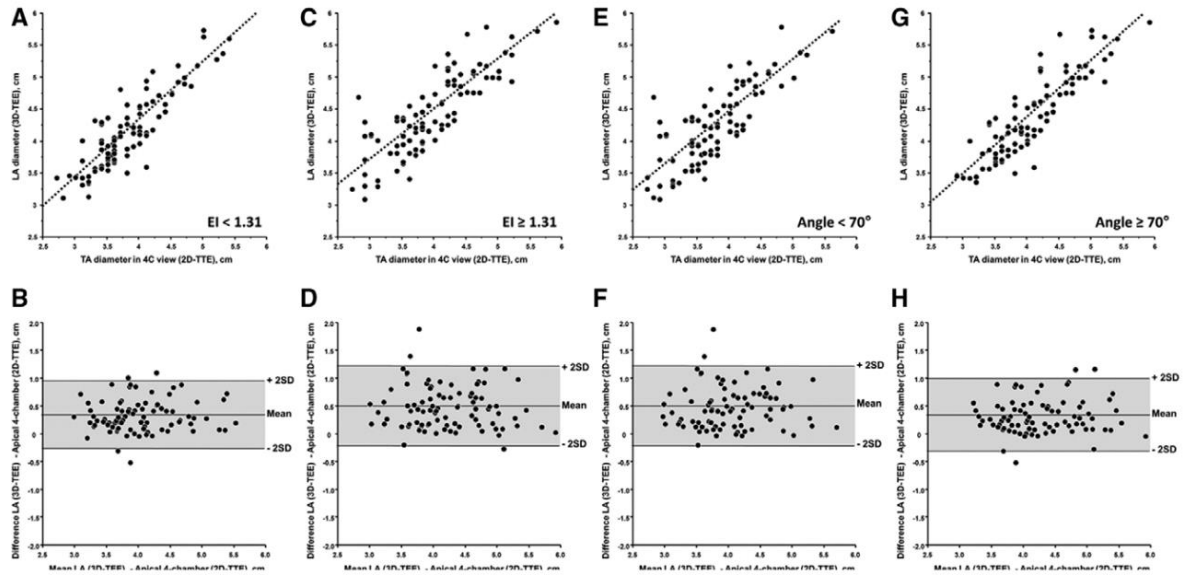


Figure 6. Impact of shape and orientation. Correlation between measurements of the tricuspid annulus (TA) diameter performed using 2-dimensional transthoracic echocardiography (2D-TTE; apical 4-chamber [4C] view) and using the 3D-transesophageal echocardiography (TEE; long axis [LA] diameter) and quality control plots using Altman and Bland analysis for the 2 methods in the subsets of patients with an eccentricity index (EI) <1.31 (A and B), with an EI ≥ 1.31 (C and D), with an angle between the long axis and the vertical axis in the surgical view < 70° (E and F) and with an angle between the long axis and the vertical axis in the surgical view $\geq 70^\circ$ (G and H). The middle line represents the mean and the upper and lower lines + or - 2 SD.

surgical measurements of TAD were performed, 3D-TEE and surgical measurements were not different (4.47 ± 0.63 versus 4.42 ± 0.79 cm; $P=0.68$) but correlation between methods was moderate ($r=0.50$; $P<0.0013$) and again a large SD of the difference was observed (0.71 cm; Figure 7). Finally, a slight traction applied on the TA orifice (stretched measurements performed in 91 patients) resulted in a >1 cm increase in surgical measurements of the TA (5.40 ± 0.76 versus 4.25 ± 0.76 cm, respectively; $P<0.0001$).

Healthy Volunteers

TAD was measured in the A4C view using 2D-TTE in 66 healthy volunteers. Mean age was 34 ± 12 years, 56% were women, and mean body surface area 1.76 ± 0.20 m². Normal values were 3.24 ± 0.46 cm (median, 3.2; 95% CI [2.37–4.17]) and 1.85 ± 0.23 cm/m² (median, 1.86; 95% CI [1.36–2.42]) and thresholds for TA enlargement, defined as mean normal value + 2 SD, were 4.2 cm and 2.3 cm/m², respectively.

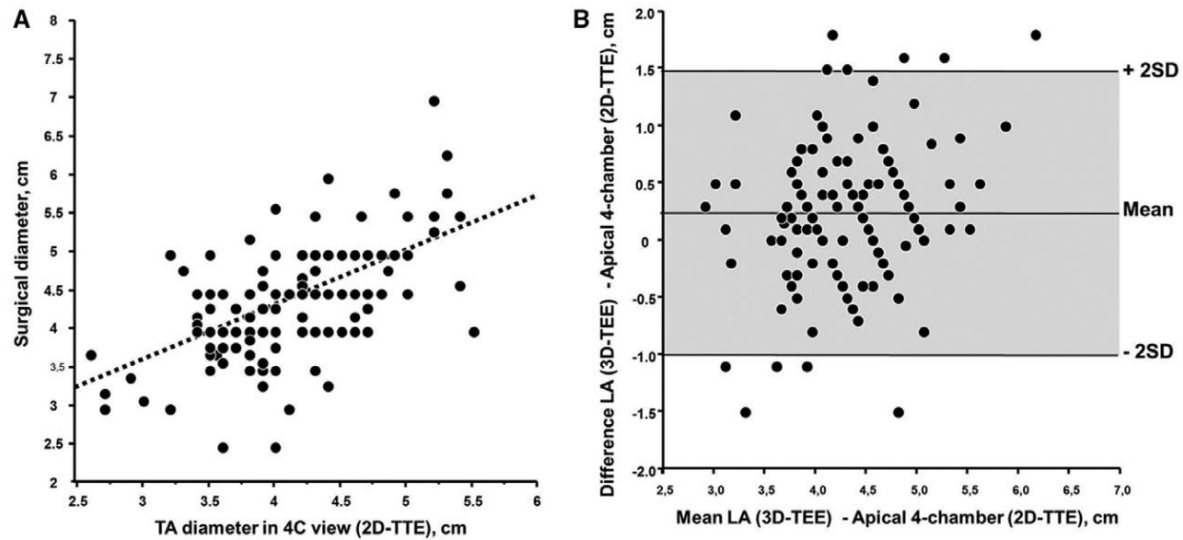


Figure 7. Comparison between surgical and 2-dimensional transthoracic echocardiography (2D-TTE) measurements of the tricuspid annulus (TA) diameter. A, Correlation between measurements of the TA diameter performed during surgery and using 2D-TTE (apical 4-chamber [4C] view). B, Quality control plots using Altman and Bland analysis for the 2 methods. The middle line represents the mean and the upper and lower lines + or - 2 SD. LA indicates long axis.

Discussion

The main results of the present study can be summarized as follows: (1) 2D-TTE measurements of the TAD were statistically different but differences were small and the A4C offered the highest feasibility and reproducibility; (2) 2D-TTE measurements were systematically smaller than the LA diameter of the TA measured using 3D-TEE but still reliably reflected the degree of TA enlargement using this method; (3) shape and orientation of the TA were highly variable among individuals but did not affect the accuracy of 2D-TEE measurements; (4) using current methodology surgical measurements were poorly reproducible as a slight traction on the TA resulted in marked changes in TA measurements; and (5) in healthy volunteers, we defined normal (3.2 cm or 1.8 cm/m²) and pathological values (4.2 cm or 2.3 cm/m²) of the TAD that could be used in clinical practice to consider the performance of a combined tricuspid annuloplasty.

TR has for a long time falsely been considered as a benign condition that could be neglected. In the past 15 years, there is a growing body of literature showing that not only is TR a marker/prognostic factor of poor outcome²² but also that TR by itself directly affects the outcome.³ There is now a consensus to correct moderate or severe TR at the same time as the left side surgery. However, the absence of moderate/severe TR is falsely reassuring and has a poor sensitivity and negative predictive value for the occurrence of late significant TR. As TA enlargement appears earlier in the course of the disease,²³ current recommendations have incorporated, in addition to TR degree, enlarged TAD as an indication for combined surgery to avoid the occurrence of significant late TR and the need for a risky redo operation. It is worth noting that this combined surgery, mainly tricuspid annuloplasty, adds little time to the mitral valve surgery and is associated with few complications.^{9,24} Such a preventive strategy is supported by a few nonrandomized studies^{13,17,18} showing that concomitant tricuspid annuloplasty prevents progression of TR and occurrence of significant late TR and promotes right ventricular reverse remodeling and thus improvement of right ventricular function. Nevertheless, neither the methodology of measurement of the TAD nor thresholds have been firmly established.

The 2D-TTE is the most common echocardiographic modality and the most common method used to assess TA size. TAD can be measured in different views and comparisons between views as well as the reproducibility of TTE measurements are rare. In the present study, we show that overall the different views were statistically different but differences were minimal and the A4C view, which is indeed the most commonly used, provided the highest feasibility and reproducibility. An important finding of the present study is to show that TA measurements performed in the A4C using TTE accurately reflected the degree of TA enlargement. Using 3D echocardiography it is now possible to visualize, under physiological conditions, the TA with high image resolution and no need for complex and time-consuming reconstruction. With technological improvements, an image of the entire TA can now be captured in 1 beat with no need for breath holding which is crucial as atrial fibrillation is common in patients with mitral valve disease. In the present study, feasibility of 3D-TEE was high and of the few patients we had to exclude

most were at the beginning of our experience. TAD measured in the A4C was smaller than the TA LA diameter measured using 3D TEE but correlations were excellent and the Bland and Altman clearly show a systematic underestimation of TTE measurements validating 2D TEE in the A4C as an accurate method to assess TA size in a large series of patients with a wide range of TA values. In addition, 3D-TEE provided an assessment of TA morphology and orientation, both of which were highly variable from 1 individual to the other but did not affect the accuracy of TTE measurements.

Direct measurements by the surgeon are intuitively regarded as more reliable and often considered as the gold standard. The present study clearly shows the current limits of surgical measurements. In contrast to 3D-TEE, surgical measurements are performed under unloaded conditions and measurements are highly dependent on the force applied to the TA. Minimal changes in the traction applied to the TA resulted in important changes in the TAD. In addition, there is no commercial tool dedicated to the measurement of TA size in contrast to the aortic annulus. Measurements were performed with a simple rule which was not always easy to precisely insert into the tricuspid valve. It is worth noting that we never achieved TAD values of 70 mm either using 3D or during surgery and most probably measurements obtained by Dreyfus and al⁹ reflected the maximum elongation of the TA. Overall our results are strong arguments to standardize surgical measurements using appropriate and dedicated tools for the assessment of TA size.

The present study deserves several comments. First, we used 3D-TEE as the reference method. In spite of the fact that we could not validate this method against a gold standard, validity and accuracy of 3D measurements are now well demonstrated.^{9,25,26} Second, no comparison with 3D-TTE was performed. In our experience, image quality of 3D-TTE is lower than that of 3D-TEE especially for posterior structures such as the mitral or tricuspid valve. Third, TR degree and TA size may vary according to loading conditions. In the present study, all TTE and TEE measurements were performed successively during the same examination and TEEs were performed under local anesthesia and midazolam. Fourth, for both TTE and TEE measurements, we assessed the intra- and interobserver variability of TA measurements but not of image acquisition. However, these acquisitions are standardized and poorly operator dependent. Fifth, our study cannot provide a definite answer on the anatomic correspondence between the 2D-TTE (A4C) and 3D-TEE (LA) measurements. Measurements in the A4C view are performed between the septal and anterior leaflet. In regard to the excellent correlation between both measurements, we may hypothesize that TTE measurements are performed in a direction grossly parallel to the LA. Further studies using ideally 3D-TTE may confirm or not this hypothesis. Sixth, not all examinations were performed in all patients. Surgical measurements were of course only performed in operated patients for whom the physician in charge asked for combined tricuspid surgery. Parts of the TEE were performed using a probe with no 3D capabilities because of logistic issues. Finally, as peroperative measurements were only performed in patients referred for combined tricuspid surgery, surgeons might have expected significant

TR or TA enlargement. Nevertheless, surgical measurements were performed blinded of echocardiographic measurements.

Accurate echocardiographic measurement of the TA has important clinical and surgical implications. Combined tricuspid valve surgery remains underused representing 10% of mitral valve operations and it is estimated that 75% of these patients have TA changes associated with functional TR.²⁷ As mentioned previously, we filled several gaps in knowledge highlighted in the current guidelines. We validated a feasible and reproducible methodology to assess the TA size and proposed thresholds that could be used in clinical practice to recommend performing a combined tricuspid surgery. Using 3D as a reference, we validated measurements performed using TTE in the A4C view and defined thresholds of TA enlargement in a subset of healthy volunteers (>42 mm or >23 mm/m² of body surface area). These thresholds were close but not identical to those suggested in the guidelines. Thus, the present study offers the appropriate methodology and thresholds to validate in future randomized prospective studies whether a preventive strategy results in improvement of the outcome of patients who undergo a mitral valve surgery.

Conclusions

In a large cohort of patients with a wide range of TA size, we validated the measurements of the TAD using TTE and the A4C view. Two-dimensional measurements in the A4C were highly feasible and reproducible and despite being systematically smaller than 3D measurements, accurately reflect the degree of TA enlargement as assessed using this method. The accuracy of the A4C was not influenced by TA orientation and shape which were highly variable among individuals. In contrast, surgical measurements, performed in unloaded conditions, were highly variable depending of the traction strength applied to the tricuspid valve highlighting the need to develop a standardized method using dedicated tools for the assessment of TA size. We propose the thresholds of 42 mm or 23 mm/m² that may lead to consider tricuspid surgery at the same time as left-sided surgery. Further prospective studies using this methodology and those thresholds are now necessary to validate whether a preventive strategy can improve outcome.

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Disclosures

None.

References

1. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Jung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Popescu BA, Von Segesser L, Badano LP, Bunc M, Claeys MJ, Drinkovic N, Filippatos G, Habib G, Kappetein AP, Kassab R, Lip GY, Moat N, Nickenig G, Otto CM, Pepper J, Piazza N, Pieper PG, Rosenhek R, Shuka

- N, Schwammenthal E, Schwitter J, Mas PT, Trindade PT, Walther T. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2012;33:2451–2496.
2. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O’Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD; ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:2440–2492. doi: 10.1161/CIR.000000000000029.
3. Messika-Zeitoun D, Thomson H, Bellamy M, Scott C, Tribouilloy C, Dearani J, Tajik AJ, Schaff H, Enriquez-Sarano M. Medical and surgical outcome of tricuspid regurgitation caused by flail leaflets. *J Thorac Cardiovasc Surg*. 2004;128:296–302. doi: 10.1016/j.jtcvs.2004.01.035.
4. Yilmaz O, Suri RM, Dearani JA, Sundt TM 3rd, Daly RC, Burkhart HM, Li Z, Enriquez-Sarano M, Schaff HV. Functional tricuspid regurgitation at the time of mitral valve repair for degenerative leaflet prolapse: the case for a selective approach. *J Thorac Cardiovasc Surg*. 2011;142:608–613. doi: 10.1016/j.jtcvs.2010.10.042.
5. Kim YJ, Kwon DA, Kim HK, Park JS, Hahn S, Kim KH, Kim KB, Sohn DW, Ahn H, Oh BH, Park YB. Determinants of surgical outcome in patients with isolated tricuspid regurgitation. *Circulation*. 2009;120:1672–1678. doi: 10.1161/CIRCULATIONAHA.109.849448.
6. Teman NR, Huffman LC, Krajačić M, Pagani FD, Haft JW, Bolling SF. “Prophylactic” tricuspid repair for functional tricuspid regurgitation. *Ann Thorac Surg*. 2014;97:1520–1524. doi: 10.1016/j.athoracsur.2013.11.049.
7. Kwon DA, Park JS, Chang HJ, Kim YJ, Sohn DW, Kim KB, Ahn H, Oh BH, Park YB, Choi YS. Prediction of outcome in patients undergoing surgery for severe tricuspid regurgitation following mitral valve surgery and role of tricuspid annular systolic velocity. *Am J Cardiol*. 2006;98:659–661. doi: 10.1016/j.amjcard.2006.03.047.
8. Desai RR, Vargas Abello LM, Klein AL, Marwick TH, Krasuski RA, Ye Y, Nowicki ER, Rajeswaran J, Blackstone EH, Pettersson GB. Tricuspid regurgitation and right ventricular function after mitral valve surgery with or without concomitant tricuspid valve procedure. *J Thorac Cardiovasc Surg*. 2013;146:1126–1132.e10. doi: 10.1016/j.jtcvs.2012.08.061.
9. Dreyfus GD, Corbi PJ, Chan KM, Bahrani T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? *Ann Thorac Surg*. 2005;79:127–132. doi: 10.1016/j.athoracsur.2004.06.057.
10. Matsunaga A, Duran CM. Progression of tricuspid regurgitation after repaired functional ischemic mitral regurgitation. *Circulation*. 2005;112(9 Suppl): I453–I457. doi: 10.1161/CIRCULATIONAHA.104.524421.
11. Matsuyama K, Matsumoto M, Sugita T, Nishizawa J, Tokuda Y, Matsuo T. Predictors of residual tricuspid regurgitation after mitral valve surgery. *Ann Thorac Surg*. 2003;75:1826–1828.
12. Song H, Kang DH, Kim JH, Park KM, Song JM, Choi KJ, Hong MK, Chung CH, Song JK, Lee JW, Park SW, Park SJ. Percutaneous mitral valvuloplasty versus surgical treatment in mitral stenosis with severe tricuspid regurgitation. *Circulation*. 2007;116(11 Suppl):I246–I250. doi: 10.1161/CIRCULATIONAHA.107.678151.
13. Benedetto U, Melina G, Angeloni E, Refice S, Roscitano A, Comito C, Sinatra R. Prophylactic tricuspid annuloplasty in patients with dilated tricuspid annulus undergoing mitral valve surgery. *J Thorac Cardiovasc Surg*. 2012;143:632–638. doi: 10.1016/j.jtcvs.2011.12.006.
14. Fukuda S, Saracino G, Matsumura Y, Daimon M, Tran H, Greenberg NL, Hozumi T, Yoshikawa J, Thomas JD, Shiota T. Three-dimensional geometry of the tricuspid annulus in healthy subjects and in patients with functional tricuspid regurgitation: a real-time, 3-dimensional echocardiographic study. *Circulation*. 2006;114(1 Suppl):I492–I498. doi: 10.1161/CIRCULATIONAHA.105.000257.
15. Ring L, Rana BS, Kydd A, Boyd J, Parker K, Rusk RA. Dynamics of the tricuspid valve annulus in normal and dilated right hearts: a three-dimensional transoesophageal echocardiography study. *Eur Heart J Cardiovasc Imaging*. 2012;13:756–762. doi: 10.1093/ehjci/jes040.
16. Ton-Nu TT, Levine RA, Handschumacher MD, Dorer DJ, Yosefy C, Fan D, Hua L, Jiang L, Hung J. Geometric determinants of functional tricuspid regurgitation: insights from 3-dimensional echocardiography. *Circulation*. 2006;114:143–149. doi: 10.1161/CIRCULATIONAHA.106.611889.
17. Van de Veire NR, Braun J, Delgado V, Versteegh MI, Dion RA, Klautz RJ, Bax JJ. Tricuspid annuloplasty prevents right ventricular dilatation and progression of tricuspid regurgitation in patients with tricuspid annular dilatation undergoing mitral valve repair. *J Thorac Cardiovasc Surg*. 2011;141:1431–1439.

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18. Colombo T, Russo C, Ciliberto GR, Lanfranconi M, Bruschi G, Agati S, Vitali E. Tricuspid regurgitation secondary to mitral valve disease: tricuspid annulus function as guide to tricuspid valve repair. *Cardiovasc Surg.* 2001;9:369–377.
19. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16:777–802. doi: 10.1016/S0894-7317(03)00335-3.
20. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr.* 1989;2:358–367.
21. Altman D, Bland J. Measurement in medicine: the analysis of method comparison studies. *The Statistician.* 1983;32:307.
22. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol.* 2004;43:405–409. doi: 10.1016/j.jacc.2003.09.036.
23. Shiran A, Sagie A. Tricuspid regurgitation in mitral valve disease incidence, prognostic implications, mechanism, and management. *J Am Coll Cardiol.* 2009;53:401–408. doi: 10.1016/j.jacc.2008.09.048.
24. Tang GH, David TE, Singh SK, Maganti MD, Armstrong S, Borger MA. Tricuspid valve repair with an annuloplasty ring results in improved long-term outcomes. *Circulation.* 2006;114(1 Suppl):I577–I581. doi: 10.1161/CIRCULATIONAHA.105.001263.
25. Mor-Avi V, Jenkins C, Kühl HP, Nesser HJ, Marwick T, Franke A, Ebner C, Freed BH, Steringer-Mascherbauer R, Pollard H, Weinert L, Niel J, Sugeng L, Lang RM. Real-time 3-dimensional echocardiographic quantification of left ventricular volumes: multicenter study for validation with magnetic resonance imaging and investigation of sources of error. *JACC Cardiovasc Imaging.* 2008;1:413–423. doi: 10.1016/j.jcmg.2008.02.009.
26. Mor-Avi V, Yodwut C, Jenkins C, Kühl H, Nesser HJ, Marwick TH, Franke A, Weinert L, Niel J, Steringer-Mascherbauer R, Freed BH, Sugeng L, Lang RM. Real-time 3D echocardiographic quantification of left atrial volume: multicenter study for validation with CMR. *JACC Cardiovasc Imaging.* 2012;5:769–777. doi: 10.1016/j.jcmg.2012.05.011.
27. Rogers JH, Bolling SF. The tricuspid valve: current perspective and evolving management of tricuspid regurgitation. *Circulation.* 2009;119:2718–2725. doi: 10.1161/CIRCULATIONAHA.108.842773.

CLINICAL PERSPECTIVE

Accurate echocardiographic measurement of the tricuspid annulus (TA) size has important clinical and surgical implications. Associated tricuspid annuloplasty is recommended during left-heart valve surgery in cases of moderate to severe tricuspid regurgitation or when the TA is dilated but combined tricuspid valve surgery remains underused and the methodology for the measurement of TA size and thresholds for TA enlargement are not clearly defined. Using 3-dimensional as a reference, we validated measurements performed using transthoracic echocardiography in the apical 4-chamber view and defined thresholds of TA enlargement in a subset of healthy volunteers (>42 mm or >23 mm/m² of body surface area). The present study thus may offer tools for future randomized prospective studies studying the impact of tricuspid annuloplasty in patients undergoing mitral valve surgery.

**Histoire naturelle de l'insuffisance tricuspide
fonctionnelle**

Article 2

**Cardiac remodelling in secondary tricuspid
regurgitation:**

**Should we look beyond the tricuspid annulus
diameter?**

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Arch Cardiovasc Dis. 2021 Apr;114(4):277-286

Article 2 : Remodelage cardiaque dans l'insuffisance tricuspide secondaire : devrait-on regarder au-delà de l'anneau tricuspide ?

L'IT fonctionnelle est secondaire à une dilatation de l'AT favorisée par à une dilatation de l'OD et/ou un tenting des feuillets valvulaires induit par une dilatation du VD⁸.

L'évaluation fiable du degré de sévérité de l'IT et du remodelage des cavités droites est un défi quotidien sachant qu'une nouvelle classification des grades de sévérité de l'IT a été proposée¹⁹ et que l'apparition progressive d'une dilatation ou d'une dysfonction VD sont des paramètres échocardiographiques proposés dans les recommandations pour réaliser un geste chirurgical en cas d'IT sévère isolée asymptomatique, sans préciser de seuil⁵⁸.

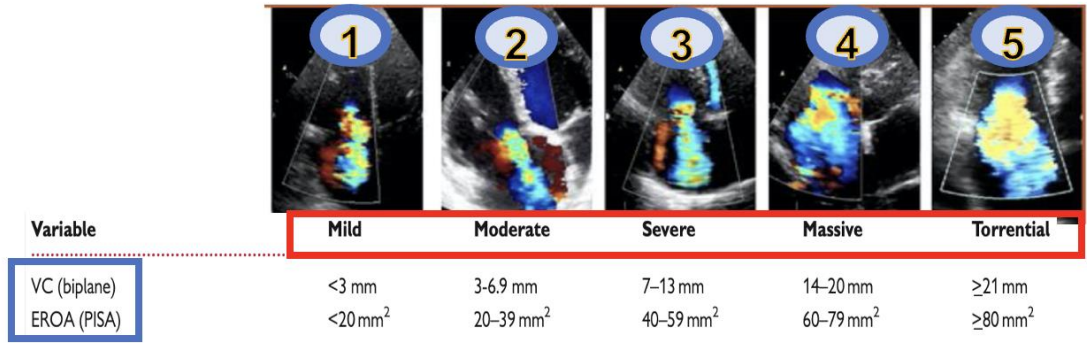
L'objectif principal de cette étude était de caractériser les déterminants échocardiographiques de la sévérité d'une IT fonctionnelle isolée chez des patients stables avec fraction d'éjection ventriculaire gauche (FEVG) préservée.

Dans un registre multicentrique (13 centres Français) « TRAP » de la Filiale d'Imagerie de la Société Française de Cardiologie, 100 patients consécutifs avec IT fonctionnelle isolée initialement sévère, pour lesquels le traitement médical a été optimisé et sans décompensation cardiaque depuis au moins 1 mois, ont été prospectivement inclus pour une évaluation échocardiographique systématisée. Toutes les mesures échocardiographiques ont été réalisées par un Core Lab.

L'évaluation du degré de sévérité de l'IT était basée sur la classification proposée par *Hahn et al.*¹⁹, la SOR par la méthode PISA étant retenue comme le paramètre de référence pour définir la sévérité de la fuite.

De nombreuses différences de gradation du degré de sévérité de l'IT étaient retrouvées selon que le paramètre utilisé était la SOR ou la vena contracta (Figure 24).

A.



B.

| | | TR severity according to EROA | | | | |
|------------------------------|------------|-------------------------------|----------|--------|---------|------------|
| | | Mild | Moderate | Severe | Massive | Torrentiel |
| TR severity according to VCW | Mild | 1 | 0 | 0 | 0 | 0 |
| | Moderate | 10 | 21 | 5 | 0 | 0 |
| | Severe | 1 | 10 | 12 | 14 | 12 |
| | Massive | 0 | 0 | 1 | 3 | 6 |
| | Torrentiel | 0 | 0 | 0 | 0 | 4 |

Figure 24. Grades de sévérité de l'insuffisance tricuspide en fonction de la surface de l'orifice régurgitant et de la vena contracta

- A. Classification en 5 grades avec seuils pour la surface de l'orifice régurgitant et la vena contracta, d'après Hahn et al¹⁹
- B. Tableau de contingence de la distribution des patients de l'étude pour chacun des grades de sévérité d'insuffisance tricuspide en fonction de la surface de l'orifice régurgitant ou de la vena contracta

Les encadrés rouges correspondent aux patients qui étaient référencés dans le même grade de sévérité d'IT quel que soit le paramètre utilisé

Les encadrés jaunes correspondent aux patients qui étaient référencés dans des grades de sévérité d'IT différents selon que le paramètre utilisé soit la surface de l'orifice régurgitant ou la vena contracta

EROA : surface de l'orifice régurgitant, TR : insuffisance tricuspide, VC biplane ou VCW: vena contracta biplan

Il existait une excellente corrélation entre le degré de sévérité de l'IT et les paramètres de dilatation des cavités droites ($P < 0.001$ pour tous les paramètres en analyse univariée) (Figure 25), notamment le volume de l'OD et la surface de tenting de la VT ($P < 0.001$ et $P = 0.005$ respectivement en analyse multivariée), en plus du diamètre de l'AT. Ainsi, si le diamètre de l'AT était ≥ 50 mm, la probabilité d'avoir une IT \geq sévère était $>70\%$, pour une augmentation de 10ml/m^2 du volume de l'OD, la SOR augmentait de $4,2\text{mm}^2$, et pour une augmentation de $0,1\text{cm}^2$ de l'aire sous la tente, la SOR augmentait de $2,35\text{mm}^2$.

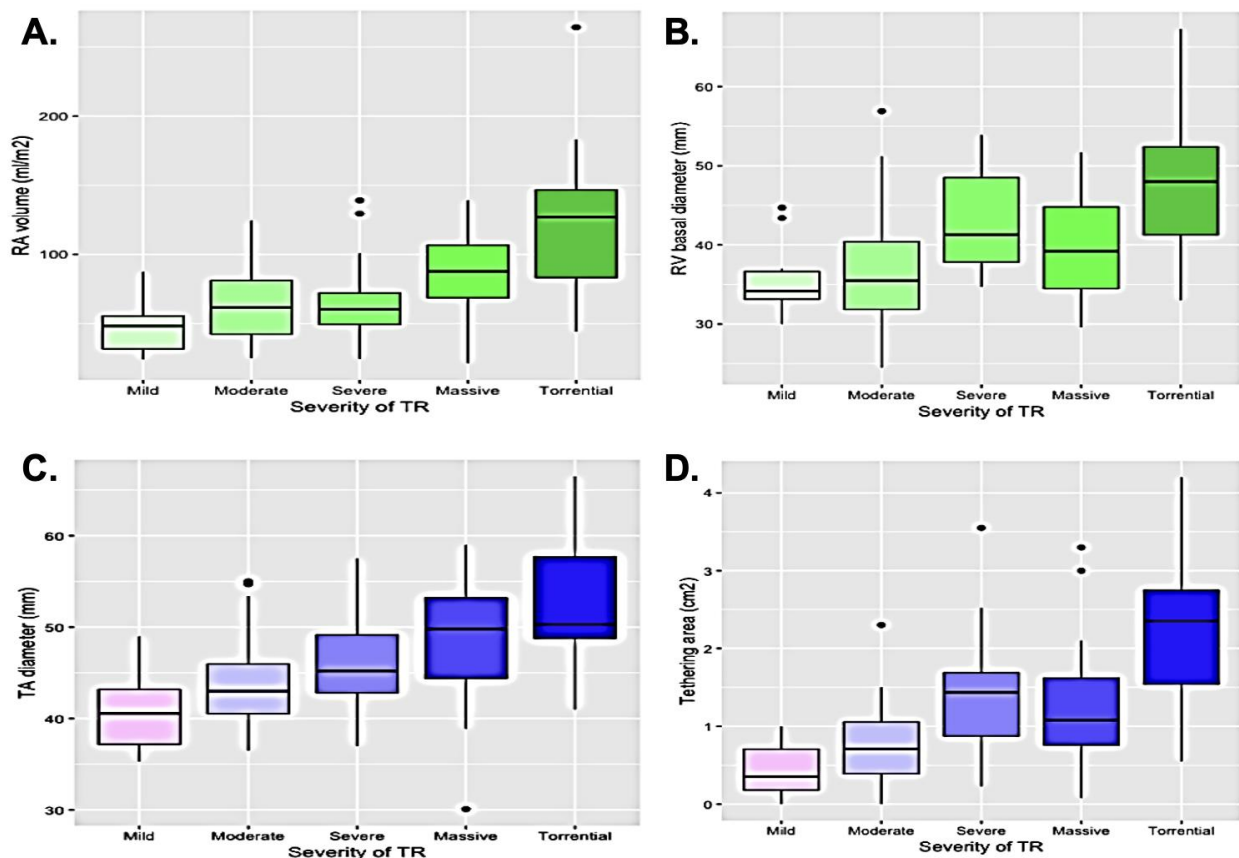


Figure 25. Diagrammes de boîtes entre le degré de sévérité de l'insuffisance tricuspide et des paramètres de remodelage de la valve tricuspide et des cavités droites

- A. Volume de l'oreille droite
- B. Diamètre basal du ventricule droit
- C. Diamètre de l'anneau tricuspide

D. Surface de tenting valvulaire tricuspide

RA : oreillette droite, RV : ventricule droit, TA : anneau tricuspide, TR : insuffisance tricuspide

A l'inverse, il n'y avait pas de corrélation entre le degré de sévérité de l'IT et les paramètres de fonction du VD ($P > 0.14$ pour tous les paramètres) (Figure 26).

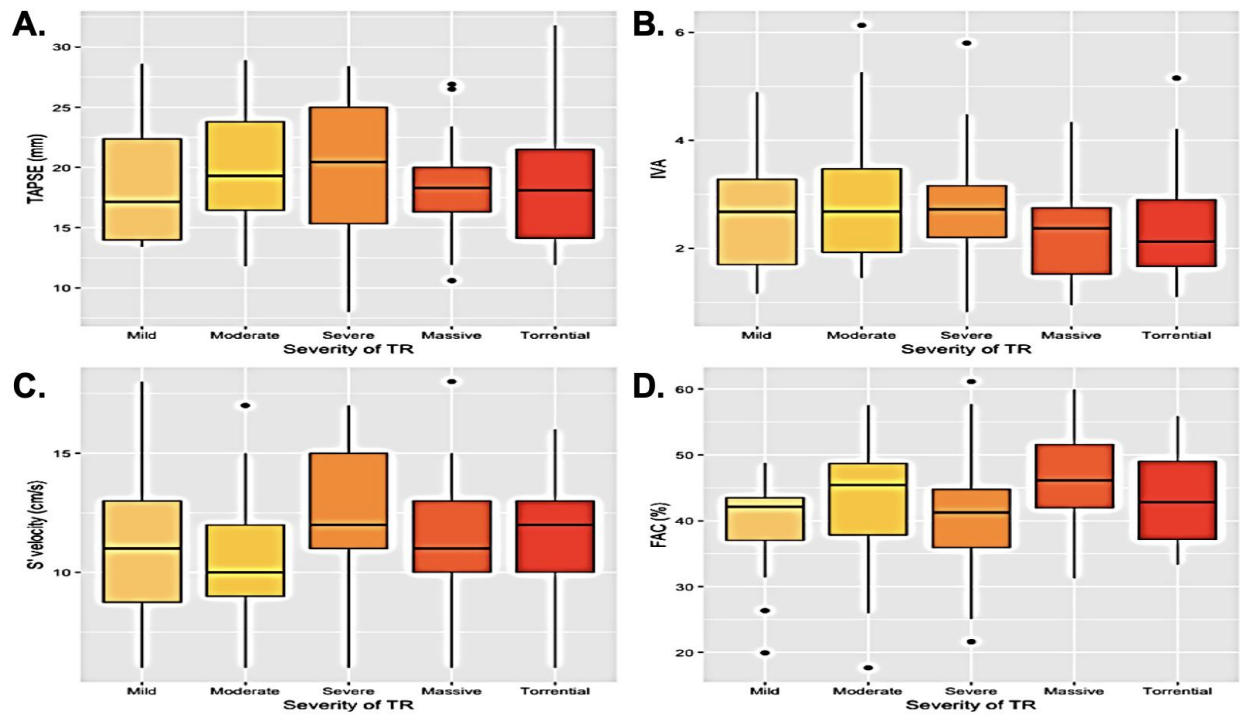


Figure 26. Diagrammes de boîtes entre le degré de sévérité de l'insuffisance tricuspide et des paramètres de fonction du ventricule droit

A. Excursion systolique du plan de l'anneau

B. Accélération de la contraction isovolumique

C. Onde S' à l'anneau tricuspide

D. Fraction de raccourcissement systolique du ventricule droit

FAC : Fraction de raccourcissement systolique du ventricule droit, IVA : accélération de la contraction isovolumique, TAPSE : excursion systolique du plan de l'anneau, TR : insuffisance tricuspide

Cette étude a donc montré que la dilatation et le remodelage des cavités droites sont bien corrélés avec le degré de sévérité de l'IT fonctionnelle, mais sans altération concomitante des paramètres de fonction ventriculaire droite. Notamment, la dilatation de l'OD avec dilatation de l'AT et/ou la restriction des feuillets valvulaires semblent être des paramètres nécessaires à l'aggravation d'une IT fonctionnelle.



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CLINICAL RESEARCH

Cardiac remodelling in secondary tricuspid regurgitation: Should we look beyond the tricuspid annulus diameter?



Remodelage cardiaque de la fuite tricuspide secondaire : devons-nous aller au-delà de la mesure de l'anneau tricuspide ?

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KEYWORDS

Tricuspid regurgitation;
 Right heart remodelling;
 Determinant

Summary

Background. – A better understanding of the mechanism of tricuspid regurgitation severity would help to improve the management of this disease.

Aim. – We sought to characterize the determinants of isolated secondary tricuspid regurgitation severity in patients with preserved left ventricular ejection fraction.

Abbreviations: EROA, effective regurgitant orifice area; LV, left ventricle/ventricular; LVEF, left ventricular ejection fraction; RA, right atrial; RV, right ventricular; PASP, pulmonary artery systolic pressure; TA, tricuspid annular; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

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Methods. — This was a prospective observational multicentre study. Patients with severe tricuspid regurgitation were asked to participate in a registry that required a control echocardiogram after optimization of medical treatment and a follow-up. Patients had to have at least mild secondary tricuspid regurgitation when clinically stable, and were classified according to five grades of tricuspid regurgitation severity, based on effective regurgitant orifice area.

Results. — One hundred patients with tricuspid regurgitation (12 mild, 31 moderate, 18 severe, 17 massive and 22 torrential) were enrolled. Right atrial indexed volume and tethering area were statistically associated with the degree of tricuspid regurgitation ($P < 0.001$ and $P = 0.005$, respectively). When the tricuspid annular diameter was ≥ 50 mm, the probability of having severe tricuspid regurgitation or a higher grade was $> 70\%$. For an increase of 10 mL/m^2 in right atrial volume, the effective regurgitant orifice area increased by 4.2 mm^2 , and for an increase of 0.1 cm^2 in the tethering area, the effective regurgitant orifice area increased by 2.35 mm^2 . The degree of right ventricular dilation and changes in tricuspid morphology were significantly related to tricuspid regurgitation severity class ($P < 0.001$). No significant difference in right ventricular function variables was observed between the tricuspid regurgitation classes.

Conclusions. — For tricuspid regurgitation to be severe or torrential, both right atrial dilatation and leaflet tethering are needed. Interestingly, right cavities dilated progressively with tricuspid regurgitation severity, without joint degradation of right ventricular systolic function variables.

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MOTS CLÉS

Insuffisance tricuspidie ; Remodelage du ventricule droit ; Déterminant

Résumé

Contexte. — Une meilleure compréhension du mécanisme de la sévérité de la régurgitation tricuspidie permettrait d'améliorer la prise en charge de cette pathologie.

Objectif. — Nous avons étudié les déterminants de la sévérité de l'insuffisance tricuspidie secondaire chez des patients ayant une fonction ventriculaire gauche préservée.

Méthodes. — L'étude est prospective et multicentrique. Les patients ayant une insuffisance tricuspidie sévère ont été sollicités afin de participer à un registre justifiant une évaluation échocardiographique systématisée de leur valvulopathie après optimisation de son traitement médical. Les patients inclus devaient avoir au moins une insuffisance tricuspidie modérée lors de l'évaluation systématisée. La fuite était caractérisée en 5 grades sur la base de la surface de l'orifice régurgitant.

Résultats. — Cent patients (12 modérée, 31 moyenne, 18 sévère, 17 massive et 22 torrentielle) ont été inclus. Le volume indexé de l'oreillette droite et l'aire sous la tente étaient significativement associés au degré de sévérité de l'insuffisance tricuspidie ($p < 0,001$ et $p = 0,005$, respectivement). Si le diamètre de l'anneau était ≥ 50 mm, la probabilité d'avoir une insuffisance tricuspidie \geq sévère était $> 70\%$. Pour une augmentation de 10 mL/m^2 du volume de l'oreillette droite, la surface de l'orifice régurgitant augmentait de $4,2 \text{ mm}^2$, et pour une augmentation de $0,1 \text{ cm}^2$ de l'aire sous la tente, la surface de l'orifice régurgitant augmentait de $2,35 \text{ mm}^2$. Il n'y avait pas de différence significative entre les paramètres de fonction ventriculaire droite selon le degré de sévérité de l'insuffisance tricuspidie.

Conclusions. — Pour être sévère ou torrentielle, la dilatation atriale droite et la restriction du jeu valvulaire sont nécessaires. De manière intéressante, la progressive dilatation des cavités droites avec l'aggravation de l'insuffisance tricuspidie ne s'accompagne pas d'une altération des paramètres d'évaluation de la fonction du ventricule droit.

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Background

The tricuspid valve is a dynamic complex structure. Based on data from the Framingham cohort, tricuspid regurgitation (TR) appears to be dominant in females in the general population, with a prevalence of 18.4% versus

14.8% in men, and the prevalence increases with age [1–3].

For many years, cardiologists have relinquished the right heart, and have focused on TR only as a marker of poor prognosis in left heart diseases [4–6]. In cohorts, mortality increases according to TR severity, regardless of pulmonary

artery pressure and left ventricular ejection fraction (LVEF) [7–9].

Secondary TR is explained by either isolated annular dilatation dependent on right atrial (RA) dilatation and/or leaflet tethering that relies on right ventricular (RV) dilatation [10]. Recently, Hahn and Zamorano proposed a new classification system for TR severity [11]. However, reliable assessment of TR severity continues to be a real challenge [11,12].

Like secondary mitral regurgitation, which remains a therapeutic challenge, treatment of secondary TR is unclear [13]. Guidelines state that surgery is recommended for patients with isolated severe TR with symptoms or progressive RV dilation/dysfunction, but the thresholds are unclear. Only tricuspid annular (TA) dilatation ≥ 40 mm is considered in these guidelines at the time of left-sided heart valve surgery, and the best indication and timing for curative treatment of TR are still a matter of debate [14–16].

Thus, much remains to be learned to optimize treatment [17]. We sought to study how cardiac remodelling is associated with isolated secondary TR and its severity. Non-invasive evaluation with transthoracic two-dimensional echocardiography is not perfectly standardized, but has been used for a better understanding of TR [18]. The main objective of our study was to characterize the determinants of isolated TR severity in stable patients with preserved LVEF.

Methods

Patient selection

We conducted a prospective observational study. Patients were recruited between January 2017 and March 2019 from thirteen French hospital centres (listed in the Appendix). The criteria for inclusion were age ≥ 18 years, at least moderate secondary TR and euvolemic status. We excluded patients with organic TR (diagnosed or suspected), congenital cardiopathy, LVEF $< 40\%$ (by Simpson's biplane method, to avoid too severe left ventricular [LV] dysfunction that would directly impact on RV shape and loading condition), significant left heart valvular disease (aortic stenosis < 1.5 cm², mitral/aortic insufficiency $\geq 2/4$, mitral stenosis < 2 cm²), primary pulmonary hypertension, life expectancy < 1 year, apart from valve disease, and poor acoustic window.

Patients were assessed long after the initial diagnosis and under well-conducted medical treatment. It was required to ensure that the patients were not decompensated (clinically) in the 4 weeks preceding the evaluation. Thus, patients could have a severe TR when they signed the consent, but a much weaker TR 4 weeks later (load dependency and "accordion" behaviour of the regurgitation). Medical history and risk factors were collected from medical files, from subject self-reporting and from physical assessment immediately preceding the echocardiographic examination. All data were reported in an online case report form.

Echocardiographic examination

All patients underwent standard transthoracic echocardiography using a Vivid 7, Vivid E9 or E95 ultrasound system (GE Healthcare, Horten, Norway) equipped with a 3S or an M5S 3.5 MHz transducer. Two-dimensional, colour-Doppler, pulsed-wave and continuous-wave Doppler images were obtained as a priority. Data were stored on a dedicated workstation for off-line analysis (EchoPAC, version 112.99, Research Release; GE Healthcare, Horten, Norway). Part of the analysis was performed on Image Arena (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). The analysis was done at Rennes CIC-IT accredited Core Lab (ISO 9001) using double-checking of the main measurements.

The volumes and function of the left atrium and left ventricle (LV) were measured by the biplane method, as recommended [19]. RA volume and RV areas and functions were also assessed according to guidelines. Tissue Doppler imaging was used to detect lateral and septal mitral annulus velocities. The ratio of early transmitral flow velocity to the tissue Doppler imaging annular velocity (E/e') was considered an index of mean LV filling pressure [20]. RV function was estimated by six performance indices, measured according to Lang et al.: TA plane systolic excursion (TAPSE); the maximal lateral TA velocity measured at tissue Doppler imaging (S' velocity); RV free wall speckle-tracking strain; RV isovolumic acceleration; RV fraction area change; and the Tei index [21]. Systolic pulmonary artery pressure (PASP) was determined, when possible, from the TR jet velocity, using the modified Bernoulli equation, and this value was combined with an estimation of right atrial pressure by means of the diameter and collapsibility of the inferior vena cava. Tricuspid leaflet coaptation was evaluated by the tethering distance (the distance between the leaflet coaptation point and the annular plane), the tenting area (the area between the closed leaflet and the annular plane) and the coaptation defect (Fig. 1). The TR severity assessment was defined according to the recommendations [22], together with the new classification of severe TR proposed by Hahn and Zamorano [11]. Severe TR was defined as an effective regurgitant orifice area (EROA) of 40–59 mm², massive TR as an EROA of 60–79 mm² and torrential TR as an EROA ≥ 80 mm². The baseline Nyquist limit shift was 28 cm/s. All measurements were averaged over three cardiac cycles in sinus rhythm, and over five cycles in atrial fibrillation. The EROA was the determinant tool for defining the severity of TR in our analysis. RV contractile function and its coupling with the pulmonary circulation has been demonstrated to be estimated by the TAPSE/PASP ratio, which is also correlated with pulmonary artery compliance [23]. This variable was assessed. The impact of TR peak velocity with the cut-off of 2.8 m/s was also tested.

Reproducibility of our measurement was required according to the standard of the Core Lab, and this was tested on 10 randomized patients. The intraclass correlation coefficient was 0.86 for the EROA, 0.93 for the TA diameter, 0.75 for the tenting height, 0.94 for the RA volume and 0.98 for the RV end-systolic area.

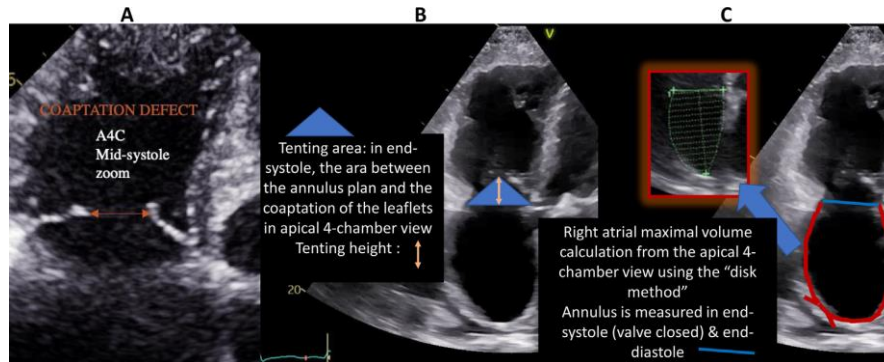


Figure 1. A. Illustration of the coaptation defect measurement in the apical four-chamber (A4C) view in mid-systole. B. Illustration of the tenting height and tenting area. C. Illustration of the measurement of right atrial volume and annulus diameter.

Statistical analysis

For descriptive analyses, categorical variables are presented as numbers and percentages and continuous variables are presented as means \pm standard deviations. A contingency table was created to compare the classification of the TR according to the vena contracta and the EROA. Comparisons between groups were made using variance analyses for quantitative variables and the χ^2 test for qualitative variables (or Fisher's test if validity conditions were not met). The distribution of quantitative variables was studied graphically. The association between the patients' echocardiographic characteristics and EROA was studied using univariate and multivariable linear regression models. Variables with a P -value < 0.20 in the univariate models were selected, and the correlation between these covariates was studied to avoid multicollinearity. If two covariates were too correlated, only one of them was included in the multivariable model, choosing the one with the most clinical interest. The final model was obtained with a step-by-step selection of variables using the stepwise bootstrap technique. The bootstrap method was used with 1000 samples created. Variables selected in at least 60% of the bootstrap models were kept in the final model. Collinearity in the final model was checked using the variable inflation factor coefficient. A P -value < 0.05 was considered statistically significant.

Finally, an ordinal logistic regression was performed by considering the five EROA classes. Each variable was studied separately in the univariate models using a proportional rating model. All analyses were performed using R Studio Version 1.1.463 (language and environment for statistical computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2018).

Ethics

Our study was conducted in accordance with the "Good Clinical Practice" guidelines of the Declaration of Helsinki, and was reviewed by an independent regional ethics committee on 28 June 2016. All patients gave their written informed consent for study participation. The National Commission for Information Technology and Privacy (CNIL) approved the

data collection conducted by the TRAP investigators on 07 November 2016 (No. 20050960v0).

Results

Patient characteristics

A total of 100 patients were enrolled. The distribution of the patients is displayed in Table 1. This contingency table encouraged the use of the EROA. Among the 100 patients assessed after optimization of pharmacological treatment, 12 had only mild TR (initially \geq severe when the informed consent was signed), 31 had moderate TR, 18 still had severe TR, 17 had massive TR and 22 had torrential TR, as defined by the EROA. Sixty-two percent of the patients were female. The demographic characteristics of the patients according to TR severity grade are described in Table 2. The tricuspid annulus was enlarged for all.

Pharmacological treatments according to TR severity grade are described in Table 2. No significant difference in treatment was observed between the different classes of secondary TR.

Description of cardiac remodelling

In our cohort, LV function was preserved, with a mean LVEF of $62.2 \pm 8.4\%$ and a global longitudinal strain of $-17.3 \pm 3.2\%$. The LV was generally of normal size and thickness: LV end-diastolic volume 83.1 ± 29.6 mL; LV end-diastolic diameter 46.1 ± 6.9 mm; and septal thickness 10.9 ± 2.5 mm. In accordance with the enrolment criteria, no significant left heart valve disease was diagnosed. Cardiac output was preserved, with an average cardiac index of 2.6 ± 0.7 L/min/m². Twenty-seven per cent of the patients had a discrete pericardial effusion (none had any haemodynamic consequence). The left atrium was enlarged (61.9 ± 30.8 mL/m²). Echocardiographic characteristics according to TR severity grade are described in Table 3. Right heart characteristics according to TR severity grade are described in Table 4. No significant difference in RV function variables was observed across the classes of secondary TR. Box-plot representations of the

Table 1 Contingency table^a of patient distribution into the different severity classes of tricuspid regurgitation according to effective regurgitant orifice area and vena contracta width.

| | TR severity according to EROA | | | | |
|------------------------------|-------------------------------|----------|--------|---------|------------|
| | Mild | Moderate | Severe | Massive | Torrential |
| TR severity according to VCV | | | | | |
| Mild | 1 | 0 | 0 | 0 | 0 |
| Moderate | 10 | 21 | 5 | 0 | 0 |
| Severe | 1 | 10 | 12 | 14 | 12 |
| Massive | 0 | 0 | 1 | 3 | 6 |
| Torrential | 0 | 0 | 0 | 0 | 4 |

EROA: effective regurgitant orifice area; TR: tricuspid regurgitation; VCV: vena contracta width.

^a This table led the analysis to focus on EROA.

main variables of cardiac morphology and RV function are provided in Figs. A.1–A.4.

RV end-systolic area was correlated ($R=0.8$; $P<0.001$) with the tenting area as well as the TR EROA.

Determinants of TR severity

Univariate (Table A.1) and multivariable analyses (Table 5; Figs. A.5 and A.6 and Table A.2 for patients with $TR < 2.8$ m/s) demonstrated that RA indexed volume and tethering area ($P < 0.001$ and $P = 0.005$, respectively) were independently and significantly associated with TR grade. At a constant tethering area, for an increase of 10 mL/m^2 in RA volume, the EROA increased by 3.9 mm^2 . At a constant RA indexed volume, for an increase of 0.25 cm^2 in the tethering area, the EROA increased by 2.35 mm^2 . Moreover, for an increase of 5 mm in the inferior vena cava diameter, the EROA increased by 4.2 mm^2 ($P = 0.03$), and for a decrease of 1 m/s in the TR velocity, the EROA increased by 25 mm^2 ($P < 0.001$).

The probability of belonging to a TR severity class according to different RV variables was analysed with ordinal logistic regression. In our cohort, when the TA diameter was $> 50 \text{ mm}$, the probability of having severe TR or a higher grade was $> 70\%$ (Fig. 2A); when the tricuspid tethering area was $> 1.5 \text{ cm}^2$, the probability of having severe TR or a higher grade was $> 70\%$ (Fig. 2B); when the RV end-diastolic area was $\geq 35 \text{ cm}^2$, the probability of having moderate or mild TR was $< 25\%$ (Fig. 2C); when the RA volume was $\geq 100 \text{ mL/m}^2$, the probability of having moderate or mild TR was $< 25\%$ (Fig. 2D); and when the TAPSE/PASP was $> 0.35 \text{ mm/mmHg}$, the probability of having moderate or mild TR was $< 25\%$ (Fig. 2E).

Discussion

Main results

TR severity graded according to the EROA was influenced by an increase in the RA indexed volume, with an increase of 3.9 mm^2 in EROA for an increase of 10 mL/m^2 in RA volume, and by an increase in tethering area, with an increase of 2.35 mm^2 for an increase of 0.25 cm^2 in tethering area. TR

severity increased in parallel with RA and RV dilatation, and with changes in the anatomy of the tricuspid valve (dilation of TA, valvular tethering and appearance of a coaptation defect). All patients had a dilated TA ($\geq 35 \text{ mm}$). No significant difference in RV function variables was highlighted among the different classes of secondary TR.

TA dilatation across TR severity

Dreyfus et al. [24] advocated for the use of three variables to analyse the severity of secondary TR: the severity of the leak (EROA, vena contracta width); the size of the TA; and the tethering area. We observed a systematic TA dilatation ($\geq 35 \text{ mm}$). The message is probably that TA enlargement is a prerequisite for any development of significant secondary TR. Recently, Badano et al. argued in favour of this statement. For the same degree of dilation, different severity grades of secondary TR can occur [25]. But TA is not a two-dimensional structure that can just be assessed by the measurement of any annular diameter [26]. The oval shape of the ring and the non-planar characteristics are certainly variables that were not tested in our study, but which will have to be treated specifically in further studies dealing with systematic three-dimensional measurements [27].

In our study, severity of TR appeared to be mainly caused by a malfunction of the leaflets, either by tethering or by a coaptation defect. Fukuda et al. showed that the persistence of a tenting height $> 8 \text{ mm}$ or a tethering area $> 1.6 \text{ cm}^2$ predicted the recurrence of secondary TR after tricuspid annuloplasty, unlike the preoperative TV annular dimensions [28].

Severe or higher grade TR: a single mechanism

A study focusing on pathogenic structural heart changes in the early stages of TR reported that RA enlargement associated with dilatation of the TA occurs early, and results in TR becoming severe via RV dilatation and papillary muscle displacement [29]. These observations, as well as ours, are questioning the hypothesis of mechanism(s) contributing to severe secondary TR. There are cases of secondary TR that are secondary to pulmonary arterial hypertension and with significant tethering and RV enlargement, but the most

| Table 2 Patient demographic characteristics. | | | | | | |
|--|----------------------|-------------------------|-----------------------|------------------------|---------------------------|---------|
| | Mild TR (n = 12) | Moderate TR (n = 31) | Severe TR (n = 18) | Massive TR (n = 17) | Torrential TR (n = 22) | P |
| Female sex | 9 (75.0) | 20 (64.5) | 12 (66.7) | 12 (70.6) | 9 (40.9) | 0.22 |
| Age (years) | 81.7 ± 9.8 | 72.5 ± 13.7 | 65.8 ± 15.7 | 76.7 ± 9.1 | 76.2 ± 6.6 | 0.005 |
| Atrial fibrillation | 10 (83.4) | 24 (77.5) | 11 (61.1) | 14 (82.4) | 20 (90.9) | 0.14 |
| Paroxysmal | 2 (16.7) | 7 (22.6) | 2 (11.1) | 2 (11.8) | 0 (0) | |
| Persistent | 0 (0) | 3 (9.7) | 1 (5.6) | 0 (0) | 1 (4.5) | |
| Permanent | 8 (66.7) | 14 (45.2) | 8 (44.4) | 12 (70.6) | 19 (86.4) | |
| High blood pressure; NA | 9 (75.0) | 22 (71.0) | 10 (55.6) | 10 (58.8); 1 (5.9) | 15 (68.2) | 0.57 |
| Diabetes; NA | 4 (33.3) | 5 (16.1) | 5 (27.8) | 1 (5.9); 1 (5.9) | 3 (13.6) | 0.32 |
| Dyslipidaemia; NA | 5 (41.7) | 16 (51.6) | 10 (55.6) | 5 (29.4); 1 (5.9) | 4 (18.2) | 0.10 |
| Coronary artery disease; NA | 5 (41.7) | 9 (29.1) | 2 (11.2) | 1 (5.9); 1 (5.9) | 2 (9.1) | 0.31 |
| CABG | 1 (8.3) | 2 (6.5) | 1 (5.6) | 1 (5.9) | 0 (0) | 0.81 |
| Aortic valve replacement | 1 (8.3) | 3 (9.7) | 1 (5.6) | 3 (17.6) | 0 (0) | 0.36 |
| Mitral surgery | 0 (0) | 2 (6.5) | 0 (0) | 2 (11.8) | 2 (9.1) | 0.39 |
| Pacemaker | 1 (8.3) | 2 (6.5) | 2 (11.1) | 4 (23.5) | 1 (4.5) | 0.32 |
| Chronic respiratory disease | 0 (0) | 2 (6.5) | 2 (11.1) | 3 (17.6) | 4 (18.2) | 0.40 |
| Past history of cancer | 3 (25) | 5 (16.1) | 1 (5.6) | 7 (41.2) | 5 (22.7) | 0.12 |
| Stroke | 1 (8.3) | 4 (12.9) | 1 (5.6) | 2 (11.8) | 2 (9.1) | 0.938 |
| Cirrhosis | 0 (0) | 1 (3.2) | 2 (11.1) | 0 (0) | 2 (9.1) | 0.47 |
| SBP (mmHg) | 129.8 ± 22.0 | 127.8 ± 20.1 | 127.6 ± 18.0 | 131.9 ± 22.2 | 129.5 ± 18.6 | 0.96 |
| DBP (mmHg) | 76.5 ± 17.7 | 72.6 ± 9.4 | 76.9 ± 12.8 | 75.6 ± 14.7 | 75.0 ± 12.6 | 0.79 |
| NYHA functional class | | | | | | 0.35 |
| I | 2 (16.7) | 5 (16.1) | 1 (5.6) | 1 (5.9) | 0 (0) | |
| II | 5 (41.7) | 15 (48.4) | 10 (55.6) | 10 (58.8) | 12 (54.5) | |
| III | 4 (33.3) | 11 (35.5) | 7 (38.9) | 6 (35.3) | 10 (45.5) | |
| IV | 1 (8.3) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | |
| Right CHF | 6 (50) | 8 (25.8) | 5 (27.8) | 10 (58.8) | 19 (86.4) | < 0.001 |
| Hospitalization for HF; NA | 4 (33.3) | 15 (48.4) | 8 (44.4); 1 (5.6) | 8 (47.1) | 16 (72.7) | 0.48 |
| Anticoagulation | 10 (83.3) | 21 (67.8) | 10 (55.6) | 15 (88.2) | 19 (86.3) | 0.15 |
| VKAs | 7 (58.3) | 10 (32.3) | 5 (27.8) | 10 (58.8) | 12 (54.5) | |
| NOACs; NA | 3 (25.0) | 11 (35.5) | 5 (27.8) | 5 (29.4); 1 (5.9) | 7 (31.8) | |
| Beta-blockers; NA | 9 (75.0) | 21 (67.7) | 9 (50.0); 1 (5.6) | 9 (52.9); 1 (5.9) | 15 (68.2) | 0.64 |
| RAAS inhibitors | 8 (66.7) | 10 (32.3) | 4 (22.2) | 8 (47.1) | 7 (31.8) | 0.11 |
| Antialdosterone; NA | 1 (8.3) | 9 (29.0) | 4 (22.2); 1 (5.6) | 4 (23.5); 1 (5.9) | 8 (36.4) | 0.52 |
| Sacubitril/valsartan; NA | 0 (0) | 0 (0) | 0 (0) | 0 (0); 1 (5.9) | 0 (0) | 1 |
| Furosemide; NA | 7 (58.3) | 23 (74.2) | 15 (83.3) | 13 (76.5); 1 (5.9) | 20 (90.9) | 0.23 |
| Daily dosage of furosemide (mg) | 159.3 ± 194.0 | 81.5 ± 53.1 | 223.6 ± 310.4 | 128.8 ± 128.4 | 171.7 ± 231.8 | 0.28 |
| Amiodarone; NA | 3 (25.0); 1 (8.3) | 4 (12.9) | 1 (5.6); 1 (5.6) | 3 (17.6); 1 (5.9) | 2 (9.1) | 0.54 |

Data are expressed as mean ± standard deviation or number (%). CABG: coronary artery bypass grafting; CHF: congestive heart failure; DBP: diastolic blood pressure; HF: heart failure; NA: not available; NOAC: non-vitamin K antagonist oral anticoagulant; NYHA: New York Heart Association; RAAS: renin-angiotensin-aldosterone system; SBP: systolic blood pressure; TR: tricuspid regurgitation; VKA: vitamin K antagonist.

Table 3 Characteristics of the left cavities and diastolic function.

| | Mild TR (n = 12) | Moderate TR (n = 31) | Severe TR (n = 18) | Massive TR (n = 17) | Torrential TR (n = 22) | P |
|--------------------------------------|---------------------|-------------------------|-----------------------|------------------------|---------------------------|---------|
| LVEF (%) | 60.2 ± 5.4 | 63.1 ± 7.0 | 62.4 ± 10.4 | 64.9 ± 6.5 | 60.0 ± 10.5 | 0.37 |
| GLS (–%) | 16.5 ± 3.9 | 17.0 ± 3.2 | 17.4 ± 2.9 | 18.7 ± 2.2 | 17.1 ± 3.8 | 0.48 |
| LVEDV (mL) | 79.2 ± 18.6 | 82.0 ± 28.7 | 85.8 ± 32.6 | 73.3 ± 25.8 | 92.1 ± 35.3 | 0.37 |
| LVEDD (mm) | 45.4 ± 5.6 | 45.4 ± 8.5 | 45.8 ± 5.8 | 45.6 ± 6.0 | 48.1 ± 6.3 | 0.65 |
| Septal thickness (mm) | 12.0 ± 2.5 | 10.9 ± 2.3 | 10.1 ± 2.3 | 11.3 ± 2.0 | 10.6 ± 3.1 | 0.28 |
| Cardiac index (L/m ²) | 2.7 ± 0.7 | 2.9 ± 0.9 | 2.4 ± 0.6 | 2.7 ± 0.7 | 2.5 ± 0.7 | 0.17 |
| Aortic valve area (cm ²) | 2.4 ± 0.7 | 2.4 ± 0.9 | 2.3 ± 0.5 | 2.3 ± 0.9 | 2.3 ± 0.7 | 0.97 |
| Pericardial effusion | 3 (25.0) | 6 (19.4) | 4 (22.2) | 4 (23.5) | 10 (45.5) | 0.28 |
| LA volume (mL/m ²) | 56.2 ± 19.3 | 66.8 ± 41.4 | 53.1 ± 18.8 | 55.6 ± 19.3 | 69.2 ± 32.0 | 0.37 |
| Mitral E velocity DT (ms) | 170.6 ± 42.4 | 178.0 ± 52.6 | 205.1 ± 62.8 | 190.0 ± 76.9 | 177.1 ± 42.0 | 0.41 |
| E/e' | 16.7 ± 5.1 | 10.6 ± 3.9 | 10.4 ± 5.2 | 11.4 ± 3.8 | 9.3 ± 2.9 | < 0.001 |

Data are expressed as mean ± standard deviation or number (%). DT: deceleration time; GLS: global longitudinal strain; LA: left atrial; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; TR: tricuspid regurgitation.

Table 4 Characteristics of right cavity dimensions, pressure and right ventricular function.

| | Mild TR (n = 12) | Moderate TR (n = 31) | Severe TR (n = 18) | Massive TR (n = 17) | Torrential TR (n = 22) | P |
|-----------------------------------|---------------------|-------------------------|-----------------------|------------------------|---------------------------|---------|
| RVOT PLAX (mm) | 35.5 ± 4.4 | 36.9 ± 7.0 | 43.0 ± 6.4 | 40.3 ± 6.6 | 47.4 ± 8.6 | < 0.001 |
| RVOT PSAX (mm) | 32.6 ± 4.0 | 35.2 ± 6.4 | 41.0 ± 5.8 | 38.3 ± 7.6 | 43.4 ± 8.2 | < 0.001 |
| RV basal diameter (mm) | 44.4 ± 6.8 | 49.3 ± 7.9 | 52.1 ± 6.8 | 55.0 ± 7.7 | 59.9 ± 8.2 | < 0.001 |
| RV mid-cavity diameter (mm) | 36.1 ± 6.0 | 39.1 ± 6.4 | 43.1 ± 7.9 | 44.3 ± 7.6 | 50.4 ± 7.0 | < 0.001 |
| RV longitudinal diameter (mm) | 67.7 ± 6.0 | 69.7 ± 9.7 | 74.9 ± 7.8 | 73.2 ± 10.3 | 79.5 ± 11.2 | 0.002 |
| RVEDA (cm ²) | 21.3 ± 4.6 | 24.9 ± 6.6 | 29.8 ± 7.0 | 31.4 ± 9.4 | 37.1 ± 8.7 | < 0.001 |
| Eccentricity index | 0.98 ± 0.09 | 1.02 ± 0.18 | 1.05 ± 0.15 | 1.12 ± 0.34 | 1.11 ± 0.24 | 0.30 |
| RA area (cm ²) | 23.7 ± 6.7 | 30.3 ± 9.0 | 31.3 ± 8.0 | 35.5 ± 8.6 | 45.7 ± 13.9 | < 0.001 |
| RA volume (mL/m ²) | 46.9 ± 18.4 | 65.7 ± 28.2 | 66.5 ± 31.3 | 85.9 ± 32.8 | 121.7 ± 50.8 | < 0.001 |
| TA diastolic diameter (mm) | 40.5 ± 4.2 | 43.7 ± 4.8 | 46.3 ± 5.3 | 48.0 ± 7.3 | 52.5 ± 6.8 | < 0.001 |
| TA systolic diameter (mm) | 33.8 ± 5.2 | 36.1 ± 4.7 | 39.5 ± 4.9 | 41.8 ± 6.5 | 46.1 ± 6.1 | < 0.001 |
| Tethering height (mm) | 4 ± 2.6 | 5.4 ± 2.9 | 8.8 ± 3.6 | 7.2 ± 3.5 | 10.1 ± 2.6 | < 0.001 |
| Tethering area (cm ²) | 0.46 ± 0.3 | 0.74 ± 0.5 | 1.4 ± 0.8 | 1.3 ± 0.9 | 2.2 ± 1.0 | < 0.001 |
| Coaptation defect (mm) | 0.2 ± 0.9 | 1.0 ± 1.6 | 2.7 ± 3.1 | 4.3 ± 4.2 | 9.1 ± 5.8 | < 0.001 |
| IVC diameter (mm) | 21.5 ± 5.6 | 21.7 ± 5.1 | 25.4 ± 7.1 | 26.3 ± 5.1 | 33.6 ± 9.1 | < 0.001 |
| TR velocity (m/s) | 3.3 ± 0.8 | 2.9 ± 0.5 | 2.7 ± 0.5 | 2.5 ± 0.4 | 2.3 ± 0.4 | < 0.001 |
| PASP + RAP (mmHg) | 54.4 ± 23.7 | 44.3 ± 15.6 | 42.7 ± 15.3 | 39.5 ± 10.1 | 35.5 ± 7.3 | 0.011 |
| FAC (%) | 38.8 ± 8.5 | 43.0 ± 8.6 | 41.2 ± 11.2 | 46.9 ± 7.8 | 43.3 ± 7.1 | 0.14 |
| RV strain (–%) | 21.9 ± 3.7 | 24.2 ± 6.4 | 23.3 ± 6.2 | 22.0 ± 5.5 | 21.9 ± 5.4 | 0.56 |
| S' velocity (cm/s) | 11.0 ± 3.3 | 10.8 ± 2.5 | 12.1 ± 3.6 | 11.2 ± 3.1 | 11.2 ± 3.1 | 0.75 |
| TAPSE (mm) | 18.5 ± 5.2 | 19.9 ± 4.7 | 20.0 ± 6.0 | 18.7 ± 4.4 | 18.1 ± 5.2 | 0.66 |
| IVA (m/s ²) | 2.7 ± 1.2 | 2.9 ± 1.3 | 2.8 ± 1.2 | 2.3 ± 1.0 | 2.4 ± 1.1 | 0.30 |
| Tei index | 0.32 ± 0.09 | 0.32 ± 0.17 | 0.33 ± 0.15 | 0.29 ± 0.16 | 0.27 ± 0.18 | 0.75 |
| TAPSE/PASP (mm/mmHg) | 0.39 ± 0.17 | 0.50 ± 0.23 | 0.52 ± 0.23 | 0.49 ± 0.14 | 0.53 ± 0.19 | 0.45 |

Data are expressed as mean ± standard deviation. FAC: fraction area change; IVA: isovolumic acceleration; IVC: inferior vena cava; PASP: pulmonary artery systolic pressure; PLAX: parasternal long axis; PSAX: parasternal short axis; RA: right atrial; RAP: right atrial pressure; RV: right ventricular; RVEDA: right ventricular end-diastolic area; RVOT: right ventricular outflow tract; TA: tricuspid annular; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation.

frequent situation is a combination of several factors [10]. Most of the time, we could consider the Carpentier classification that is conventionally used as being inappropriate for secondary TR. We observed that for a large majority of cases of severe TR, characteristics of both type I and type IIIb

from the Carpentier classification are actually required to generate the most severe TR [17]. Fukuda et al. highlighted that TA dilatation was correlated with both RA dilation and RV enlargement and change in geometry [28,30]. The interdependence of these mechanisms could explain why

Table 5 Multivariable linear regression model explaining the factors determining the increase in effective regurgitant orifice area.

| | Coefficient | Standard deviation | P |
|-----------------------------------|-------------|--------------------|---------|
| RA volume (mL/m ²) | 0.39 | 0.07 | < 0.001 |
| Tethering area (cm ²) | 9.4 | 3.3 | 0.005 |
| TR velocity (m/s) | -25.6 | 4.3 | < 0.001 |
| IVC diameter (mm) | 0.84 | 0.4 | 0.03 |

IVC: inferior vena cava; RA: right atrial; TR: tricuspid regurgitation.

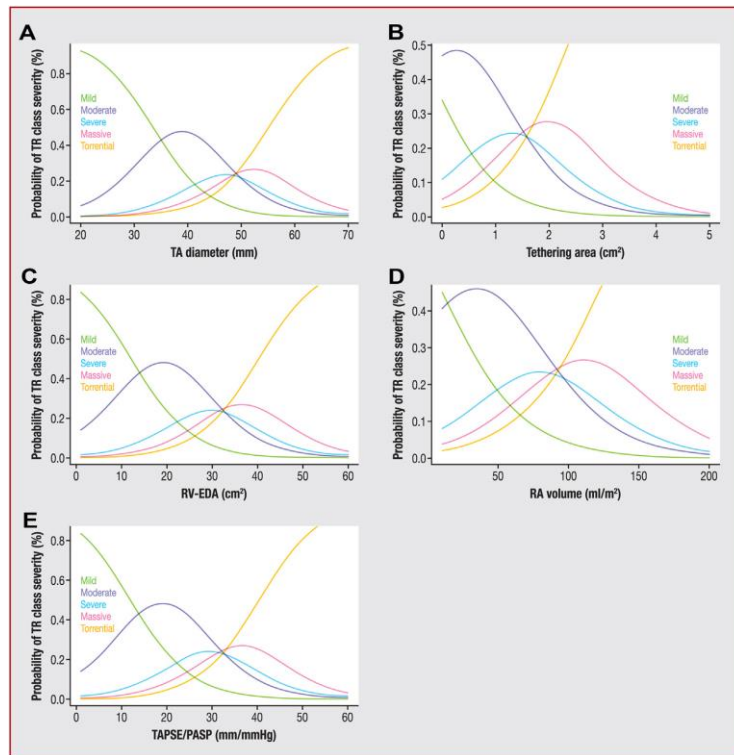


Figure 2. A. Ordinal logistic regression representing the probability of tricuspid regurgitation (TR) class severity according to different variables. A. Tricuspid annular (TA) diameter. B. Tethering area. C. Right ventricular end-diastolic area (RVEDA). D. Right atrial (RA) indexed volume. E. Tricuspid annular plane systolic excursion/pulmonary artery systolic pressure (TAPSE/PASP).

dilation of the RV predominates at the basal level and in width at the medial level (RV conical deformation) [31]. The remodelling of the right heart cavities causes volume overload, which itself is responsible for the amplification of remodelling by dilation of the right cavities. Finally, secondary TR begets secondary TR in a vicious circle.

RV functional changes across TR severity

It is interesting to note that, contrary to our expectations, the severity of TR was not associated with objectified RV systolic dysfunction as assessed by conventional variables

(TAPSE, S', etc.). TR is a self-worsening disease, as RV volume overload caused by regurgitation worsens TR. Also, secondary TR is a marker of right heart dilatation — either the right atrium and/or the right ventricle. Just as it has been used for mitral or aortic regurgitations to define an indication for surgery, independent of any quantification of RV systolic function, the degree of RV end-systolic dilatation could be considered as a marker of RV intrinsic dysfunction that needs an action. Studies are needed to examine the impact of this RV remodelling on ventricular cavity interdependence. Of note, we found that the greater the TR, the lower the left heart E/e' [32].

It is worth recalling that Topilsky et al. [30] highlighted a link between the severity of TR and mortality, regardless of the function and volume of the RV. Our study showed a significant increase in right congestive heart failure with the increase in the severity of TR, but without significant difference in RV systolic function variables [31]. Further analyses in a larger group of patients with secondary TR and longer follow-up should focus on the influence of RV function and remodelling on cardiovascular morbidity and mortality. The precise understanding of right heart adaptation in this setting is desirable, and might have an impact on the development of emerging therapeutic innovations.

Study limitations

The choice of EROA to assess TR severity can be questioned because of the dynamic regurgitant orifice with a complex geometric configuration, but the EROA remains one of the most reproducible and easy-to-perform quantitative variables in clinical practice. The vena contracta width was not retained because of its uneven distribution among the different classes of TR severity. Three-dimensional echocardiography (vena contracta width area, regurgitant jet area) looks promising, but is also challenging [33]; thus, in this multicentre study, we were unable to use this tool in every single patient. Three-dimensional echocardiography seems important for our understanding of the TR via the precise characterization of annular 3D deformation, with accurate measurement of right heart cavities and their functions. The bootstrap technique and ordinal regression were preferred to classical multivariable linear regression. It provides graphical simulations, which are based on the measurements made, and provides meaningful graphs that could have been easy to display with numbers.

Conclusions

A constant TA enlargement was demonstrated in secondary isolated TR. Furthermore, increases in tethering area and RA indexed volume were associated with aggravation of TR severity. This right heart dilatation progressively worsens the TR (vicious circle), but without joint degradation of the conventional variables of RV systolic function.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.acvd.2020.11.002>.

References

- [1] Guerin A, Dreyfus J, Le Tourneau T, et al. Secondary tricuspid regurgitation: do we understand what we would like to treat? *Arch Cardiovasc Dis* 2019;112:642–51.
- [2] Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol* 1999;83:897–902.
- [3] Topilsky Y, Maltais S, Medina Inojosa J, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging* 2019;12:433–42.
- [4] Hung J, Koelling T, Semigran MJ, Dec GW, Levine RA, Di Salvo TG. Usefulness of echocardiographic determined tricuspid regurgitation in predicting event-free survival in severe heart failure secondary to idiopathic-dilated cardiomyopathy or to ischemic cardiomyopathy. *Am J Cardiol* 1998;82:1301–3 [A10].
- [5] Koelling TM, Aaronson KD, Cody RJ, Bach DS, Armstrong WF. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. *Am Heart J* 2002;144:524–9.
- [6] Neuhold S, Huelsmann M, Pernicka E, et al. Impact of tricuspid regurgitation on survival in patients with chronic heart failure: unexpected findings of a long-term observational study. *Eur Heart J* 2013;34:844–52.
- [7] Mascherbauer J, Kammertander AA, Zotter-Tufaro C, et al. Presence of isolated tricuspid regurgitation should prompt the suspicion of heart failure with preserved ejection fraction. *PLoS One* 2017;12:e0171542.
- [8] Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* 2004;43:405–9.
- [9] Topilsky Y, Nkomo VT, Vatury O, et al. Clinical outcome of isolated tricuspid regurgitation. *JACC Cardiovasc Imaging* 2014;7:1185–94.
- [10] Spinner EM, Shannon P, Buice D, et al. In vitro characterization of the mechanisms responsible for functional tricuspid regurgitation. *Circulation* 2011;124:920–9.
- [11] Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. *Eur Heart J Cardiovasc Imaging* 2017;18:1342–3.
- [12] Hahn RT, Thomas JD, Khalique OK, Cavalcante JL, Praz F, Zoghbi WA. Imaging assessment of tricuspid regurgitation severity. *JACC Cardiovasc Imaging* 2019;12:469–90.
- [13] Zack CJ, Fender EA, Chandrashekar P, et al. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol* 2017;70:2953–60.
- [14] Axtell AL, Bhambhani V, Moonsamy P, et al. Surgery does not improve survival in patients with isolated severe tricuspid regurgitation. *J Am Coll Cardiol* 2019;74:715–25.
- [15] Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739–91.
- [16] Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129:e521–643.
- [17] Huttin O, Voilliot D, Mandry D, Venner C, Juilliere Y, Selton-Suty C. All you need to know about the tricuspid valve: tricuspid

- valve imaging and tricuspid regurgitation analysis. *Arch Cardiovasc Dis* 2016;109:67–80.
- [18] Prihadi EA, Delgado V, Leon MB, Enriquez-Sarano M, Topilsky Y, Bax JJ. Morphologic types of tricuspid regurgitation: characteristics and prognostic implications. *JACC Cardiovasc Imaging* 2019;12:491–9.
- [19] Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233–70.
- [20] Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016;17:1321–60.
- [21] Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;23:685–713 [quiz 86–8].
- [22] Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;14:611–44.
- [23] Guazzi M. Use of TAPSE/PASP ratio in pulmonary arterial hypertension: an easy shortcut in a congested road. *Int J Cardiol* 2018;266:242–4.
- [24] Dreyfus GD, Martin RP, Chan KM, Dulguerov F, Alexandrescu C. Functional tricuspid regurgitation: a need to revise our understanding. *J Am Coll Cardiol* 2015;65:2331–6.
- [25] Badano LP, Hahn R, Rodriguez-Zanella H, Araiza Garaygordobil D, Ochoa-Jimenez RC, Muraru D. Morphological assessment of the tricuspid apparatus and grading regurgitation severity in patients with functional tricuspid regurgitation: thinking outside the box. *JACC Cardiovasc Imaging* 2019;12:652–64.
- [26] Dreyfus J, Durand-Viel G, Raffoul R, et al. Comparison of 2-dimensional, 3-dimensional, and surgical measurements of the tricuspid annulus size: clinical implications. *Circ Cardiovasc Imaging* 2015;8:e003241.
- [27] Muraru D, Hahn RT, Soliman OI, Faletra FF, Basso C, Badano LP. 3-dimensional echocardiography in imaging the tricuspid valve. *JACC Cardiovasc Imaging* 2019;12:500–15.
- [28] Fukuda S, Song JM, Gillinov AM, et al. Tricuspid valve tethering predicts residual tricuspid regurgitation after tricuspid annuloplasty. *Circulation* 2005;111:975–9.
- [29] Nemoto N, Lesser JR, Pedersen WR, et al. Pathogenic structural heart changes in early tricuspid regurgitation. *J Thorac Cardiovasc Surg* 2015;150:323–30.
- [30] Topilsky Y, Khanna A, Le Tourneau T, et al. Clinical context and mechanism of functional tricuspid regurgitation in patients with and without pulmonary hypertension. *Circ Cardiovasc Imaging* 2012;5:314–23.
- [31] Fukuda S, Gillinov AM, Song JM, et al. Echocardiographic insights into atrial and ventricular mechanisms of functional tricuspid regurgitation. *Am Heart J* 2006;152:1208–14.
- [32] Friedberg MK. Imaging right–left ventricular interactions. *JACC Cardiovasc Imaging* 2018;11:755–71.
- [33] Chen TE, Kwon SH, Enriquez-Sarano M, Wong BF, Mankad SV. Three-dimensional color Doppler echocardiographic quantification of tricuspid regurgitation orifice area: comparison with conventional two-dimensional measures. *J Am Soc Echocardiogr* 2013;26:1143–52.

**Prise en charge médicale, chirurgicale et percutanée de
l'insuffisance tricuspide**

Article 3

**Tricuspid regurgitation: frequency, management and
outcome among patients with severe left-sided valvular
heart disease**

**Dreyfus J, Komar, M, Attias, D, De Bonis M, Ruschitzka F,
Popescu BA, Laroche C, Tribouilloy C, Prokophiev AB,
Mizariene V, Bax JJ, Maggioni AP, Vahanian A, Iung B, on
behalf of the EORP VHD II Registry Investigators Group**

Article soumis

Article 3 : Insuffisance tricuspide : fréquence, prise en charge et pronostic parmi les patients ayant une valvulopathie sévère du cœur gauche en Europe

L'IT est secondaire à une valvulopathie du cœur gauche chez environ 50% des patients ayant une IT significative (moyenne/sévère)¹¹ mais la prévalence et le grade d'IT en fonction de chaque valvulopathie du cœur gauche n'ont pas été bien décrits.

Les recommandations Américaines et Européennes pour réaliser un geste concomitant sur la VT au moment d'une chirurgie valvulaire du cœur gauche sont actuellement bien codifiées avec une indication de classe I pour les patients ayant une IT sévère en pré-opératoire et une indication de classe IIa pour les patients ayant une dilatation de l'AT quel que soit le degré de sévérité de l'IT^{39,40}.

Les objectifs de cette étude étaient :

- Evaluer la fréquence et le grade de sévérité de l'IT chez les patients ayant une valvulopathie sévère du cœur gauche, dans l'ensemble et en fonction de chaque valvulopathie
- Analyser la présentation des patients en fonction du grade d'IT
- Analyser la survie globale et cardiovasculaire à 6 mois selon le grade d'IT chez les patients ayant une valvulopathie sévère du cœur gauche, dans l'ensemble et en fonction de chaque valvulopathie
- Analyser les taux d'intervention sur la VT au moment d'une intervention valvulaire du cœur gauche, dans l'ensemble et en fonction de chaque valvulopathie
- Evaluer la concordance entre les recommandations et les pratiques pour la réalisation d'un geste concomitant sur la VT au moment d'une chirurgie valvulaire du cœur gauche pour les patients ayant une indication de classe I (IT sévère)

Parmi 6883 patients ayant une valvulopathie sévère du cœur gauche ou un antécédent d'intervention valvulaire du cœur gauche inclus dans le registre prospectif « EURObservational Research Programme » de la Société Européenne de Cardiologie mené dans 222 centres à travers 28 pays, une IT significative (moyenne/sévère) était rare chez les patients ayant une valvulopathie

aortique sévère (<5 %) mais fréquente chez les patients ayant une valvulopathie mitrale sévère, retrouvée chez 30 % des patients ayant une sténose mitrale serrée, 30 % des patients ayant une IM organique et 46 % des patients ayant une IM fonctionnelle (Figure 27).

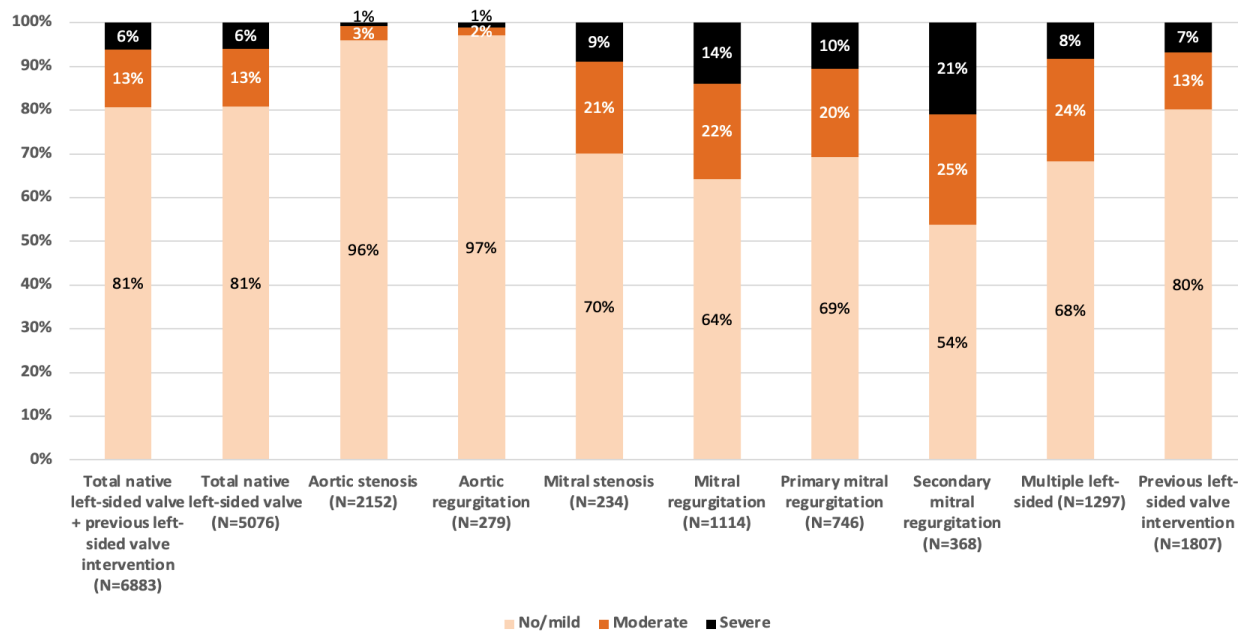


Figure 27. Fréquence et grade de sévérité de l'insuffisance tricuspide chez les patients ayant une valvulopathie sévère du cœur gauche (native ou antécédent d'intervention valvulaire du cœur gauche), dans l'ensemble et en fonction de chaque valvulopathie

Un grade d'IT plus sévère était associé à une présentation cardiaque et non cardiaque plus grave, avec plus d'hospitalisations pour insuffisance cardiaque au cours de l'année précédente, plus de diurétiques, plus souvent en classe fonctionnelle New York Heart Association (NYHA) III/IV, plus de signes d'insuffisance cardiaque congestive au moment de l'examen, une mobilité plus réduite, plus de FA, plus d'atteintes hépatiques, des pressions artérielles pulmonaires systoliques (PAPS) plus élevées, un indice de Charlson et un EuroSCORE II plus élevés, ainsi qu'une clairance de la créatinine et une FEVG plus basses (P <0.001 pour tous).

Plus l'IT était sévère, plus la mortalité globale à 6 mois augmentait (respectivement 5% pour les patients avec une IT minime à modérée, 8% pour une IT modérée à moyenne et 11% pour une IT sévère, $P < 0.001$), y compris après ajustement sur l'EuroSCORE II ou l'indice de comorbidité de Charlson. Il en était de même pour la mortalité cardio-vasculaire à 6 mois (respectivement 2% pour les patients avec une IT minime à modérée, 3% pour une IT modérée à moyenne et 5% pour une IT sévère, $P < 0.001$) (Figure 28). Ces résultats étaient retrouvés quelle que soit la valvulopathie.

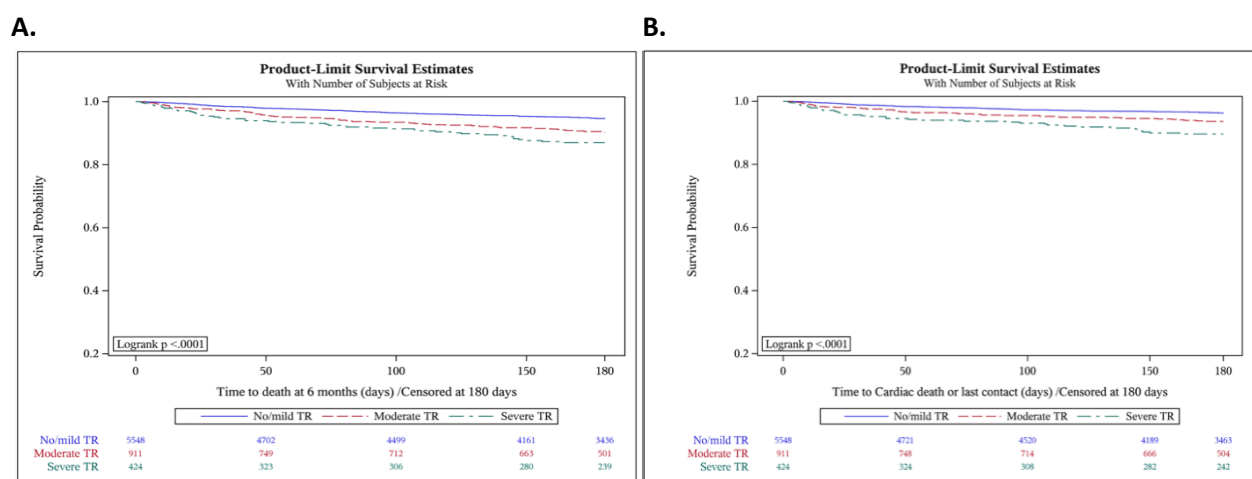


Figure 28. Impact du grade de sévérité de l'insuffisance tricuspide sur la survie

Courbes de Kaplan-Meier de survie à 6 mois chez les patients ayant une valvulopathie sévère du cœur gauche (native ou antécédent d'intervention valvulaire du cœur gauche) en fonction du grade de sévérité de l'insuffisance tricuspide

A. *Survie globale*

B. *Survie cardiovasculaire*

Parmi 2081 patients ayant eu une intervention pour valvulopathie sévère du cœur gauche, les taux d'intervention sur la VT au moment d'une intervention valvulaire du cœur gauche étaient élevés au moment d'une chirurgie valvulaire mitrale (plus de 40%) mais très faibles au moment

d'une chirurgie valvulaire aortique (1 à 2%) (Figure 29). A noter qu'un tiers des patients traités pour une valvulopathie du cœur gauche ont eu un geste percutané et qu'aucun patient n'a eu de geste percutané sur la VT dans ce registre qui a été réalisé en 2017.

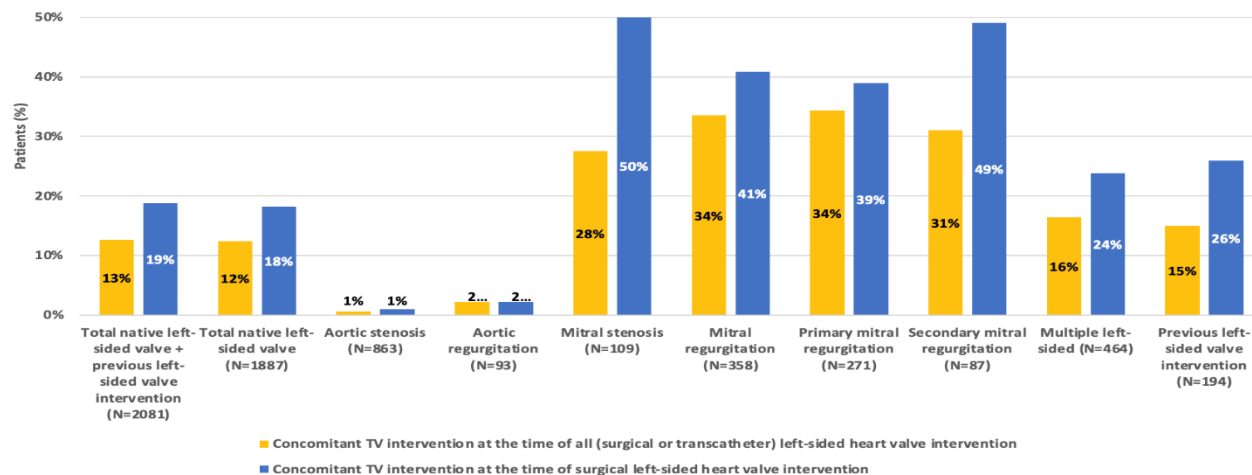


Figure 29. Taux d'interventions concomitantes sur la valve tricuspide au moment d'une intervention valvulaire du coeur gauche, dans l'ensemble et en fonction de chaque valvulopathie

TV : valve tricuspide

La concordance entre les indications de classe I pour la réalisation d'un geste concomitant sur la VT au moment d'une chirurgie valvulaire du coeur gauche selon les recommandations Européennes et Américaines^{39,40} et la décision thérapeutique en pratique réelle était très bonne (88 % dans l'ensemble), en particulier pour les patients opérés pour une IM (95 %) (Figure 30).

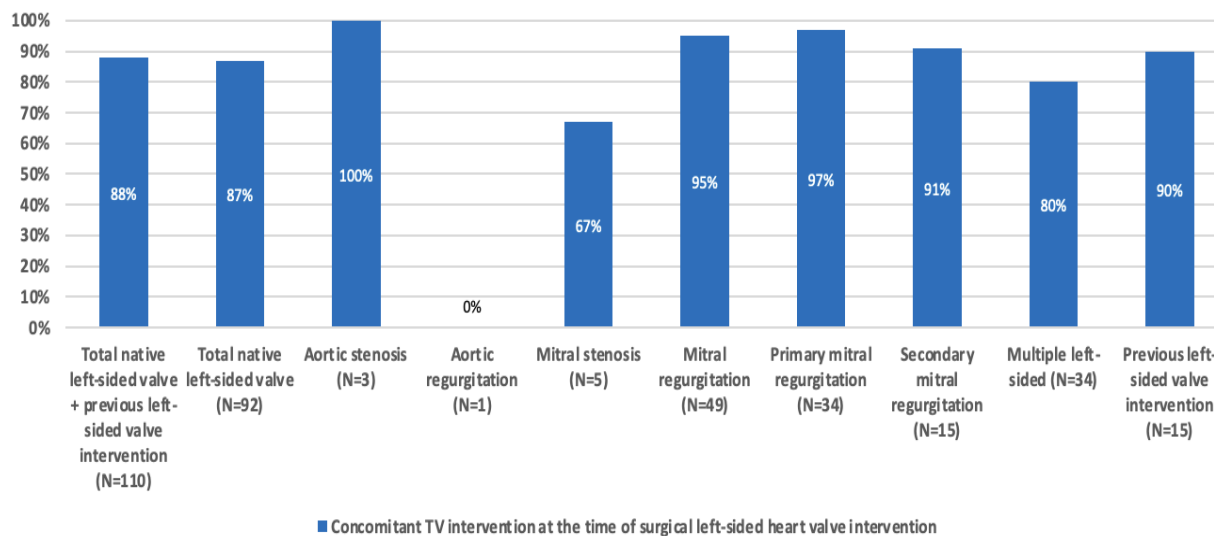


Figure 30. Taux d'interventions concomitantes sur la valve tricuspide au moment d'une chirurgie valvulaire du coeur gauche chez les patients ayant une insuffisance tricuspide sévère, dans l'ensemble et en fonction de chaque valvulopathie : concordance entre les indications de classe I pour une intervention valvulaire tricuspide concomitante (recommandations Européennes et Américaines^{39,40}) et la décision thérapeutique

Cette étude a donc montré que l'IT est fréquente chez les patients ayant une valvulopathie mitrale sévère, qu'un grade d'IT plus sévère est associé à une présentation cardiaque et non cardiaque plus grave et que l'IT est associée à un pronostic d'autant plus sombre qu'elle est sévère, même après ajustement.

Sur le plan thérapeutique, un geste concomitant sur la VT au moment d'une intervention valvulaire du coeur gauche est fréquent au moment d'une chirurgie valvulaire mitrale et les recommandations pour la pratique d'un geste concomitant sur la VT au moment d'une chirurgie valvulaire du coeur gauche semblent bien respectées en pratique pour les patients ayant une indication de classe I.

**Tricuspid regurgitation: frequency, management and outcome among patients with severe left-sided
valvular heart disease.**

BRIEF TITLE: Tricuspid regurgitation and left valve disease.

Julien Dreyfus, MD¹; Monika Komar, MD²; David Attias, MD¹; Michele De Bonis, MD³; Frank Ruschitzka, MD⁴; Bogdan A. Popescu, MD, PhD⁵; Cécile Laroche⁶; Christophe Tribouilloy, MD, PhD⁷; Alexander Bogachev Prokophiev, MD⁸; Vaida Mizariene, MD⁹; Jeroen J. Bax, MD, PhD¹⁰; Aldo Pietro Maggioni, MD⁶; Alec Vahanian, MD¹¹; Bernard lung, MD¹²; on behalf of the EORP VHD II Registry Investigators Group*

*Listed in the Appendix.

WORD COUNT

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|------------------------------------|------------|
| Abstract | 299 words |
| Text (Introduction to conclusion) | 3375 words |
| References | 939 words |
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| Figure legends | 369 words |
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ABSTRACT

Background. Tricuspid regurgitation (TR) is frequent among patients with severe left-sided valvular heart disease (LS-VHD).

Objectives. We sought to assess TR frequency, management and outcome in this population.

Methods. Among 6883 patients with severe LS-VHD or previous valvular intervention in the EURObservational Research Programme prospective VHD II survey (28 countries, 222 centers), we analyzed frequency and grade of TR according to LS-VHD, and 6-month overall and cardiovascular survival according to TR grade. Among 2081 patients who underwent an intervention for severe LS-VHD, we analyzed frequency and outcome of concomitant tricuspid valve (TV) intervention, and concordance between Class I indications for concomitant TV surgery (patients with severe TR) and real-practice decision-making.

Results. Moderate to severe TR was frequent among patients with severe mitral VHD ($\geq 30\%$), especially with secondary mitral regurgitation (46%), and rare among patients with aortic VHD ($< 5\%$). Higher TR grade was associated with a poorer 6-month overall and cardiovascular survival ($P < 0.001$). Rates of concomitant TV intervention at the time of left-sided heart valve surgery (LS-HVS) were high at the time of mitral valve surgery (more than 40%) but very low at the time of aortic valve surgery (1 to 2%). Concomitant TV intervention at the time of LS-HVS was performed in patients with a better general status but a more severe cardiac than patients without concomitant TV intervention, with no difference between the 2 groups in in-hospital and 6-month mortality ($P = 0.93$ and $P = 0.60$ respectively). Concordance between Class I indications for concomitant TV surgery at the time of LS-HVS according to guidelines and real-practice decision-making was very good (88% overall).

Conclusion. TR was frequent in patients with mitral VHD and was associated with a poorer outcome as TR grade increased. Adherence to guidelines for Class I indications for concomitant TV surgery at the time of LS-HVS was very good.

KEYWORDS: tricuspid regurgitation, left-sided heart valve disease, management, outcome, guidelines.

CONDENSED ABSTRACT

In this large international prospective EURObservational Research Programme Valvular Heart Disease (VHD) II survey, among 6883 patients with severe left-sided VHD or previous valvular intervention, tricuspid regurgitation (TR) was frequent in patients with mitral VHD and was associated with a poorer outcome as TR grade increased. Compliance to guidelines for Class I indications (patients with severe TR) for concomitant TV surgery at the time of left-sided heart valve surgery was very good. With the trend toward more transcatheter treatment for left-sided VHD, there is a critical need for safe and efficient TV transcatheter treatment for patients with concomitant TR.

ABBREVIATIONS LIST:

ACC: American College of Cardiology

AHA: American Heart Association

EACTS: European Association for Cardiothoracic Surgery

ESC: European Society of Cardiology

LS-HVS: Left-Sided Heart Valve Surgery

LS-VHD: Left-Sided Valvular Heart Disease

NYHA: New York Heart Association

TR: Tricuspid Regurgitation

TV: Tricuspid Valve

VHD: Valvular Heart Disease

INTRODUCTION

Moderate or severe tricuspid regurgitation (TR) is a frequent condition, affecting over 1.6 million individuals in the US.¹⁰ In approximately half of those patients, TR is secondary to left-sided valvular heart disease (LS-VHD)¹¹ but prevalence and grade of TR according to each LS-VHD have not been well described.

TR is an independent prognosis factor associated with significant morbidity and mortality, that increases with TR grade, whatever its mechanism or etiology.^{26,30,31,35,59,60} TR often persists or even progresses after successful correction of mitral or aortic valve disease, including surgical or transcatheter interventions, when the tricuspid valve (TV) is left untreated at the time of left-sided valvular intervention, with an adverse prognosis for those patients.^{36,61} Hence, both European Society of Cardiology (ESC) / European Association for Cardiothoracic Surgery (EACTS) and American College of Cardiology (ACC) / American Heart Association (AHA) have provided well-codified recommendations for concomitant TV intervention at the time of left-sided heart valve surgery with a Class I indication for patients with severe TR and a Class IIa indication for patients with less than severe TR with specific stipulations.^{39,40}

This study aimed to use data from the international VHD II survey, designed by the ESC EURObservational Research Programme (EORP)⁶² to assess TR frequency, management and outcome among patients with severe left-sided VHD in a large recent multicentric cohort in Europe.

METHODS

Study population

The VHD II Survey was prospectively designed to assess adherence to guidelines and was conducted between January and August 2017 in 222 centers across 28 countries; 7247 patients were recruited over a 3-month period in each center if they had at least one severe native LS-VHD or if they had previously undergone a valvular intervention. Details concerning inclusion criteria and data collection have been

previously described.⁶² Severe aortic or mitral VHD and grades of TR, divided into no/mild, moderate and severe, were defined by echocardiography using an integrative approach.

The VHD II Survey was approved for the ESC by the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTRS) (5 October 2016) and the Commission Nationale Informatique et Liberté (CNIL) (14 April 2017). National coordinators, in conjunction with local centres, [or] participating centers [depending on whether they are country/centre based] managed the approvals of national or regional ethics committees or Institutional Review Boards (IRBs), according to local regulations.

TR and severe LS-VHD

In a total of 6883 patients with severe LS-VHD or previous left-sided valvular intervention (patients with isolated right-sided VHD or previous right-sided valvular intervention were excluded from the overall population), we specifically studied frequency and grade of TR according to left-sided VHD as well as characteristics and 6-month overall and cardiovascular survival of patients according to TR grade.

Concomitant TV intervention at the time of left-sided heart valve intervention

In a total of 2081 patients who underwent an intervention for severe LS-VHD during the study period, we analyzed the rates of surgical and transcatheter intervention on left heart valve disease and the frequency of concomitant TV intervention. More specifically, we studied the concordance between Class I indications for concomitant TV intervention from the 2012 ESC/EACTS and 2014 ACC/AHA guidelines which were applicable at the time of the survey^{63,64} and therapeutic decision-making. Characteristics of patients and 6-month overall and cardiovascular survival according to concomitant TV intervention were also reported.

Statistical analysis

Variables were expressed as median [interquartile range] for continuous variables and number of patients (percentage) for categorical variables. Comparisons between groups of patients with severe left-sided VHD according to TR grade and between patients undergoing an intervention for severe left-sided VHD according to concomitant TV intervention were performed with a χ^2 or Fischer-exact test for categorical variables and a Kruskal-Wallis test for continuous variables.

Concordance with Class I recommendations for concomitant TV intervention according to 2012 ESC/EACTS and 2014 ACC/AHA guidelines^{63,64} and therapeutic decision-making was assessed by the frequency of concomitant TV interventions which were performed in patients who underwent interventions for severe LS-VHD and had severe TR.

Six-month overall and cardiovascular (heart failure, infective endocarditis, re-intervention, stroke) survival rates, according to TR grade among patients with severe LS-VHD and according to concomitant TV intervention among patients who underwent an intervention for severe LS-VHD, were assessed using the Kaplan-Meier method and compared with a log-rank test. Follow-up at six months was 85% completed for both. The relationships between overall 6-month survival and TR grade, and between overall 6-month survival and concomitant TV intervention were analyzed using an unadjusted Cox proportional hazard model and two different Cox models, adjusted according to EuroSCORE II or Charlson Comorbidity Index.

Analyses were performed at the two-tailed $P < 0.05$ level, using SAS statistical software version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Frequency and grade of TR in patients with severe left-sided VHD

Among 6883 patients with severe LS-VHD, 5548 (81%) had no or mild TR, 911 (13%) had moderate TR and 424 (6%) had severe TR, with no difference between patients with native LS-VHD or previous left-

sided valvular intervention ($P=0.47$). Moderate to severe TR was rare in patients with severe aortic valve disease (4% for aortic stenosis and 3% for aortic regurgitation) but frequent in patients with severe mitral valve disease (30% for mitral stenosis, 31% for primary mitral regurgitation and 46% for secondary mitral regurgitation). Similarly, moderate to severe TR was frequent in patients with severe multiple LS-VHD (32%) (Figure 1 and Table S1).

Characteristics and outcome of patients with severe LS-VHD according to TR grade

Overall, there was a parallelism between the severity of the TR grade and the severity of the clinical, biological and echocardiographic presentation as described in Table 1. Thus, higher TR grade was associated with a more severe cardiac and non-cardiac presentation, as patients had more permanent pacemakers, previous hospitalization for heart failure during the last year, diuretics, NYHA functional Class III/IV, congestive heart failure signs at the time of examination, limited mobility, atrial fibrillation, liver dysfunction, higher systolic pulmonary artery pressure, Charlson index and EuroSCORE II, as well as reduced creatinine clearance and left-ventricular ejection fraction ($P<0.001$ for all).

Moreover, overall, TR grade was associated with 6-month overall mortality that significantly increased with TR severity (respectively 5% for patients with no or mild TR, 8% for moderate TR and 11% for severe TR, $P<0.001$) (Figure 2A), even after adjustment for EuroSCORE II or Charlson Comorbidity Index (Table 2). It was the same for 6-month cardiovascular mortality (respectively 2% for patients with no or mild TR, 3% for moderate TR and 5% for severe TR, $P<0.001$) (Figure 2B).

Concomitant TV intervention at the time of left-sided heart valve intervention

Overall, a concomitant TV intervention was performed in 13% of the 2081 patients who underwent (surgical or transcatheter) left-sided valvular heart interventions during the survey period, accounting for 19% of all left-sided heart valve surgical interventions (Figure 3A).

Most of concomitant TV surgeries at the time of left-sided heart valve surgery were performed for patients with less than severe TR, as patients with Class I recommendation represented only 27% of all patients who underwent a concomitant tricuspid valve and left-sided heart valve surgery (LS-HVS).

TV surgery was mostly a repair (96% of all the TV procedures) while biological and mechanical prostheses were rarely implanted in the tricuspid position (3% and 1% respectively). Rates of concomitant TV intervention at the time of left-sided heart valve surgery were very low for aortic valve surgery (1% for aortic stenosis and 2% for aortic regurgitation) but high for mitral valve surgery, as it was performed in more than 40% in case of surgery for mitral regurgitation and up to 50% for mitral stenosis (Figure 3A).

Transcatheter interventions represented overall one third of all left-sided heart valve interventions. No patient who underwent a transcatheter intervention at the left-sided heart valve level had a concomitant transcatheter TV intervention (Figures 3B, 4A and 4B).

Concordance between Class I indications for concomitant TV intervention and therapeutic decision

Overall, a concomitant TV intervention was performed at the time of LS-HVS in 88% of patients with a Class I indication for severe TR, according to ESC/EACTS and ACC/AHA guidelines.^{63,64} This rate rose to 95% at the time of mitral valve surgery for mitral regurgitation (Figure 3B).

Characteristics and outcome of patients undergoing an intervention for severe LS-VHD according to concomitant TV intervention

Overall, among patients who underwent left-sided heart valve intervention, those who had a concomitant TV intervention had a better general status than those without concomitant TV intervention, as they were younger, with less frequent hypertension, previous coronary intervention, lower limb atherosclerosis and lower Charlson score than patients who underwent an isolated left-sided heart valve intervention. However, they had a more serious cardiac condition, with more frequent hospitalizations for

heart failure during the previous year, more frequent use of diuretics, more NYHA functional Class III/IV, congestive heart failure at the time of examination, atrial fibrillation, higher systolic pulmonary artery pressure, more severe TR and reduced LV ejection fraction (all $P < 0.05$) (Table 3).

Overall, there was no difference between patients who underwent left-sided heart valve intervention according to concomitant TV intervention for in-hospital mortality (2% in both groups, $P = 0.93$) and no significant difference for post-operative permanent pacemaker (6% in the group without concomitant TV intervention and 8% in the group with concomitant TV intervention, $P = 0.40$).

Concomitant TV intervention was not associated with 6-month overall mortality (5% in the group without concomitant TV intervention and 4% in the group with concomitant TV intervention, $P = 0.61$) and cardiovascular mortality (3% in the group without concomitant TV intervention and 2% in the group with concomitant TV intervention, $P = 0.56$) (Figure 5A and 5B), even after adjustment for EuroSCORE II or Charlson Comorbidity Index (Table S2).

DISCUSSION

In this large recent international prospective survey of patients with severe LS-VHD during a three-month period in 2017 in Europe, the main results can be summarized as follows (Graphical Abstract): 1) moderate to severe TR was frequent among patients with severe mitral valve disease ($\geq 30\%$), especially those with secondary mitral regurgitation (46%), and rare among patients with aortic valve disease ($< 5\%$); 2) an increase in TR grade was associated with a more severe clinical presentation and a poorer overall and cardiovascular survival at six months; 3) rates of concomitant TV intervention at the time of left-sided heart valve surgery were high at the time of mitral valve surgery (more than 40% in case of surgery for mitral regurgitation and 50% for mitral stenosis) but very low at the time of aortic valve surgery (1 to 2%); 4) concordance between Class I indications (patients with severe TR) for concomitant TV surgery at the time of left-sided valvular heart surgery according to ESC/EACTS guidelines and real-practice decision-

making was very good (88% overall), especially for patients undergoing surgery for mitral regurgitation (95%); 5) patients who underwent a concomitant TV intervention at the time of left-sided heart valve intervention had a better general status but a more severe cardiac condition than patients who underwent a left-sided heart valve intervention without concomitant TV intervention, with no difference between the 2 groups in in-hospital mortality and overall and cardiovascular mortality at six months.

This study is the first to depict frequency and grade of TR associated with severe LS-VHD, not only overall, but also according to specific settings such as previous valvular intervention, multiple left-sided VHD or primary/secondary mitral regurgitation. In a recent study, Chancellor et al.⁶⁰ have shown that among 17,483 patients undergoing aortic valve replacement, 6% had moderate and 1% had severe TR, which is concordant with our results showing that severe TR is rare among patients with severe aortic stenosis (3% had moderate and 1% had severe TR in our study). Conversely, rates of moderate to severe TR were particularly high in patients with severe mitral VHD, especially secondary mitral regurgitation, probably stressed by both older age and atrial fibrillation, which is consistent with a recent series of 606 patients treated with transcatheter repair for mitral regurgitation in whom 57% had moderate to severe TR at baseline.⁶⁵

TR is a serious condition and an independent predictive factor of outcome with a poorer outcome related to its grade.^{26,30,31} Previous studies had shown that presence of severe TR before treatment of LS-VHD was a predictor of poor outcome for both patients with aortic stenosis^{59,66} and mitral regurgitation,^{36,61,65,67} regardless of the treatment strategy (surgery or transcatheter) for left-sided VHD. This study is the first to show a parallel between the severity of the TR grade and overall and cardiovascular mortality in the setting of all severe left-sided VHD, which is a very common situation, as it represents approximately half of patients with TR.¹¹ In our population, it was also striking to see that severity of the TR grade was associated with a poorer clinical, biological and echocardiographic presentation, with notably more congestive heart failure, atrial fibrillation, renal and liver failure.

The vast majority of TV surgery is performed at the time of LS-HVS (86% of overall TV surgery in the Society of Thoracic Surgeons database in the USA⁶⁸ and 92% in France),⁶⁹ especially at the time of mitral valve surgery,^{49,70} as mitral VHD is frequently associated with TV disease. Thus, in our study, a concomitant surgical treatment of TR was frequently performed at the time of mitral valve surgical interventions (50% for patients with mitral stenosis, 39% for primary MR and 49% for secondary MR) but only in 1% of surgical interventions for aortic stenosis. Our results are fairly consistent with the literature. Indeed, among 17,483 patients who underwent surgical aortic valve replacement in a regional Society of Thoracic Surgeons database between 2001 and 2017, only 0.6% underwent a concomitant TV intervention.⁶⁰ On the contrary, among all mitral valve surgeries performed for MR in France between 2014 and 2016, a concomitant TV intervention was performed in 20% of the 7,593 patients with primary MR and 27% of the 2,935 patients with secondary MR.⁷¹

This survey highlighted a very good adherence to ESC/EACTS and ACC/AHA guidelines, as a concomitant TV intervention was performed at the time of LS-HVS in 88% of overall patients with a Class I indication for severe TR according to 2012 ESC/EACTS and 2014 ACC/AHA guidelines,^{63,64} rate that raised up to 95% at the time of mitral valve surgery for mitral regurgitation and 100% at the time of aortic valve surgery for aortic stenosis. Those results were consistent with the steady increase over time in the number of combined TV surgery at the time of left-sided heart valve surgery,^{69,72} a trend that should continue, as those recommendations were maintained in the last American and European guidelines.^{63,64}

In the VHD II survey, like in other studies,⁴⁹ most of concomitant TV surgeries at the time of left-sided heart valve surgery were performed for patients with less than severe TR, as patients with Class I recommendation represented only 27% of all patients who underwent a concomitant tricuspid valve and left-sided heart valve surgery, which can explain the very high rate of TV repair (96%) to treat tricuspid annulus dilatation and prevent long-term significant TR.

Moreover, our results reinforced among 2081 patients that concomitant TV surgery at the time of left-sided heart valve surgery does not increase in-hospital mortality in comparison to isolated LS-HVS.^{46,47,49,73} In this survey, like in most other studies,^{46,47,49} rate of post-operative permanent pacemaker in the group of patients with concomitant TV surgery was relatively low (8%) and not significantly different than in the group of patients without concomitant TV surgery, on the contrary to a recent randomized trial that has shown a higher rate of post-operative permanent pacemaker in the group of patients with concomitant TV surgery (14%).⁷³

When the survey was conducted, transcatheter treatment represented one third of all curative interventions for severe LS-VHD, with a higher proportion for patients with aortic stenosis, mitral stenosis or previous left-sided intervention. The number of transcatheter treatment for severe LS-VHD is currently significantly growing with the advent of transcatheter aortic valve replacement for aortic stenosis and also the development of transcatheter mitral valve repair or replacement, especially transcatheter edge-to-edge repair. Population ageing, previous valve surgery (26% of our population), addition of indications for transcatheter treatment of mitral regurgitation in selected patients and extension of indications for transcatheter treatment of aortic stenosis toward low-risk patients in the last guidelines will intensify this trend.^{39,40}

Transcatheter treatment for TR, that can be a repair or a replacement for patients with high surgical risk,⁷⁴ is currently under development and available only within the scope of trials in expert centers.⁷⁵ Ongoing randomized controlled trials (TRILUMINATE Pivotal Trial, TRI-FR,⁷⁶ CLASP II TR, TRISCEND II Pivotal trial) will try to demonstrate the safety and effectiveness of transcatheter treatments in improving clinical outcomes in comparison to medical therapy. In a recent study, Mehr et al.⁷⁷ have shown that concurrent correction of mitral and tricuspid regurgitation with transcatheter edge-to-edge valve repair was associated with a higher 1-year survival rate compared with isolated transcatheter edge-to-edge mitral valve repair in patients with

severe MR and severe TR. Further studies are mandatory to carefully evaluate the benefit of combined mitral and tricuspid valve transcatheter interventions as well as the best strategy (1 or 2 procedures) if combined interventions appear to be useful. In our survey, no patient received a transcatheter treatment for TR. While waiting for the use in routine practice of transcatheter treatment for TR, the presence of severe TR associated with severe LS-VHD should be taken into consideration, especially for mitral valve diseases, in the choice of the best therapeutic option between concomitant mitral and tricuspid surgical correction versus isolated mitral transcatheter intervention.

Study limitations

The present study deserves several comments. First, this voluntary survey was not population-based and there may be legitimate concerns concerning its ability to represent wider practice due to potential selection, referral and treatment bias. However, the design of the present survey allows for a detailed analysis of the relationship between patient characteristics and therapeutic decision-making in the light of ESC guidelines in a wide spectrum of healthcare structures and countries. Thus, we could not affirm the exact prevalence and grade of TR in patients with severe LS-VHD but we can assume that the frequency found in this registry should be close to its prevalence in the population, thanks to a very large number of patients (6883) in many centers (222) across many countries (28). Moreover, we do not have data on massive or torrential TR as those grades were suggested after the end of the survey. Second, we were not able to assess adherence to Class IIa recommendations for patients with less than severe TR but dilated tricuspid annulus, as tricuspid annulus diameter in transthoracic echocardiography was not collected in this registry. In the same way, we could not assess improvement of TR grade at six months according to TV intervention, as this data was not collected. Third, follow-up was limited to six months in the VHD II protocol, a time span that is usually too short to demonstrate any benefit of concomitant TV

intervention on overall mortality, especially as most patients who underwent surgery had less than severe TR at baseline. Fourth, in-hospital mortality and overall and cardiovascular mortality at six months in patients with left-sided heart valve intervention according to concomitant TV intervention should be interpreted bearing in mind that groups were not randomized. Indeed, concomitant TV surgery at the time of LS-HVS seemed to be performed in patients with a more advanced cardiac disease but a better general condition, patients being younger and with a lower Charlson's index. However, results were unchanged after adjustment for EuroSCORE II or Charlson Comorbidity Index and were consistent with the literature.⁴⁹

CONCLUSION

In this large, international, prospective survey among patients with severe LS-VHD, we have shown that TR was frequent in patients with mitral VHD and was associated with a poorer outcome as TR grade increased. Concomitant TV intervention at the time of left-sided heart valve surgery was not associated with an increased in-hospital mortality and there was a very good concordance between guidelines and real-practice decision-making for Class I indications (patients with severe TR) for concomitant TV surgery at the time of left-sided heart valve surgery. As more and more patients have a transcatheter rather than a surgical treatment for aortic and mitral VHD, there is a critical need for safe and efficient transcatheter TV treatment for patients with concomitant, significant TR.

CLINICAL PERSPECTIVES

Competency in patient care and procedural skills:

Tricuspid regurgitation is frequent in patients with mitral valvular heart disease and is associated with a poorer outcome as tricuspid regurgitation grade increases.

Adherence to guidelines for Class I indications for concomitant tricuspid valve surgery at the time of left-sided heart valve surgery, assessed for the first time in this survey, is very good.

Translational outlook

With the trend toward more transcatheter treatment for left-sided valvular heart disease, there is a critical need for safe and efficient tricuspid valve transcatheter treatment for patients with concomitant tricuspid regurgitation.

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REFERENCES

1. Stuge O, Liddicoat J. Emerging opportunities for cardiac surgeons within structural heart disease. *J Thorac Cardiovasc Surg* 2006;132:1258-61.
2. Topilsky Y, Maltais S, Medina Inojosa J et al. Burden of Tricuspid Regurgitation in Patients Diagnosed in the Community Setting. *JACC Cardiovasc Imaging* 2019;12:433-442.
3. Amano M, Izumi C, Taniguchi T et al. Impact of concomitant tricuspid regurgitation on long-term outcomes in severe aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2018;20:353-360.
4. Chancellor WZ, Mehaffey JH, Beller JP et al. Impact of tricuspid regurgitation with and without repair during aortic valve replacement. *J Thorac Cardiovasc Surg* 2020;162:44-50 e2.
5. Essayagh B, Antoine C, Benfari G et al. Functional tricuspid regurgitation of degenerative mitral valve disease: a crucial determinant of survival. *Eur Heart J* 2020;41:1918-1929.
6. Messika-Zeitoun D, Thomson H, Bellamy M et al. Medical and surgical outcome of tricuspid regurgitation caused by flail leaflets. *J Thorac Cardiovasc Surg* 2004;128:296-302.
7. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* 2004;43:405-9.
8. Wang N, Fulcher J, Abeysuriya N et al. Tricuspid regurgitation is associated with increased mortality independent of pulmonary pressures and right heart failure: a systematic review and meta-analysis. *Eur Heart J* 2018;40:476-484.

9. Kalbacher D, Schafer U, von Bardeleben RS et al. Impact of tricuspid valve regurgitation in surgical high-risk patients undergoing MitraClip implantation: results from the TRAMI registry. *EuroIntervention* 2017;12:e1809-e1816.
10. Pavasini R, Ruggerini S, Grapsa J et al. Role of the tricuspid regurgitation after mitralclip and transcatheter aortic valve implantation: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging* 2017;19:654-659.
11. Otto CM, Nishimura RA, Bonow RO et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;143:e72-e227.
12. Vahanian A, Beyersdorf F, Praz F et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2021.
13. Iung B, Delgado V, Rosenhek R et al. Contemporary Presentation and Management of Valvular Heart Disease: The EURObservational Research Programme Valvular Heart Disease II Survey. *Circulation* 2019;140:1156-1169.
14. Nishimura RA, Otto CM, Bonow RO et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129:e521-643.
15. Vahanian A, Alfieri O, Andreotti F et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012;33:2451-96.
16. Geyer M, Keller K, Bachmann K et al. Concomitant tricuspid regurgitation severity and its secondary reduction determine long-term prognosis after transcatheter mitral valve edge-to-edge repair. *Clin Res Cardiol* 2021;110:676-688.

17. Shamekhi J, Sugiura A, Tabata N et al. Impact of Tricuspid Regurgitation in Patients Undergoing Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv* 2020;13:1135-1137.
18. Hahn RT, Asch F, Weissman NJ et al. Impact of Tricuspid Regurgitation on Clinical Outcomes: The COAPT Trial. *J Am Coll Cardiol* 2020;76:1305-1314.
19. Kilic A, Saha-Chaudhuri P, Rankin JS, Conte JV. Trends and outcomes of tricuspid valve surgery in North America: an analysis of more than 50,000 patients from the Society of Thoracic Surgeons database. *Ann Thorac Surg* 2013;96:1546-52; discussion 1552.
20. Dreyfus J, Flagiello M, Bazire B et al. Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes. *Eur Heart J* 2020;41:4304-4317.
21. Brescia AA, Ward ST, Watt TMF et al. Outcomes of Guideline-Directed Concomitant Annuloplasty for Functional Tricuspid Regurgitation. *Ann Thorac Surg* 2020;109:1227-1232.
22. Dreyfus G, Essayagh B, Benfari G et al. Outcome of consistent guideline-based tricuspid management in patients undergoing degenerative mitral regurgitation correction. *JTCVS Open* 2021.
23. Messika-Zeitoun D, Candolfi P, Enriquez-Sarano M et al. Presentation and outcomes of mitral valve surgery in France in the recent era: a nationwide perspective. *Open Heart* 2020;7.
24. Vassileva CM, Shabosky J, Boley T, Markwell S, Hazelrigg S. Tricuspid valve surgery: the past 10 years from the Nationwide Inpatient Sample (NIS) database. *J Thorac Cardiovasc Surg* 2012;143:1043-9.

25. Badhwar V, Rankin JS, He M et al. Performing Concomitant Tricuspid Valve Repair at the Time of Mitral Valve Operations Is Not Associated With Increased Operative Mortality. *Ann Thorac Surg* 2016;103:587-593.
26. Chikwe J, Itagaki S, Anyanwu A, Adams DH. Impact of Concomitant Tricuspid Annuloplasty on Tricuspid Regurgitation, Right Ventricular Function, and Pulmonary Artery Hypertension After Repair of Mitral Valve Prolapse. *J Am Coll Cardiol* 2015;65:1931-8.
27. Gammie JS CM, Falk V, Overbey JR, Moskowitz AJ, Gillinov M, Mack MJ, Voisine P, Krane M, Yerokun B, Bowdish ME, Conradi L, Bolling SF, Miller MA, Taddei-Peters WC, Jeffries NO, Parides MK, Weisel R, Jessup M, Rose EA, Mullen JC, Raymond S, Moquete EG, O'Sullivan K, Marks ME, Iribarne A, Beyersdorf F, Borger MA, Geirsson A, Bagiella E, Hung J, Gelijns AC, O'Gara PT, Ailawadi G; CTSN Investigators. Concomitant Tricuspid Repair in Patients with Degenerative Mitral Regurgitation. *NEJM* 2021.
28. Dreyfus J, Audureau E, Bohbot Y et al. TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. *Eur Heart J* 2021.
29. Taramasso M, Benfari G, van der Bijl P et al. Transcatheter Versus Medical Treatment of Patients With Symptomatic Severe Tricuspid Regurgitation. *J Am Coll Cardiol* 2019;74:2998-3008.
30. Donal E, Leurent G, Ganivet A et al. Multicentric randomized evaluation of a tricuspid valve percutaneous repair system (clip for the tricuspid valve) in the treatment of severe secondary tricuspid regurgitation Tri.Fr Design paper. *Eur Heart J Cardiovasc Imaging* 2021.

31. Mehr M, Karam N, Taramasso M et al. Combined Tricuspid and Mitral Versus Isolated Mitral Valve Repair for Severe MR and TR: An Analysis From the TriValve and TRAMI Registries. *JACC Cardiovasc Interv* 2020;13:543-550.

FIGURE LEGENDS

Central Illustration. Tricuspid regurgitation among patients with severe left-sided valvular heart disease.

Insights from the ESC-EORP Valvular Heart Disease II survey among 6883 patients with severe left-sided valvular heart disease across 28 countries during a 3-month period in 2017.

A. Frequency and grade of tricuspid regurgitation (TR) in patients with severe left-sided valvular heart disease according to left-sided valve disease.

B. Survival in patients with severe left-sided valvular heart disease according to TR grade

C. Frequency of concomitant tricuspid valve intervention for patients with severe TR at the time of left-sided heart valve surgery: concordance between class I indications for concomitant tricuspid valve intervention (ESC and ACC/AHA guidelines) and therapeutic decision.

EORP: EURObservational Research Programme, ESC: European Society of Cardiology, TR: Tricuspid Regurgitation.

Figure 1. Frequency and grade of tricuspid regurgitation.

Frequency and grade of tricuspid regurgitation in patients with severe left-sided valvular heart disease (native or previous left-sided valvular intervention) according to left-sided valve disease.

Figure 2. Impact of tricuspid regurgitation grade on survival.

Kaplan Meier 6-month survival in patients with severe left-sided valvular heart disease (native or previous left-sided valvular intervention) according to tricuspid regurgitation grade.

A. Overall survival.

B. Cardiovascular survival.

Figure 3. Concomitant tricuspid and left-sided valve intervention.

Concomitant tricuspid valve (TV) intervention at the time of all (surgical or transcatheter) or only surgical left-sided heart valve intervention according to left-sided heart valve disease (native or previous left-sided valvular intervention).

A. Overall frequency of concomitant TV intervention.

B. Frequency of concomitant TV intervention for patients with severe tricuspid regurgitation: concordance between Class I indications for concomitant TV intervention (ESC and ACC/AHA guidelines) and therapeutic decision.

TV: Tricuspid Valve.

Figure 4. Rates of surgical versus transcatheter left-sided heart valve intervention.

Rates of surgical versus transcatheter intervention among patients who underwent a left-sided heart valve intervention according to left-sided heart valve disease (native or previous left-sided valvular intervention).

A. Overall.

B. Among patients with severe tricuspid regurgitation.

Figure 5. Impact of concomitant tricuspid valve intervention on survival.

Kaplan Meier 6-month survival in patients who underwent an intervention for severe left-sided valvular heart disease (native or previous left-sided valvular intervention) according to concomitant tricuspid valve (TV) intervention.

A. Overall survival.

B. Cardiovascular survival.

Table 1: Characteristics of patients with severe left-sided valvular heart disease according to tricuspid regurgitation grade.

| | No/mild TR (N=5548) | Moderate TR (N=911) | Severe TR (N=424) | P-Value |
|--|------------------------|------------------------|----------------------|---------|
| Patient characteristics | | | | |
| Age, years | 71.0 [61.0-80.0] | 74.0 [64.0-81.0] | 71.0 [61.0-79.0] | <0.001 |
| Female sex | 2441 (44) | 499 (55) | 248 (59) | <0.001 |
| Body mass index, kg/m ² | 27.0 [24.1-30.3] | 26.5 [23.6-29.8] | 26.0 [23.4-29.7] | <0.001 |
| Previous coronary intervention | 905/5526 (16) | 182/904 (20) | 62/419 (15) | 0.011 |
| Permanent pacemaker | 285/5026 (6) | 89/801 (11) | 52/366 (14) | <0.001 |
| Hospitalization for heart failure during the last year | 912/5547 (16) | 261 (29) | 159 (38) | <0.001 |
| NYHA Class | | | | |
| I | 1494 (27) | 106 (12) | 35 (8) | |
| II | 2200 (40) | 319 (35) | 125 (30) | <0.001 |
| III | 1662 (30) | 418 (46) | 207 (49) | |
| IV | 192 (4) | 68 (8) | 57 (13) | |
| Congestive heart failure | 941 (17) | 341 (37) | 205 (48) | <0.001 |
| Atrial fibrillation/flutter | 1049/5531 (19) | 440/910 (48) | 242/422 (57) | <0.001 |
| Creatinine clearance, ml/min | 69.9 [49.6-94.0] | 59.5 [42.0-80.2] | 57.2 [40.8-79.2] | <0.001 |
| Risk factors | | | | |
| Hypertension | 3733 (67) | 662 (73) | 254 (60) | <0.001 |
| Diabetes | 1201/5547 (22) | 201 (22) | 90 (21) | 0.936 |
| Comorbidities | | | | |
| Chronic dialysis | 59 (1) | 10 (1) | 6 (1) | 0.797 |
| Chronic pulmonary disease | 591/5511 (11) | 125/900 (14) | 56/421 (13) | 0.009 |
| Liver dysfunction | 92/5459 (2) | 30/876 (3) | 36/418 (9) | <0.001 |

| | | | | |
|---|----------------|---------------|---------------|------------------|
| Previous myocardial infarction | 514/5510 (9) | 120/895 (13) | 45/417 (11) | <0.001 |
| Previous stroke/TIA | 417 (8) | 69 (8) | 42 (10) | 0.203 |
| Lower limbs atherosclerosis | 249/5103 (5) | 46/797 (6) | 17/376 (5) | 0.514 |
| Limited mobility | 325 (6) | 87 (10) | 53 (13) | <0.001 |
| Charlson comorbidity index | 3.0 [2.0-5.0] | 4.0 [3.0-6.0] | 4.0 [3.0-6.0] | <0.001 |
| EuroSCORE II | 1.9 [1.0-3.7] | 3.0 [1.6-6.5] | 3.8 [2.0-7.3] | <0.001 |
| Left-sided valvular heart disease | | | | |
| aortic valve disease | 2335 (42) | 77 (9) | 19 (5) | <0.001 |
| mitral valve disease | 879 (16) | 293 (32) | 176 (42) | <0.001 |
| multiple valve disease | 885 (16) | 305 (34) | 107 (25) | <0.001 |
| previous intervention | 1449 (26) | 236 (26) | 122 (29) | 0.472 |
| Drug therapy at admission | | | | |
| Diuretics | 2808/4867 (58) | 662/842 (79) | 339/392 (87) | <0.001 |
| Transthoracic echocardiography | | | | |
| LV ejection fraction <60% | 2825/5447 (52) | 579/894 (65) | 299/417 (72) | <0.001 |
| Systolic pulmonary artery pressure >55mmHg | 499/5041 (10) | 289/880 (33) | 226/405 (56) | <0.001 |

Values are number of patients (percentage) or median [interquartile range]; bolded results are statistically significant at the p<0.05 level.

LV: Left Ventricle, NYHA: New York Heart Association, TR: Tricuspid Regurgitation.

Table 2: Hazard ratios for 6-month overall death in patients with severe LS-VHD according to TR grade.

| | Hazard ratio | 95% Confidence Interval | p |
|---|---------------------|--------------------------------|----------|
| Unadjusted | | | |
| Moderate/severe TR vs no/mild TR | 2.08 | 1.67-2.58 | <0.001 |
| Adjusted on EuroSCORE II | | | |
| Moderate/severe TR vs no/mild TR | 1.81 | 1.44-2.29 | <0.001 |
| EuroSCORE II (per 1-% increase) | 1.04 | 1.03-1.05 | <0.001 |
| Adjusted on Charlson Comorbidity Index | | | |
| Moderate/severe TR vs no/mild TR | 1.97 | 1.57-2.44 | <0.001 |
| Charlson Comorbidity Index (per 1-point increase) | 1.14 | 1.11-1.16 | <0.001 |

LS-VHD: Left-Sided Valvular Heart Disease, TR: Tricuspid Regurgitation.

Table 3: Characteristics of patients undergoing an intervention for severe LS-VHD according to concomitant TV intervention.

| | Concomitant TV intervention | | P-Value |
|--|-----------------------------|------------------|---------|
| | No (N=1819) | Yes (N=262) | |
| Patient characteristics | | | |
| Age, years | 71.0 [61.0-81.0] | 64.0 [57.0-70.0] | <0.001 |
| Female sex | 829 (46) | 137 (52) | 0.042 |
| Body mass index, kg/m ² | 27.4 [24.2-30.8] | 26.3 [23.2-29.9] | 0.011 |
| Previous coronary intervention | 302/1812 (17) | 19 (7) | <0.001 |
| Permanent pacemaker | 87/1576 (6) | 9/212 (4) | 0.439 |
| Hospitalization for heart failure during the last year | 374 (21) | 84 (32) | <0.001 |
| NYHA Class | | | |
| I | 217 (12) | 27 (10) | |
| II | 708 (39) | 78 (30) | 0.012 |
| III | 819 (45) | 145 (55) | |
| IV | 75 (4) | 12 (5) | |
| Congestive heart failure | 306 (17) | 81 (31) | <0.001 |
| Atrial fibrillation | 340 (19) | 139 (53) | <0.001 |
| Creatinine clearance, ml/min | 68.5 [49.6-92.8] | 71.5 [54.7-93.2] | 0.192 |
| Risk factors | | | |
| Hypertension | 1280 (70) | 152 (58) | <0.001 |
| Diabetes | 399 (22) | 37 (14) | 0.004 |
| Comorbidities | | | |

| | | | |
|---|---------------|---------------|------------------|
| Chronic dialysis | 18 (1) | 2 (1) | >0.999 |
| Chronic pulmonary disease | 217/1805 (12) | 30/259 (12) | 0.839 |
| Liver dysfunction | 28/1787 (2) | 8/260 (3) | 0.122 |
| Previous myocardial infarction | 147/1807 (8) | 20/261 (8) | 0.794 |
| Previous stroke | 142 (8) | 23 (9) | 0.586 |
| Lower limbs atherosclerosis | 83/1711 (5) | 2/255 (1) | 0.003 |
| Limited mobility | 100 (6) | 8 (3) | 0.095 |
| Charlson's index | 4.0 [2.0-5.0] | 3.0 [1.0-4.0] | <0.001 |
| EuroSCORE II | 2.0 [1.1-4.0] | 2.1 [1.3-3.7] | 0.335 |
| Left-sided valvular heart disease | | | |
| aortic valve disease | 949 (52) | 7 (3) | <0.001 |
| mitral valve disease | 317 (18) | 150 (57) | <0.001 |
| multiple valve disease | 388 (21) | 76 (29) | 0.005 |
| previous intervention | 165 (9) | 29 (11) | 0.298 |
| Drug therapy at admission | | | |
| Diuretics | 946/1579 (60) | 161/223 (72) | <0.001 |
| Transthoracic echocardiography | | | |
| LV ejection fraction <60% | 945/1785 (53) | 157/260 (60) | <0.001 |
| Systolic pulmonary artery pressure ≥55mmHg | 226/1618 (14) | 84/251 (34) | <0.001 |
| Degree of tricuspid regurgitation | | | |
| No/mild | 1640 (90) | 73 (28) | |
| Moderate | 142 (8) | 119 (45) | <0.001 |
| Severe | 37 (2) | 70 (27) | |

Values are number of patients (percentage) or median [interquartile range]; bolded results are statistically significant at the p<0.05 level.

LS-VHD: Left-Sided Valvular Heart Disease, LV: Left Ventricle, NYHA: New York Heart Association, TV: Tricuspid Valve.

Figure 1.

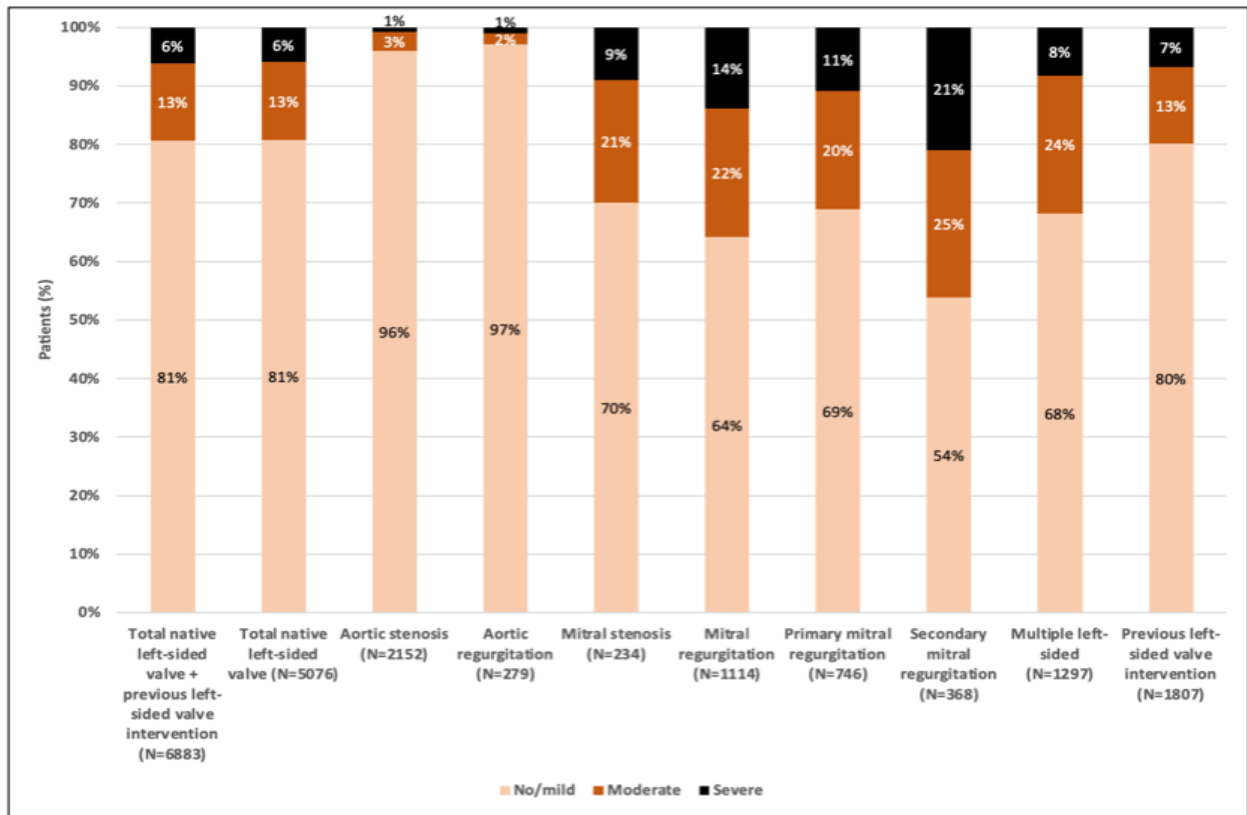
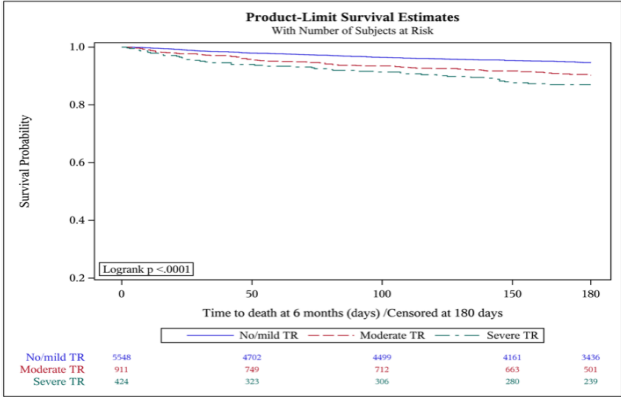


Figure 2.

A.



B.

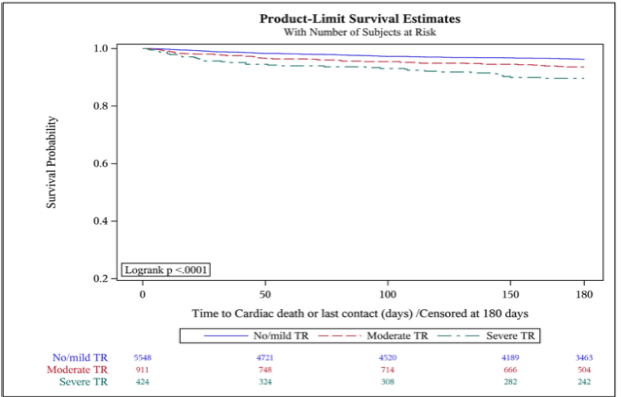
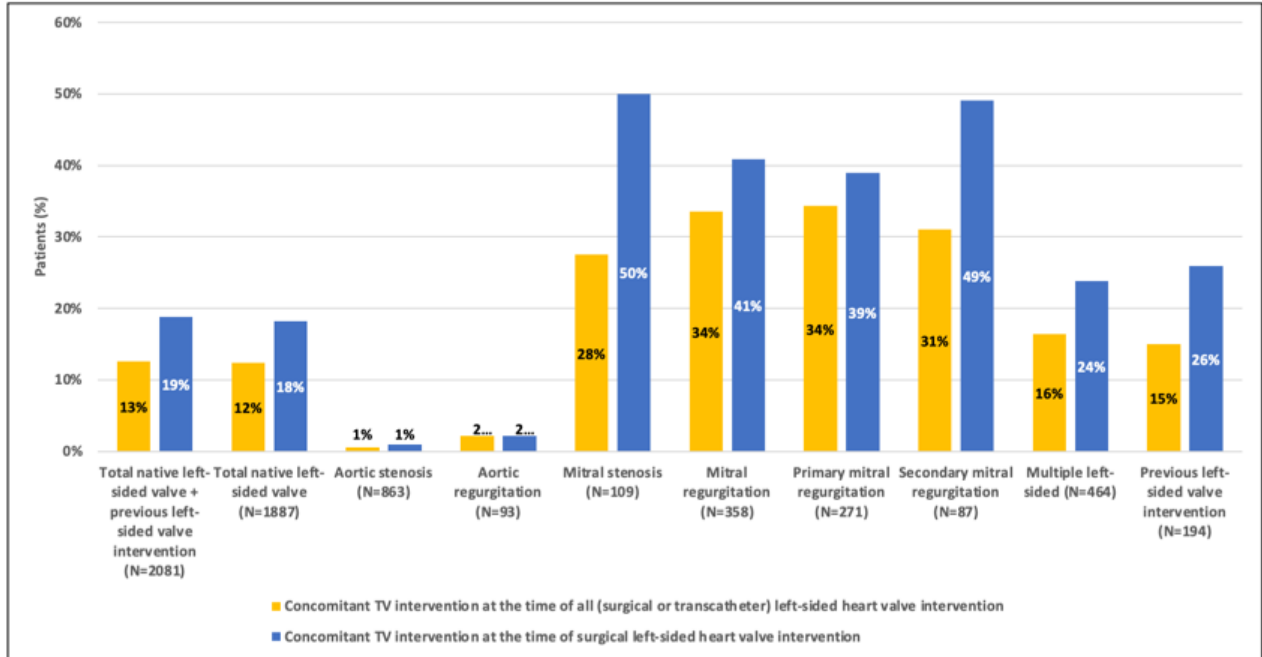


Figure 3.

A.



B.

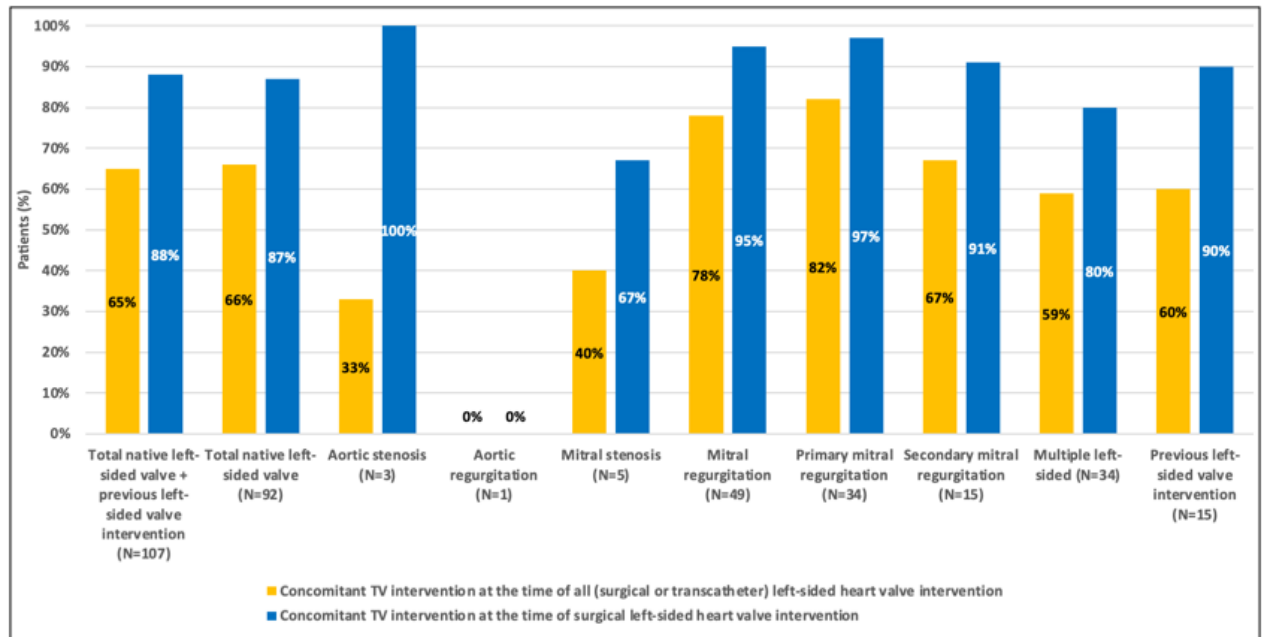
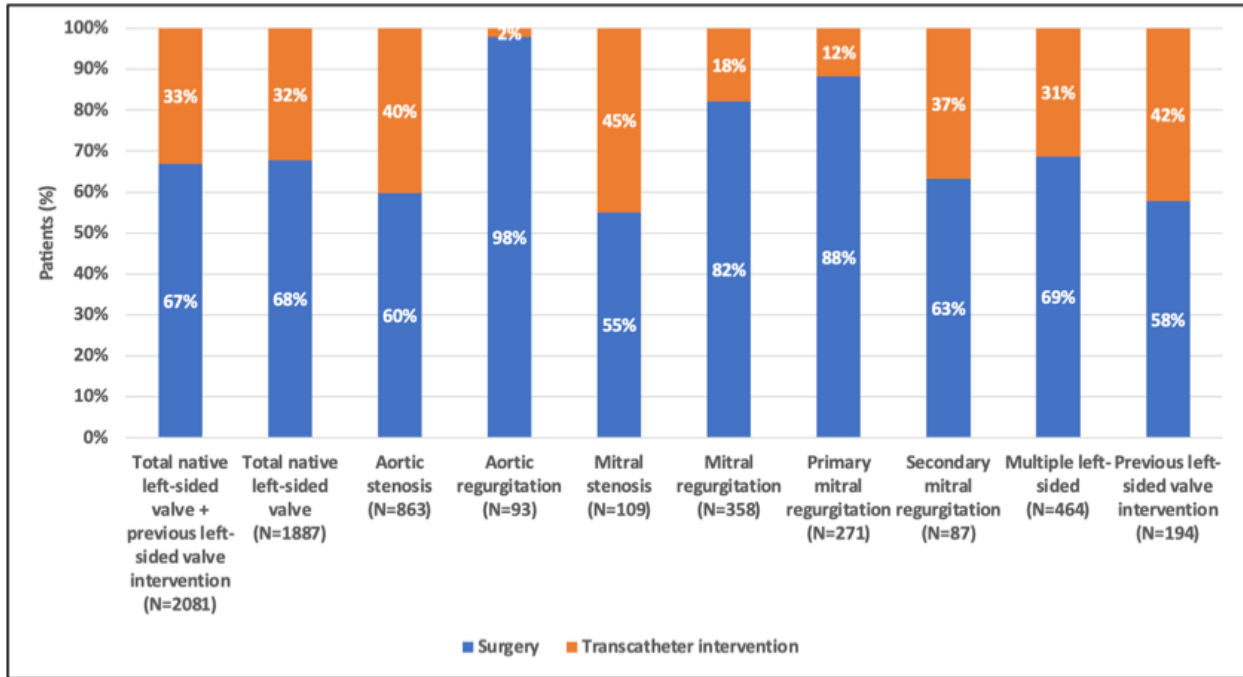


Figure 4.

A.



B.

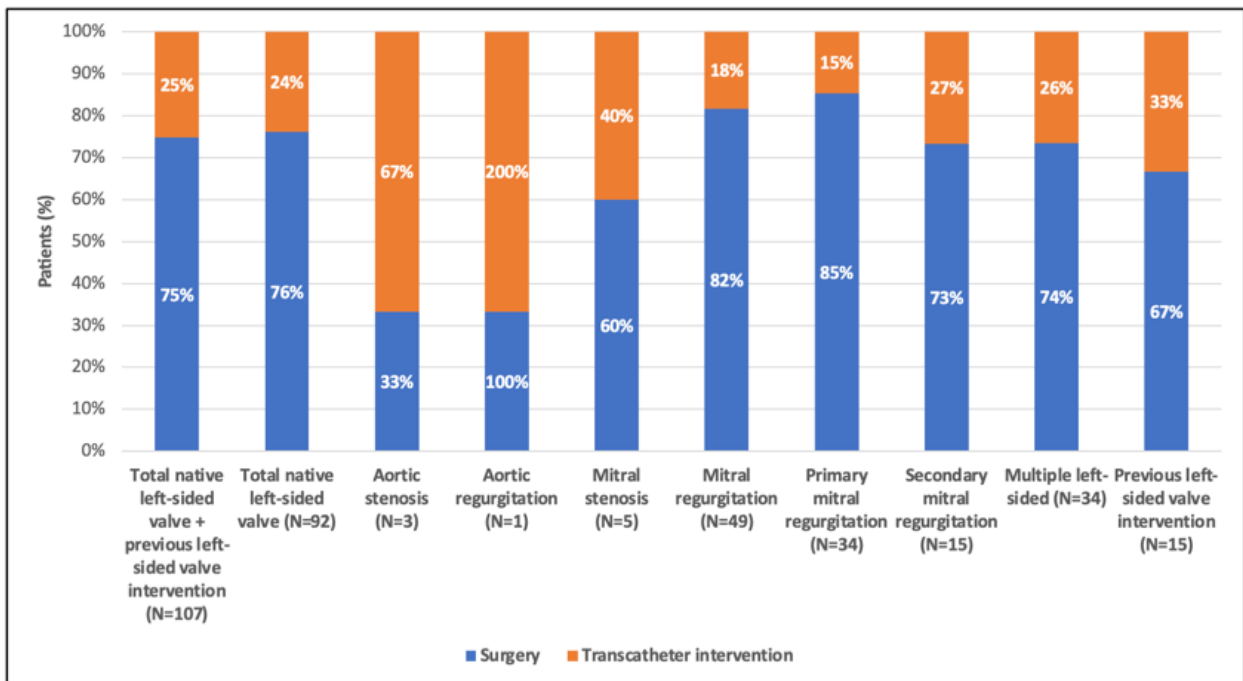
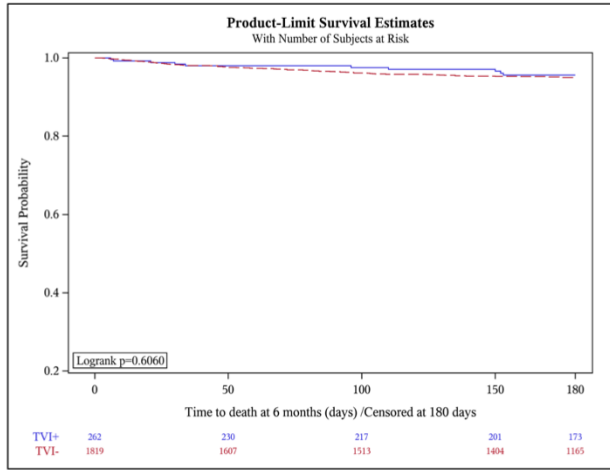
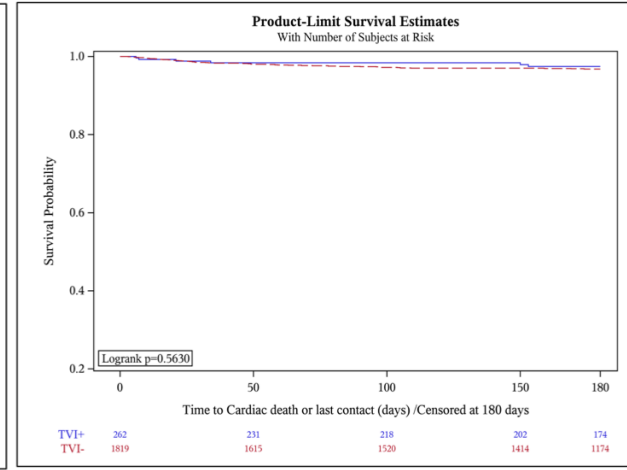


Figure 5.

A.



B.



Central Illustration.



SUPPLEMENTAL MATERIAL

Table S1: Frequency and grade of TR according to LS-VHD.

| Degree of tricuspid regurgitation | Overall | Total native left-sided valve | Aortic stenosis | Aortic regurgitation | Mitral Stenosis | Mitral regurgitation | Primary mitral regurgitation | Secondary mitral regurgitation | Multiple left-sided valve | Previous |
|-----------------------------------|-----------|-------------------------------|-----------------|----------------------|-----------------|----------------------|------------------------------|--------------------------------|---------------------------|-------------------------|
| | | | | | | | | | | left-sided intervention |
| | (N=6883) | (N=5076) | (N=2152) | (N=279) | (N=234) | (N=1114) | (N=746) | (N=368) | (N=1297) | (N=1807) |
| No/mild | 5548 (81) | 4099 (81) | 2064 (96) | 271 (97) | 164 (70) | 715 (64) | 517 (69) | 198 (54) | 885 (68) | 1449 (80) |
| Moderate | 911 (13) | 675 (13) | 72 (3) | 5 (2) | 49 (21) | 244 (22) | 151 (20) | 93 (25) | 305 (24) | 236 (13) |
| Severe | 424 (6) | 302 (6) | 16 (1) | 3 (1) | 21 (9) | 155 (14) | 78 (11) | 77 (21) | 107 (8) | 122 (7) |

Values are number of patients (percentage).

LS-VHD: Left-Sided Valvular Heart Disease, TR: Tricuspid Regurgitation.

Table S2: Hazard ratios for 6-month overall death following an intervention for severe LS-VHD according to concomitant TV intervention.

| | Hazard ratio | 95% Confidence Interval | p |
|---|--------------|-------------------------|--------|
| Unadjusted | | | |
| Concomitant TV intervention | 0.84 | 0.44-1.62 | 0.607 |
| Adjusted on EuroSCORE II | | | |
| Concomitant TV intervention | 0.85 | 0.42-1.70 | 0.642 |
| EuroSCORE II (per 1-% increase) | 1.06 | 1.04-1.07 | <0.001 |
| Adjusted on Charlson Comorbidity Index | | | |
| Concomitant TV intervention | 1.06 | 0.52-2.13 | 0.877 |
| Charlson Comorbidity Index (per 1-point increase) | 1.20 | 1.12-1.29 | <0.001 |

LS-VHD: Left-Sided Valvular Heart Disease, TV: Tricuspid Valve.

Article 4

Management and Outcome of Patients Admitted With Tricuspid Regurgitation in France

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Can J Cardiol. 2021 Jul;37(7):1078-1085

Article 4 : Prise en charge et pronostic des patients hospitalisés pour insuffisance tricuspide en France

De nombreuses études montrent que l'IT est associée à un excès de mortalité et d'événements cardiovasculaires, quel que soit le contexte^{27,31}, mais est sous-traitée. Toutefois, des données issues de larges registres nationaux évaluant la prise en charge et le devenir des patients présentant une IT sont rares.

Les objectifs de cette étude étaient d'évaluer la présentation, la prise en charge et le devenir des patients hospitalisés pour IT à l'échelon national.

A partir des données nationales du Programme de Médicalisation des Systèmes d'Information (PMSI), tous les patients hospitalisés (hôpitaux publics et privés) en France en 2014-2015 en raison d'un diagnostic d'IT ont pu être inclus et leurs données analysées.

Parmi 17 676 patients consécutifs hospitalisés pour IT fonctionnelle (les patients ayant une atteinte congénitale, rhumatismale ou une endocardite infectieuse étant exclus), l'âge moyen était de 75 ± 14 ans (44% des patients avaient 80 ans ou plus), 51% étaient des femmes, 56% présentaient un indice de Charlson ≥ 2 et 46% étaient en IC. L'IT était associée à un antécédent de chirurgie cardiaque, une cardiomyopathie dilatée ou ischémique ou à une IM dans 73% des cas.

Dans l'ensemble de la population, seuls 10 % des patients présentant une IT ont été opérés sur la VT. Parmi les patients opérés sur la valve mitrale, 67% ont eu un geste concomitant sur la VT (Figure 31).

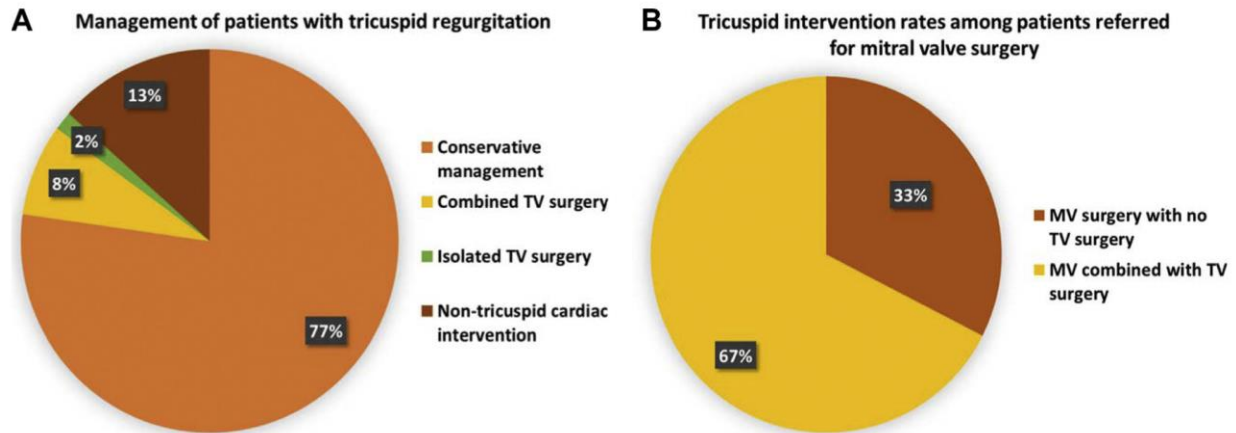


Figure 31. Prise en charge des patients hospitalisés en France avec insuffisance tricuspide

- A. Prise en charge des patients avec insuffisance tricuspide dans la population globale
 B. Taux d'intervention concomitante sur la valve tricuspide au moment d'une chirurgie valvulaire mitrale

MV: valve mitrale, TV: valve tricuspide

Parmi les 13 654 patients pris en charge médicalement, les taux de mortalité hospitalière, de mortalité à 1 an et de mortalité à 1 an ou réhospitalisation pour IC étaient respectivement de 5.1%, 17.8% et 41% dans l'ensemble de la population, et 5.3%, 17.2% et 37% chez ceux présentant une IT en l'absence d'antécédent de chirurgie cardiaque ou de cardiopathie du cœur gauche, sans différence statistiquement significative entre les différents sous-groupes (Figure 32). A noter que ces taux étaient huit fois plus élevés que ceux attendus dans une population de même âge et de même sexe.

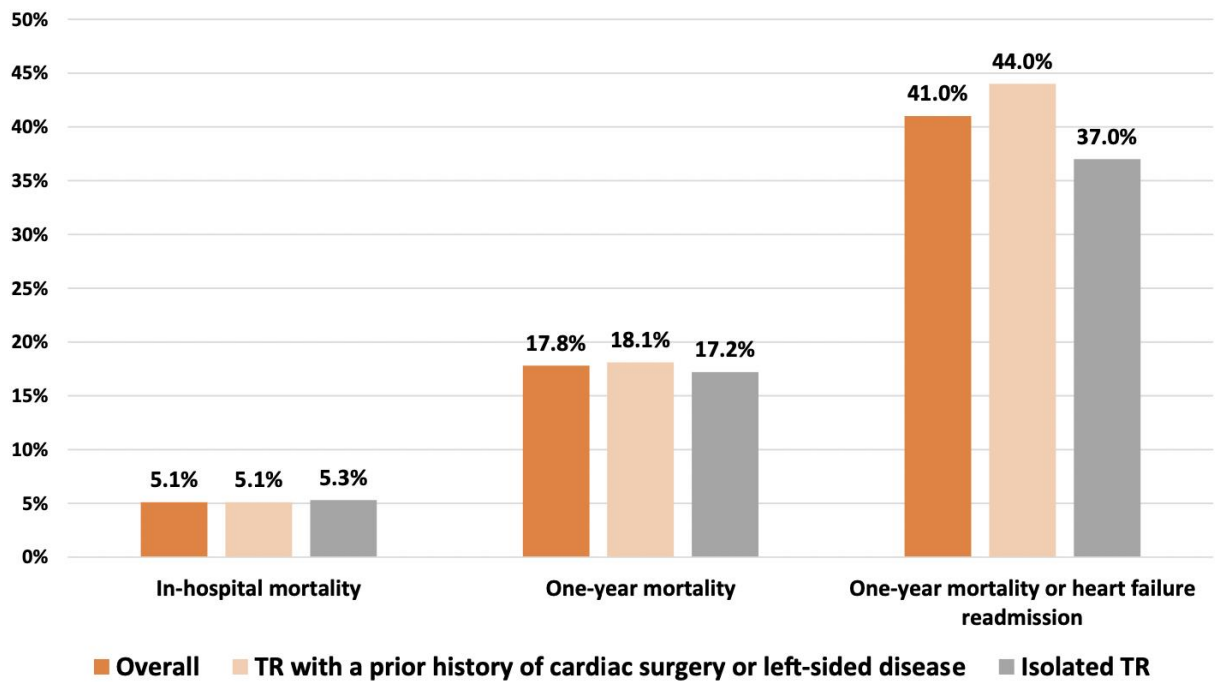


Figure 32. Taux d'événements chez les patients présentant une insuffisance tricuspide traitée médicalement, dans l'ensemble de la population, dans le sous-groupe de patients avec antécédent de chirurgie cardiaque ou de cardiopathie du cœur gauche, et dans le sous-groupe de patients avec insuffisance tricuspide isolée

TR : insuffisance tricuspide

Cette étude a montré que la majorité des patients hospitalisés avec IT sont âgés et avec des comorbidités, et que seuls 10% d'entre eux bénéficient d'un traitement curatif chirurgical sur la VT alors que la mortalité et la morbidité à court terme des patients pris en charge médicalement est considérable.

Clinical Research

Management and Outcome of Patients Admitted With Tricuspid Regurgitation in France

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See editorial by Ong and Connelly, pages xxx-xxx of this issue.

ABSTRACT

Background: Growing evidence shows a major outcome impact and undertreatment of tricuspid regurgitation (TR), but large and comprehensive contemporary reports of management and outcome at the nationwide level are lacking.

Methods: We gathered all consecutive patients admitted with a diagnosis of likely functional TR in 2014–2015 in France from the Programme de Médicalisation des Systèmes d'Information national database and collected rate of surgery, in-hospital mortality, 1-year mortality, or heart failure (HF) readmission rates.

RÉSUMÉ

Contexte : De plus en plus de données montrent que l'insuffisance tricuspide (IT) influence le pronostic et est fréquemment sous-traitée. Toutefois, des données issues de larges registres nationaux évaluant la prise en charge et le devenir des patients présentant une IT sont rares. **Méthodologie :** Nous avons extrait de la base de données nationale du Programme de médicalisation des systèmes d'information (France) les renseignements relatifs aux patients consécutifs admis en 2014–2015 dans un hôpital français en raison d'un diagnostic de IT vraisemblablement fonctionnelle, afin d'examiner les taux d'intervention

Tricuspid regurgitation (TR) is a common condition. Recent epidemiologic studies have shown a high prevalence of moderate or severe TR in the community, with overall rates of 0.55% and up to 3% after 75 years of age, similar to rates seen for aortic stenosis.^{1,2} Moderate or severe TR is estimated to affect > 1.6 million individuals in the United States.³ Although traditional management of TR has been conservative, recent single-center studies in various contexts, such as patients with reduced left ventricular ejection fraction (LVEF), isolated functional TR, or flail tricuspid leaflets, have

suggested that the presence and severity of TR are associated with an increased risk of death and cardiovascular events.^{2,4–11} In a recent meta-analysis, moderate and severe TR were associated with a > 2-fold increase in cardiac mortality independently of pulmonary pressures, LVEF, and right ventricular (RV) dysfunction.¹² In a large, contemporary, patient-level database of almost half a million US patients with heart failure (HF), TR was associated with marked increases in mortality risk overall and across all patient subgroups based on age, gender, rhythm, associated comorbidities, prior cardiac surgery, or LVEF.¹³ Although highly prevalent and associated with a marked increased risk of mortality and cardiovascular events, TR is often left untreated, with < 10,000 patients undergoing tricuspid surgery per year in the US, mostly at the time of mitral valve surgery.^{14,15}

Most epidemiologic studies have been based on limited geographically defined areas with small populations that may

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See page 6 for disclosure information.

Results: In 2014-2015, 17,676 consecutive patients (75 ± 14 years of age, 51% female) were admitted with a TR diagnosis. Charlson index was ≥ 2 in 56% of the population and 46% presented with HF. TR was associated with prior cardiac surgery, ischemic/dilated cardiomyopathy, or mitral regurgitation in 73% of patients. Only 10% of TR patients overall and 67% of those undergoing mitral valve surgery received a tricuspid valve intervention. Among the 13,654 (77%) conservatively managed patients, in-hospital mortality, 1-year mortality, and 1-year mortality or HF readmission rates were 5.1%, 17.8%, and 41%, respectively, overall, and 5.3%, 17.2%, and 37%, respectively, among those with no underlying medical conditions (8-fold higher than predicted for age and gender).

Conclusions: This nationwide cohort of patients admitted with TR included elderly patients with frequent comorbidities/underlying cardiac diseases. In patients conservatively managed, mortality and morbidity were considerably high over a short time span. Despite this poor prognosis, only 10% of patients underwent a tricuspid valve intervention. These nationwide data showing a considerable risk and potential underuse of treatment highlight the critical need to develop strategies to improve the management and outcomes of TR patients.

not be applicable to the general population. There are few nationwide data that would provide large-population, comprehensive assessment, and contemporary information on management and outcome of patients with TR. The Programme de Médicalisation des Systèmes d'Information (PMSI) is a French comprehensive national database that collects information on all consecutive patients admitted to public and private hospitals in the entire territory of France, as participation is mandatory for all French health-care institutions. The PMSI offers the unique opportunity to evaluate the presentation, outcome, and management of patients admitted with TR nationwide, and to examine the hypotheses that TR hospital admission is predominant in elderly patients and is associated with poor outcome and underuse of TR surgical treatments.

Methods

Study design

All health-care institutions in France are mandated to transfer information regarding their activity into the PMSI database. The PMSI data set includes information about the patient (age and sex), the hospital, the dates of admission and discharge, pathologies, procedures, and in-hospital outcome.¹⁶ Primary and secondary diagnoses are coded using the *International Statistical Classification of Diseases and Related Health Problems—10th revision*. Procedures are coded using a French standardised classification.¹⁷

We collected all admissions data in France from both public and private hospitals in 2014 and 2015 for patients ≥ 30 years

chirurgicale, de mortalité hospitalière, de mortalité à 1 an et de réadmission pour insuffisance cardiaque.

Résultats : En 2014-2015, 17 676 patients consécutifs (75 ± 14 ans, 51 % de femmes) ont été hospitalisés avec un diagnostic d'IT ; 56 % présentaient un indice de Charlson ≥ 2 et 46 % une insuffisance cardiaque. L'IT était associée à un antécédent de chirurgie cardiaque, une cardiomyopathie dilatée ou ischémique ou à une insuffisance mitrale dans 73 % des cas. Dans l'ensemble de la population, seuls 10 % des patients présentant une IT ont été opérés sur la valve tricuspide et seulement 67 % de ceux opérés sur la valve mitrale ont bénéficié d'une chirurgie concomitante sur la valve tricuspide. Parmi les 13 654 patients pris en charge médicalement, le taux de mortalité hospitalière, de mortalité à 1 an et de mortalité à un an ou de réadmission pour insuffisance cardiaque étaient respectivement de 5,1 %, 17,8 % et 41 % dans l'ensemble de la population et 5,3 %, 17,2 % et 37 % chez ceux présentant une IT en l'absence de pathologie associée (taux huit fois plus élevés que ceux attendu dans une population de même âge et sexe).

Conclusions : Dans cette large cohorte française regroupant tous les patients admis pour une IT en 2014-2015, la majorité des patients était âgés avec de fréquentes comorbidités. La mortalité et morbidité à court terme des patients pris en charge médicalement était considérable. Malgré ce sombre pronostic, seuls 10 % des patients ont bénéficié d'une chirurgie tricuspide. Ces données, montrent à l'échelle nationale, l'insuffisance de traitement et risque considérable encouru par les patients présentant une IT et la nécessité de développer de nouvelles approches pour améliorer leur prise en charge et leur devenir.

of age with non-rheumatic TR as a primary or secondary discharge code (I361). We excluded patients who presented with codes related to rheumatic tricuspid valve disease (regurgitation or stenosis), congenital diseases, infective endocarditis, and cardiac transplantation. The Charlson index was used to assess the burden of patients' comorbidities.¹⁸ Ethics approval was not required as all data were anonymised.

Outcome

In-hospital mortality was defined as death occurring during the same hospital stay. We also collected from the PMSI all in-hospital death and readmissions for HF that occurred during the year after the index hospitalisation. To avoid misleading comparisons, in-hospital mortality was not provided in patients undergoing an intervention as the intervention was not performed during the index admission in up to one third of patients.

Statistics

Continuous variables are expressed as mean ± standard deviation or median and interquartile range (25%-75%), and categorical variables are presented as number of patients (percent). Differences between groups were calculated using the χ^2 test for categorical variables and Student *t* test or Wilcoxon/Kruskal-Wallis tests for continuous variables as appropriate. Observed mortality was compared with expected 1-year mortality rates according to age and sex obtained from the Institut National de la Statistique et des études Économiques (www.insee.fr/fr/statistiques/3311422:sommaire=3311425). All tests were 2-sided and performed using JMP

version 9.0 (SAS Institute, Cary, NC). $P < 0.05$ was considered statistically significant.

Results

Population

In 2014-2015, 17,676 patients with a diagnosis of TR (excluding rheumatic, congenital, and infective endocarditis etiologies) were admitted in French public and private hospitals. Characteristics of the population are presented in Table 1. Mean age was 75 years (44% were ≥ 80 years of age) and 51% were female. Most of the patients presented with comorbidities; mean Charlson index was 2.5 ± 2.7 , and was ≥ 2.0 in 56% of the population. Forty-six percent (8171 patients) presented with HF. TR was associated with underlying medical conditions in most cases (prior cardiac surgery, ischemic or dilated cardiomyopathy or MR in 73%). In 27% of patients, TR was considered isolated and as being free of these conditions. In-hospital and 1-year mortality were 4.8% and 15.9%, respectively. One-year mortality or HF readmission rate was 39%.

Management of patients with TR

A cardiac intervention was performed in 4022 patients (23%), whereas 13,654 (77%) were managed conservatively. Among the 4022 patients who underwent an intervention, 2369 (13%) underwent non-tricuspid valve (non-TV) intervention (not exclusive: aortic valve replacement [N = 1448], coronary artery bypass graft [N = 684], and mitral valve [MV] surgery [N = 540]), 1374 patients (8%) underwent combined TV surgery (not exclusive: combined with MV surgery [N = 1119], aortic valve replacement [N = 316], and coronary artery bypass graft [N = 177]), and 279 patients (2%) underwent isolated TV surgery (Fig. 1). Interestingly, of the 1659 patients who underwent MV surgery, TV intervention was performed concomitantly in only 1119 patients (67%). Thus, no TV intervention was performed in 59% of patients referred for a cardiac intervention overall and in 33% of those undergoing MV surgery.

A comparison between patients who underwent TV surgery (combined or isolated) and those who underwent a non-TV intervention is shown in right portion of Table 1. Patients who underwent TV surgery were slightly younger, more frequently female, had less ischemic cardiomyopathy, and presented more often with HF than those who did not, but prevalence of MR was similar between groups. One-year mortality rate and rate of death or HF readmission were also higher in patients who underwent TV surgery, but were substantial in both subsets (12.6% and 38%, respectively, in patients who underwent TV surgery and 7.4% and 28% in those who did not).

Outcomes of patients with TR managed conservatively

Baseline characteristics, mortality rate, and readmission rates of this subset are presented in Table 1 and Figure 2. In-hospital mortality, 1-year mortality, and 1-year mortality or HF readmission rates were 5.1%, 17.8%, and 41%, respectively. Importantly, the observed 1-year mortality rates according to age and gender were markedly higher than

expected with an average 8-fold increased mortality rate (Table 2).

Compared with patients with a history of cardiac surgery or left-sided heart disease, patients with isolated TR were younger (72 ± 17 vs 77 ± 12 years, $P < 0.0001$), more frequently female (58% vs 50%, $P < 0.0001$), had a lower Charlson index (2.4 ± 3.0 vs 2.9 ± 2.7 , $P < 0.0001$), and had a lower prevalence of HF (45% vs 54%). However, in-hospital (5.3% vs 5.1%, $P = 0.46$) and 1-year (17.2% vs 18.1%, $P = 0.17$) mortality rates were not different. The 1-year mortality or HF readmission rate was lower (37% vs 44%, $P < 0.0001$) (Fig. 2).

Discussion

In this first nationwide report on TR hospital admission, we have reported on the management and outcomes of consecutive patients with TR admitted in France in the contemporary era. This unique study design demonstrates first that TR is a common diagnosis code at admission and is often related to elderly patients with frequent comorbidities and HF. Second, the vast majority of TR patients were conservatively managed and only 10% underwent a TV surgery. Third, most TV surgeries were performed with another intervention, mostly MV surgery, whereas only a few were performed without any concomitant intervention. Even in the context of MV surgery, TR was not intervened upon in a third of patients. Finally, TR was associated with considerable short-term mortality and HF readmission rates, underscoring the dismal outcome of patients admitted with TR and highlighting the importance of efforts to relieve this considerable burden of untoward outcomes.

Management of patients with TR

Paradoxically, TR has been considered for years as both a benign condition that could be neglected and as a simple marker of increased mortality and morbidity. Increasing evidence supports that TR is an independent prognostic factor and a cause *per se* of the observed increased mortality and cardiovascular event rates. The magnitude of the difference between the prevalence of TR and the number of TV interventions suggests a marked undertreatment.¹⁹ However, reports on the management of patients with TR are limited and come mainly from single-center studies. As such, unbiased information on the management and outcomes of patients with TR are scarce. In the present study, using the PMSI nationwide database, we were able to collect data on all patients admitted in France with a diagnosis of TR, in both public and private hospitals. To the best of our knowledge, this study is the first to identify all patients with TR admitted at the nationwide level in the contemporary era. Most TR patients were elderly and presented with comorbidities, and HF and left-sided heart disease was present in the majority of patients. Only 10% of the population underwent a TV intervention within 1 year of the index admission and the vast majority of patients were managed conservatively, thus highlighting a potential undertreatment of this condition. An important finding from the present study is that TR was often neglected even in patients referred for an intervention. Both the European Society of Cardiology and the American College of Cardiology / American Heart Association recommend TV

Table 1. Characteristics and outcome of the overall population with tricuspid regurgitation and according to the type of management

| | Overall population (N = 17,676) | Patients conservatively managed (N = 13,654) | Patients referred for a cardiac intervention (N = 4022) | | Patients referred for a cardiac intervention | | |
|---|------------------------------------|---|---|---------------------------------------|---|------------|----------|
| | | | P value | Tricuspid valve surgery (N = 1653) | Non-tricuspid cardiac intervention (N = 2369) | P value | |
| Age | 75 ± 14 | 76 ± 14 | 71 ± 12 | < 0.0001 | 69 ± 12 | 73 ± 11 | < 0.0001 |
| Females | 9017 (51%) | 7215 (53%) | 1802 (45%) | < 0.0001 | 789 (48%) | 1013 (43%) | 0.002 |
| Previous cardiac surgery | 3791 (21%) | 2521 (18%) | 1270 (32%) | < 0.0001 | 494 (30%) | 776 (33%) | 0.05 |
| Ischemic cardiomyopathy | 3125 (18%) | 2494 (18%) | 631 (16%) | 0.0002 | 167 (10%) | 464 (20%) | < 0.0001 |
| Dilated cardiomyopathy | 1941 (11%) | 1652 (12%) | 289 (7%) | < 0.0001 | 125 (8%) | 164 (7%) | 0.44 |
| Mitral regurgitation | 9179 (52%) | 6679 (49%) | 2500 (62%) | < 0.0001 | 1051 (64%) | 1449 (61%) | 0.12 |
| Tricuspid regurgitation with no other known cardiac disease | 4753 (27%) | 4605 (34%) | 148 (4%) | < 0.0001 | 148 (9%) | 0 | — |
| Congestive heart failure | 8171 (46%) | 6955 (51%) | 1216 (30%) | < 0.0001 | 595 (36%) | 621 (26%) | < 0.0001 |
| Charlson index | 2.5 ± 2.7 | 2.7 ± 2.8 | 1.7 ± 2.1 | < 0.0001 | 1.7 ± 2.2 | 1.7 ± 2.0 | 0.58 |
| Charlson index median (IQR) | 2 (1-3) | 2 (1-4) | 1 (1-4) | — | 1 (0-2) | 1 (0-2) | — |
| Charlson index ≥ 2 | 9974 (56%) | 8351 (61%) | 1623 (41%) | < 0.0001 | 661 (40%) | 962 (41%) | 0.69 |
| Public hospital | 13,093 (74%) | 10,132 (74%) | 2961 (74%) | 0.46 | 1225 (74%) | 1736 (73%) | 0.56 |
| In-hospital mortality | 845 (4.8%) | 703 (5.1%) | — | — | — | — | — |
| One-year mortality | 2814 (15.9%) | 2429 (17.8%) | 385 (9.6%) | < 0.0001 | 208 (12.6%) | 177 (7.4%) | < 0.0001 |
| One-year mortality/heart failure readmission | 6932 (39%) | 5658 (41%) | 1274 (32%) | < 0.0001 | 620 (38%) | 654 (28%) | < 0.0001 |

Number are mean ± standard deviation or number of patients (%).
IQR, interquartile range.

surgery at the time of the MV surgery in patients with moderate/severe TR.²⁰⁻²² However, TR was not addressed in one third of the patients at the time of MV surgery in our cohort, despite a TR diagnoses and the clear recommendations for intervention (including for patients with moderate TR). Thus, our study strongly supports that TR is undertreated, even at the time of MV surgery.

One-year mortality rate and the combined endpoint of 1-year mortality or HF readmissions rates in the subset of patients who underwent TV surgery were remarkably high (12.6% and 38%, respectively) and in the same range as those of patients managed conservatively. Considering the usual mortality rates observed in patients referred for MV surgery, coronary artery bypass graft, or aortic valve replacement, these rates suggest that patients were referred at an advanced stage of the disease. The presence of significant TR at the time of MV intervention reflects long-lasting MV disease with right ventricular enlargement and the development of functional TR. Thus, we have extended previous findings that, in the contemporary era, patients with MR are still often referred late in the course of the disease,²³ despite guideline recommendations.²⁰⁻²² It is important to emphasise that comparisons of outcomes between patients who underwent TV intervention with those who did not in the present study should be made cautiously as patients are likely sicker in the former group and an unadjusted comparison may be misleading. Thus, if 1-year mortality and HF readmissions rates were higher in patients who underwent TV surgery than in those who underwent cardiac intervention without TV

intervention, the type of cardiac intervention and the underlying diseases would be markedly different. Most patients who underwent TV intervention had MV surgery, whereas those who did not underwent predominantly an aortic valve replacement, including transcatheter approaches. Importantly, the present study was not designed for or capable of evaluating whether performance of concomitant TV surgery improves clinical outcomes.

Outcome of patients with TR conservatively managed

Most patients diagnosed with TR were managed conservatively. The majority of patients were elderly, with 49% ≥ 80 years of age and half of them presenting with HF. The lower prevalence of females compared with previous data probably relates to the inclusion in the present study of patients with both isolated and combined TR like associated with ischemic cardiomyopathy where there is a male predominance. In capturing all consecutive admissions in France, we have clearly shown that TR patients managed conservatively have a poor prognosis. In-hospital and 1-year mortality rates were 5.1% and 17.8%, respectively. At 1 year, 40% of patients were either dead or readmitted for HF. The 1-year mortality rates were markedly higher than expected irrespective of gender and in every age category (except in nonagenarians), as shown in Table 2. Most patients presented with a history of cardiac surgery or a left-sided disease. Nevertheless, TR was considered isolated in 27% of the population, occurring in the absence of any history of cardiac

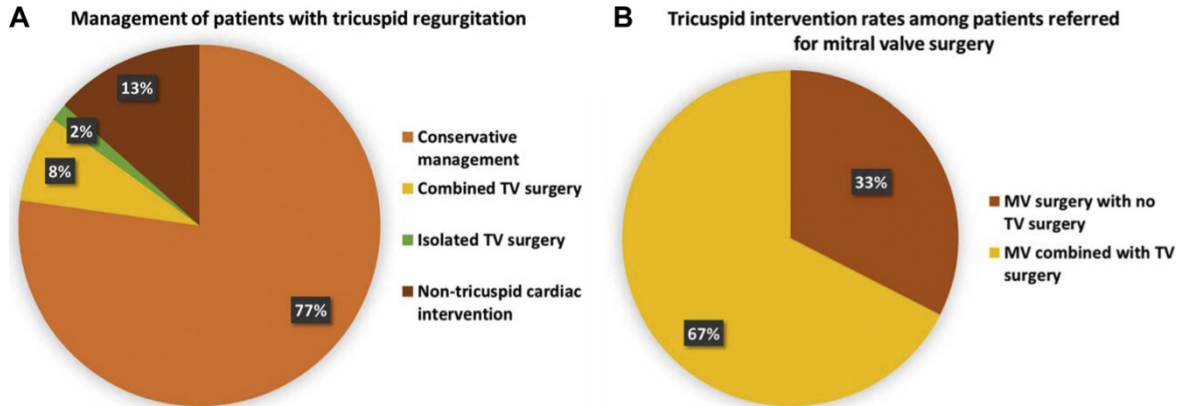


Figure 1. (A) Management of the overall population. (B) Rate of combined TV intervention among patients referred for MV surgery. MV, mitral valve; TV, tricuspid valve.

surgery, dilated/ischemic cardiomyopathy, or mitral regurgitation. Even in this subset, both in-hospital and 1-year mortality rates were high and similar to those observed in patients with a history of cardiac surgery or left-sided heart disease, suggesting that TR is independently associated with the observed increased mortality rate. Thus, the present study clearly shows the poor prognosis of hospitalised patients with TR.

Clinical implications

Despite clear guidelines for Class I recommendations,²⁰⁻²² TR was not addressed in most patients at the time of intervention, even in those undergoing MV surgery. It is worth noting that almost all MV interventions were surgical and that

transcatheter MV interventions were seldom performed in France in 2014-2015. In addition, transcatheter TR interventions were also not available at that time. Whether due to the erroneous belief that TR interventions increase the risk of MV surgery,^{24,25} insufficient knowledge on the evaluation and management of patients with valvular heart diseases,²⁶ or the incorrect assumption that the condition will resolve after the MV surgery,^{27,28} the present study highlights an important and substantial opportunity to improve the outcomes in these patients. In this regard, we as well as others have shown that combined TV interventions at the time of the MV surgery do not increase the in-hospital mortality rates if performed when indicated.^{24,25} The gap between recommendations of scientific societies and real-life practice should be regarded as a strong incentive for development of

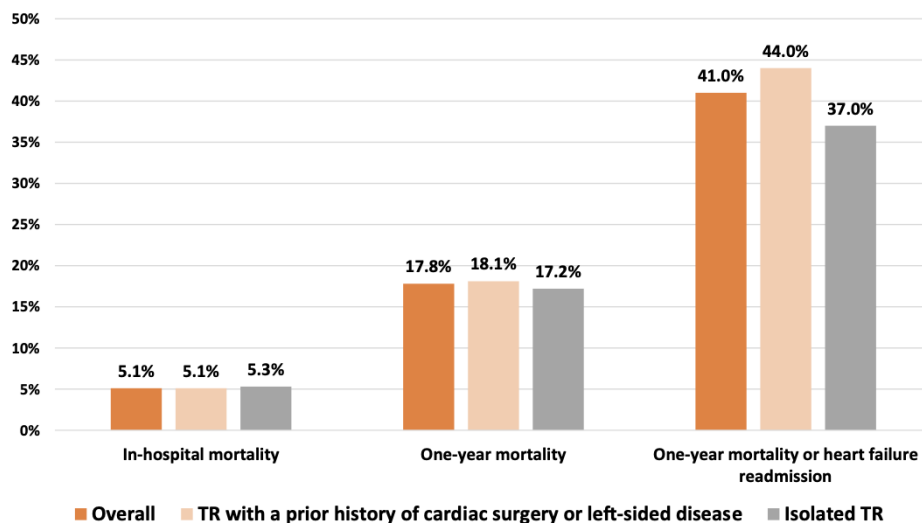


Figure 2. Event rates in patients with tricuspid regurgitation managed conservatively, overall, in the subsets with prior cardiac surgery or left-sided disease and in the subset of isolated tricuspid regurgitation. TR, tricuspid regurgitation.

Table 2. Observed and predicted 1-year mortality rates according to age and gender from the Institut National de la Statistique et des études Economiques in the conservatively managed subset of patients (N = 13,654)

| Age category | Males | | Females | |
|--------------|----------|----------|----------|----------|
| | Observed | Expected | Observed | Expected |
| Mean age * | 19.2% | 2.3% | 16.6% | 1.9% |
| < 60 years | 8.3% | 1.0% | 7.8% | 0.4% |
| 60-70 years | 15.0% | 1.3% | 11.4% | 0.6% |
| 70-80 years | 20.4% | 2.7% | 13.6% | 1.4% |
| 80-90 years | 24.2% | 8.3% | 20.1% | 5.2% |
| ≥ 90 years | 24.7% | 24.7% | 20.5% | 19.8% |

* For males, this was 73 years and for females it was 79 years.

educational programmes for health-care providers to reduce the number of patients referred at an advanced stage of the disease and for the implementation of Heart Valve Centers of Excellence.

TR was found to be a common diagnosis code. There were approximately 27,000,000 yearly admissions in France during the study period, including 1,470,000 related to cardiovascular diseases. When admissions and readmissions were added (14,759 yearly admissions), the number of TR-related admissions accounted for 0.05% of all admissions and 1% of cardiovascular admissions. Most patients admitted with a diagnosis of TR were managed conservatively despite incurring high mortality and HF readmissions rates, including those with isolated TR. Although we acknowledge that isolated TR intervention should only be performed in cases of severe TR, the remarkably low rate of TV intervention (10%), strongly suggests a marked undertreatment in our population. Thus, assuming that severe TR only accounted for one third of the population and that all surgeries were performed in this subset, two thirds remained conservatively managed (23% i.e. [33%-10%] / 33%). Convincing evidence of the direct impact of TR on outcome can be derived from patients with TV flail leaflets (a model of isolated severe organic TR),⁹ or from patients with isolated severe functional TR.²⁹ However, the impact of TR correction on survival is disputed, with contradictory retrospective evaluations.^{30,31} Randomised, controlled trials are currently evaluating the impact of transcatheter interventions, a less invasive alternative to surgery.³²⁻³⁶ These studies will close the loop and formally demonstrate whether TR correction can improve clinical outcome.

Strengths and limitations

The present study deserves several comments. First, there are inherent limitations to the PMSI database relating to the limited granularity of the available data. Variables such as New York Heart Association functional class, creatinine, LVEF, right ventricular systolic pressure, or right ventricular function and size are not available and our assessment of comorbidity burden relied on the Charlson index (no surgical risk score could be calculated). However, we were able to capture all consecutive patients admitted with TR at the nationwide level in France during the study period to document their management and their mortality and morbidity outcomes. Second, the database has no information regarding TR severity or

grade. However, TR was considered severe enough by the treating physicians to include a TR diagnosis code in the discharge summary and thus was likely to reflect at least moderate severity. TR is a heterogeneous disease and TR etiology was not available in the PMSI, but, based on our exclusion criteria, we suspect that most of our patients presented with functional TR (easily the most common TR etiology). Third, in-hospital mortality rate among patients referred for an intervention could not be provided, as the intervention was performed during a separate hospital admission after the index admission in more than one third of patients, making comparisons of in-hospital mortality rates inappropriate. Fourth, only in-hospital death (at admission or during follow-up) and HF readmissions are captured in the PMSI. Therefore, death and HF rates may have been underestimated, which further emphasises our findings. Finally, the cause of death was not recorded and only associations other than causation could be attributed to TR and the clinical endpoints. The cause of death is often difficult to ascertain but the inclusion of TR as a diagnosis code strongly suggests that TR was considered severe enough to have played a role in the patient's admission and complications.

Conclusions

This large contemporary nationwide cohort of patients admitted with TR included elderly patients with frequent comorbidities. TR was often associated with underlying cardiac conditions and less commonly isolated, but both subsets were associated with high mortality and HF readmission rates. Approximately 20% of TR patients underwent an intervention, but TR was not addressed in more than half of these patients and in up to one third of patients referred for MV surgery. Patients who underwent a TV intervention incurred high event rates, suggesting that these patients were referred late in the course of their disease. Patients who were managed conservatively, representing the vast majority of patients, exhibited high mortality and HF readmissions rates with an 8-fold increased mortality rate at 1 year. These findings highlight the public health issue related to TR and the critical need to develop strategies to improve the management and outcomes of patients with this condition.

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Disclosures

Dr Messika-Zeitoun is a consultant for Edwards Lifesciences and received research grants from Edwards Lifesciences. Drs Candolfi, Verta, and Feldman are Edwards Lifesciences employees. Dr Lung has received consultant fees from Edwards Lifesciences and speaker's fees from Boehringer Ingelheim and Novartis. Dr Vahanian has received speaker's fees from Edwards Lifesciences and Abbott Vascular and is consultant for Cardiawave. Maurice Enriquez-Sarano has received research grants from Edwards Lifesciences. Drs

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References

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;368:1005-11.
2. Topilsky Y, Maltais S, Medina Inojosa J, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging* 2019;12:433-42.
3. Stuge O, Liddicoat J. Emerging opportunities for cardiac surgeons within structural heart disease. *J Thorac Cardiovasc Surg* 2006;132:1258-61.
4. Hung J, Koelling T, Semigran MJ, Dec GW, Levine RA, Di Salvo TG. Usefulness of echocardiographic determined tricuspid regurgitation in predicting event-free survival in severe heart failure secondary to idiopathic-dilated cardiomyopathy or to ischemic cardiomyopathy. *Am J Cardiol* 1998;82:1301-3. A1310.
5. Koelling TM, Aaronson KD, Cody RJ, Bach DS, Armstrong WF. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. *Am Heart J* 2002;144:524-9.
6. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* 2004;43:405-9.
7. Topilsky Y, Inojosa JM, Benfari G, et al. Clinical presentation and outcome of tricuspid regurgitation in patients with systolic dysfunction. *Eur Heart J* 2018;39:3584-92.
8. Bartko PE, Arfsten H, Frey MK, et al. Natural history of functional tricuspid regurgitation: implications of quantitative Doppler assessment. *JACC Cardiovasc Imaging* 2019;12:389-97.
9. Messika-Zeitoun D, Thomson H, Bellamy M, et al. Medical and surgical outcome of tricuspid regurgitation caused by flail leaflets. *J Thorac Cardiovasc Surg* 2004;128:296-302.
10. Benfari G, Antoine C, Miller WL, et al. Excess mortality associated with functional tricuspid regurgitation complicating heart failure with reduced ejection fraction. *Circulation* 2019;140:196-206.
11. Chorin E, Rozenbaum Z, Topilsky Y, et al. Tricuspid regurgitation and long-term clinical outcomes. *Eur Heart J Cardiovasc Imaging* 2020;21:157-65.
12. Wang N, Fulcher J, Abeysuriya N, et al. Tricuspid regurgitation is associated with increased mortality independent of pulmonary pressures and right heart failure: a systematic review and meta-analysis. *Eur Heart J* 2019;40:476-84.
13. Messika-Zeitoun D, Verta P, Gregson J, et al. Impact of tricuspid regurgitation on survival in patients with heart failure: a large electronic health record patient-level database analysis. *Eur J Heart Fail* 2020;22:1803-13.
14. Vassileva CM, Shabosky J, Boley T, Markwell S, Hazelrigg S. Tricuspid valve surgery: the past 10 years from the Nationwide Inpatient Sample (NIS) database. *J Thorac Cardiovasc Surg* 2012;143:1043-9.
15. Zack CJ, Fender EA, Chandrashekar P, et al. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol* 2017;70:2953-60.
16. Programme de médicalisation des systèmes d'informations (PMSI). 2012. Available at: <http://www.drees.sante.gouv.fr/redressements-du-programme-de-medicalisation-des-systemes-d-informations-pmsi>. Accessed May 18, 2021.
17. Classification commune des actes médicaux (CCAM). Available at: <http://www.ameli.fr/accueil-de-la-ccam/trouver-un-acte/index.php>. Accessed May 18, 2021.
18. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;47:1245-51.
19. Dreyfus J, Ghalem N, Garbarz E, et al. Timing of referral of patients with severe isolated tricuspid valve regurgitation to surgeons (from a French Nationwide Database). *Am J Cardiol* 2018;122:323-6.
20. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease: the Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2017;38:2739-91.
21. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017;135:e1159-95.
22. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: Executive Summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129:2440-92.
23. Gammie JS, Chikwe J, Badhwar V, et al. Isolated mitral valve surgery: the Society of Thoracic Surgeons Adult Cardiac Surgery Database Analysis. *Ann Thorac Surg* 2018;106:716-27.
24. Chikwe J, Itagaki S, Anyanwu A, Adams DH. Impact of concomitant tricuspid annuloplasty on tricuspid regurgitation, right ventricular function, and pulmonary artery hypertension after repair of mitral valve prolapse. *J Am Coll Cardiol* 2015;65:1931-8.
25. Verdonk C, Darmon A, Cimadevilla C, et al. Is tricuspid annuloplasty increasing surgical mortality and morbidity during mitral valve replacement? A single-centre experience. *Arch Cardiovasc Dis* 2017;111:480-6.
26. Lung B, Delgado V, Lazure P, et al. Educational needs and application of guidelines in the management of patients with mitral regurgitation. A European mixed-methods study. *Eur Heart J* 2018;39:1295-303.
27. Matsuyama K, Matsumoto M, Sugita T, Nishizawa J, Tokuda Y, Matsuo T. Predictors of residual tricuspid regurgitation after mitral valve surgery. *Ann Thorac Surg* 2003;75:1826-8.
28. Song JM, Kang DH, Song JK, et al. Outcome of significant functional tricuspid regurgitation after percutaneous mitral valvuloplasty. *Am Heart J* 2003;145:371-6.
29. Topilsky Y, Nkomo VT, Vatury O, et al. Clinical outcome of isolated tricuspid regurgitation. *JACC Cardiovasc Imaging* 2014;7:1185-94.
30. Axtell AL, Bhamhani V, Moonsamy P, et al. Surgery does not improve survival in patients with isolated severe tricuspid regurgitation. *J Am Coll Cardiol* 2019;74:715-25.
31. Taramasso M, Benfari G, van der Bijl P, et al. Transcatheter versus medical treatment of symptomatic severe tricuspid regurgitation. *J Am Coll Cardiol* 2019;74:2998-3008.
32. Hahn RT, Meduri CU, Davidson CJ, et al. Early feasibility study of a transcatheter tricuspid valve annuloplasty: SCOUT Trial 30-day results. *J Am Coll Cardiol* 2017;69:1795-806.

33. Nickenig G, Kowalski M, Hausleiter J, et al. Transcatheter treatment of severe tricuspid regurgitation with the edge-to-edge MitraClip technique. *Circulation* 2017;135:1802-14.
34. Rodes-Cabau J, Hahn RT, Latib A, et al. Transcatheter therapies for treating tricuspid regurgitation. *J Am Coll Cardiol* 2016;67:1829-45.
35. Schueler R, Hammerstingl C, Werner N, Nickenig G. Interventional direct annuloplasty for functional tricuspid regurgitation. *JACC Cardiovasc Interv* 2017;10:415-6.
36. Taramasso M, Pozzoli A, Guidotti A, et al. Percutaneous tricuspid valve therapies: the new frontier. *Eur Heart J* 2017;38:639-47.

Article 5

Timing of Referral of Patients With Severe Isolated Tricuspid Valve Regurgitation to Surgeons (from a French Nationwide Database)

Dreyfus J, Ghalem N, Garbarz E, Cimadevilla C, Nataf P, Vahanian A, Caranhac G, Messika-Zeitoun D

Am J Cardiol. 2018 Jul 15;122(2):323-326

Article 5 : Moment de la prise en charge chirurgicale des patients avec insuffisance tricuspide sévère isolée à l'échelon national

La chirurgie isolée de la VT n'est que rarement réalisée car considérée comme une intervention à haut risque opératoire mais les données publiées étaient limitées, le plus souvent sur des petits registres ou avec de longues périodes d'inclusion⁷⁸.

Les objectifs de cette étude étaient d'évaluer le devenir immédiat des patients après chirurgie isolée de la VT et les déterminants des complications hospitalières.

A partir des données nationales du PMSI, tous les patients adultes opérés pour une chirurgie isolée de la VT (les patients ayant eu un autre geste opératoire concomitant comme une chirurgie valvulaire du cœur gauche, des pontages aorto-coronariens ou une fermeture de communication inter-atriale, étaient exclus) en France sur une période de 2 ans (2013-2014) ont été inclus et leurs données analysées.

Une chirurgie isolée de la VT n'a été que rarement réalisée (241 patients sur 2 ans). Il s'agissait le plus souvent d'un remplacement valvulaire (65% de RVT vs 35% de réparations de la VT).

L'âge moyen était de 61 ± 16 ans, 53% étaient des femmes, 36% étaient en FA, 26% étaient en IC et 21% avaient déjà été opérés d'une valvulopathie du cœur gauche.

L'indication de la chirurgie était une endocardite infectieuse dans 20% des cas.

Le taux de mortalité hospitalière était élevé (10%), de même que le taux de complications post-opératoires graves (incluant mortalité, nécessité de dialyse ou d'une assistance hémodynamique extra-corporelle), qui était de 19% (Figure 33). A noter qu'il n'avait pas différence statistique entre les patients ayant eu un remplacement ou une réparation de la VT.

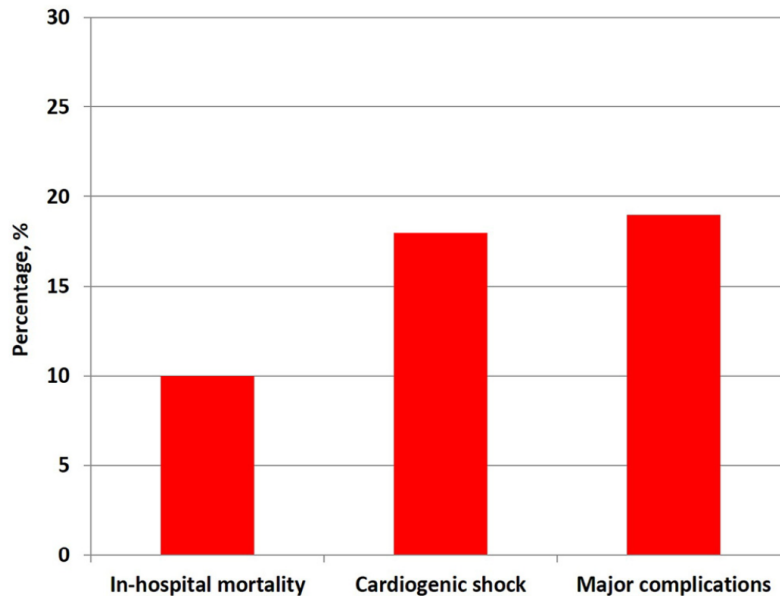


Figure 33. Taux de mortalité hospitalière, choc cardiogénique et complications graves après chirurgie valvulaire tricuspide isolée

Les durées de séjours étaient longues (26 ± 40 jours, avec une médiane de 16 jours [11 à 28] pour la durée totale de séjour, et 10 ± 18 jours, avec une médiane de 15 jours [2 à 12] pour la durée de séjour en soins intensifs).

La présence de signes cliniques d'IC en pré-opératoire était un facteur prédictif du risque de mortalité et de complications post-opératoires graves ($P = 0.001$ pour les 2), et l'atteinte hépatique pré-opératoire était associée au risque de complications post-opératoires graves ($P = 0.02$). Il y avait également une tendance entre l'insuffisance rénale pré-opératoire et le risque de complications post-opératoires graves ($P = 0.07$). A noter que l'antécédent de chirurgie valvulaire du cœur gauche et la présence d'une endocardite infectieuse n'étaient pas associés aux complications post-opératoires ($P = 0.23$ et 0.38 respectivement).

Cette étude a montré à l'échelon national qu'un traitement curatif de l'IT par chirurgie isolée de la VT n'est que très rarement réalisé et que cette intervention est associée à des taux de mortalité et de complications post-opératoires immédiates très élevés. La

**présentation pré-opératoire (insuffisance cardiaque, atteinte hépatique, insuffisance rénale)
semble être prédictive du devenir post-opératoire des patients.**

Timing of Referral of Patients With Severe Isolated Tricuspid Valve Regurgitation to Surgeons (from a French Nationwide Database)



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Series evaluating the results of isolated tricuspid valve surgery (ITVS) are rare and often limited by small sample size, selection bias, and/or long period of enrollment. Based on a mandatory administrative national database, we collected all consecutive ITVS performed in France during a 2-year period (2013 and 2014), the type of intervention, clinical profile, and in-hospital mortality and complications. During the 2-year period, 241 patients underwent an ITVS in France (84 repairs and 157 replacements). In-hospital mortality was high (10%), and most patients experienced at least 1 complication (65%) with a 19% rate of major complications (death, need for dialysis, or need for mechanical support using extracorporeal membrane oxygenation). Consequently, hospital duration was remarkably long (26 ± 40 days). Congestive heart failure at presentation was associated with mortality and major complications rates (both $p = 0.01$). In conclusion, in a contemporary and consecutive series, ITVS was associated with a high mortality and morbidity predicted by clinical presentation at baseline. Our results suggest that patients are often referred too late and that an earlier intervention may improve immediate and possibly midterm outcomes. With the availability of transcatheter therapies in a near future, optimal timing of intervention in this population will be of utmost importance. © 2018 Elsevier Inc. All rights reserved. (Am J Cardiol 2018;122:323–326)

Tricuspid regurgitation (TR) is an independent prognostic factor associated with a significant excess mortality and morbidity that increases with TR grade.^{1,2} Surgery is mostly performed at the time of left-sided valve surgery for secondary TR, whereas isolated tricuspid valve surgery (ITVS) is rarely performed and recommended in patients with severe TR who are either symptomatic or are facing a progressive right ventricle dilation/dysfunction.^{3,4} However, the optimal timing for surgery is difficult to determine as patients may be asymptomatic for a long period of time, symptoms are usually not specific, and right ventricle size and function are difficult to assess in routine clinical practice. Series of isolated tricuspid valve (TV) surgery are rare, often biased, single-center, based on small sample sizes, and covering long time period.^{5–9} Based on the French Programme de Médicalisation des Systèmes d'Information (PMSI),¹⁰ a mandatory administrative database, we aimed to evaluate the immediate outcomes of all consecutive patients who underwent an ITVS

in France in 2013 and 2014 and the determinants of in-hospital complications.

Methods

Since the 1991 law on health-care reform, all health-care institutions are mandated to analyze their own activity and transfer the information to the State and to the national health insurance. To achieve this, the PMSI database was created to collect data on patients' diagnoses, procedures, and in-hospital outcome. Each hospitalization is encoded in a standardized dataset which includes patient's information, length of stay, pathologies, and procedures. Diagnoses are coded using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).¹¹ Procedures are coded using a French standardized classification.¹²

All patients who underwent an ITVS, either repair or replacement, in a public or a private institution in France between January 1, 2013 and December 31, 2014, were identified from the PMSI. We excluded patients who underwent any concomitant surgical procedure such as left-sided heart valve surgery, coronary artery bypass, or atrial septal defect closure. Major complications were defined as in-hospital death, post-operative need for dialysis, or mechanical support for hemodynamic failure (extracorporeal membrane oxygenation [ECMO]). Ethical approval was not required as all data are anonymized. The French Data Protection Authority granted access to the PMSI data.

Variables were expressed as mean ± standard deviation or median [percentile 25 and 75] for continuous variables and

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See page 326 for disclosure information.

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Table 1
Baseline characteristics and in-hospital complications of the population

| Variables | Overall (N = 241) | Tricuspid valve repair (N = 84) | Tricuspid valve replacement (N = 157) | p |
|--|-------------------|---------------------------------|---------------------------------------|-------|
| BASELINE CHARACTERISTICS | | | | |
| Age (years) | 61 ± 16 | 63 ± 15 | 59 ± 16 | 0.06 |
| Women | 128 (53%) | 44 (52%) | 84 (54%) | 0.87 |
| Previous left-heart valve surgery | 51 (21%) | 8 (10%) | 43 (27%) | 0.001 |
| Coronary artery disease | 24 (10%) | 13 (15%) | 11 (7%) | 0.04 |
| Pacemaker | 28 (12%) | 21 (13%) | 7 (8%) | 0.24 |
| Congestive heart failure | 63 (26%) | 22 (26%) | 41 (26%) | 0.99 |
| Atrial fibrillation | 87 (36%) | 13 (15%) | 51 (32%) | 0.11 |
| Renal failure | 25 (10%) | 9 (11%) | 16 (10%) | 0.90 |
| Liver disease | 9 (4%) | 2 (2%) | 7 (4%) | 0.42 |
| Infective endocarditis | 48 (20%) | 10 (12%) | 38 (24%) | 0.02 |
| IN-HOSPITAL COMPLICATIONS | | | | |
| In-hospital Death | 25 (10%) | 11 (13%) | 14 (9%) | 0.31 |
| New congestive heart failure | 40 (17%) | 14 (17%) | 26 (17%) | 0.98 |
| New atrial-fibrillation | 42 (17%) | 17 (20%) | 25 (16%) | 0.40 |
| New pacemaker | 44 (18%) | 12 (14%) | 32 (20%) | 0.24 |
| Acute respiratory failure | 67 (28%) | 23 (27%) | 44 (28%) | 0.92 |
| Tamponade | 38 (16%) | 13 (15%) | 25 (15%) | 0.93 |
| Acute renal failure | 69 (29%) | 23 (27%) | 46 (29%) | 0.75 |
| Dialysis | 33 (14%) | 12 (14%) | 21 (13%) | 0.84 |
| Cardiogenic shock | 46 (19%) | 15 (18%) | 31 (20%) | 0.72 |
| Shock and/or systemic inflammatory response syndrome | 68 (28%) | 23 (27%) | 45 (29%) | 0.83 |
| Mechanical support for hemodynamic failure | 16 (7%) | 11 (13%) | 5 (3%) | 0.003 |
| All complications | 157 (65%) | 50 (60%) | 107 (68%) | 0.18 |
| Major complications | 45 (19%) | 17 (20%) | 28 (19%) | 0.65 |
| Total length of stay (days) | 26 ± 40 | 29 ± 61 | 25 ± 21 | 0.37 |
| Length of stay in the intensive care unit (days) | 10 ± 18 | 11 ± 21 | 10 ± 15 | 0.71 |

Data presented are number of patients (percent) or mean ± standard-deviation.

percentage for categorical variables. Group comparisons were performed using analysis of variance, chi-square, or *t* test as appropriate. Logistic regressions in univariate and multivariate analysis (including all variables with $p < 0.10$ in univariate analysis) were used to assess the determinants of in-hospital death or in-hospital major complications. Data were analyzed with JMP (version 9.0; SAS Institute, Cary, North Carolina). All tests were 2-sided and a p value < 0.05 was considered statistically significant.

Results

A total of 241 consecutive patients underwent an ITVS in France during the 2-year study period. Clinical characteristics of this population are presented in Table 1. Mean age was 61 ± 16 years and 128 patients (53%) were women. Eighty-seven patients (36%) had atrial fibrillation, 63 patients (26%) presented with congestive heart failure, and 51 (21%) had a previous left-sided heart valve surgery. TV surgery was performed because of infective endocarditis in 48 patients (20%). Most of the patients underwent a TV replacement ($n = 157$, 65%), whereas TV repair was performed in 84 patients (35%). Comparison between repair and replacement is presented in Table 1.

In-hospital mortality was 10% ($n = 25$). Rate of postoperative complications were very high, and most of the patients experienced at least one complication ($n = 157$, 65%) (Table 1). Thus, 69 patients (29%) presented postoperative acute renal failure, 46 patients (19%) presented cardiogenic shock, and

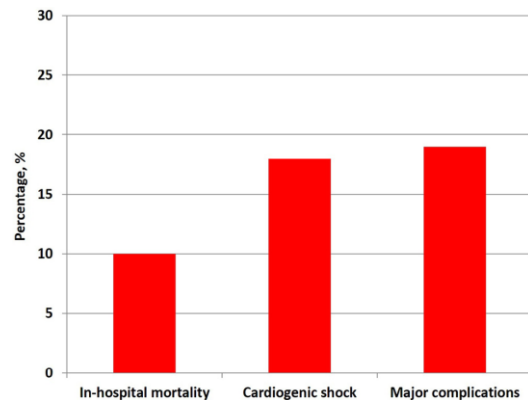


Figure 1. Bar graph showing in-hospital mortality and complications rates.

40 patients (17%) presented an episode of congestive heart failure. The rate of major complications was also very high ($n = 45$, 19%; Figure 1). Consequently, in-hospital lengths of stay (total and in the intensive care units) were remarkably long (26 ± 40 days, median 16 days [11 to 28], and 10 ± 18 days, median 5 days [2 to 12], respectively). Postoperative mortality and complications rates were not statistically different between patients who underwent a TV repair and patients who underwent a TV replacement (Table 1).

In univariate analysis, after adjustment for age and gender, congestive heart failure at presentation was the only determinant of in-hospital mortality ($p = 0.01$), whereas other factors such as previous cardiac surgery ($p = 0.23$) and infective endocarditis ($p = 0.38$) were not. Similarly, congestive heart failure at presentation was a major determinant of major postoperative complications defined as death, need for dialysis, or need for ECMO ($p = 0.01$). Preoperative renal failure ($p = 0.07$) and liver disease ($p = 0.05$) were also predictive of major complications in univariate analysis, whereas endocarditis ($p = 0.26$) and previous surgery ($p = 0.44$) were not. In multivariate analysis, after adjustment for age and gender, preoperative congestive heart failure ($p = 0.01$) and liver disease ($p = 0.02$) were both predictive of in-hospital major complications, whereas renal failure was of borderline statistical significance ($p = 0.08$).

Discussion

In this large contemporary and consecutive series, ITVS was (1) associated with a high (10%) mortality, (2) responsible for high morbidity with a 19% major complication rate and consequently a remarkably long in-hospital length of stay, and (3) preoperative clinical presentation was an important predictor of in-hospital death and major complication rates. Our results suggest that these patients are often referred too late and that an earlier intervention may improve immediate and possibly midterm outcomes. With the availability of transcatheter therapies in a near future, optimal timing of intervention in this population will be of utmost importance.

Surgery is the only curative treatment for severe TR and medical therapy—mainly diuretics—is only palliative. As for other valvular heart diseases, there is a marked trend toward a more aggressive approach in surgical indications and transcatheter tricuspid therapies are emerging.¹³ Thus, in patients with left-sided valve diseases, indications for combined TV surgery rely not only on TR degree but also on the severity of right chambers remodeling and tricuspid annulus size.^{14–17} Surgical indications for ITVS are based upon the functional status and/or the degree of right ventricular enlargement/dysfunction.^{3,4} However, management of isolated severe TR remained strongly influenced by 2 long-lasting contradictory beliefs: (1) that severe TR is a benign disease and (2) that ITVS is a high-risk surgery. It is now well established that TR presence and degree are independent and strong prognostic factors.^{18,19} Although performed in different settings, in-hospital mortality after ITVS ranged between 10% and up to 30%.^{5–9,20} As ITVS is performed much less often than mitral or aortic valve surgery, most of the previous series came from high-volume tertiary institutions and gathered patients from a long period of time and/or did not differentiate isolated from combined TV surgery.^{5–9,20–23} Thus, we undertook the present study to specifically assess the in-hospital mortality and its potential determinants in a contemporary and consecutive series of all patients who underwent an ITVS in our country during a 2-year period.

We observed that ITVS was associated with high mortality and morbidity rates. The remarkably high complications rate translated into a long in-hospital length of stay, far much longer than any other valve surgery. The high morbidity and mortality is even more striking as regards the relatively young

age of the population. TV surgery is relatively simple and well codified, and we may hypothesize that the high rate of complications may be either due to associated co-morbidities or to the very advanced clinical presentation of the patients. The association between congestive heart failure at presentation and the high rates of dialysis and ECMO suggests that advance disease stage plays a major role. We are certainly not implying that co-morbidities and previous surgery have no impact on outcome, but our point is to highlight that in patients who underwent an ITVS, clinical presentation and advanced course of the disease have played a major role which superseded medical history and co-morbidities. Similarly, the overall advance disease stage may have prevented us from observing an outcome difference between repair and replacement, the latter usually being associated with a worse clinical profile. A recent U.S. study based on National Inpatient Sample files has shown that number of ITVS has increased from 2004 to 2013 but that the mortality has remained unchanged (8.8%) and predicted by expected consequences of severe long-lasting TV disease as coagulopathy and end-stage renal disease.²⁴ It is worth noting that the observed mortality in the United States was very similar to ours although they excluded patients with a history of infective endocarditis or congenital disease. Altogether these findings further support the hypothesis that late referral is the major reason for the observed excess mortality.

There are 2 clinical implications of the present study. First, it strongly advocates a preventive strategy to avoid occurrence of late severe TR requiring surgery in patients who undergo a left-sided valve disease. Although debated,^{25,26} a strategy based not only on TR degree but also on the dimension of the tricuspid annulus size should be recommended even if the level of evidence needs to be improved.^{17,27–29} Second, in patients with severe TR, as for the other valve diseases, a more aggressive approach should be recommended to avoid performing surgery in patients with end-stage congestive heart failure or severe right ventricular dysfunction. It should be noted that we have only presented the illuminated face of the moon as patients who have been judged too severe and contraindicated for surgery were not captured. Thus, in our opinion, the paradigm should be shifted; it is not the surgery per se which is responsible for the high mortality and morbidity rates but the late referral to surgery. Refinement of the evaluation of right ventricular function and size is definitively needed, but in our clinical practice, we are now considering surgery when diuretics have to be increased to control symptoms or when significant/progressive right ventricular enlargement is observed. Development of transcatheter therapies may potentially represent in the near future an alternative to surgery and will further push for an early intervention if proved to be safe and efficient.

Strengths and limitations of the present study need to be discussed. As participation in our administrative database (PMSI) is not voluntary, we were able to identify all cases of ITVS that were performed in France during the study period. Nevertheless, use of administrative data also has limitations. Limited population's characteristics were available, and they relied on coding quality. Thus, except for infective endocarditis, we were not able to further refine the etiology of the disease. Type and nature of heart failure symptoms were

not accessible. No echocardiographic data were available and our ability to detect prognostic factors was thus relatively limited. Midterm outcome also could not be obtained from the PMSI as there is no current possibility to link to other databases. Finally, we are only providing indirect arguments, suggesting that the high mortality and morbidity observed are related to late surgical referral and that an earlier surgery may improve outcome. A direct proof would require a randomized controlled trial.

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Disclosures

None of the authors has conflict of interest or disclosure related to the present study.

- Koelling TM, Aaronson KD, Cody RJ, Bach DS, Armstrong WF. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. *Am Heart J* 2002;144:524–529.
- Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* 2004;43:405–409.
- Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Muñoz DR, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL. 2017 ESC/EACTS Guidelines for the management of valvular heart disease: the Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2017;38:2739–2791.
- Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O’Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017;135:e1159–e1195.
- De Meester P, Van De Bruene A, Voigt JU, Herijgers P, Budts W. Outcome and determinants of prognosis in patients undergoing isolated tricuspid valve surgery: retrospective single center analysis. *Int J Cardiol* 2014;175:333–339.
- Kim YJ, Kwon DA, Kim HK, Park JS, Hahn S, Kim KH, Kim KB, Sohn DW, Ahn H, Oh BH, Park YB. Determinants of surgical outcome in patients with isolated tricuspid regurgitation. *Circulation* 2009;120:1672–1678.
- Kim JB, Jung SH, Choo SJ, Chung CH, Lee JW. Clinical and echocardiographic outcomes after surgery for severe isolated tricuspid regurgitation. *J Thorac Cardiovasc Surg* 2012;146:278–284.
- Teman NR, Huffman LC, Krajacic M, Pagani FD, Haft JW, Bolling SF. “Prophylactic” tricuspid repair for functional tricuspid regurgitation. *Ann Thorac Surg* 2014;97:1520–1524.
- Jeganathan R, Armstrong S, Al-Alao B, David T. The risk and outcomes of reoperative tricuspid valve surgery. *Ann Thorac Surg* 2013;95:119–124.
- PMSI. Programme de médicalisation des systèmes d’informations (PMSI). 2012. Available at: <http://www.drees.sante.gouv.fr/redressements-du-programme-de-medicalisation-des-systemes-d-informations-pmsi>. Accessed on January 29, 2010.
- Problems WHOISC-toDaRH. International Statistical Classification of Diseases and Related Health Problems 10th Revision. 2012. Available at: <http://apps.who.int/classifications/icd10/browse/2010/en>. Accessed on January 1, 2012.
- Maladie A. Classification commune des actes médicaux (CCAM). 2012. Available at: <http://www.ameli.fr/accueil-de-la-ccam/trouver-un-acte/index.php>. Accessed on January 1, 2018.
- Rodes-Cabau J, Taramasso M, O’Gara PT. Diagnosis and treatment of tricuspid valve disease: current and future perspectives. *Lancet* 2016;388:2431–2442.
- Matsuyama K, Matsumoto M, Sugita T, Nishizawa J, Tokuda Y, Matsuo T. Predictors of residual tricuspid regurgitation after mitral valve surgery. *Ann Thorac Surg* 2003;75:1826–1828.
- Dreyfus GD, Corbi PJ, Chan KM, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? *Ann Thorac Surg* 2005;79:127–132.
- Desai RR, Vargas Abello LM, Klein AL, Marwick TH, Krasuski RA, Ye Y, Nowicki ER, Rajeswaran J, Blackstone EH, Pettersson GB. Tricuspid regurgitation and right ventricular function after mitral valve surgery with or without concomitant tricuspid valve procedure. *J Thorac Cardiovasc Surg* 2013;146:1126–1132.
- Van de Veire NR, Braun J, Delgado V, Versteegh MI, Dion RA, Klautz RJ, Bax JJ. Tricuspid annuloplasty prevents right ventricular dilatation and progression of tricuspid regurgitation in patients with tricuspid annular dilatation undergoing mitral valve repair. *J Thorac Cardiovasc Surg* 2011;141:1431–1439.
- Messika-Zeitoun D, Thomson H, Bellamy M, Scott C, Tribouilloy C, Dearani J, Tajik AJ, Schaff H, Enriquez-Sarano M. Medical and surgical outcome of tricuspid regurgitation caused by flail leaflets. *J Thorac Cardiovasc Surg* 2004;128:296–302.
- Topilsky Y, Nkomo VT, Vatury O, Michelena HI, Letourneau T, Suri RM, Pislaru S, Park S, Mahoney DW, Biner S, Enriquez-Sarano M. Clinical outcome of isolated tricuspid regurgitation. *JACC Cardiovasc Imaging* 2014;7:1185–1194.
- Pfannmuller B, Moz M, Misfeld M, Borger MA, Funkat AK, Garbade J, Mohr FW. Isolated tricuspid valve surgery in patients with previous cardiac surgery. *J Thorac Cardiovasc Surg* 2013;146:841–847.
- Kim JB, Yoo DG, Kim GS, Song H, Jung SH, Choo SJ, Chung CH, Lee JW. Mild-to-moderate functional tricuspid regurgitation in patients undergoing valve replacement for rheumatic mitral disease: the influence of tricuspid valve repair on clinical and echocardiographic outcomes. *Heart* 2012;98:24–30.
- Topilsky Y, Khanna AD, Oh JK, Nishimura RA, Enriquez-Sarano M, Jeon YB, Sundt TM, Schaff HV, Park SJ. Preoperative factors associated with adverse outcome after tricuspid valve replacement. *Circulation* 2011;123:1929–1939.
- Marquis-Gravel G, Bouchard D, Perrault LP, Page P, Jeanmart H, Demers P, Carrier M, Cartier R, Poirier NC, Hebert Y, Pellerin M. Retrospective cohort analysis of 926 tricuspid valve surgeries: clinical and hemodynamic outcomes with propensity score analysis. *Am Heart J* 2012;163:851–858.
- Zack CJ, Fender EA, Chandrashekar P, Reddy YNV, Bennett CE, Stulak JM, Miller VM, Nishimura RA. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol* 2017;70:2953–2960.
- Chan V, Burwash IG, Lam BK, Auyeung T, Tran A, Mesana TG, Ruel M. Clinical and echocardiographic impact of functional tricuspid regurgitation repair at the time of mitral valve replacement. *Ann Thorac Surg* 2009;88:1209–1215.
- Yilmaz O, Suri RM, Dearani JA, Sundt TM 3rd, Daly RC, Burkhart HM, Li Z, Enriquez-Sarano M, Schaff HV. Functional tricuspid regurgitation at the time of mitral valve repair for degenerative leaflet prolapse: the case for a selective approach. *J Thorac Cardiovasc Surg* 2011;142:608–613.
- Benedetto U, Melina G, Angeloni E, Refice S, Roscitano A, Comito C, Sinatra R. Prophylactic tricuspid annuloplasty in patients with dilated tricuspid annulus undergoing mitral valve surgery. *J Thorac Cardiovasc Surg* 2012;143:632–638.
- Chikwe J, Itagaki S, Anyanwu A, Adams DH. Impact of concomitant tricuspid annuloplasty on tricuspid regurgitation, right ventricular function, and pulmonary artery hypertension after repair of mitral valve prolapse. *J Am Coll Cardiol* 2015;65:1931–1938.
- De Meester P, De Cock D, Van De Bruene A, Gabriels C, Buys R, Helsen F, Voigt JU, Herijgers P, Herregods MC, Budts W. Additional tricuspid annuloplasty in mitral valve surgery results in better clinical outcome. *Heart* 2015;101:720–726.

Article 6

Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes

Dreyfus J, Flagiello M, Bazire B, Eggenpieler F, Viau F, Riant E, Mbaki Y, Bohbot Y, Eyharts D, Senage T, Dubrulle H, Nicol M, Doguet F, Nguyen V, Coisne A, Le Tourneau T, Lavie-Badie Y, Tribouilloy C, Donal E, Tomasi J, Habib G, Selton-Suty C, Raffoul R, Iung B, Obadia JF, Messika-Zeitoun D

Eur Heart J. 2020 Dec 1;41(45):4304-4317

Article 6 : Chirurgie valvulaire tricuspide isolée : impact de l'étiologie et de la présentation clinique sur le pronostic

La chirurgie isolée de la VT est associée à une mortalité et à une morbidité post-opératoires élevées mais ces résultats sont basés sur des études monocentriques avec un faible nombre de patients ou des registres administratifs avec peu de données cliniques, biologiques et échocardiographiques, et un suivi limité^{79,80}. De plus, l'IT peut être fonctionnelle ou organique, avec des étiologies multiples qui n'étaient pas prises en compte dans ces études.

Les objectifs de cette étude étaient d'évaluer les déterminants du pronostic intra-hospitalier et à moyen terme après chirurgie isolée de la VT en fonction du mécanisme et de l'étiologie de l'IT, et plus spécifiquement l'impact de la présentation pré-opératoire.

A partir des données du PMSI local, tous les patients adultes consécutifs opérés d'une chirurgie de la VT dans 12 centres tertiaires Français sur une période de 11 ans (2007-2017) ont été inclus. Parmi ces 5 661 patients, 466 (8% de toutes les chirurgies de la VT) ont été identifiés comme ayant eu une chirurgie isolée de la VT pour IT sévère non congénitale sur valve native alors que plus de 90% ont eu un geste sur la VT concomitant d'un autre geste chirurgical (chirurgie valvulaire du cœur gauche, pontages aorto-coronariens ou fermeture de communication inter-atriale) (Figure 34).

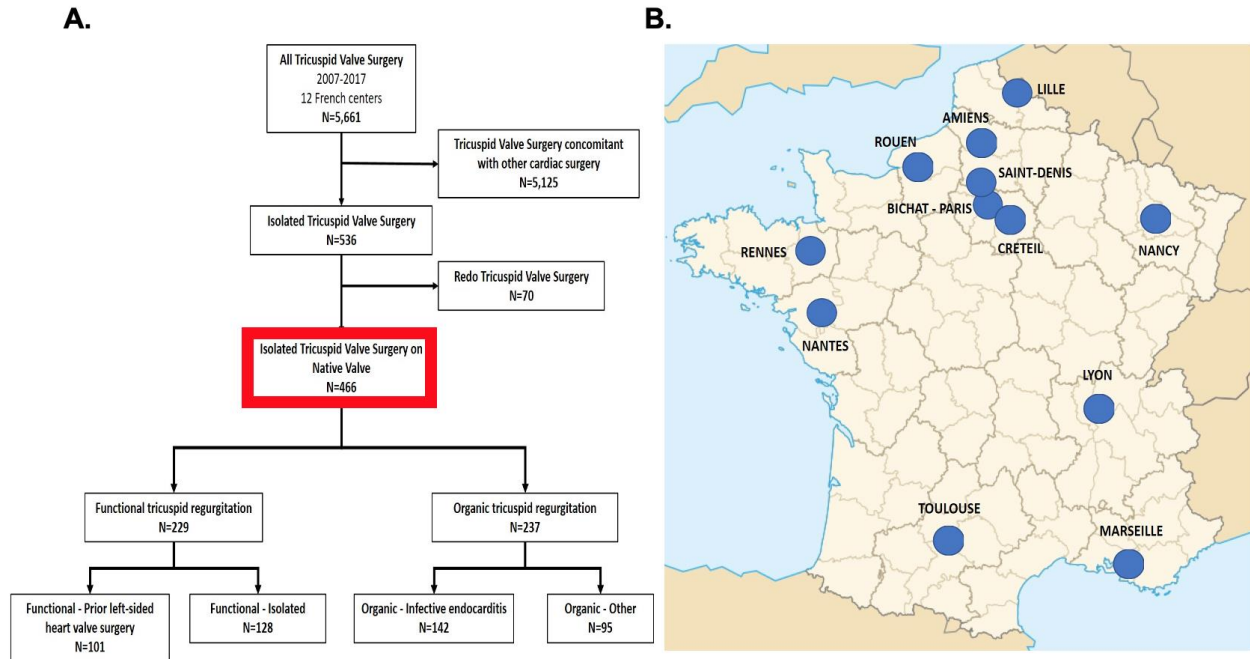


Figure 34. Population de l'étude et centres participants

- A. Organigramme des patients opérés de la valve tricuspide dans 12 centres tertiaires Français sur une période de 11 ans*
L'encadré rouge correspond à la population de l'étude
- B. Carte représentant les centres participants*

Au cours de cette période, le nombre de chirurgie de la VT augmentait de façon significative (2.8 fois d'interventions en 2017 par rapport à 2007), en rapport avec une augmentation du nombre de chirurgies de la VT au moment d'une autre intervention alors que le nombre de chirurgies isolées de la VT augmentait peu et restait faible (Figure 35).

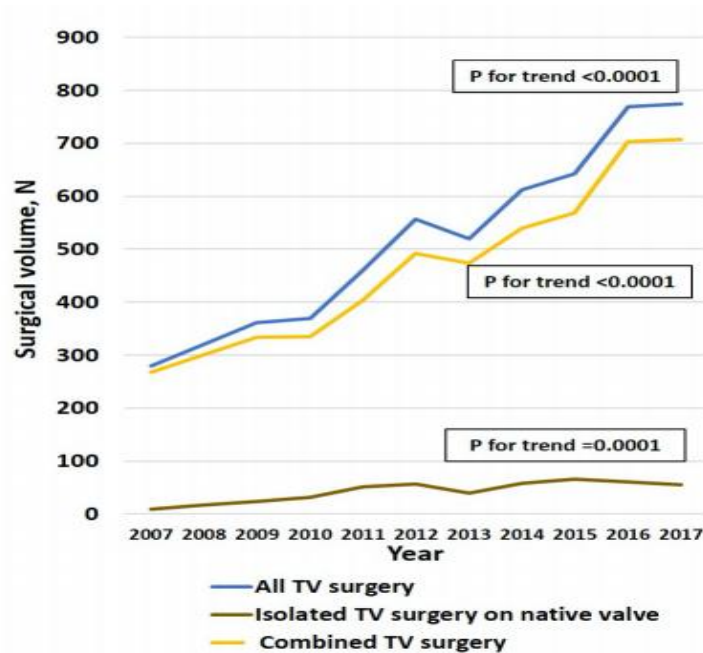


Figure 35. Nombre et évolution du nombre de chirurgies de la valve tricuspide réalisées dans 12 centres tertiaires Français sur une période de 11 ans

Les patients opérés d'une chirurgie isolée de la VT constituaient la population d'intérêt. La chirurgie était réalisée pour une IT fonctionnelle chez 49% des patients (22% avec un antécédent chirurgie valvulaire du cœur gauche et 27% isolées) et organique chez les 51% autres (31% avec une endocardite et 20% avec une autre cause organique) (Figure 34).

L'âge moyen était de 60 ± 16 ans, 49% étaient des femmes et la plupart des patients étaient très symptomatiques (47% avec un stade NYHA III/IV et 57% avec des signes d'IC droite). Alors que la très grande majorité (96%) des patients opérés sur la VT au moment d'une autre intervention avaient un geste de réparation au niveau de la VT, la majorité des patients opérés pour un geste isolé sur la VT avaient l'implantation d'une prothèse (57%), quasi-exclusivement biologique (<2% de prothèses mécaniques) (Figure 36).

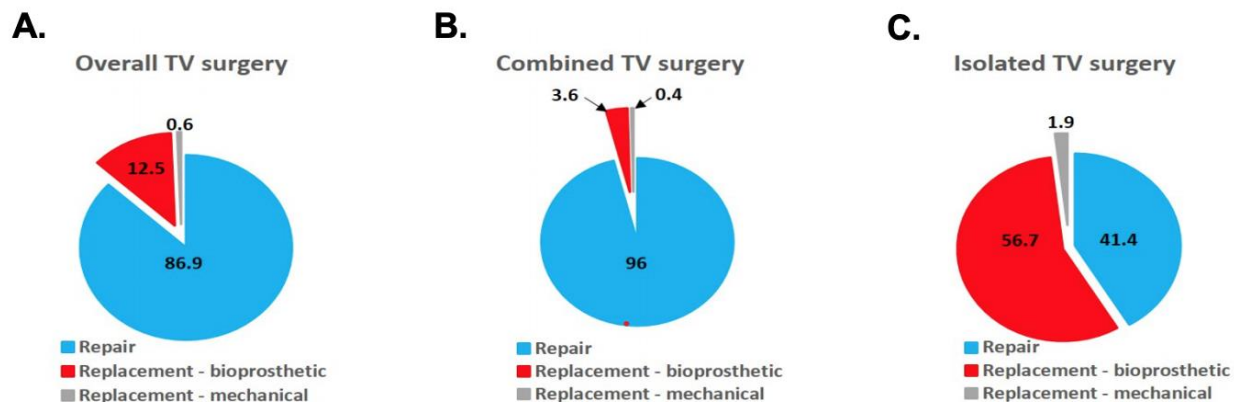


Figure 36. Types de chirurgie de la valve tricuspide (réparation, bioprothèse ou prothèse mécanique)

- A. Chez l'ensemble des patients opérés sur la valve tricuspide
- B. Chez les patients opérés sur la valve tricuspide combinée à une autre intervention
- C. Chez les patients opérés pour une chirurgie isolée de la valve tricuspide

TV : valve tricuspide

Les taux de mortalité hospitalière et de complications post-opératoires graves (incluant mortalité, choc, tamponnade, insuffisance rénale aiguë nécessitant la dialyse ou ventilation mécanique >72 heures) étaient respectivement de 10% et 31%. Ces taux masquaient de grandes disparités selon les mécanismes/étiologies de l'IT, les patients ayant une IT fonctionnelle ayant des taux de mortalité hospitalière et de complications post-opératoires graves plus élevés que les patients opérés pour IT organique (P =0.004 et P < 0.0001 respectivement) (Figure 37).

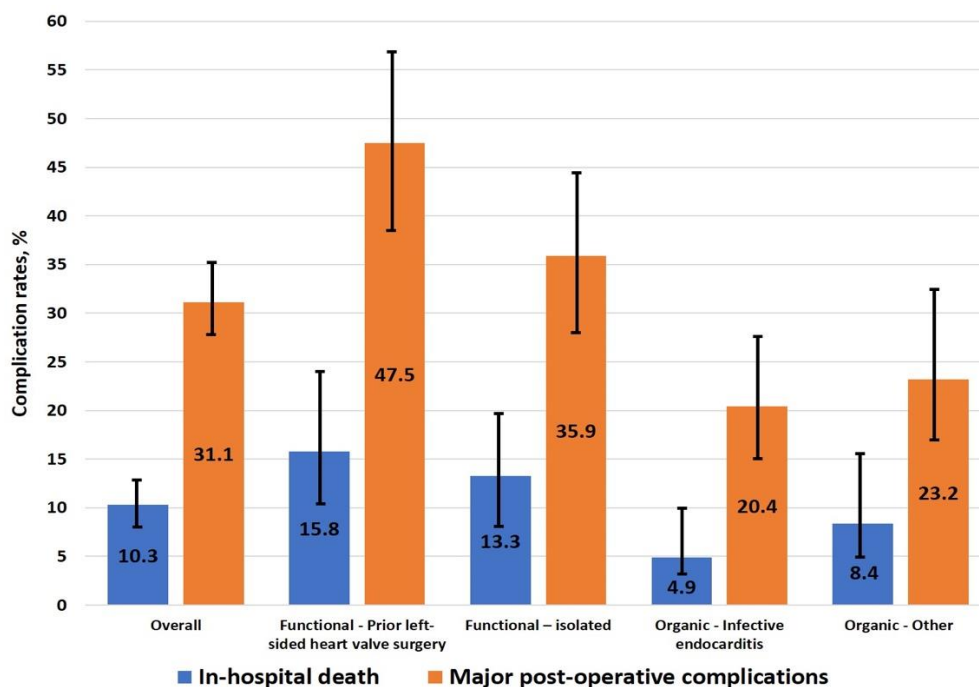


Figure 37. Taux de mortalité hospitalière et de complications post-opératoires graves après chirurgie isolée de la valve tricuspide, dans l'ensemble de la population et selon l'étiologie de l'insuffisance tricuspide

Les taux de survie, de survie sans réhospitalisation cardio-vasculaire et de survie sans réhospitalisation pour IC étaient respectivement de 86%, 73% et 79% à 1 an, et 75%, 44% et 62% à 5 ans avec un pronostic plus sombre pour les patients ayant une IT fonctionnelle comparativement aux patients ayant une IT organique ($P < 0.007$ pour les 3 courbes de survie) (Figure 38).

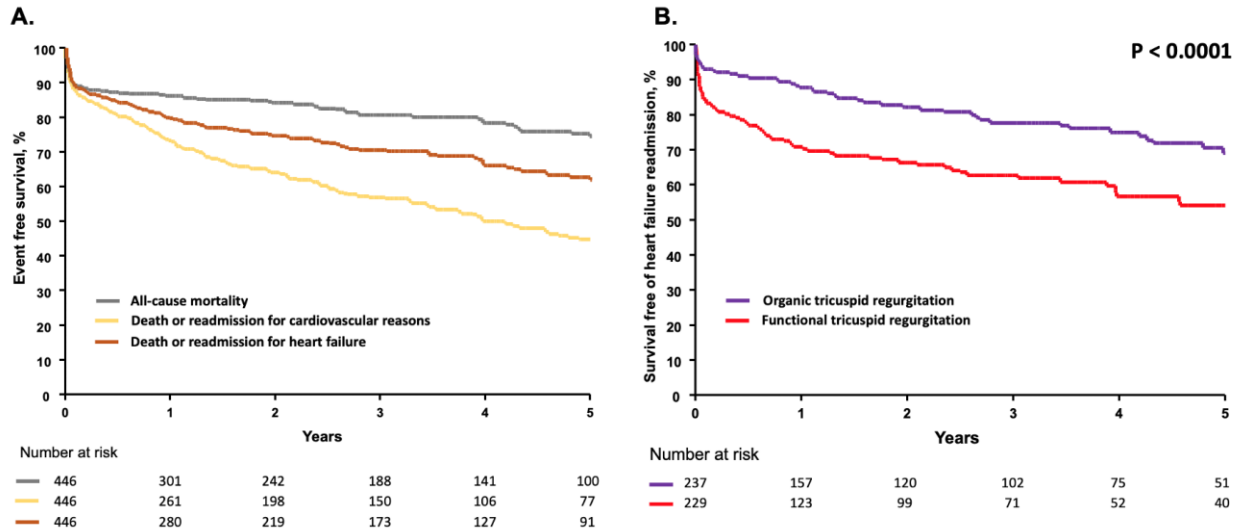


Figure 38. Taux d'événements après chirurgie isolée de la valve tricuspide

- A. Courbes de Kaplan-Meier de survie, de survie sans réhospitalisation cardio-vasculaire et de survie sans réhospitalisation pour insuffisance cardiaque dans l'ensemble de la population
- B. Courbes de Kaplan-Meier de survie sans réhospitalisation pour insuffisance cardiaque en fonction du mécanisme (fonctionnel ou organique)

En analyse univariée et multivariée, les facteurs prédictifs du pronostic post-opératoire et à moyen terme étaient les paramètres correspondants à la présentation pré-opératoire clinique (âge élevé, classe fonctionnelle NYHA III/IV, signes cliniques d'IC droite), biologique (débit de filtration glomérulaire (DFG) altéré, temps de prothrombine abaissé) et échocardiographique (dilatation et/ou dysfonction VD modérée/sévère). A noter que les mécanismes/étiologies de l'IT ne ressortaient pas comme des facteurs prédictifs du pronostic après cette intervention, de même que l'antécédent de chirurgie valvulaire du cœur gauche.

Cette étude a montré que la chirurgie isolée de la VT n'est que rarement réalisée et est associée à une mortalité et une morbidité élevées, à la fois en post-opératoire immédiat et pendant le suivi, prédite par la sévérité de la présentation pré-opératoire mais pas par le mécanisme de l'IT.

Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes

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Aims

The aim of this study was to identify determinants of in-hospital and mid-term outcomes after isolated tricuspid valve surgery (ITVS) and more specifically the impact of tricuspid regurgitation (TR) mechanism and clinical presentation.

Methods and results

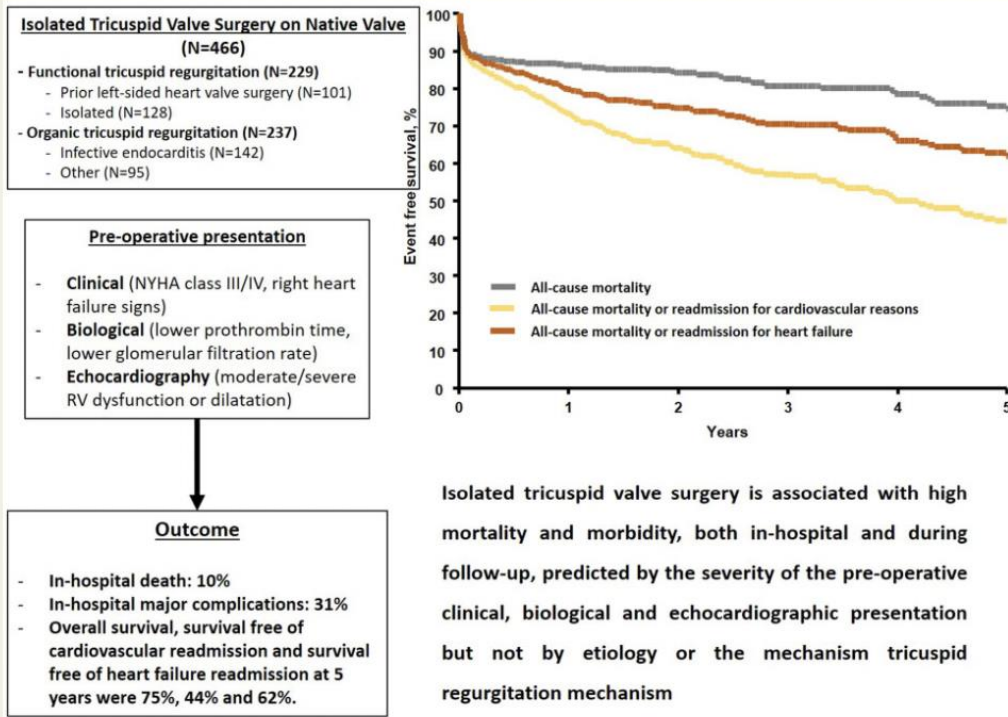
Among 5661 consecutive adult patients who underwent a tricuspid valve (TV) surgery at 12 French tertiary centres in 2007–2017 collected from a mandatory administrative database, we identified 466 patients (8% of all tricuspid surgeries) who underwent an ITVS. Most patients presented with advanced disease [47% in New York Heart Association (NYHA) III/IV, 57% with right-sided heart failure (HF) signs]. Tricuspid regurgitation was functional in 49% (22% with prior left-sided heart valve surgery and 27% isolated) and organic in 51% (infective endocarditis in 31% and other causes in 20%). In-hospital mortality and major complications rates were 10% and 31%, respectively. Rates of survival and survival free of HF readmission were 75% and 62% at 5 years. Patients with functional TR incurred a worse in-hospital mortality than those with organic TR (14% vs. 6%, $P=0.004$), but presentation was more severe. Independent determinants of outcomes were NYHA Class III/IV [odds ratios (OR) = 2.7 (1.2–6.1), $P=0.01$], moderate/severe right ventricular dysfunction [OR = 2.6 (1.2–5.8), $P=0.02$], lower prothrombin time [OR = 0.98 (0.96–0.99), $P=0.008$], and with borderline statistical significance, right-sided HF signs [OR = 2.4 (0.9–6.5), $P=0.06$] while TR mechanism was not [OR = 0.7 (0.3–1.8), $P=0.88$].

Conclusion

Isolated TV surgery was associated with high mortality and morbidity, both in hospital and during follow-up, predicted by the severity of the presentation but not by TR mechanism. Our results suggest that TV intervention should be performed earlier in the course of the disease.

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Graphical Abstract



Keywords

Tricuspid regurgitation • Surgery • Outcome

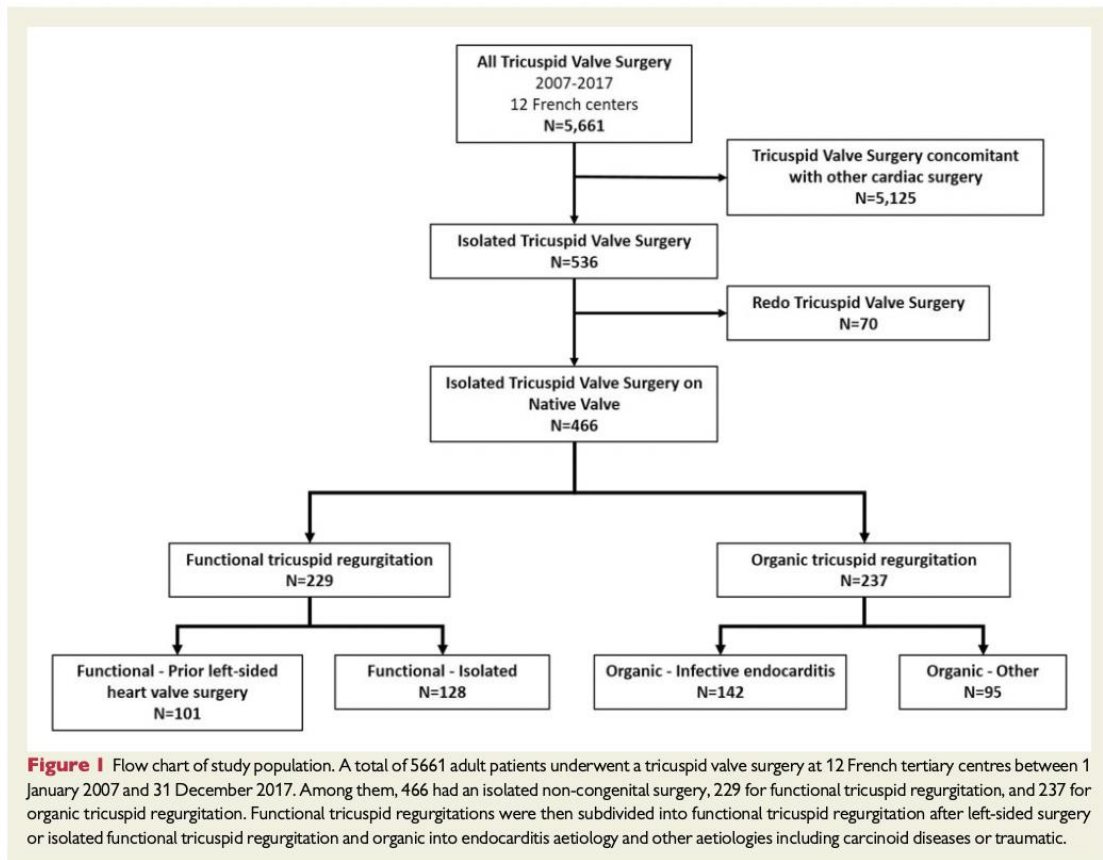
Introduction

Tricuspid regurgitation (TR) is a frequent condition that has been overlooked compared to left-sided valve diseases. Epidemiological studies suggest that moderate or severe TR affects over 1.6 million individuals in the USA.^{1,2} Multiple studies, in various settings such as heart failure (HF) with reduced left ventricular ejection fraction (LVEF), tricuspid flail, or isolated functional TR, have shown that the presence and severity of TR are associated with an increased risk of mortality and of cardiovascular (CV) events.³⁻⁸ In a recent meta-analysis, moderate/severe TR was associated with more than a two-fold increased cardiac mortality independently of pulmonary pressures, LVEF, and right ventricular (RV) dysfunction.⁹ Despite its high prevalence, TR is often left untreated and the number of tricuspid valve (TV) surgeries, mostly performed at the time of mitral valve surgery, remains remarkably low.¹⁰

Isolated tricuspid valve surgery (ITVS) is reputed to be a high-risk surgery with a 10% in-hospital mortality rate that had remained

constant across studies and time despite improvement in surgical techniques and post-operative management.¹⁰⁻¹² However, most studies relied on small single-centre studies or on administrative databases with limited clinical, biological, and echocardiographic information and limited follow-up. Thus, determinants of outcome after ITVS have remained so far elusive. In a previous study, using the French Programme de Médicalisation des Systèmes d'Information (PMSI), a mandatory administrative database, congestive heart failure (CHF) at presentation was associated with mortality and major complications rates.¹² However, granularity was limited and we were not able to account for the severity of the clinical presentation and echocardiographic features. In addition, TR mechanism may be either functional or organic and encompass multiple aetiologies. Consequently, patients referred for ITVS represent a heterogeneous population. Impact of TR aetiology on outcome remained unclear and data are very limited.

In the present study, relying on in depth characterization of patients' medical history, functional status, laboratory, and echocardiography results, we aimed to evaluate the determinants of in-hospital



and mid-term outcomes after ITVS according to TR mechanism and aetiology and more specifically the impact of the severity of the clinical presentation.

Methods

Study design

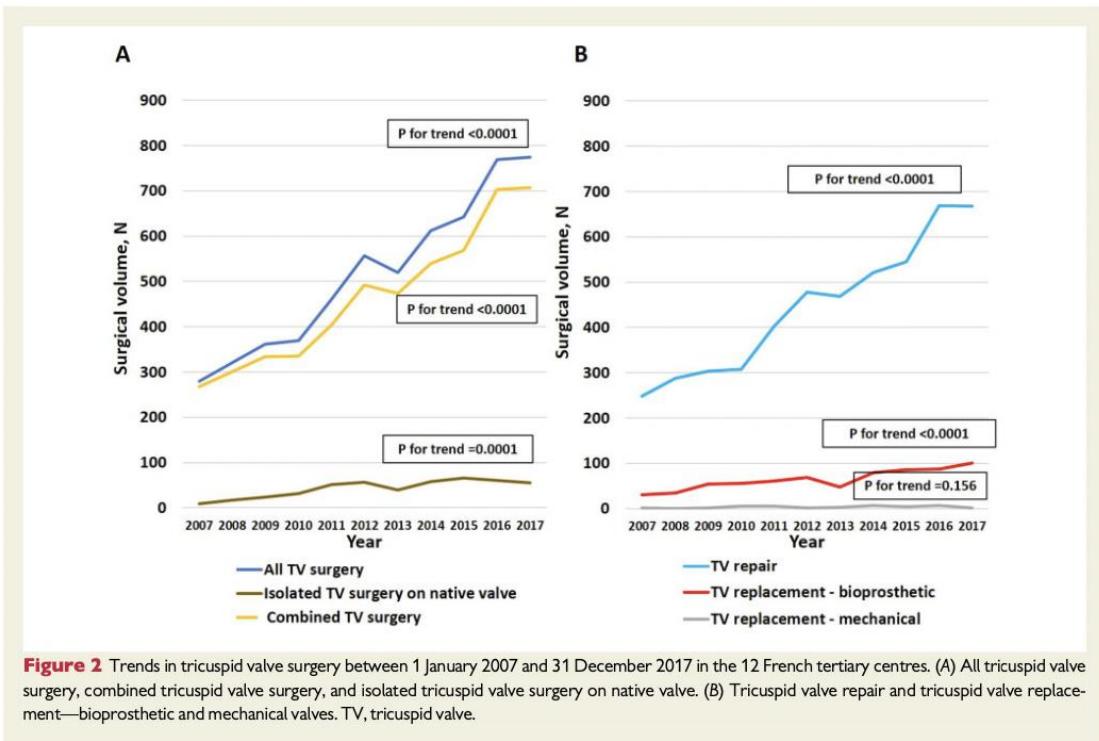
Using the local PMSI database,¹³ we collected all consecutive cases of TV surgery performed in adult patients at 12 French tertiary centres between 1 January 2007 and 31 December 2017 (Supplementary material online, Figure S1). Tricuspid valve interventions were identified using Common Classification of Medical Procedures classification (DBKA004, DBMA008, or DBMA012).¹⁴ All healthcare institutions in France are mandated to transfer information regarding their activity into the PMSI database and the PMSI database is therefore considered exhaustive. Among all TV surgery cases performed in these centres, we excluded congenital TRs and patients who underwent a combined TV surgery, meaning a TV surgery concomitant with other cardiac surgery such as mitral valve surgery, coronary artery bypass graft, or atrial septal defect closure. Finally, we excluded all redo TV surgery either on native or prosthetic valves and our study population consisted of all patients who underwent an isolated non-congenital TV surgery performed on

native valve. Clinical presentation, laboratory results, echocardiography, and immediate and mid-term outcome were retrospectively collected locally at each centre. The study was approved by each local institutional review board.

Patients' characteristics

Information regarding clinical presentation, past medical history, and laboratory results were retrospectively collected from patients' charts. Glomerular filtration rate was calculated using the Cockcroft–Gault formula according to sex. Surgical risk scores [logistic EuroSCORE, EuroSCORE II, and Society of Thoracic Surgeons (STS)] were calculated; mitral valve repair intervention was used for the STS as there is no dedicated score for ITVS.^{15,16} The Charlson index was used to assess for patients' comorbidities.

All echocardiographic reports before intervention were reviewed and when needed measurements were retrospectively performed on digitally stored images. Tricuspid regurgitation aetiology was first classified as functional (no intrinsic tricuspid disease) or organic (due to abnormalities of the tricuspid leaflets or chordae). Functional TR was then subdivided into functional TR after left-sided valve surgery or isolated functional TR, and organic into endocarditis and other aetiologies including carcinoid diseases or traumatic. Left ventricular ejection fraction was measured visually or using the biplane method of discs (modified Simpson's rule). Right ventricular size was visually assessed as normal, mildly, moderately



or severely enlarged. The RV basal diameter and the tricuspid annulus (TA) diameter (TA) were measured in diastole in the apical four-chamber view.¹⁷ Right ventricular function was semi-quantitatively assessed using an integrative approach based on visual assessment, tricuspid annulus plane systolic excursion (TAPSE), and Doppler tissue imaging peak systolic annular velocity S' as recommended.^{18,19} Pulmonary artery systolic pressure was measured using the peak systolic trans-tricuspid pressure gradient and estimated right atrial pressure according to the diameter of the inferior vena cava and its variation with respiration, applying the Bernoulli equation.

Outcome

In-hospital mortality was defined as death occurring between the intervention and hospital discharge during the same hospital stay. Major post-operative complications were defined as death, shock, tamponade, and acute renal failure requiring dialysis or prolonged (>72 h) mechanical ventilation. Lengths of stay (total and intensive care unit) were calculated as the time duration between the admission and hospital discharge. During follow-up, all-cause death and CV readmissions, defined as due to CHF, atrial fibrillation (AF), infective endocarditis, stroke, acute coronary syndrome, re-intervention (tamponade, sternum infection), or pacemaker related, were also collected based on hospital chart reviews and telephone interviews with patients or family members.

Statistics

Variables were expressed as mean \pm standard deviation or median (percentile 25 and 75) for continuous variables and number of patients

(percentage) for categorical variables. Trends in the number and type of TV surgery were estimated by the Mann–Kendall trend test. Comparisons between groups of TR mechanism/aetiologies were performed using ANOVA, χ^2 , Student's *t*-test or non-parametric Wilcoxon test as appropriate. Complication rates were expressed as percentage and 95% confidence intervals. Logistic regressions in univariate and multivariate analyses (including variables with $P < 0.10$ in univariate analysis) were used to assess the determinants of in-hospital death and major post-operative complications. Variables independently associated with mortality in each category (clinical, laboratory, and echocardiographic) were entered into the final model. Multiple comparisons for continuous variables were tested with the Bonferroni correction. Odd ratios (OR) along with 95% confidence intervals were reported. We assessed the risks of death and CV readmission overall and according to TR mechanism/aetiology using Kaplan–Meier estimates and Cox proportional hazard models. Data were analysed using JMP version 9.0 (SAS Institute) or XLSTAT (Microsoft, Redmond, WA, USA). All tests were two-sided and a P -value of <0.05 was considered statistically significant.

Results

Trends in tricuspid valve surgery

A total of 5661 adult patients underwent a TV surgery (Supplementary material online, Figure S2) at the 12 participating French tertiary centres between 1 January 2007 and 31 December 2017. Among them, 466 patients (8%) had a non-congenital isolated

Table 1 Baseline characteristics of the population overall and according to the aetiology of the tricuspid regurgitation

| Characteristics | Overall (N = 466) | Functional (N = 229) | Organic (N = 237) | P-value | Functional—prior left-sided heart valve surgery (N = 101) | Functional—isolated (N = 128) | Organic—infected endocarditis (N = 142) | Organic—other (N = 95) | P-value |
|--|-------------------|----------------------|-------------------|---------|---|-------------------------------|---|------------------------|---------|
| Age (years) | 60 ± 16 | 66 ± 11 | 53 ± 18 | <0.0001 | 66 ± 11 | 67 ± 12 | 49 ± 17 | 61 ± 15 | <0.0001 |
| Female gender | 229 (49) | 137 (60) | 92 (39) | <0.0001 | 64 (63) | 73 (57) | 43 (30) | 49 (52) | <0.0001 |
| Body mass index (kg/m ²) | 25 ± 5 | 27 ± 6 | 24 ± 5 | <0.0001 | 26 ± 5 | 27 ± 6 | 24 ± 5 | 25 ± 5 | <0.0001 |
| Hypertension | 190 (41) | 120 (52) | 70 (30) | <0.0001 | 47 (47) | 73 (57) | 31 (22) | 39 (41) | <0.0001 |
| Diabetes mellitus | 62 (13) | 40 (18) | 22 (9) | 0.009 | 19 (19) | 21 (16) | 13 (9) | 9 (10) | 0.07 |
| Chronic lung disease | 51 (11) | 30 (13) | 21 (9) | 0.14 | 14 (14) | 16 (13) | 13 (9) | 8 (8) | 0.52 |
| Peripheral vascular disease | 16 (3) | 5 (2) | 11 (5) | 0.15 | 1 (1) | 4 (3) | 8 (6) | 3 (3) | 0.27 |
| Prior stroke | 41 (9) | 24 (11) | 17 (7) | 0.21 | 15 (15) | 9 (7) | 9 (6) | 8 (8) | 0.10 |
| Prior left-sided heart valve surgery | 111 (24) | 101 (44) | 10 (4) | <0.0001 | 101 (100) | 0 (0) | 1 (1) | 9 (10) | <0.0001 |
| Coronary artery disease | 59 (13) | 35 (15) | 24 (10) | 0.09 | 20 (20) | 15 (12) | 12 (9) | 12 (13) | 0.07 |
| Chronic kidney disease | 154 (33) | 100 (44) | 54 (23) | <0.0001 | 52 (51) | 48 (38) | 28 (20) | 26 (27) | <0.0001 |
| Chronic liver disease | 54 (12) | 31 (14) | 23 (10) | 0.20 | 16 (16) | 15 (12) | 10 (7) | 13 (14) | 0.17 |
| Liver cirrhosis | 11 (2) | 7 (3) | 4 (2) | 0.33 | 5 (5) | 2 (2) | 0 (0) | 4 (4) | 0.04 |
| Permanent pacemaker | 104 (22) | 54 (24) | 50 (21) | 0.52 | 26 (26) | 28 (22) | 29 (20) | 21 (22) | 0.80 |
| Hospitalization for congestive heart failure (<1 year) | 163 (35) | 121 (53) | 42 (18) | <0.0001 | 57 (56) | 64 (50) | 16 (11) | 26 (27) | <0.0001 |
| Systolic blood pressure (mmHg) | 125 ± 19 | 126 ± 19 | 124 ± 20 | 0.36 | 123 ± 19 | 127 ± 19 | 122 ± 19 | 127 ± 20 | 0.10 |
| Diastolic blood pressure (mmHg) | 73 ± 13 | 72 ± 13 | 73 ± 14 | 0.35 | 70 ± 13 | 74 ± 13 | 73 ± 14 | 74 ± 14 | 0.16 |
| NYHA functional Class III–IV | 217 (47) | 136 (59) | 81 (34) | <0.0001 | 62 (61) | 74 (58) | 41 (29) | 40 (42) | <0.0001 |
| Right-sided heart failure signs | 264 (57) | 166 (73) | 98 (41) | <0.0001 | 80 (79) | 86 (67) | 48 (34) | 50 (53) | <0.0001 |
| Ascites | 39 (8) | 29 (13) | 10 (4) | 0.001 | 15 (15) | 14 (11) | 1 (1) | 9 (10) | 0.0005 |
| Loop diuretics | 301/451 (67) | 194/222 (87) | 107/229 (47) | <0.0001 | 96 (95) | 98/121 (81) | 49/136 (36) | 58/93 (62) | <0.0001 |
| Daily dose of loop diuretics (mg) | 40 (0–80) | 60 (40–120) | 0 (0–40) | 0.0006 | 80 (40–125) | 40 (20–120) | 0 (0–40) | 40 (0–80) | 0.003 |
| Atrial fibrillation | 180 (39) | 142 (62) | 39 (17) | <0.0001 | 66 (65) | 76 (59) | 17 (12) | 22 (23) | <0.0001 |
| Haemoglobin (g/dL) | 12.3 ± 2.3 | 12.5 ± 2.0 | 12.1 ± 2.5 | 0.06 | 12.1 ± 1.9 | 12.8 ± 2.0 | 11.2 ± 2.5 | 13.4 ± 2.0 | <0.0001 |
| Glomerular filtration rate (mL/min) | 72 ± 39 | 61 ± 29 | 82 ± 44 | <0.0001 | 60 ± 28 | 60 ± 30 | 93 ± 49 | 67 ± 32 | <0.0001 |
| Elevated ALT and/or AST | 73/393 (19) | 31/195 (16) | 42/198 (21) | 0.18 | 14/91 (15) | 17/104 (16) | 31/112 (28) | 11/86 (13) | 0.03 |
| Elevated GGT and/or ALP | 189/397 (48) | 102/195 (52) | 87/202 (43) | 0.07 | 55/93 (59) | 47/102 (46) | 50/120 (42) | 37/82 (45) | 0.07 |
| Total bilirubin (μmol/L) | 15.8 ± 11.9 | 17 ± 13 | 15 ± 11 | 0.07 | 19.1 ± 14.2 | 15.1 ± 11.4 | 13.3 ± 10.4 | 16.6 ± 11.2 | 0.006 |
| Prothrombin time | 74 ± 20 | 67 ± 21 | 80 ± 16 | <0.0001 | 62 ± 22 | 71 ± 19 | 78 ± 16 | 82 ± 16 | <0.0001 |
| LV ejection fraction | 58 ± 9 | 57 ± 8 | 59 ± 9 | 0.03 | 55 ± 9 | 58 ± 8 | 59 ± 10 | 59 ± 8 | 0.02 |
| RV basal diameter (mm) | 48 ± 11 | 52 ± 11 | 44 ± 9 | <0.0001 | 52 ± 7 | 51 ± 12 | 42 ± 9 | 49 ± 8 | <0.0001 |
| Moderate/severe RV dilatation | 245/450 (54) | 148/222 (67) | 97/228 (43) | <0.0001 | 62/99 (63) | 86/123 (70) | 48/135 (36) | 49/93 (53) | <0.0001 |
| TAPSE (mm) | 20 ± 7 | 18 ± 5 | 22 ± 7 | <0.0001 | 16 ± 4 | 19 ± 6 | 23 ± 8 | 22 ± 7 | <0.0001 |
| Peak systolic annular velocity S' (cm/s) | 11.9 ± 4.1 | 10.7 ± 3.1 | 13.5 ± 4.6 | <0.0001 | 9.5 ± 2.1 | 11.6 ± 3.5 | 13.8 ± 4.9 | 13.2 ± 4.1 | <0.0001 |
| Moderate/severe RV dysfunction | 76/446 (17) | 50/221 (23) | 26/225 (12) | 0.002 | 31/98 (32) | 19/123 (15) | 14/134 (10) | 12/91 (13) | 0.0002 |

Continued

Table 1 Continued

| Characteristics | Overall (N = 466) | Functional (N = 229) | Organic (N = 237) | P- value | Functional—prior left-sided heart valve surgery (N = 101) | Functional—iso- lated (N = 128) | Organic—infected endocarditis (N = 142) | Organic— other (N = 95) | P- value |
|--|----------------------|-------------------------|----------------------|-------------|---|------------------------------------|---|-------------------------------|-------------|
| Tricuspid annulus diameter in apical four-chamber view (mm) | 44 ± 9 | 47 ± 7 | 41 ± 9 | <0.0001 | 46 ± 7 | 47 ± 7 | 38 ± 9 | 44 ± 9 | <0.0001 |
| Systolic pulmonary artery pressure (mmHg) | 40 ± 11 | 43 ± 11 | 37 ± 10 | <0.0001 | 43 ± 10 | 43 ± 12 | 36 ± 9.1 | 39 ± 11 | <0.0001 |
| Logistic EuroSCORE | 5.2 (3.0–9.2) | 5.2 (3.3–9.7) | 5.2 (2.6–8.8) | 0.78 | 7.0 (4.8–12.3) | 4.3 (2.7–7.6) | 6.0 (3.6–11.3) | 3.3 (1.5–6.0) | <0.0001 |
| EuroSCORE II | 2.7 (1.4–5.0) | 3.4 (1.9–6) | 2.0 (1.2–4.7) | 0.03 | 5.0 (3.6–7.5) | 2.1 (1.3–4.3) | 2.1 (1.4–5.0) | 1.9 (0.9–3.4) | <0.0001 |
| STS predicted risk of mortality | 3.0 (1.6–5.5) | 3.6 (2.2–6.1) | 2.3 (1.1–4.8) | 0.05 | 4.9 (3.0–7.3) | 3.0 (1.6–4.9) | 2.3 (1.0–5.1) | 2.3 (1.3–4.3) | 0.0008 |
| Charlson comorbidity index | 3 (1–4) | 4 (2–5) | 2 (0–4) | <0.0001 | 4 (2–4) | 3 (2–5) | 1 (0–3) | 3 (1–5) | <0.0001 |
| Charlson comorbidity index ≥ 2 | 324 (70) | 196 (86) | 128 (54) | <0.0001 | 86 (85) | 110 (86) | 63 (44) | 65 (68) | <0.0001 |

Values are number of patients (percentage), mean ± standard deviation, or median (inter-quartiles).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LV, left ventricle; NYHA, New York Heart Association; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; STS, Society of Thoracic Surgery.

TV surgery on native valve (Figure 1). Trends in TV surgery are presented in Figure 2. The number of TV surgery increased from 280 in 2007 to 774 in 2017 (P for trend < 0.0001). The increase in number of TV surgery performed was mainly related to a marked increase in the number of combined TV surgery (P for trend < 0.0001) although isolated TV modestly but significantly increased during the study period (P for trend = 0.0001).

Clinical presentation and aetiologies of isolated tricuspid valve surgery

Characteristics of the 466 patients with a non-congenital isolated TV surgery on native valve are presented in Table 1. Overall mean age was 60 ± 16 years and 229 patients (49%) were female. One hundred and eleven patients (24%) had a previous left-sided heart surgery. Close to half of the patients were severely symptomatic [47% in New York Heart Association (NYHA) functional Class III/IV] and 163 (35%) were admitted for CHF within the year preceding the surgery. Right-sided HF signs were present in 264 patients (57%) in whom 39 (8%) had ascites. Chronic kidney disease was present in 154 patients (33%) and chronic liver disease in 54 patients (12%). Mean LVEF was $58 \pm 9\%$. A moderate/severe RV dilatation was present in 54% of patients and a moderate/severe RV dysfunction in 17%. The mean systolic pulmonary artery pressure was 40 ± 11 mmHg (≥ 50 mmHg in 19%). The median Charlson comorbidity index was high [3.0 (1–4)], and 324 patients (70%) had a Charlson comorbidity index of ≥ 2 .

Tricuspid regurgitation mechanism was functional in 229 patients (49%) and organic in 237 patients (51%). Among patients with functional TR, 101 patients (22%) had a prior left-sided heart valve surgery and 128 (27%) patients had an isolated functional TR (Figure 1). Among the 237 patients with organic disease, TR was due to infective endocarditis in 142 patients (31%) and to other causes in 95 patients (20%). Patients with functional TR were older, more frequently female and presented more often with CV risk factors and comorbidities than those with organic TR. Importantly clinical presentation was also more severe. Patients with functional TR presented more advanced signs of HF signs, worse laboratory results, and more often moderate/severe RV enlargement and dysfunction than patients with organic TR. The Charlson index was twice as high in patients with functional TR than in patients with organic TR. As expected, TV infective endocarditis affected a younger mainly male population with infrequent CV risk factors. Clinical and echocardiographic RV parameters also tended to be less severe than those of the three other groups. Comparisons of baseline characteristics between functional and organic TR and between TR aetiologies are presented in Table 1.

In-hospital outcomes of isolated tricuspid valve surgery

A TV repair was performed in 193 patients (41%) and a replacement in 273 patients (59%) (Supplementary material online, Figure S2). A TV replacement was more often performed when the TV surgery was performed isolated than concomitant with other cardiac interventions (59% vs. 4%, $P < 0.0001$). In most cases of ITVS, a bioprosthetic valve was used ($n = 264$, 57%) while a mechanical valve was implanted in only nine patients (2%). Surgery was urgent in 102 patients (22%). Overall, in-hospital mortality rate was 10% ($n = 48$) and major post-operative complications rate was 31% ($n = 145$).

Table 2 In-hospital outcome overall and according to the aetiology of the tricuspid regurgitation

| Characteristics | Overall (N = 466) | Functional (N = 229) | Organic (N = 237) | P-value | Functional—prior left-sided heart valve surgery (N = 101) | Functional—isolated (N = 128) | Organic—infected endocarditis (N = 142) | Organic—other (N = 95) | P-value |
|---|----------------------|-------------------------|----------------------|---------|---|----------------------------------|---|---------------------------|---------|
| Urgent surgery | 102 (22) | 14 (6) | 88 (37) | <0.0001 | 5 (5) | 9 (7) | 83 (58) | 5 (5) | <0.0001 |
| TV replacement | 273 (57) | 135 (59) | 138 (58) | 0.87 | 76 (75) | 59 (46) | 78 (55) | 60 (63) | <0.0001 |
| In-hospital death | 48 (10) | 33 (14) | 15 (6) | 0.004 | 16 (16) | 17 (13) | 7 (5) | 8 (8) | 0.02 |
| Major post-operative complications | 145 (31) | 94 (41) | 51 (22) | <0.0001 | 48 (48) | 46 (36) | 29 (20) | 22 (23) | <0.0001 |
| Shock | 107 (23) | 73 (32) | 34 (14) | <0.0001 | 39 (39) | 34 (27) | 21 (15) | 13 (14) | 0.0004 |
| Cardiogenic shock | 87 (19) | 63 (28) | 24 (10) | <0.0001 | 32 (32) | 31 (24) | 12 (8) | 12 (13) | 0.0001 |
| Tamponade | 36 (8) | 26 (11) | 10 (4) | 0.004 | 13 (13) | 13 (10) | 5 (4) | 5 (5) | 0.03 |
| Acute renal failure | 123 (26) | 74 (32) | 49 (21) | 0.004 | 34 (34) | 40 (31) | 32 (23) | 17 (18) | 0.01 |
| Acute renal failure requiring dialysis | 49 (11) | 32 (14) | 17 (7) | 0.02 | 17 (17) | 15 (12) | 11 (8) | 6 (6) | 0.02 |
| Prolonged mechanical ventilation | 40 (9) | 24 (10) | 16 (7) | 0.15 | 14 (14) | 10 (8) | 11 (8) | 5 (5) | 0.13 |
| New permanent pacemaker implantation | 84 (18) | 37 (16) | 47 (20) | 0.30 | 16 (16) | 21 (16) | 29 (20) | 18 (19) | 0.43 |
| Length of stay in intensive care unit (days) | 4 (2–8) | 4 (2–9) | 3 (2–7) | 0.04 | 5 (3–11) | 4 (2–7) | 3 (2–7) | 4 (2–7) | 0.002 |
| Length of stay in hospital (days) | 18 (12–29) | 17 (12–29) | 18 (12–29) | 0.35 | 22 (15–35) | 15 (10–25) | 21 (14–37) | 15 (11–23) | <0.0001 |
| Tricuspid regurgitation \leq 2 at discharge | 408 (98) | 192 (98) | 216 (97) | 0.66 | 83 (98) | 109 (98) | 130 (92) | 86 (99) | 0.58 |
| Systolic pulmonary artery pres- sure at discharge (mmHg) | 36 \pm 11 | 40 \pm 12 | 31 \pm 8 | <0.0001 | 40 \pm 11 | 40 \pm 13 | 29 \pm 8 | 33 \pm 9 | <0.0001 |

Values are number of patients (percentage), mean \pm standard deviation, or median (inter-quartiles). Major post-operative complications were defined as death, shock, tamponade, acute renal failure requiring dialysis, or prolonged mechanical ventilation (>72 h). TV, tricuspid valve.

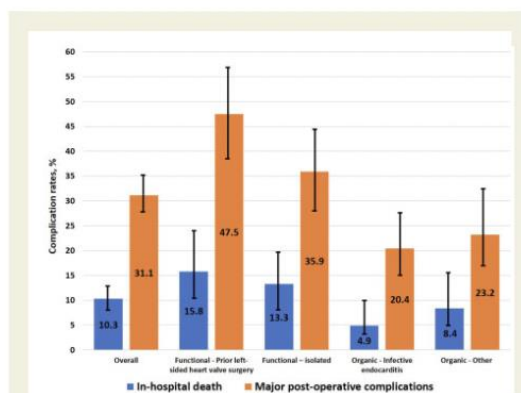


Figure 3 In-hospital mortality and major post-operative complications rates overall and according to the aetiology of the tricuspid regurgitation.

(Table 2 and Figure 3). In the post-operative period, 87 patients (19%) presented a cardiogenic shock, 36 patients (8%) a tamponade, and 123 (26%) acute renal failure, of whom 49 (11%) requiring dialysis, 40 (9%) a prolonged mechanical ventilation, and 84 (18%) needed a definitive pacemaker. The median intensive care unit and total lengths of stay were 4 days (2–8) and 18 days (12–29), respectively. Residual TR was rare and 98% of patients alive at discharge presented with less than moderate TR.

Factors associated with in-hospital death in univariate analysis are presented in Table 3. In-hospital mortality was associated with older age and more severe presentation based on clinical, laboratory, and echocardiographic assessment such as history of CHF, severe symptoms (NYHA Class III/IV), presence of ascites, cirrhosis, dose of loop diuretics, kidney impairment, comorbidity index, and surgical risk scores and degree of RV dilatation and dysfunction. Functional TR was also associated with higher in-hospital mortality rate than organic aetiology (14% vs. 6%, $P=0.004$) while history of previous left-sided heart valve surgery was not ($P=0.10$). Mortality rates according to TR aetiology were 16% for functional TR after left-sided valve surgery, 13% for isolated functional TR, 5% for infective endocarditis, and 8% for organic TR of other aetiology ($P=0.02$) (Figure 3). In multivariate analysis, independent determinants of in-hospital death were NYHA Class III/IV [OR = 2.7 (1.2–6.1), $P=0.01$], moderate/severe RV dysfunction [OR = 2.6 (1.2–5.8), $P=0.02$], lower prothrombin time [OR = 0.98 (0.96–0.99), $P=0.008$], and with borderline statistical significance, presence of right CHF signs [OR = 2.4 (0.9–6.5), $P=0.06$] while mechanism was not [OR = 0.7 (0.3–1.8), $P=0.88$]. Systolic pulmonary artery pressure ≥ 50 mmHg was also of borderline statistical significance [OR = 2.5 (0.9–7.0), $P=0.08$]. Independent determinants of major in-hospital complications in multivariate analysis were similar, with moderate/severe RV dysfunction [OR = 2.2 (1.2–4.1), $P=0.01$], lower glomerular filtration rate [OR = 0.98 (0.96–0.99), $P=0.006$], lower prothrombin time [OR = 0.98 (0.97–0.99), $P=0.02$], and with borderline statistical significance, NYHA Class III/IV [OR = 1.6 (0.95–1.1), $P=0.07$], AF [OR = 1.7 (0.9–3.1), $P=0.08$] and moderate/severe RV dilatation

[OR = 1.6 (0.95–2.6), $P=0.08$]. Excluding patients with permanent pacemaker at the time of the surgery did not change our results. Our results also remained similar after the exclusion of patients with infective endocarditis or if the prothrombin time was not included into the model.

Mid-term outcomes of isolated tricuspid valve surgery

Follow-up was 90% complete. During an overall mean follow-up duration of 3.1 ± 2.7 years [median 2.6 years (0.8–4.9), up to 11.8 years], there were 40 additional deaths (all-cause) and 138 patients were readmitted for CV reasons including 64 patients for CHF. Overall rates of survival, survival free of CV readmission, and survival free of HF readmission were 86%, 73%, and 79% at 1 year and 75%, 44%, and 62% at 5 years, respectively (Figure 4A, Take home figure). Event rates among the 371 patients alive at 30 days and with available follow-up were 98%, 83%, and 90% at 1 year and 85%, 50%, and 70% at 5 years (Figure 4B). Survival, survival free of CV readmission, and survival free of HF readmission curves according to TR aetiology are presented in Figure 5 and were significantly worse for functional than for organic TR (all $P < 0.01$). Mortality and CV events according to TR aetiologies were also significantly different when subdivided into functional TR after left-sided valve surgery, isolated functional TR, organic TR due to infective endocarditis, and organic TR due to other aetiologies (all $P < 0.05$) (Supplementary material online, Figure S3). However, outcome of both functional groups was not different (all $P > 0.40$).

In the multivariate analysis, independent determinants of all-cause mortality were NYHA Class III/IV [HR = 1.7 (1.1–2.8), $P=0.04$], presence of right CHF signs [OR = 1.8 (1.01–3.3), $P < 0.05$], lower prothrombin time [OR = 0.98 (0.97–0.99), $P=0.04$], and with borderline statistical significance, functional aetiology [OR = 0.6 (0.3–1.1), $P=0.07$], lower glomerular filtration rate [OR = 0.99 (0.98–1.01), $P=0.09$], and moderate/severe RV dilatation [OR = 1.6 (0.9–2.7), $P=0.08$]. Similar determinants were observed for all-cause mortality or CV readmissions {NYHA Class III/IV [OR = 1.4 (1.0–2.0), $P=0.05$], presence of right CHF signs [OR = 1.8 (1.2–2.6), $P=0.002$], lower prothrombin time [OR = 0.99 (0.99–0.99), $P=0.03$], and moderate/severe RV dilatation [OR = 1.6 (1.1–2.3), $P=0.006$]} and for all-cause mortality or HF readmissions {NYHA Class III/IV [OR = 1.7 (1.1–2.3), $P=0.02$], presence of right CHF signs [OR = 1.9 (1.2–3.1), $P=0.006$], and moderate/severe RV dilatation [OR = 2.0 (1.3–3.1), $P=0.002$]}). Functional aetiology was not an independent determinant of mortality or (CV or HF) readmissions [OR = 0.9 (0.6–1.4), $P=0.67$ and OR = 0.9 (0.5–1.3), $P=0.37$, respectively].

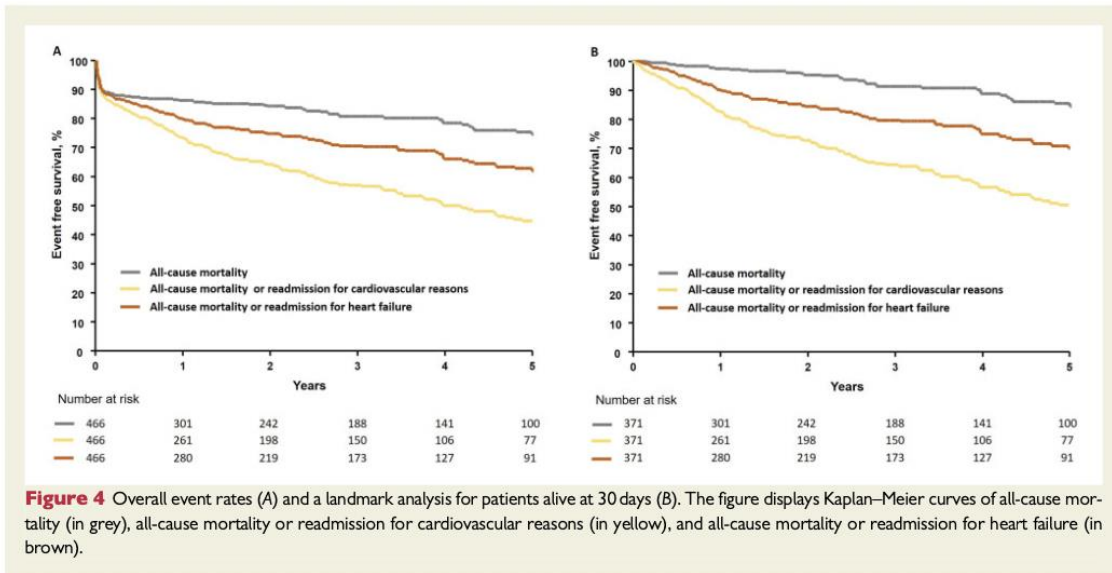
Discussion

In this retrospective series, we collected all cases of TV surgery performed at 12 French tertiary centres between 1 January 2007 and 31 December 2017 and assessed the clinical, biological, and echocardiographic presentation and immediate and mid-term outcomes of ITVS. Main results of the present study can be summarized as follows: (i) although total numbers had increased over time, TV surgery remained seldom performed; (ii) TV surgery was mainly concomitant with another surgical procedure and rarely isolated; (iii) ITVS was performed in approximately half of cases for functional TR (after left-sided valve

Table 3 Univariate logistic regression for predictors of in-hospital death in adult patients undergoing an isolated tricuspid valve surgery and odd ratios (95% confidence interval) for the variables entered in the final model

| Characteristics | In-hospital death (N = 48) | Discharged alive (N = 418) | P-value | Odds ratios (95% CI) | P-value |
|--|----------------------------|----------------------------|---------|----------------------|---------|
| Age (years) | 68 ± 12 | 59 ± 16 | <0.0001 | 1.01 (0.97–1.04) | 0.63 |
| Female gender | 24 (50) | 205 (49) | 0.90 | | |
| Body mass index (kg/m ²) | 26 ± 6 | 25 ± 5 | 0.61 | | |
| Hypertension | 24 (50) | 166 (40) | 0.17 | | |
| Diabetes mellitus | 6 (13) | 56 (13) | 0.86 | | |
| Chronic lung disease | 8 (17) | 43 (10) | 0.18 | | |
| Peripheral vascular disease | 2 (4) | 14 (3) | 0.77 | | |
| Prior stroke | 3 (6) | 38 (9) | 0.51 | | |
| Prior left-sided heart valve surgery | 16 (33) | 95 (23) | 0.10 | | |
| Coronary artery disease | 9 (19) | 50 (12) | 0.18 | | |
| Chronic kidney disease | 20 (42) | 134 (32) | 0.18 | | |
| Chronic liver disease | 12 (25) | 42 (10) | 0.002 | | |
| Liver cirrhosis | 3 (6) | 8 (2) | 0.008 | | |
| Prior pacemaker | 16 (33) | 88 (21) | 0.05 | | |
| Hospitalization for congestive heart failure (<1 year) | 25 (52) | 128 (33) | 0.009 | | |
| Systolic blood pressure (mmHg) | 122 ± 17 | 125 ± 20 | 0.49 | | |
| Diastolic blood pressure (mmHg) | 70 ± 14 | 73 ± 13 | 0.20 | | |
| NYHA functional Class III–IV | 33 (69) | 184 (44) | 0.001 | 2.7 (1.2–6.1) | 0.01 |
| Right-sided heart failure signs | 41 (85) | 223 (53) | <0.0001 | 2.4 (0.9–6.5) | 0.06 |
| Ascites | 10 (21) | 29 (7) | 0.001 | | |
| Loop diuretics | 41/47 (87) | 260/404 (64) | 0.002 | | |
| Daily dose of loop diuretics (mg) | 80 (40–250) | 40 (0–80) | <0.0001 | | |
| Atrial fibrillation | 27 (56) | 154 (37) | 0.009 | 1.5 (0.6–3.3) | 0.37 |
| Haemoglobin (g/dL) | 11.9 ± 1.8 | 12.3 ± 2.3 | 0.21 | | |
| Glomerular filtration rate (mL/min) | 58 ± 30 | 73 ± 40 | 0.02 | 0.99 (0.98–1.01) | 0.41 |
| Elevated ALT and/or AST | 11/38 (29) | 62/355 (18) | 0.08 | | |
| Elevated GGT and/or ALP | 25/38 (26) | 164/359 (46) | 0.02 | | |
| Total bilirubin (μmol/L) | 27.3 ± 24.0 | 14.6 ± 9.1 | <0.0001 | | |
| Prothrombin time | 62 ± 19 | 75 ± 19 | <0.0001 | 0.98 (0.96–0.99) | 0.008 |
| Left ventricular ejection fraction | 54 ± 9 | 58 ± 9 | 0.005 | | |
| RV basal diameter (mm) | 54 ± 8 | 47 ± 12 | 0.001 | | |
| Moderate/severe RV dilatation | 33 (69) | 212/402 (53) | 0.04 | 1.38 (0.65–2.94) | 0.40 |
| TAPSE (mm) | 17 ± 6 | 20 ± 7 | 0.01 | | |
| Peak systolic annular velocity S' (cm/s) | 10.7 ± 3.3 | 12.1 ± 4.1 | 0.07 | | |
| Moderate/severe RV dysfunction | 16 (33) | 60/398 (15) | 0.002 | 2.6 (1.2–5.8) | 0.02 |
| Tricuspid annulus diameter in apical four-chamber view | 46 ± 8 | 44 ± 9 | 0.29 | | |
| Systolic pulmonary artery pressure (mmHg) | 45 ± 10 | 40 ± 11 | 0.01 | | |
| Functional aetiology of the tricuspid regurgitation | 33 (69) | 196 (47) | 0.004 | 0.7 (0.3–1.8) | 0.88 |
| Logistic EuroSCORE | 7.6 (4.4–15.9) | 5 (2.8–8.6) | <0.0001 | | |
| EuroSCORE II | 3.7 (2.5–6.7) | 2.5 (1.3–5) | 0.004 | | |
| STS predicted risk of mortality | 4.3 (2.4–7.1) | 2.9 (1.6–5.2) | 0.005 | | |
| Charlson comorbidity index | 4 (3–6) | 3 (1–4) | <0.0001 | | |
| Charlson comorbidity index ≥ 2 | 43 (90) | 280 (67) | 0.001 | | |
| Urgent surgery | 9 (19) | 93 (22) | 0.58 | | |
| Tricuspid valve replacement | 33 (69) | 240 (57) | 0.13 | | |

ALP, alkaline phosphatases; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase; NYHA, New York Heart Association; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; STS, Society of Thoracic Surgery.

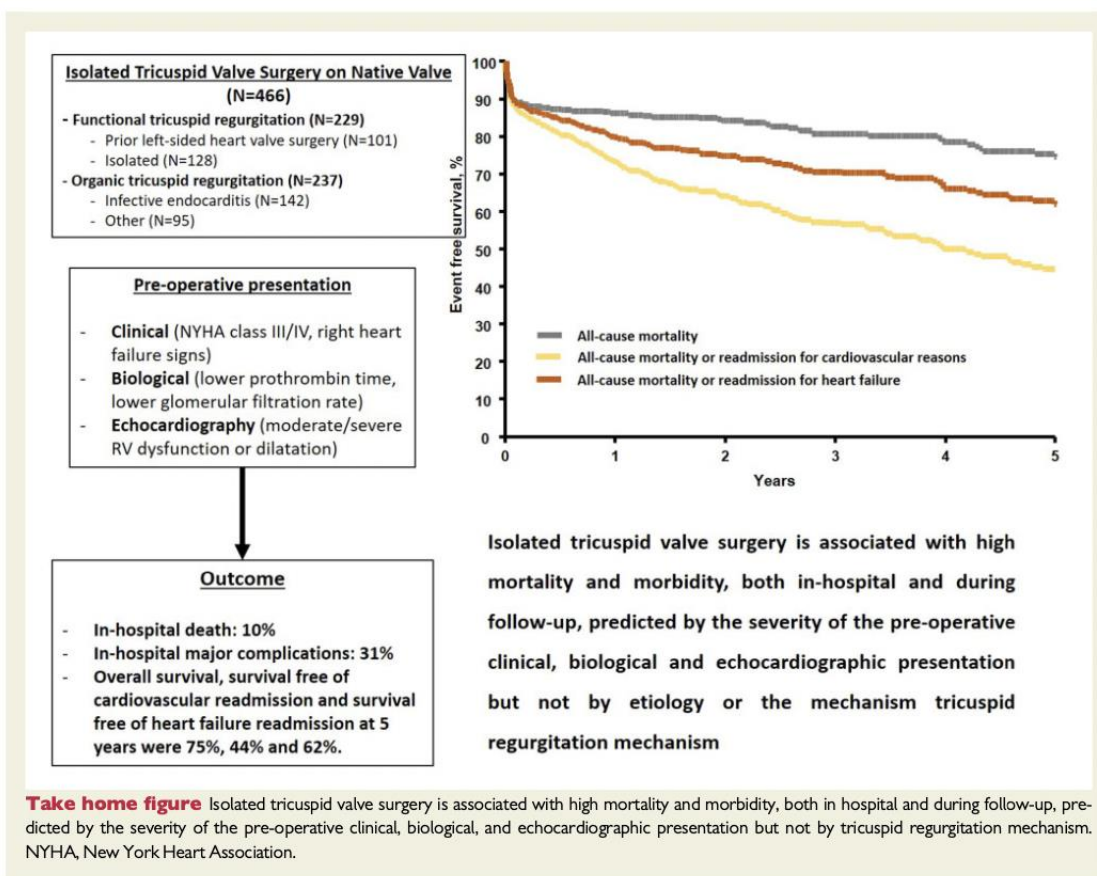


surgery in 46% and for isolated functional TR in 54%) and in the other half for organic TR (due to infective endocarditis in 60%); (iv) patients were often referred late in the course of the disease with severe symptoms, frequent impairment of liver and kidney functions, and advanced RV consequences; (v) in-hospital mortality and CV events rates were high with long in-hospital lengths of stay; (vi) although in-hospital mortality and morbidity were significantly worse for functional TR than for organic TR, outcome was more related to the severity of the clinical presentation observed in this subgroup than to TR mechanism or aetiology, which portended limited independent prognostic information; and (vii) mid-term outcomes showed substantial rates of death and readmissions also predicted by the severity of the presentation.

Using the PMSI, a mandatory French administrative database, we were able to identify all TV surgeries performed at 12 French tertiary centres over the past 10 years. Based on our previous nationwide study, these 12 centres accounted for 40% of all TV surgery performed in France.¹² The number of TV surgeries increased over time, from less than 300 in 2007 to close to 800 in 2017, but remained far from the number of aortic valve replacements (>10 000/year) or mitral valve interventions (>6000/year) currently performed in France.²⁰ The vast majority of TV interventions consisted of a TV repair performed concomitant with another procedure, mostly with left-sided valve surgery. Both the American College of Cardiology/American Heart Association and the European Society of Cardiology guidelines recommend performance of a combined TV surgery during left-sided valve surgery in case of moderate–severe TR or TV annulus diameter >40 mm.^{21,22} Assuming that the number of mitral valve surgeries has remained stable during the study period, the present study suggests a wider adoption of these recommendations but also suggests that a substantial number of patients with qualifying indication for combined TV interventions remain neglected.

Recent epidemiological studies have shown that TR prevalence was similar to that of aortic stenosis and mitral regurgitation.^{2,23} In the community, prevalence of significant—moderate or severe—TR was estimated to be as high as 0.55% and up to 3% after 75 years.¹ Despite its high prevalence and its strong association with poor outcomes,^{3–5,9,24,25} TR is often left untreated. Intervention (surgery or transcatheter) is the only curative treatment for severe TR and medical therapy should be considered as only palliative. The magnitude of the gap between the estimated TR prevalence and the observed rates of interventions for TR (~40/year ITVS in the present study, 100–120/year at the nationwide level) is thus striking. Management of isolated severe TR often relies on two contradictory beliefs: one that severe TR is a benign condition and the other that ITVS is a high-risk surgery. In clinical practice, patients are often initially not referred for an intervention arguing that it is too early until they are deemed at too high risk and denied surgery due to a too advanced disease. The literature is fairly consistent showing that in-hospital mortality of ITVS is ~10% and has remained stable over time.^{10,12} The present study confirms these findings with a similar 10% in-hospital mortality rate. In addition, we also showed that mid-term mortality and CV event rates were substantial. At 5 years, one quarter of patients are dead, more than half are either dead or admitted for CV reasons, and one-third dead or admitted for HF.

Importantly, mortality rates are highly variable according to patients' characteristics. In contrast to previous studies including ours, we were able to obtain much more details regarding TR aetiology and clinical presentation including laboratory and echocardiographic results and to evaluate the determinants of outcomes after ITVS. Most patients presented with advanced disease, severe CHF, kidney, liver, or RV dilatation/dysfunction. It is worth noting that the Charlson index in the present study was more than twice as high as the Charlson index observed in patients referred for transcatheter aortic valve implantation in the early days.²⁰ Functional TR accounted



in France insuring generalizability of our findings. Second, in contrast to previously published studies using administrative databases, which lack granularity, and with limited follow-up, we were able to provide in-depth assessment of patients' presentation including laboratories and echocardiographic results. Such level of details, as well as our sample size, unique in the literature, enabled us to identify the mechanism of TR and determinants of in-hospital and mid-term outcomes. Third, echocardiographic evaluation relied on centres' evaluation and not on a centralized laboratory. Assessment of RV dilatation or dysfunction was based on an integrative approach performed by each centre, and we could not provide specific thresholds for RV dilatation or dysfunction that could have guided surgical indications. Nevertheless, as an internal validation, RV basal diameter was markedly different between patients classified as presenting a moderate/severe RV dilatation compared to those who did not (54 ± 8 vs. 42 ± 10 mm, $P < 0.0001$), and TAPSE and Doppler tissue imaging peak systolic annular velocity S' were markedly different between patients who presented with moderate/severe RV dysfunction compared to those who did not (13 ± 4 vs. 21 ± 6 mm and 7.6 ± 1.5 vs. 12.4 ± 3.2 cm/s, respectively, both $P < 0.0001$). Fourth, as a retrospective study, not all laboratory and echocardiographic parameters

could be collected for all patients. However, main parameters of interest were available in the vast majority of our population. In addition, we did not collect information regarding right catheterization performance and results. It is probable that patients with high systolic pulmonary pressure would be those with the highest event rates and those who might benefit the less from the intervention. Systolic pulmonary artery pressure measured using echocardiography was of borderline statistical significance but was only available in 274 patients (59%) and may be underestimated in patients with severe/laminar TR. Fifth, TA diameter was not predictive of outcome in the overall population and in the subgroup of patients with functional TR. These findings should be interpreted in light of the baseline characteristics of our population as most patients presented with significant TA enlargement while prognostic value of TA diameter has been shown in less selected patients.²⁶ Sixth, assessment of TR aetiology and mechanism may be challenging in few patients in particular in the presence of permanent pacemaker. However, our results remained unchanged after exclusion of the 104 patients with pacemaker. Finally, we could only infer that the high mortality and morbidity observed in the present study are related to a late surgical referral and that an earlier surgery would have improved the outcome. However, the limited

impact of TR aetiology on in-hospital and mid-term outcomes compared to the weight of the clinical presentation including laboratory and echocardiographic TR consequences strongly supports this hypothesis. Future randomized controlled trials will evaluate the impact of TR correction on outcome and identify patients who will benefit the most of an intervention.

With regard to clinical implications, the present study highlights the need to prevent the occurrence of late TR after left-sided surgery and the importance of timely referral for TV interventions. As mentioned above, although debated, a more aggressive approach on TV intervention at the time of the left-sided surgery should be advocated to prevent the occurrence of late TR and the need for a repeat intervention seldom performed in real life. The high mortality and morbidity rates observed during ITVS for functional TR after left-sided valve surgery should be regarded as a strong incentive for the performance of concomitant TV surgery when indicated. On the other hand, timely referral for the intervention of patients with severe TR is also critical. Current guidelines^{21,22} are quite vague with no Class I recommendation for intervention, but as for other valvular diseases, patients with severe TR should be referred earlier in the course of the disease avoiding the performance of TV intervention in patients with advanced disease at a desperate stage. In this regard, evaluation of RV size and function, often challenging especially in the setting of severe TR, should be refined. It is worth noting that we have illuminated only part of the problem as many patients with severe TR are often conservatively managed and denied any intervention. Thus, mortality and morbidity related to TR are likely underestimated. In a near future, the development of transcatheter therapies may represent an alternative to surgery and will further push for an early intervention if proved to be safe and efficient. As for functional mitral regurgitation,^{27,28} patients' selection will be critical and 'early' intervention before the occurrence of irreversible consequences will be key. Impact of TR correction on outcome has been recently disputed.^{29,30} A later referral in surgical than transcatheter series may explain the contradictory results reported in the literature. Compared to our population, patients who underwent a transcatheter intervention were older (77 years), the vast majority presented with functional TR in AF (90% and 83%, respectively) with concomitant 3+/4+ mitral regurgitation while pulmonary pressure was similar. Patients referred for surgery were of similar age, similarly symptomatic than our functional TR subset but presented with higher systolic pulmonary pressures.

Conclusion

In this large multicentre series, we collected all cases of TV surgery performed at 12 French tertiary centres between 1 January 2007 and 31 December 2017 and assessed the clinical presentation and immediate and mid-term outcomes of ITVS. Compared to aortic or mitral valve surgery, tricuspid surgery remained uncommon and mainly performed at the time of left-sided surgery. Isolated TV surgery was rare, associated with high mortality and morbidity, both in hospital and during follow-up, predicted by the severity of the clinical presentation, while TR mechanism/aetiology had limited impact. Our results suggest adopting a more aggressive approach for TV intervention, either at the time of left-sided surgery to prevent the occurrence of

late TR, or intervening earlier in the course of the disease for patients with severe isolated TR, whatever the mechanism, before the occurrence of advanced/irreversible consequences and intractable HF.

Data sharing

Data sharing with qualified researchers may be considered after submission of a proposal to Docteur Dreyfus.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: B.I. received consultant fees from Edwards Lifesciences. J.-F.O. received consultant fees for Abbott Vascular, Carmat, Delacroix-Chevalier, Landanger, Medtronic, and Sorin. D.M.-Z. received consultant fees from Edwards Lifesciences. All other authors declared no conflict of interest.

References

1. Topilsky Y, Maltais S, Medina Inojosa J, Oguz D, Michelena H, Maalouf J, Mahoney DW, Enriquez-Sarano M. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging* 2019;**12**:433–442.
2. Stuge O, Liddicoat J. Emerging opportunities for cardiac surgeons within structural heart disease. *J Thorac Cardiovasc Surg* 2006;**132**:1258–1261.
3. Benfari G, Antoine C, Miller WL, Thapa P, Topilsky Y, Rossi A, Michelena HI, Pislaru S, Enriquez-Sarano M. Excess mortality associated with functional tricuspid regurgitation complicating heart failure with reduced ejection fraction. *Circulation* 2019;**140**:196–206.
4. Messika-Zeitoun D, Thomson H, Bellamy M, Scott C, Tribouilloy C, Dearani J, Tajik AJ, Schaff H, Enriquez-Sarano M. Medical and surgical outcome of tricuspid regurgitation caused by flail leaflets. *J Thorac Cardiovasc Surg* 2004;**128**:296–302.
5. Topilsky Y, Inojosa JM, Benfari G, Vaturi O, Maltais S, Michelena H, Mankad S, Enriquez-Sarano M. Clinical presentation and outcome of tricuspid regurgitation in patients with systolic dysfunction. *Eur Heart J* 2018;**39**:3584–3592.
6. Koelling TM, Aaronson KD, Cody RJ, Bach DS, Armstrong WF. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. *Am Heart J* 2002;**144**:524–529.
7. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* 2004;**43**:405–409.
8. Neuhold S, Huelsmann M, Pernicka E, Graf A, Bonderman D, Adlbrecht C, Binder T, Maurer G, Pacher R, Mascherbauer J. Impact of tricuspid regurgitation on survival in patients with chronic heart failure: unexpected findings of a long-term observational study. *Eur Heart J* 2013;**34**:844–852.
9. Wang N, Fulcher J, Abeyesuriya N, McGrady M, Wilcox I, Celermajor D, Lal S. Tricuspid regurgitation is associated with increased mortality independent of pulmonary pressures and right heart failure: a systematic review and meta-analysis. *Eur Heart J* 2019;**40**:476–484.
10. Zack CJ, Fender EA, Chandrashekar P, Reddy YNV, Bennett CE, Stulak JM, Miller VM, Nishimura RA. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol* 2017;**70**:2953–2960.
11. De Meester P, Van De Bruaene A, Voigt JU, Herijgers P, Budts W. Outcome and determinants of prognosis in patients undergoing isolated tricuspid valve surgery: retrospective single center analysis. *Int J Cardiol* 2014;**175**:333–339.
12. Dreyfus J, Ghalem N, Garbarz E, Cimadevilla C, Nataf P, Vahanian A, Caranhac G, Messika-Zeitoun D. Timing of referral of patients with severe isolated tricuspid valve regurgitation to surgeons (from a French Nationwide Database). *Am J Cardiol* 2018;**122**:323–326.
13. PMSI. Programme de médicalisation des systèmes d'informations (PMSI). 2012. <https://drees.solidarites-sante.gouv.fr/etudes-et-statistiques/publications/documents-de-travail/serie-statistiques/article/redressements-du-programme-de-medicalisation-des-systemes-d-informations-pmsi>.
14. CCAM. Classification commune des actes médicaux (CCAM). 2012. <https://www.ameli.fr/etablissement/exercice-professionnel/nomenclatures-et-codage/codage-actes-medicaux-ccam>.
15. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;**16**:9–13.

16. O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2— isolated valve surgery. *Ann Thorac Surg* 2009;**88**(1 Suppl):S23–S42.
17. Dreyfus J, Durand-Viel G, Raffoul R, Alkhoder S, Hvass U, Radu C, Al-Attar N, Ghodbhane W, Attias D, Nataf P, Vahanian A, Messika-Zeitoun D. Comparison of 2-dimensional, 3-dimensional, and surgical measurements of the tricuspid annulus size: clinical implications. *Circ Cardiovasc Imaging* 2015;**8**:e003241.
18. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, Little SH, Shah DJ, Sherman S, Thavendiranathan P, Thomas JD, Weissman NJ. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;**30**:303–371.
19. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;**16**:777–802.
20. Nguyen V, Michel M, Eltchaninoff H, Gilard M, Dindorf C, Iung B, Mossialos E, Cribier A, Vahanian A, Chevreul K, Messika-Zeitoun D. Implementation of transcatheter aortic valve replacement in France. *J Am Coll Cardiol* 2018;**71**: 1614–1627.
21. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease: the Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2017;**38**:2739–2791.
22. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM, Thompson A. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the Management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017;**135**:e1159–e1195.
23. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;**368**: 1005–1011.
24. Prihadi EA, van der Bijl P, Gursoy E, Abou R, Mara Vollema E, Hahn RT, Stone GW, Leon MB, Ajmone Marsan N, Delgado V, Bax JJ. Development of significant tricuspid regurgitation over time and prognostic implications: new insights into natural history. *Eur Heart J* 2018;**39**:3574–3581.
25. Topilsky Y, Nkomo VT, Vatury O, Michelena HI, Letourneau T, Suri RM, Pislaru S, Park S, Mahoney DW, Biner S, Enriquez-Sarano M. Clinical outcome of isolated tricuspid regurgitation. *JACC Cardiovasc Imaging* 2014;**7**:1185–1194.
26. Dietz MF, Prihadi EA, van der Bijl P, Goedemans L, Mertens BJA, Gursoy E, van Genderen OS, Ajmone Marsan N, Delgado V, Bax JJ. Prognostic implications of right ventricular remodeling and function in patients with significant secondary tricuspid regurgitation. *Circulation* 2019;**140**:836–845.
27. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefevre T, Piot C, Rouleau F, Carrie D, Nejari M, Ohlmann P, Leclercq F, Saint Etienne C, Teiger E, Leroux L, Karam N, Michel N, Gilard M, Donal E, Trochu JN, Cormier B, Armoiry X, Boutitie F, Maucort-Boulch D, Barnel C, Samson G, Guerin P, Vahanian A, Mewton N. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018;**379**:2297–2306.
28. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembok IJ, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;**379**:2307–2318.
29. Axtell AL, Bhambhani V, Moonsamy P, Healy EW, Picard MH, Sundt TM 3rd, Wasfy JH. Surgery does not improve survival in patients with isolated severe tricuspid regurgitation. *J Am Coll Cardiol* 2019;**74**:715–725.
30. Taramasso M, Benfari G, van der Bijl P, Alessandrini H, Attinger-Toller A, Biasco L, Lurz P, Braun D, Brochet E, Connelly KA, de Bruijn S, Denti P, Deuschl F, Estevez-Loureiro R, Fam N, Frerker C, Gavazzoni M, Hausleiter JR, Ho E, Juliard JM, Kaple R, Besler C, Kodali S, Kreidel F, Kuck KH, Latib A, Lauten A, Monivas V, Mehr M, Muntane-Carol G, Nazif T, Nickening G, Pedrazzini G, Philippon F, Pozzoli A, Praz F, Puri R, Rodes-Cabau J, Schafer U, Schofer J, Sievert H, Tang GH, Thiele H, Topilsky Y, Rommel KP, Delgado V, Vahanian A, Von Bardeleben RS, Webb JG, Weber M, Windecker S, Winkel M, Zuber M, Leon MB, Hahn RT, Bax JJ, Enriquez-Sarano M, Maisano F. Transcatheter versus medical treatment of symptomatic severe tricuspid regurgitation. *J Am Coll Cardiol* 2019;**74**:2998–3008.

Article 7

TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery

Dreyfus J, Audureau E, Bohbot Y, Coisne A, Lavie-Badie Y, Bouchery M, Flagiello M, Bazire B, Eggenspieler F, Viau F, Riant E, Mbaki Y, Eyharts D, Senage T, Modine T, Nicol M, Doguet F, Nguyen V, Le Tourneau T, Tribouilloy C, Donal E, Tomasi J, Habib G, Selton-Suty C, Raffoul R, Iung B, Obadia JF, Messika-Zeitoun D

Eur Heart J. 2022 Feb 12;43(7):654-662

Article 7 : TRI-SCORE : un nouveau score de risque pour prédire la mortalité hospitalière après chirurgie valvulaire tricuspide isolée

La chirurgie isolée de la VT n'est que très rarement pratiquée car considérée à haut risque avec une mortalité post-opératoire élevée, estimée aux alentours de 10% dans la littérature^{69,80}. Pour autant, nous avons montré que la mortalité post-opératoire après cette intervention était très variable d'un patient à l'autre et qu'elle était prédite par la présentation clinique, biologique et échocardiographique pré-opératoire du patient⁶⁹. Néanmoins, il n'existe aucun score de risque permettant de prédire ce risque à l'échelon individuel sachant que l'EuroSCORE et l'EuroSCORE II n'ont pas été développés pour cette intervention et qu'il n'y a pas de score de la Société des Chirurgiens Thoraciques (STS) spécifique à la VT⁸¹⁻⁸³.

L'objectif de cette étude était de développer un score de risque spécifiquement dédié à la prédiction à l'échelon individuel du risque de mortalité post-opératoire intra-hospitalière après chirurgie isolée de la VT.

A partir des 466 patients (60±16 ans, 49% de femmes, 49% avec IT fonctionnelle) consécutifs opérés d'une chirurgie isolée de la VT pour IT sévère non congénitale sur valve native dans 12 centres Français entre 2007 et 2017, dont le taux de mortalité intra-hospitalière était de 10% et pour lesquels des données cliniques, biologiques et échocardiographiques détaillées ont été collectées, nous avons développé et validé un score de risque pour prédire la mortalité hospitalière à l'aide d'une régression logistique multivariée et d'un bootstrap avec 1000 ré-échantillonnages.

Le score de risque final, nommé TRI-SCORE, incluait 8 paramètres, 4 cliniques (âge ≥70 ans, classe fonctionnelle NYHA III ou IV, signes cliniques d'IC droite (turgescence jugulaire, ascite et/ou œdème des membres inférieurs), dose quotidienne de furosémide ≥125 mg), 2 biologiques (DFG <30 ml/min, taux de bilirubine totale élevé (au-dessus du seuil pathologique du laboratoire)) et 2 échocardiographiques (FEVG <60%, dysfonction VD significative (TAPSE <17mm et/ou pic de vélocité de l'onde S' à l'anneau tricuspide en Doppler tissulaire <9.5cm/sec et/ou évaluation visuelle)). Le score variait de 0 à 12 points, chaque paramètre étant associé à un nombre de points arrondi en fonction de son odd-ratio. (Figure 39).

| Risk factors (final model from multivariate analysis) | Scoring |
|---|-----------|
| Age \geq 70 years | 1 |
| NYHA functional class III-IV | 1 |
| Right-sided heart failure signs | 2 |
| Daily dose of furosemide \geq 125mg | 2 |
| Glomerular filtration rate $<$ 30 ml/min | 2 |
| Elevated total bilirubin | 2 |
| Left ventricular ejection fraction $<$ 60% | 1 |
| Moderate/severe right ventricular dysfunction | 1 |
| Total | 12 |

Figure 39. Facteurs de risque et nombre de points correspondants dans le TRI-SCORE pour prédire la mortalité hospitalière après chirurgie isolée de la valve tricuspide
 NYHA : New York Heart Association

Les taux de mortalité hospitalière observés et les risques prédits augmentaient avec le nombre de points, allant respectivement de 0% et 1% pour 0 point à 60% et 65% pour 9 points ou plus. (Figure 40).

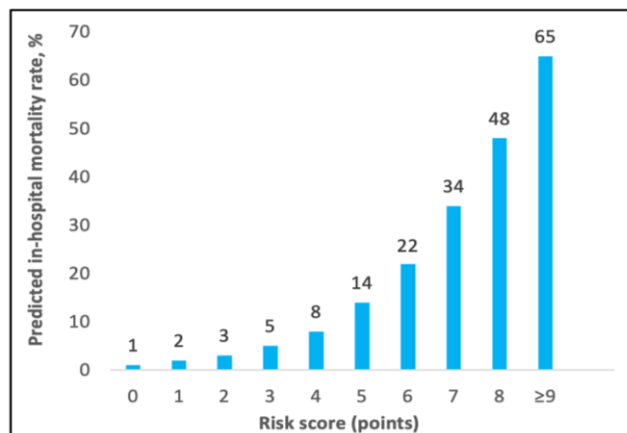


Figure 40. Taux de mortalité hospitalière après chirurgie isolée sur la valve tricuspide prédit en fonction du TRI-SCORE

Le TRI-SCORE était associé à une très bonne performance de discrimination avec une aire sous la courbe (AUC) de 81% (75% après correction des biais), bien supérieure à celles de l'EuroSCORE (67%) et de l'EuroSCORE II (63%) (Figure 41).

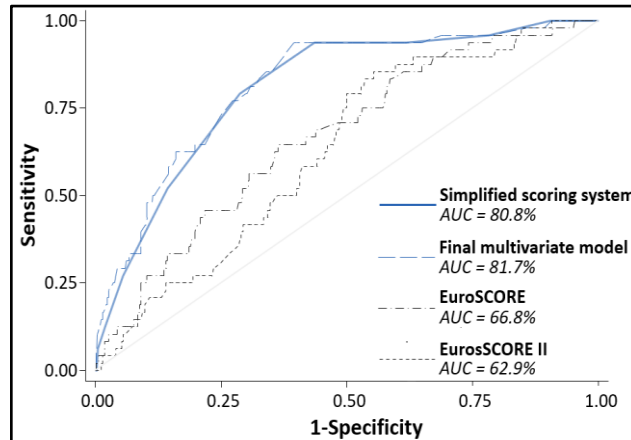


Figure 41. Courbes sensibilité/spécificité pour le score de risque final multivarié, le score de risque simplifié (TRI-SCORE), l'EuroSCORE et l'EuroSCORE II pour prédire la mortalité hospitalière après chirurgie isolée sur la valve tricuspide

AUC : aire sous la courbe

Sa calibration était appropriée lorsque l'on comparait le risque prédit et la mortalité intra-hospitalière observée pour les probabilités allant jusqu'à 50%, avec une discrète surestimation du modèle pour les plus fortes probabilités (Figure 42).

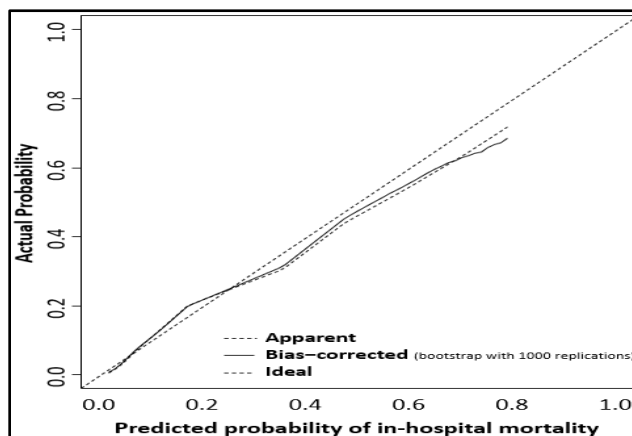


Figure 42. Calibration du score de risque final : probabilité prédite par le TRI-SCORE vs. probabilité réelle de mortalité hospitalière après chirurgie isolée sur la valve tricuspide

Le score moyen de la cohorte était de 3.5 ± 2.1 points. Bien que la mortalité intra-hospitalière était plus élevée pour les IT fonctionnelles que pour les IT organiques, le mécanisme de l'IT n'était pas un facteur prédictif indépendant de mortalité intra-hospitalière. En effet, le plus mauvais pronostic des patients avec IT fonctionnelle était lié à une prise en charge plus tardive avec une présentation pré-opératoire plus grave traduite par un score significativement plus élevé (4.3 ± 2.0 points) que celui des patients avec IT organique (2.7 ± 1.9 points, $P < 0.001$), sachant qu'à nombre de points égal, la mortalité était la même quel que soit le mécanisme (Figure 43).

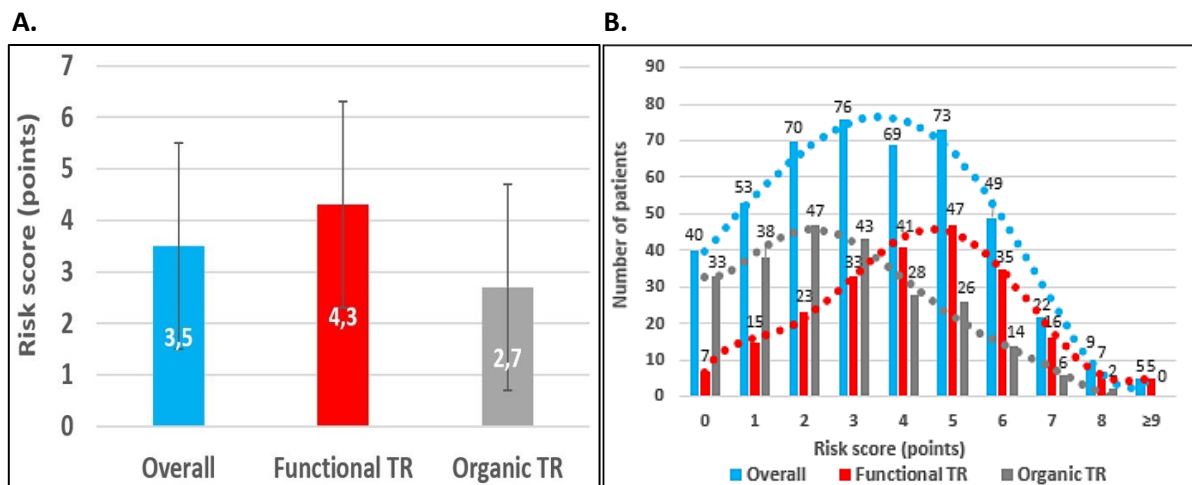


Figure 43. Valeur du TRI-SCORE et distribution dans l'ensemble de la cohorte et en fonction du mécanisme de l'insuffisance tricuspide

A. Histogrammes du nombre de points, avec les valeurs minimales et maximales

B. Nombre de patients présentant chaque valeur de score et tendances

Bien que le score ait été développé pour prédire la mortalité intra-hospitalière, il était également significativement associé aux complications post-opératoires graves (incluant mortalité, choc, tamponnade, insuffisance rénale aiguë nécessitant la dialyse ou ventilation mécanique >72 heures) (AUC =0.71) et à la mortalité à 1 an (AUC =0.78).

Dans ce registre exhaustif de « vraie vie », la moitié des patients (51%) étaient opérés avec un score bas (entre 0 et 3) et avaient un excellent pronostic (taux de mortalité hospitalière $\leq 4\%$). A l'inverse, l'autre moitié (49%) était opérée à un stade plus évolué de la maladie, ce qui avait un impact négatif sur le pronostic puisque les patients avec un score ≥ 4 avaient un taux de mortalité hospitalière $\geq 10\%$ et ceux avec un score ≥ 6 un taux $\geq 25\%$ (Figure 44).

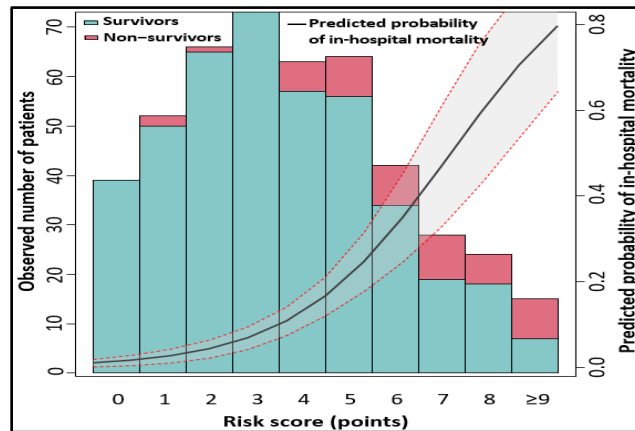


Figure 44. Distribution du nombre de patients et probabilité prédite de mortalité hospitalière après chirurgie isolée sur la valve tricuspide en fonction du TRI-SCORE

Les histogrammes représentent la distribution du nombre de patients pour chaque valeur du TRI-SCORE

La courbe représente la probabilité prédite de mortalité hospitalière en fonction du TRI-SCORE

Nous avons développé le premier score de risque spécifiquement dédié à la prédiction à l'échelon individuel du risque de mortalité hospitalière après chirurgie isolée de la VT pour IT sévère sur valve native, indépendamment du mécanisme de l'IT, avec une très bonne discrimination et calibration. Ce score, le TRI-SCORE, basé sur 8 paramètres simples à recueillir qui traduisent le retentissement de l'IT sur le VD et les autres organes, va permettre d'informer les patients et les médecins sur le risque de cette intervention et contribuer à la discussion thérapeutique médico-chirurgicale chez les patients ayant une IT sévère. Afin de faciliter son utilisation en routine par les cardiologues et les chirurgiens cardiaques, un calculateur en ligne est accessible gratuitement (www.tri-score.com).

TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery

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Aims

Isolated tricuspid valve surgery (ITVS) is considered to be a high-risk procedure, but in-hospital mortality is markedly variable. This study sought to develop a dedicated risk score model to predict the outcome of patients after ITVS for severe tricuspid regurgitation (TR).

Methods and results

All consecutive adult patients who underwent ITVS for severe non-congenital TR at 12 French centres between 2007 and 2017 were included. We identified 466 patients (60 ± 16 years, 49% female, functional TR in 49%). In-hospital mortality rate was 10%. We derived and internally validated a scoring system to predict in-hospital mortality using multivariable logistic regression and bootstrapping with 1000 re-samples. The final risk score ranged from 0 to 12 points and included eight parameters: age ≥70 years, New York Heart Association Class III–IV, right-sided

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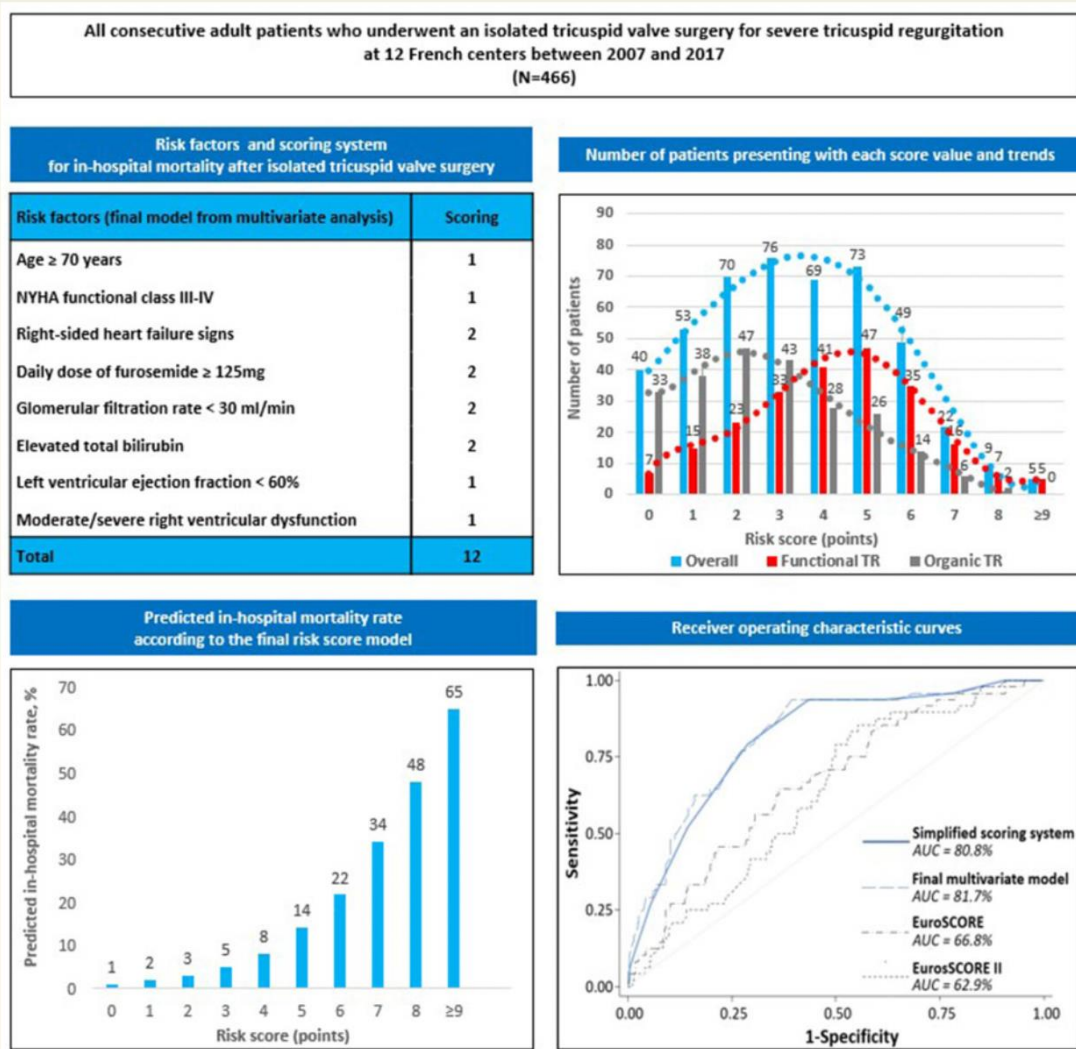
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heart failure signs, daily dose of furosemide ≥ 125 mg, glomerular filtration rate < 30 mL/min, elevated bilirubin, left ventricular ejection fraction $< 60\%$, and moderate/severe right ventricular dysfunction. Tricuspid regurgitation mechanism was not an independent predictor of outcome. Observed and predicted in-hospital mortality rates increased from 0% to 60% and from 1% to 65%, respectively, as the score increased from 0 up to ≥ 9 points. Apparent and bias-corrected areas under the receiver operating characteristic curves were 0.81 and 0.75, respectively, much higher than the logistic EuroSCORE (0.67) or EuroSCORE II (0.63).

Conclusion

We propose TRI-SCORE as a dedicated risk score model based on eight easy to ascertain parameters to inform patients and physicians regarding the risk of ITVS and guide the clinical decision-making process of patients with severe TR, especially as transcatheter therapies are emerging (www.tri-score.com).

Graphical Abstract



TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. AUC: area under the curve; TR: tricuspid regurgitation.

Keywords

Risk score • Tricuspid regurgitation • Surgery • Outcome

Introduction

In the community, prevalence of significant—moderate or severe—tricuspid regurgitation (TR) is estimated to be as high as 0.55% and up to 3% after 75 years, a prevalence that is similar to that of aortic stenosis or mitral regurgitation.¹ Epidemiological studies suggest that moderate or severe TR affects over 1.6 million individuals in the USA¹ and is associated with a twofold increased cardiac mortality that persists after adjustment for potential confounders.^{2,3}

Despite its high prevalence and its association with a dismal prognosis, TR remains often conservatively managed and the number of tricuspid valve (TV) surgeries, mostly performed at the time of mitral valve surgery, is remarkably low.^{4–7} If the management of significant TR at the time of mitral surgery is relatively well codified, the management of patients with isolated—organic or functional—TR is less established.^{8,9} Isolated tricuspid valve surgery (ITVS) is rarely performed (few hundred interventions yearly in the USA)^{4–6} based upon its reported high mortality rates. If the literature is consistent showing that overall in-hospital mortality is ~10% both in the USA and in Europe, we have previously shown that it was markedly variable and that it was predicted by the severity of the clinical presentation while TR mechanism/aetiology had a limited impact.⁴

With the recent development of transcatheter interventions, there is a critical need to accurately predict in-hospital mortality rates for ITVS that could be used in routine practice and support clinical decisions. Both the Society of Thoracic Surgeons (STS) cardiac surgery risk model and the logistic EuroSCORE/EuroSCORE II were not designed to predict outcomes of this type of rare interventions. There have been few attempts to develop a specific risk score model for ITVS,¹⁰ but so far an accurate and dedicated risk score model capturing main parameters of interest in the setting of TR is cruelly lacking. In particular, no score has integrated liver function or right ventricular (RV) consequences, which are main prognostic factors in TR, in a risk score model for ITVS.

Relying on a multicentre consecutive cohort of patients who underwent ITVS for severe TR at 12 French tertiary centres, we aimed to develop a dedicated risk score model to accurately predict the outcome of patients after ITVS.

Methods

Study design

Using the local Programme de Médicalisation des Systèmes d'Information (PMSI) database,¹¹ among 5661 consecutive cases of TV surgery performed in adult patients at 12 tertiary French centres between 1 January 2007 and 31 December 2017, we identified 466 patients who underwent an ITVS on native valve for severe non-congenital TR. The design of the study has been previously reported.⁴ Clinical information and immediate and mid-term outcome were retrospectively collected locally at each centre. Right-sided heart failure signs were defined as severe jugular venous distention, ascites, and/or marked peripheral oedema. Tricuspid regurgitation mechanism was classified as functional (no intrinsic TV disease) or organic (due to abnormalities of the tricuspid leaflets or chordae). Glomerular filtration rate was calculated using the Cockcroft–Gault formula according to sex. Left ventricular (LV) ejection fraction was measured visually or using the biplane method of discs (modified Simpson's rule). Right ventricular size was visually assessed as normal,

mildly, moderately, or severely enlarged. Right ventricular function was semi-quantitatively assessed using an integrative multi-parametric approach, as recommended.^{12–14} Moderate/severe RV dysfunction was defined by a tricuspid annular plane systolic excursion (TAPSE) <17 mm and/or a Doppler tissue imaging peak systolic annular velocity S' <9.5 cm/s and/or a markedly reduced fractional area change based on visual assessment. Logistic EuroSCORE and EuroSCORE II were calculated.^{15,16} The Charlson index was used to assess patient comorbidities. Urgent surgery was defined as non-elective and within the same hospital admission. Centres were divided into quartiles according to average yearly number of interventions performed. The study was approved by each local institutional review board.

Outcome

In-hospital mortality was defined as death occurring between the intervention and hospital discharge during the same hospital stay. Major post-operative complications were defined as death, shock, tamponade, acute renal failure requiring dialysis, or prolonged (>72 h) mechanical ventilation. One-year mortality was also collected based on hospital chart reviews and telephone interviews with patients or family members.

Statistical analysis and risk score modelling

For risk score development, variables associated at the P -value <0.2 level in univariate logistic regression were entered into multivariate analysis, using a stepwise backward procedure based on the Akaike information criterion (AIC) for variable selection, sequentially removing items until the best final model with the lowest AIC was obtained. For the sake of simplicity of use, continuous variables were dichotomized before incorporation into regression analyses by means of recursive partitioning analysis and/or accounting for clinically relevant thresholds.¹⁷ Regression coefficients of the final model were then considered for use as weights to compute a simplified scoring system, by multiplying and rounding coefficients to their closest integer, following the approach from Cole to determine the optimal multiplier.¹⁸ Model discrimination was evaluated by the area under the receiver operating characteristic curve (AUROC), and calibration by plotting calibration curves to evaluate the concordance between observed and predicted survival probability. Internal validation was performed using 1000 bootstrap re-samples, providing bias-corrected AUROC and calibration curves to estimate and account for the amount of optimism in model discrimination and calibration.¹⁹ To reduce potential bias arising from complete-case analysis, all regression models were performed after missing data imputation using the non-parametric missForest method²⁰ and Rubin's rules.²¹ Additional details are given in [Supplementary material online, Methods](#), regarding the missing data imputation and modelling strategy.

Analyses were performed at the two-tailed P -value <0.05 level, using Stata v16.1 (StataCorp, College Station, TX, USA) for descriptive analyses, and R v4.0.3 (R Foundation for Statistical Computing, Vienna, Austria; packages *party*, *MASS*, *rms*, *missForest*) for missing data imputation and model development and validation.

Results

Study population

The characteristics of the 466 consecutive patients who underwent ITVS on native valve at our 12 tertiary French centres during the 10-year period are presented in [Table 1](#) and [Supplementary material online, Table S1](#). Briefly, the mean age was 60 ± 16 years, 229 patients (49%) were female, and TR mechanism was functional in 229 patients

Table 1 Baseline characteristics overall and according to discharge vital status (raw data only), and univariate logistic regression (with imputed data) for predictors of in-hospital mortality

| Characteristics | Overall (n = 466) | By vital status | | P-value | Univariate | | |
|--|----------------------|-------------------------------|-------------------------------|------------------|---------------|-----------|------------------|
| | | Discharged alive (n = 418) | In-hospital death (n = 48) | | Odds ratio | 95% CI | P-value |
| Age (years) | 60 ± 16 | 59 ± 16 | 68 ± 12 | <0.001 | 1.05 | 1.02–1.07 | <0.001 |
| Age ≥70 years | 141 (30) | 117 (28) | 24 (50) | 0.003 | 2.57 | 1.41–4.71 | 0.003 |
| Female sex | 229 (49) | 205 (49) | 24 (50) | 1.00 | 1.04 | 0.57–1.89 | 0.90 |
| Body mass index (kg/m ²) | 25 ± 5 | 25 ± 5 | 26 ± 6 | 0.66 | 1.02 | 0.96–1.07 | 0.60 |
| Hypertension | 190 (41) | 166 (40) | 24 (50) | 0.22 | 1.52 | 0.83–2.76 | 0.18 |
| Diabetes mellitus | 62 (13) | 56 (13) | 6 (13) | 1.00 | 0.92 | 0.38–2.27 | 0.90 |
| Chronic lung disease | 51 (11) | 43 (10) | 8 (17) | 0.27 | 1.74 | 0.77–3.97 | 0.20 |
| Peripheral vascular disease | 16 (3) | 14 (3) | 2 (4) | 0.68 | 1.25 | 0.28–5.69 | 0.73 |
| Prior stroke | 41 (9) | 38 (9) | 3 (6) | 0.79 | 0.67 | 0.20–2.25 | 0.55 |
| Prior left-sided heart valve surgery | 111 (24) | 95 (23) | 16 (33) | 0.15 | 1.70 | 0.89–3.23 | 0.11 |
| Coronary artery disease | 59 (13) | 50 (12) | 9 (19) | 0.27 | 1.70 | 0.78–3.72 | 0.20 |
| Chronic kidney disease | 154 (33) | 134 (32) | 20 (42) | 0.24 | 1.51 | 0.82–2.78 | 0.19 |
| Permanent pacemaker | 104 (22) | 88 (21) | 16 (33) | 0.08 | 1.88 | 0.98–3.57 | 0.06 |
| Hospitalization for congestive heart failure (<1 year) | 163 (35) | 138 (33) | 25 (52) | 0.01 | 2.21 | 1.21–4.03 | 0.01 |
| Systolic blood pressure (mmHg) | 125 ± 19 | 125 ± 20 | 122 ± 17 | 0.44 | 0.99 | 0.98–1.01 | 0.42 |
| Diastolic blood pressure (mmHg) | 73 ± 13 | 73 ± 13 | 70 ± 14 | 0.21 | 0.98 | 0.95–1.00 | 0.11 |
| NYHA functional Class III–IV | 217 (47) | 184 (44) | 33 (69) | 0.002 | 2.80 | 1.48–5.31 | 0.001 |
| Right-sided heart failure signs | 264 (57) | 223 (53) | 41 (85) | <0.001 | 5.12 | 2.25–11.7 | <0.001 |
| Ascites | 39 (8) | 29 (7) | 10 (21) | 0.003 | 3.53 | 1.60–7.79 | 0.004 |
| Loop diuretics | 301/451 (67) | 260/404 (64) | 41/47 (87) | 0.003 | 3.68 | 1.53–8.86 | 0.001 |
| Daily dose of furosemide (mg) | 40 (0–80) | 40 (0–80) | 80 (40–250) | 0.008 | 1.00 | 1.00–1.00 | <0.001 |
| Daily dose of furosemide ≥125 mg | 67 (15) | 48 (12) | 19 (40) | <0.001 | 5.05 | 2.63–9.69 | <0.001 |
| Atrial fibrillation | 181 (39) | 154 (37) | 27 (56) | 0.01 | 2.20 | 1.20–4.03 | 0.01 |
| Haemoglobin (g/dL) | 12.3 ± 2.3 | 12.3 ± 2.3 | 11.9 ± 1.8 | 0.13 | 0.91 | 0.80–1.05 | 0.19 |
| Glomerular filtration rate (mL/min) | 72 ± 39 | 73 ± 40 | 58 ± 30 | 0.003 | 0.99 | 0.98–1.00 | 0.008 |
| Glomerular filtration rate <30 mL/min | 32/442 (7) | 24/398 (6) | 8/44 (18) | 0.003 | 3.28 | 1.38–7.79 | <0.001 |
| Elevated ALT and/or AST | 73/393 (19) | 62/355 (18) | 11/38 (29) | 0.13 | 1.88 | 0.95–3.73 | 0.08 |
| Elevated GGT and/or ALP | 189/397 (48) | 164/359 (46) | 25/38 (66) | 0.03 | 2.59 | 1.38–4.87 | 0.003 |
| Elevated total bilirubin | 143/389 (37) | 119/352 (34) | 24/37 (65) | <0.001 | 3.78 | 2.03–7.02 | <0.001 |
| Left ventricular ejection fraction (%) | 58 ± 9 | 58 ± 9 | 54 ± 9 | 0.009 | 0.96 | 0.93–0.99 | 0.005 |
| Left ventricular ejection fraction <60% | 199/452 (44) | 169/404 (42) | 30 (63) | 0.01 | 0.38 | 0.19–0.79 | 0.006 |
| Moderate/severe right ventricular dilatation | 245/450 (54) | 212/402 (53) | 33 (69) | 0.05 | 2.08 | 1.10–3.94 | 0.02 |
| TAPSE (mm) | 20 ± 7 | 20 ± 7 | 17 ± 6 | 0.004 | 0.90 | 0.85–0.95 | <0.001 |
| Peak systolic annular velocity S' (cm/s) | 11.9 ± 4.1 | 12.1 ± 4.1 | 10.7 ± 3.3 | 0.04 | 0.83 | 0.74–0.92 | 0.001 |
| Moderate/severe right ventricular dysfunction | 76/446 (17) | 60/398 (15) | 16 (33) | 0.003 | 2.98 | 1.54–5.77 | 0.002 |
| Tricuspid annulus diameter (mm) | 44 ± 9 | 44 ± 8 | 46 ± 8 | 0.30 | 1.04 | 1.00–1.08 | 0.07 |
| Systolic pulmonary artery pressure (mmHg) | 40 ± 11 | 40 ± 11 | 45 ± 10 | 0.01 | 1.05 | 1.02–1.09 | 0.001 |
| Systolic pulmonary artery pressure ≥50 mmHg | 52/274 (19) | 42/247 (17) | 10/27 (37) | 0.02 | 1.93 | 0.80–4.63 | 0.16 |
| Functional aetiology of the tricuspid regurgitation | 229 (49) | 196 (47) | 33 (69) | 0.007 | 2.49 | 1.31–4.73 | 0.004 |
| Logistic EuroSCORE | 5.2 (3.0–9.2) | 5 (2.8–8.6) | 7.6 (4.4–15.9) | 0.01 | 1.05 | 1.02–1.08 | 0.002 |
| EuroSCORE II | 2.7 (1.4–5.0) | 2.5 (1.3–5) | 3.7 (2.5–6.7) | 0.09 | 1.03 | 0.98–1.08 | 0.21 |
| Charlson comorbidity index | 3 (1–4) | 3 (1–4) | 4 (3–6) | <0.001 | 1.29 | 1.14–1.45 | <0.001 |
| Charlson comorbidity index ≥2 | 324 (70) | 281 (67) | 43 (90) | 0.003 | 4.19 | 1.62–10.8 | 0.001 |
| Urgent surgery | 102 (22) | 93 (22) | 9 (19) | 0.71 | 0.81 | 0.38–1.73 | 0.60 |
| Beating heart | 98 (25) | 84 (23) | 14 (37) | 0.10 | 1.57 | 0.81–3.05 | 0.20 |
| Tricuspid valve replacement | 273 (59) | 240 (57) | 33 (69) | 0.18 | 1.63 | 0.86–3.10 | 0.13 |
| Major post-operative complications | 145 (31) | — | — | — | — | — | — |
| Mortality at 1 year | 55 (12) | — | — | — | — | — | — |

Values are mean ± standard deviation, n (%), or median (interquartile range); bolded results are statistically significant at the P-value <0.05 level.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion.

Table 2 Risk factors for in-hospital mortality: final model from multivariate analysis and scoring system

| Risk factors | Odds ratio | 95% CI | Regression coefficient | Final scoring |
|---|------------|-----------|------------------------|---------------|
| Age ≥70 years | 1.65 | 0.84–3.21 | 0.50 | 1 |
| NYHA functional Class III–IV | 1.76 | 0.88–3.55 | 0.57 | 1 |
| Right-sided heart failure signs | 2.62 | 1.08–6.35 | 0.96 | 2 |
| Daily dose of furosemide ≥125 mg | 2.25 | 1.08–4.68 | 0.81 | 2 |
| Glomerular filtration rate <30 mL/min | 2.47 | 0.92–6.62 | 0.90 | 2 |
| Elevated total bilirubin | 2.89 | 1.48–5.63 | 1.06 | 2 |
| Left ventricular ejection fraction <60% | 1.97 | 0.91–4.28 | 0.68 | 1 |
| Moderate/severe right ventricular dysfunction | 1.93 | 0.93–4.01 | 0.66 | 1 |
| Total | | | | 12 |

CI, confidence interval; NYHA, New York Heart Association.

Table 3 Predicted vs. observed in-hospital mortality rates according to the risk score value

| Score | Number of patients | Predicted in-hospital mortality (%) | Observed in-hospital mortality (%) |
|-------|--------------------|-------------------------------------|------------------------------------|
| 0 | 40 | 1 | 0 |
| 1 | 53 | 2 | 4 |
| 2 | 70 | 3 | 1 |
| 3 | 76 | 5 | 0 |
| 4 | 69 | 8 | 10 |
| 5 | 73 | 14 | 18 |
| 6 | 49 | 22 | 25 |
| 7 | 22 | 34 | 32 |
| 8 | 9 | 48 | 33 |
| ≥9 | 5 | 65 | 60 |

(49%) and organic in 237 patients (51%). Overall, in-hospital mortality rate was 10% ($n = 48$), major post-operative complications rate was 31% ($n = 145$), and 1-year mortality rate was 12% ($n = 55$). In-hospital and 1-year follow-up were 100% and 90% complete, respectively.

Univariate analysis

Factors associated with in-hospital death in univariate analysis are presented in Table 1, showing comparisons according to final vital status based on raw data in the left section, and unadjusted odds ratios from logistic regression on imputed data in the right section. In-hospital mortality was statistically significantly associated with older age and more severe presentation based on clinical, laboratory, and echocardiographic assessment such as history of congestive heart failure, severe symptoms [New York Heart Association (NYHA) Class III/IV, right-sided heart failure signs], dose of furosemide, kidney or liver impairment, TR mechanism, degree of RV dilatation and dysfunction, but not with previous left-sided heart valve surgery ($P = 0.11$). When centres were divided into quartiles according to average year-number of interventions, we did not observe an impact of centre

volume on in-hospital mortality (from the lowest-volume quartile to the highest-volume quartile: 13%, 9%, 12%, and 9%, respectively; $P = 0.83$).

Predictive model development and scoring

Variables associated at the P -value < 0.2 level in univariate analysis were entered into multivariate modelling. To develop a simplified scoring system, continuous variables were dichotomized before incorporation into regression analyses and were defined as follows: age ≥70 years, daily dose of furosemide ≥125 mg, glomerular filtration rate <30 mL/min, abnormal total bilirubin, alanine aminotransferase/aspartate aminotransferase and gamma-glutamyl transferase/alkaline phosphatases levels, LV ejection fraction <60%, systolic pulmonary artery pressure ≥50 mmHg and Charlson comorbidity index ≥2. Using stepwise multivariate analysis based on AIC, eight variables were selected in the final model: age, NYHA functional Class III–IV, right-sided heart failure signs, daily dose of furosemide, glomerular filtration rate, total bilirubin level, LV ejection fraction and moderate/severe RV dysfunction. In the final simplified scoring model, 1 point was attributed to a risk factor when odds ratio was between 1 and 2 and 2 points when odds ratio was ≥2 (Table 2).

Predictive model validation and calibration

Observed and predicted in-hospital mortality rates according to the score from the risk score model ranged from 0% to 60% and from 1% to 65%, respectively, for a score of 0 to a score of 9 or more, with exponential increased mortality rates as the score increased (Table 3 and Figure 1A). Good discrimination performance was found for the final simplified risk score model with an apparent AUROC of 0.808 (0.817 for the raw regression model without scaling/rounding of coefficients) and a bias-corrected AUROC of 0.753 (0.762) from internal validation. These results were found to be substantially higher than those obtained with both logistic EuroSCORE and EuroSCORE II (AUROC 0.668 and 0.629, respectively) (Figure 1B and C). Calibration of the risk score model was appropriate, as shown in calibration curves demonstrating very good agreement between actual

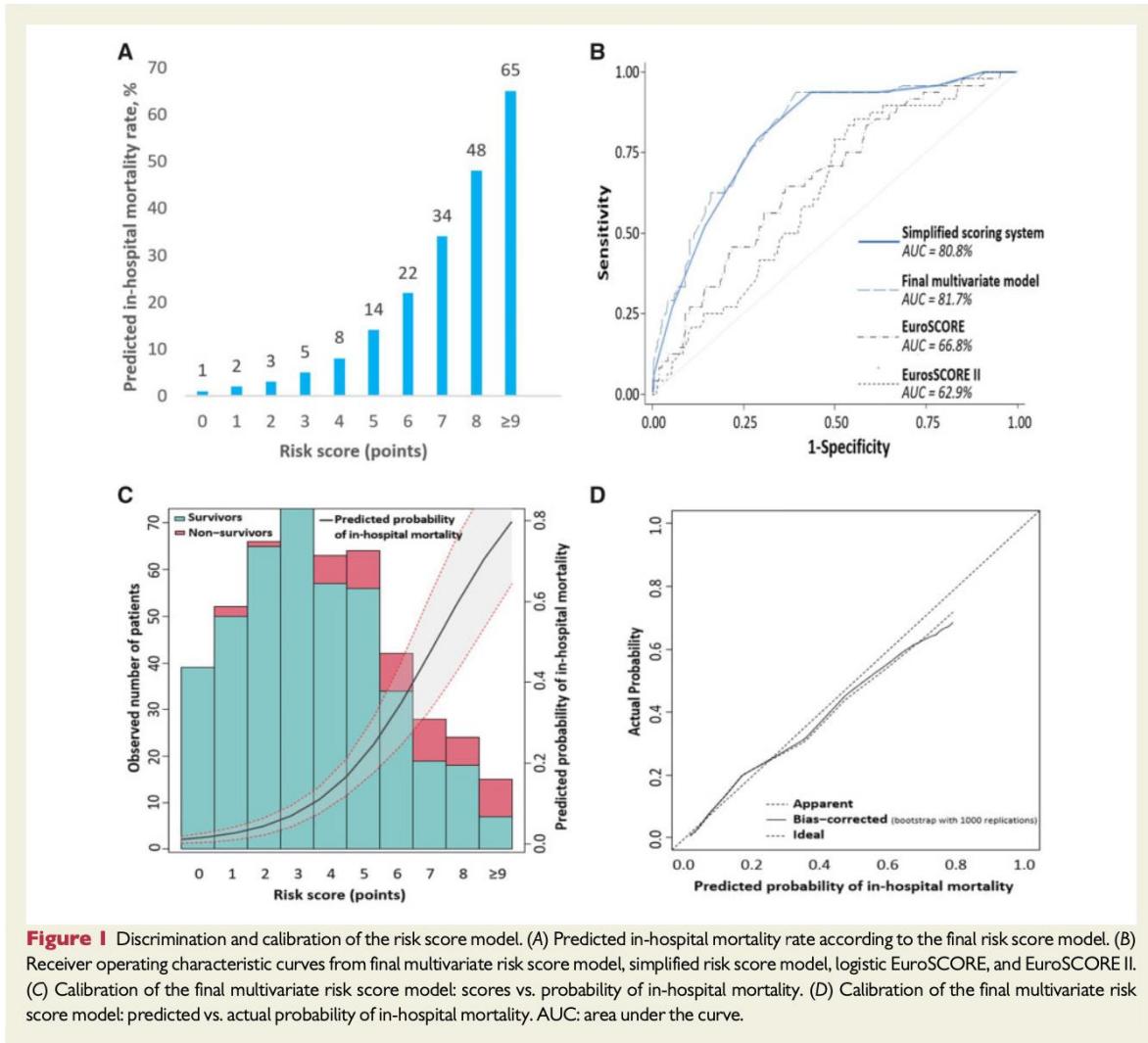


Figure 1 Discrimination and calibration of the risk score model. (A) Predicted in-hospital mortality rate according to the final risk score model. (B) Receiver operating characteristic curves from final multivariate risk score model, simplified risk score model, logistic EuroSCORE, and EuroSCORE II. (C) Calibration of the final multivariate risk score model: scores vs. probability of in-hospital mortality. (D) Calibration of the final multivariate risk score model: predicted vs. actual probability of in-hospital mortality. AUC: area under the curve.

and predicted probability of death for probabilities up to 50%, with a slight overestimation of the model for higher probabilities (Figure 1D).

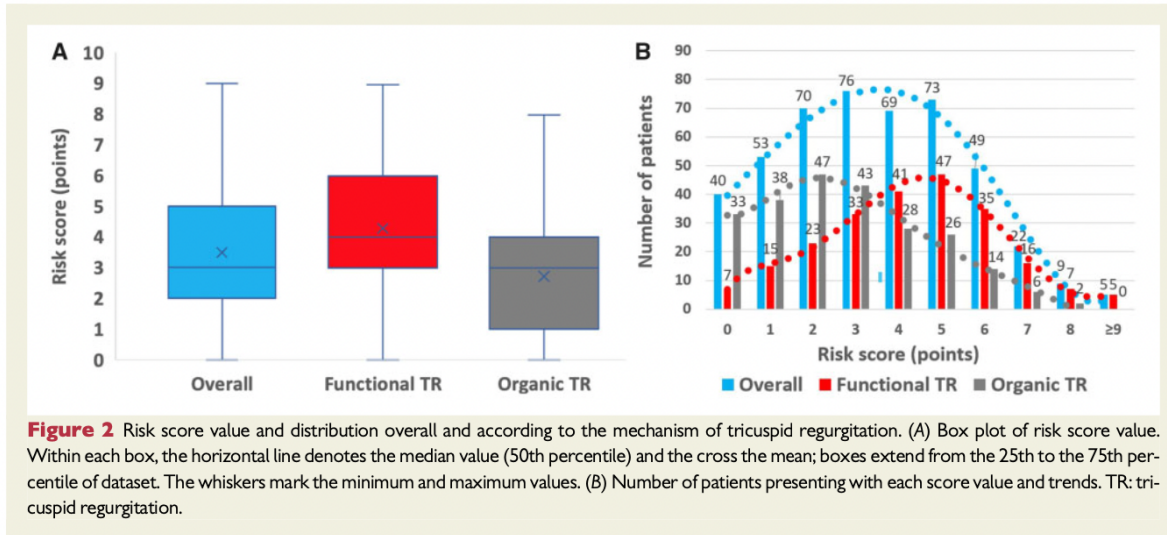
Distribution of the risk score model according to tricuspid regurgitation mechanism

Overall, mean score value was 3.5 ± 2.1 [median: 3 (2–5)] (Figure 2A) and distribution (number of patients presenting with each score value) is presented in Figure 2B. In-hospital mortality was worse for functional than for organic TR, but the mechanism was not an independent predictor of outcome and worse outcome observed in patients with functional TR was related to the worse clinical presentation in this subgroup. Thus, patients with functional TR were operated with a higher-risk score than patients with organic TR [4.3 ± 2.0 [median: 4 (3–6)] vs. 2.7 ± 1.9 [median: 3 (1–4)], $P < 0.001$] (Figure

2A) and there was a shift towards the right of the distribution of the score in patients with functional TR compared to those with organic TR (Figure 2B).

Predictive value of the score for in-hospital major complications and 1-year mortality

Although the risk score model was originally designed to predict in-hospital mortality, it was also significantly associated with major post-operative complications (C-index 0.71) and 1-year mortality rates (C-index 0.78). Major post-operative complications and 1-year mortality rates according to the score value ranged from 15% to 80% and from 3% to 60%, respectively, for a score value of 0 to a score of 9 or more, with a progressive increase in event rates as the score increased (Supplementary material online, Table S2).



Discussion

In this study, based on a large consecutive cohort of patients who underwent ITVS for severe TR at 12 French tertiary centres with in-depth clinical, laboratory, and echocardiographic characterization, we developed a dedicated risk score model to predict in-hospital mortality. The risk score model relied on eight parameters, four clinical parameters (age ≥ 70 years, NYHA functional Class III–IV, right-sided heart failure signs, daily dose of furosemide ≥ 125 mg), two laboratory parameters (glomerular filtration rate < 30 mL/min, elevated total bilirubin), and two echocardiographic parameters (LV ejection fraction $< 60\%$, moderate/severe RV dysfunction) (*Graphical Abstract*). The risk score model showed both an excellent discrimination and calibration. Although designed to predict in-hospital mortality, our risk score model also predicted in-hospital major complication rates and 1-year mortality rates with good accuracy.

Despite its high prevalence and association with increased mortality and morbidity, surgery for isolated TR remains rarely performed. Thus, only 10% of patients admitted in France with a diagnosis of TR are referred for an intervention.⁷ Management of patients with severe TR relied on two apparent contradictory beliefs, on the one hand that TR is benign and on the other hand that surgical risk for ITVS is prohibitive. In contrast to aortic stenosis or mitral regurgitation, TR is a slowly progressive disease and adverse consequences often occurred after decades explaining its falsely benign reputation.²² It is also true that the literature is fairly consistent showing an overall high in-hospital mortality rate of 8–10%.^{4–6,10,23–25} We also observed that overall in-hospital mortality rate was indeed 10%,⁴ but in the present paper we clearly showed that this 10% mortality rate is hiding important disparities with in-hospital mortality rates ranging from 0% to 60%. We have previously shown that outcomes were predicted by the severity of the presentation while TR mechanism or aetiology played a limited role. However, our findings were of limited use to predict immediate and mid-term results of ITVS at the individual level

and a risk score model that could support clinical decisions for cardiologists and cardiac surgeons was crucially lacking.

The STS risk score model does not individualize ITVS as a specific intervention contrary to aortic or mitral valve surgeries and thus does not provide any specific risk calculation. The logistic EuroSCORE and the EuroSCORE II were not designed for ITVS; interestingly the EuroSCORE II population only encompassed 85 patients who underwent ITVS. Consequently, as shown in the present study, both the logistic EuroSCORE and the EuroSCORE II poorly predicted in-hospital mortality after ITVS (C-index 0.67 and 0.63, respectively). In an attempt to better assess the surgical risk of ITVS, LaPar *et al.*¹⁰ proposed a dedicated risk score model derived from a subset of the STS database from the states of Virginia and Michigan. Although the authors should be commended for their seminal work and indeed their risk model was an important step towards a better risk stratification of patients referred for ITVS, it suffered from two important limitations. First, because of the limited granularity of the STS database, important prognostic factors in the setting of TR as RV consequences and liver function were not accounted for.²⁶ Second, their risk model was not well calibrated for high-risk patients with a maximum predicted mortality rate of 34%. The Model for End-Stage Liver Disease (MELD) score, which is used to stratify patients awaiting liver transplantation, has also been shown to predict mortality after TV surgery in a cohort of 168 patients but in whom only 22 patients underwent ITVS.^{27,28} The MELD relies on three variables that reflect liver and renal function [international normalized ratio (INR), total bilirubin, and creatinine]. However, it is worth noting that this score may be unsuitable for most patients who underwent ITVS as the majority of patients in our population were under oral anticoagulation treatment (vitamin K antagonist or direct oral anticoagulant), which increases the INR, and thus make this score likely not interpretable.

In contrast, in the present study, relying on the in-depth characterization of our population, we were able to develop a dedicated, simple, and accurate risk score model for ITVS that could guide the

clinical decision-making process. We collected all consecutive patients who underwent ITVS for severe TR at 12 tertiary French centres. Our risk score model was based on eight clinical, laboratory and echocardiographic parameters easy to capture and to measure, including those capturing the clinical sequelae of TR on the liver and the right ventricle. Our risk score model, on a 0–12 point scale, provided both excellent discrimination (C-index > 0.75) and calibration with a predicted mortality up to 65%. Interestingly, systolic pulmonary artery pressure was not an independent predictor of outcome. In the setting of severe TR, a laminar flow is commonly observed, and echocardiographic assessment of systolic pulmonary artery pressure may be not valid or may be underestimated in this situation. It is also worth noting that as patients with functional TR presented with more advanced disease than patients with organic TR, their risk score was significantly higher and the distribution of the proportion of patients with each score value was right-shifted (Figure 2). Importantly, our risk score model designed to predict in-hospital mortality also provided good predictive value for both in-hospital major complications and 1-year mortality rates that are also critical to appraise when ITVS is considered.

Study limitations

The present study deserves several comments. First, our sample size was relatively small (466 patients), but ITVS is a rare intervention. Our population, one of the largest to date, captured all ITVS performed at 12 centres during a period of >10 years representing >40% of all ITVS at the national level with in-depth clinical, laboratory and echocardiographic characterization. Nevertheless, we were not able to develop and validate a risk score model in different population subsets and further external validation of our score is desirable. Second, our study was retrospective but the low rate of ITVS precluded the prospective collection of a large number of patients referred for ITVS. Third, not all variables were available for each patient, and we performed imputation for missing variables. However, we performed multiple sensitivity analyses that found similar results; it is also noteworthy that all variables retained in the final model had clinical relevance, thus supporting the robustness of our findings. Fourth, we voluntarily did not use prothrombin time in our score as most patients were under oral anticoagulation treatment in our cohort, which can mislead its interpretation, especially if we consider the increased use of direct oral anticoagulants in recent years. Fifth, assessment of RV function relied on an integrative approach and not a single parameter with a well-defined threshold. However, each echocardiographic parameter proposed for the assessment of RV systolic function suffers from intrinsic limitations and have not been well validated in the setting of severe TR. Thus, an integrative approach was deemed the most accurate and reliable way to assess RV systolic function and is the recommended approach.^{12,13,27} As an internal validation, TAPSE and peak systolic annular velocity S' were markedly different between patients who presented with moderate/severe RV dysfunction compared to those who did not (13 ± 4 vs. 21 ± 6 mm and 7.6 ± 1.5 vs. 12.4 ± 3.2 cm/s respectively, both $P < 0.0001$). In addition, RV function, as the other echocardiographic parameters, was assessed locally by each centre with no centralized evaluation. Finally, we cannot exclude a centre effect on outcome after ITVS, but the very low rate overall (from two to six ITVS/year/centre) precludes any formal conclusion.

Clinical implications

The main aim of our risk score model is to provide reliable information to patients, cardiologists, and cardiac surgeons regarding the risk of ITVS for severe TR at an individual level and to guide the clinical decision-making process. The present score model is easy to use and calculate as relying on eight parameters that are part of the routine examination of all patients with severe TR. It helps stratifying the mortality risk when an isolated TV intervention is considered. A risk score ≤ 3 could define a low surgical risk, a score of 4–5 an intermediate risk, and a score ≥ 6 a high surgical risk. To enable wide use of this new score (TRI-SCORE), we have developed an online calculator to support physicians in their risk assessment (www.tri-score.com).

Severe TR is associated with a dismal prognosis with progressive RV dysfunction, renal and liver failure, chronic right heart failure, and need for increasing doses of diuretics. In the present study, we captured the full spectrum of disease stages, and we clearly show that a substantial proportion are still referred for an intervention late in the course of the disease with high scores (30% at intermediate risk and 18% at high risk based on the above proposed thresholds) and therefore high mortality rates. On the other hand, excellent outcomes can be achieved when the intervention is timely performed early in the course of the disease with a low score. Thus, the paradigm should be shifted, the poor outcome of ITVS observed overall is not related to the complexity of the procedure *per se* but to the late referral and the advanced disease stage of many patients. Our results should be seen as a strong incentive to consider a TV intervention earlier in the disease course avoiding performance of TV intervention in patients at a late or desperate disease stage. Nevertheless, we only provided indirect evidence that earlier intervention is likely beneficial and best timing remained to be determined.

With the rapid development of transcatheter interventions, our risk score model will provide a unique tool to select the patients who might be better suitable for surgery or for transcatheter interventions. Importantly, most patients with severe TR still remain conservatively managed. Transcatheter therapies, as a less-invasive alternative to surgery, will further push for an early intervention as well as for an extension of the number of patients treated if proved to be safe and efficient. It is also worth noting that availability of transcatheter TV replacement might circumvent one main limitation of edge-to-edge repair, i.e. significant residual TR. Ongoing and future randomized controlled trials (TRILUMINATE Pivotal Trial, TRI-FR, CLASP II TR, TRISCEND II Pivotal trial) will hopefully provide more evidence regarding most appropriate timing and recommended type of intervention to improve the outcome of this population.

Finally, the main accepted explanation of the discordant results between MITRA-FR and COAPT trials is the enrolment of different subsets of patients with functional mitral regurgitation.^{29,30} TRI-SCORE will provide a unique tool to characterize and compare populations enrolled in ongoing randomized controlled trials evaluating the benefit of TR correction.

Conclusion

We propose TRI-SCORE as a dedicated risk score model based on eight easy to ascertain parameters to inform both patients and physicians regarding the risk of ITVS. This risk score will guide the

clinical decision-making process at the bedside level, and we do hope leads to earlier and wider interventions for patients with severe TR before the occurrence of irreversible consequences that markedly affect prognosis, especially as transcatheter therapies are emerging (www.tri-score.com).

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

Data sharing with qualified researchers may be considered after submission of a proposal to Doctor Julien Dreyfus.

References

- Topilsky Y, Maltais S, Medina Inojosa J, Oguz D, Michelena H, Maalouf J, Mahoney DW, Enriquez-Sarano M. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging* 2019;**12**:433–442.
- Wang N, Fulcher J, Abesuriya N, McGrady M, Wilcox I, Celermajer D, Lal S. Tricuspid regurgitation is associated with increased mortality independent of pulmonary pressures and right heart failure: a systematic review and meta-analysis. *Eur Heart J* 2019;**40**:476–484.
- Messika-Zeitoun D, Verta P, Gregson J, Pocock SJ, Boero I, Feldman TE, Abraham WT, Lindenfeld J, Bax J, Leon M, Enriquez-Sarano M. Impact of tricuspid regurgitation on survival in patients with heart failure: a large electronic health record patient-level database analysis. *Eur J Heart Fail* 2020;**22**:1803–1813.
- Dreyfus J, Flagiello M, Bazire B, Eggenspieler F, Viau F, Riant E, Mbaki Y, Bohbot Y, Eyharts D, Senage T, Dubrulle H, Nicol M, Doguet F, Nguyen V, Coisne A, Le Tourneau T, Lavie-Badie Y, Tribouilloy C, Donal E, Tomasi J, Habib G, Selton-Suty C, Raffoul R, lung B, Obadia JF, Messika-Zeitoun D. Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes. *Eur Heart J* 2020;**41**:4304–4317.
- Dreyfus J, Ghalem N, Garbarz E, Cimadevilla C, Nataf P, Vahanian A, Caranhac G, Messika-Zeitoun D. Timing of referral of patients with severe isolated tricuspid valve regurgitation to surgeons (from a French Nationwide Database). *Am J Cardiol* 2018;**122**:323–326.
- Zack CJ, Fender EA, Chandrashekar P, Reddy YNV, Bennett CE, Stulak JM, Miller VM, Nishimura RA. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol* 2017;**70**:2953–2960.
- Messika-Zeitoun D, Candolfi P, Dreyfus J, Burwash IG, lung B, Philippon JF, Toussaint JM, Verta P, Feldman TE, Obadia JF, Vahanian A, Mesana T, Enriquez-Sarano M. Management and outcome of patients admitted with tricuspid regurgitation in France. *Can J Cardiol* 2021;**37**:1078–1085.
- Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Gilard M, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, Wojakowski W; ESC/EACTS Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2021;doi:10.1093/eurheartj/ehab395.
- Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O’Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A, Toly C. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;143:e35–e71.
- LaPar DJ, Likosky DS, Zhang M, Theurer P, Fonner CE, Kern JA, Bolling SF, Drake DH, Speir AM, Rich JB, Kron IL, Prager RL, Ailawadi G. Development of a risk prediction model and clinical risk score for isolated tricuspid valve surgery. *Ann Thorac Surg* 2018;**106**:129–136.
- PMSI. Programme de Médicalisation des Systèmes d’Information (PMSI). 2012. <https://drees.solidarites-sante.gouv.fr/redressements-du-programme-de-medicalisation-des-systemes-d-informations-pmsi>.
- Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, Little SH, Shah DJ, Sherman S, Thavendiranathan P, Thomas JD, Weissman NJ. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;**30**:303–371.
- Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;**16**:777–802.
- Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsov T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233–270.
- Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;**16**:9–13.
- Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. *Eur J Cardiothorac Surg* 2012;**41**:734–744.
- Hothorn T, Hornik K, Zeileis A. Unbiased recursive partitioning: a conditional inference framework. *J Comput Graphical Stat* 2006;**15**:651–674.
- Cole T. Scaling and rounding regression coefficients to integers. *J R Stat Soc Series C Appl Stat* 1993;**42**:261–268.
- Steyerberg E. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. New York: Springer-Verlag; 2009.
- Stekhoven DJ, Bühlmann P. MissForest—non-parametric missing value imputation for mixed-type data. *Bioinformatics* 2012;**28**:112–118.
- Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York: Wiley; 1987.
- Messika-Zeitoun D, Thomson H, Bellamy M, Scott C, Tribouilloy C, Dearani J, Tajik AJ, Schaff H, Enriquez-Sarano M. Medical and surgical outcome of tricuspid regurgitation caused by flail leaflets. *J Thorac Cardiovasc Surg* 2004;**128**:296–302.
- Gammie JS, Chikwe J, Badhwar V, Thibault DP, Vemulapalli S, Thourani VH, Gillinov M, Adams DH, Rankin JS, Ghoreishi M, Wang A, Ailawadi G, Jacobs JP, Suri RM, Bolling SF, Foster NW, Quinn RW. Isolated mitral valve surgery: the Society of Thoracic Surgeons Adult cardiac surgery database analysis. *Ann Thorac Surg* 2018;**106**:716–727.
- Kim YJ, Kwon DA, Kim HK, Park JS, Hahn S, Kim KH, Kim KB, Sohn DW, Ahn H, Oh BH, Park YB. Determinants of surgical outcome in patients with isolated tricuspid regurgitation. *Circulation* 2009;**120**:1672–1678.
- Topilsky Y, Khanna AD, Oh JK, Nishimura RA, Enriquez-Sarano M, Jeon YB, Sundt TM, Schaff HV, Park SJ. Preoperative factors associated with adverse outcome after tricuspid valve replacement. *Circulation* 2011;**123**:1929–1939.
- Yates MT, Anyanwu AC. Invited commentary. *Ann Thorac Surg* 2018;**106**:136–137.
- Martin AP, Bartels M, Hauss J, Fangmann J. Overview of the MELD score and the UNOS adult liver allocation system. *Transplant Proc* 2007;**39**:3169–3174.
- Ailawadi G, Lapar DJ, Swenson BR, Siefert SA, Lau C, Kern JA, Peeler BB, Littlewood KE, Kron IL. Model for end-stage liver disease predicts mortality for tricuspid valve surgery. *Ann Thorac Surg* 2009;**87**:1460–1467.
- Obadia JF, Messika-Zeitoun D, Leurent G, lung B, Bonnet G, Piriou N, Lefevre T, Piot C, Rouleau F, Carrie D, Nejari M, Ohlmann P, Leclercq F, Saint Etienne C, Teiger E, Leroux L, Karam N, Michel N, Gilard M, Donal E, Trochu JN, Cormier B, Armoiry X, Boutitie F, Maucort-Boulch D, Barnel C, Samson G, Guerin P, Vahanian A, Mewton N; MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018;**379**:2297–2306.
- Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ, Coapt I. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;**379**:2307–2318.

Article 8

Predictive value of the TRI-SCORE for in-hospital mortality after redo isolated tricuspid valve surgery

Dreyfus J, Bohbot Y, Coisne A, Lavie-Badie Y, Flagiello M, Bazire B, Eggenpieler F, Viau F, Riant E, Mbaki Y, Eyharts D, Senage T, Modine T, Nicol M, Doguet F, Nguyen V, Le Tourneau T, Tribouilloy C, Donal E, Tomasi J, Habib G, Selton-Suty C, Raffoul R, Iung B, Obadia JF, Audureau E, Messika-Zeitoun D

Heart. 2023 Feb 24:heartjnl-2022-322167

Article 8 : Fiabilité du TRI-SCORE pour prédire la mortalité hospitalière après chirurgie redux isolée de la valve tricuspide

Après réparation ou remplacement chirurgical de la VT, une chirurgie redux isolée de la VT n'est que très rarement réalisée car considérée à haut risque. Pour autant, les données sont très limitées concernant cette population et nous ne disposons pas de score de risque pour prédire la mortalité post-opératoire après cette intervention. Nous avons montré que le TRI-SCORE prédit de façon fiable la mortalité hospitalière après chirurgie isolée de la VT sur valve native, mais ce score n'a pas été testé dans la population des patients redux sur la VT⁸⁴.

Les objectifs de cette étude étaient :

- Evaluer la fiabilité du TRI-SCORE pour prédire la mortalité hospitalière après chirurgie isolée redux de la VT
- Comparer la valeur prédictive du TRI-SCORE aux autres scores de risque chirurgicaux

A partir des données du PMSI, nous avons identifiés 70 patients consécutifs qui ont eu une chirurgie isolée redux de la VT dans 12 centres tertiaires Français entre 2007 et 2017 (Figure 45).

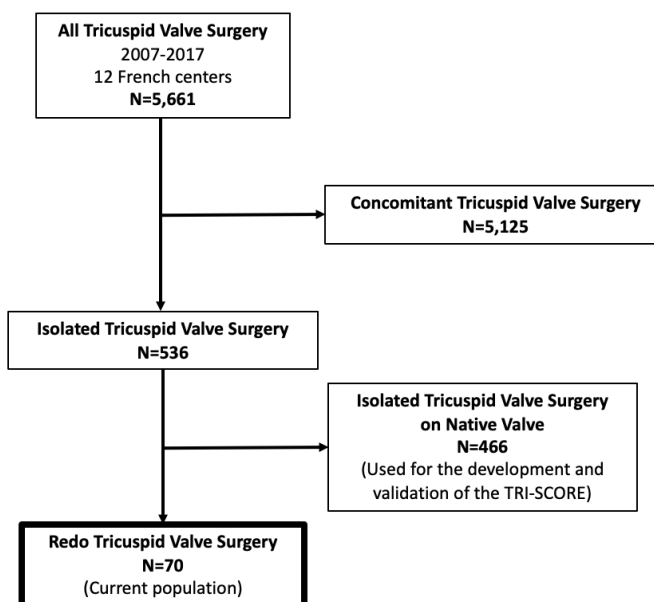


Figure 45. Organigramme montrant la population à partir de laquelle a été développée la population de l'étude

L'encadré noir correspond à la population de l'étude

L'âge moyen était de 54 ± 15 ans, 63% des patients étaient des femmes, et la plupart étaient très symptomatiques (53% ont été hospitalisés au cours de la dernière année pour IC, 56% avaient une classe fonctionnelle NYHA III ou IV, 63% avaient des signes cliniques d'IC droite et 76% étaient traités par diurétiques de l'anse), 56% avaient une dilatation significative du VD et 34% une dysfonction VD significative. Le TRI-SCORE était bas (entre 0 et 3) chez 44% des patients, intermédiaire (4-5) chez 27% et élevé (≥ 6) chez 29%.

Les patients avaient tous déjà été opérés sur la VT, avec un antécédent de réparation de la VT dans 51% des cas et de remplacement dans 49% des cas, intervention qui avait été combinée à une chirurgie valvulaire du cœur gauche (mitrale le plus souvent) dans 41% des cas. Les réparations de la VT avaient été réalisées principalement pour une IT fonctionnelle (66%) au moment d'une chirurgie valvulaire du cœur gauche (56%), à l'aide d'un anneau rigide (58%), tandis que les remplacements de la VT étaient principalement des chirurgies isolées de la VT (74%) pour IT organique (82%), souvent due à une endocardite infectieuse (62%), en implantant une bioprothèse (91%).

La chirurgie redux sur la VT était réalisée quasi-exclusivement pour IT fonctionnelle après réparation (94%) et principalement pour dégénérescence de bioprothèse après remplacement, en moyenne 10 ± 9 ans après. Chez les patients avec antécédent de remplacement de la VT, les thromboses de prothèses représentaient 9% des chirurgies redux sur la VT et les endocardites infectieuses et/ou fuites périprothétiques 18%.

Les patients avec antécédent de réparation de la VT avaient une présentation pré-opératoire plus grave que ceux avec antécédent de remplacement. En effet, ils étaient plus âgés, plus souvent sévèrement symptomatiques (classe fonctionnelle NYHA III ou IV, signes cliniques d'IC droite), en FA, avec anémie, insuffisance rénale et hépatique avec ascite, dilatation significative du VD et HTAP (tous les $P < 0.05$). Cette présentation pré-opératoire était concordante avec des TRI-SCORE plus élevés (5 [2-7] vs. 3 [1-5], $P = 0.05$).

Pour la chirurgie redux sur la VT, un remplacement a été réalisé après sternotomie chez tous les patients, dont 31% à cœur battant. Une bioprothèse a été implantée chez la majorité des patients (86%) et 21% ont été implantés d'un stimulateur cardiaque permanent.

Les taux de mortalité hospitalière et de complications postopératoires graves (incluant mortalité, choc, tamponnade, insuffisance rénale aigue nécessitant la dialyse ou ventilation mécanique >72 heures) étaient respectivement de 10% et 34% en moyenne dans l'ensemble de la population.

A la sortie de l'hôpital, l'IT était complètement corrigée (absente ou minime) chez tous les patients.

En analyse univariée, les facteurs prédictifs de la mortalité hospitalière après chirurgie redux isolée de la VT étaient la sévérité des symptômes (classe fonctionnelle NYHA III ou IV, signes cliniques d'IC droite), la dose quotidienne de diurétiques de l'anse, l'atteinte rénale et l'atteinte hépatique. Les patients avec antécédent de réparation de la VT avaient tendance à avoir une mortalité hospitalière plus élevée que ceux avec antécédent de remplacement, même si elle n'atteignait pas la significativité statistique (respectivement 14% vs 6 %, P =0.43).

Le TRI-SCORE était le seul score de risque chirurgical associé à la mortalité hospitalière (P =0.005 vs P =0.50 pour l'EuroSCORE et P =0.35 pour l'EuroSCORE II).

Les taux de mortalité hospitalière observés et prédits selon le TRI-SCORE variaient de 0% et 3% pour un score ≤ 3 à 25% et 38% respectivement pour un score ≥ 6 , avec une augmentation significative des taux de mortalité lorsque le TRI-SCORE augmentait.

Le TRI-SCORE était associé à une très bonne performance de discrimination avec une AUC de 83%, beaucoup plus élevée que l'EuroSCORE (58%) ou l'EuroSCORE II (61%) (Figure 46).

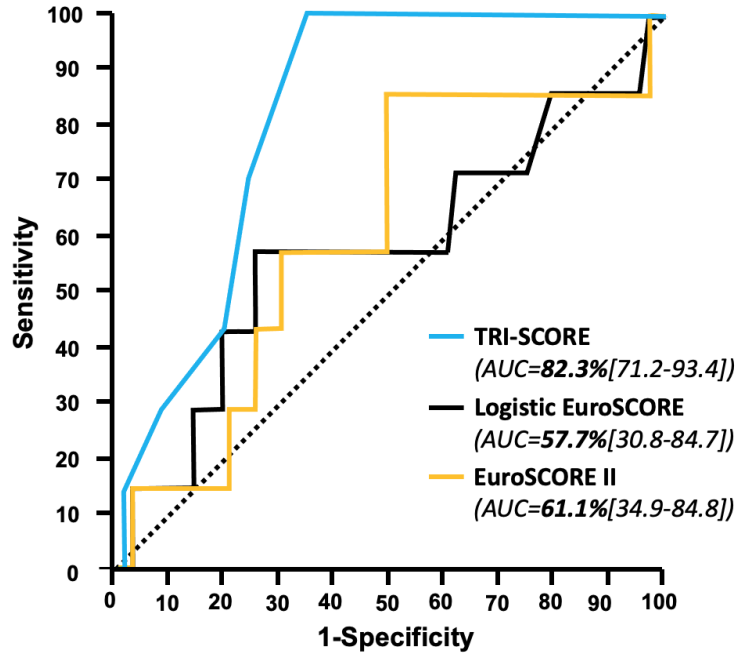


Figure 46. Courbes sensibilité/spécificité pour le le TRI-SCORE, l'EuroSCORE et l'EuroSCORE II pour prédire la mortalité après chirurgie redux isolée sur la VT
AUC : aire sous la courbe

Le TRI-SCORE était également associé aux complications post-opératoires graves puisque ce taux augmentait avec le TRI-SCORE, allant de 10% pour un score ≤ 3 , à 44% pour un score de 4 ou 5, et jusqu'à 65% pour un score ≥ 6 .

Le TRI-SCORE était également associé au pronostic à moyen terme. Dans l'ensemble de la population, les taux estimés de survie et de survie sans ré-hospitalisation pour IC étaient respectivement de 85% et 80% à 1 an, et de 79% et 71% à 5 ans. Les courbes de survie et de survie sans ré-hospitalisation pour IC en fonction du TRI-SCORE étaient excellentes pour les patients avec un TRI-SCORE ≤ 3 (respectivement 95% et 90% à 5 ans) mais se dégradait nettement à mesure que le TRI-SCORE augmentait (tous les $P < 0.05$) (Figure 47).

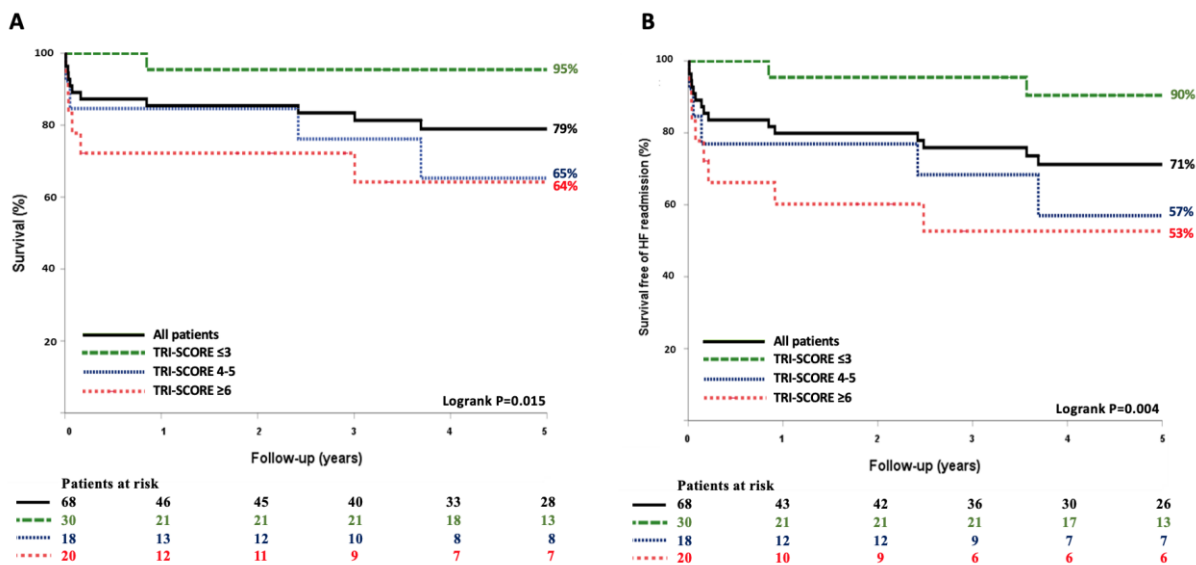


Figure 47. Taux d'événements à 5 ans après chirurgie redux isolée de la valve tricuspide, dans l'ensemble de la population et en fonction du TRI-SCORE divisé en 3 grades









A. Courbes de Kaplan-Meier de survie

B. Courbes de Kaplan-Meier de survie sans ré-hospitalisation pour insuffisance cardiaque

Cette étude a montré que la chirurgie redux isolée de la VT est rarement réalisée et associée à une mortalité et une morbidité hospitalières globalement élevées mais qui cachent d'importantes disparités individuelles, en rapport avec la présentation pré-opératoire. Contrairement aux autres scores de risque chirurgicaux, le TRI-SCORE prédisait de façon fiable la mortalité hospitalière, les complications post-opératoires graves ainsi que le pronostic à moyen terme après chirurgie redux isolée de la VT. Le TRI-SCORE pourrait informer les patients, les cardiologues et les chirurgiens sur le risque opératoire de cette intervention à l'échelon individuel et aider à la prise de décision lorsqu'une nouvelle intervention sur la VT est envisagée.

Original research

Predictive value of the TRI-SCORE for in-hospital mortality after redo isolated tricuspid valve surgery

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► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/heartjnl-2022-322167>).

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JD and YB contributed equally.

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ABSTRACT

Objectives The TRI-SCORE reliably predicts in-hospital mortality after isolated tricuspid valve surgery (ITVS) on native valve but has not been tested in the setting of redo interventions. We aimed to evaluate the predictive value of the TRI-SCORE for in-hospital mortality in patients with redo ITVS and to compare its accuracy with conventional surgical risk scores.

Methods Using a mandatory administrative database, we identified all consecutive adult patients who underwent a redo ITVS at 12 French tertiary centres between 2007 and 2017. Baseline characteristics and outcomes were collected from chart review and surgical scores were calculated.

Results We identified 70 patients who underwent a redo ITVS (54±15 years, 63% female). Prior intervention was a tricuspid valve repair in 51% and a replacement in 49%, and was combined with another surgery in 41%. A tricuspid valve replacement was performed in all patients for the redo surgery. Overall, in-hospital mortality and major postoperative complication rates were 10% and 34%, respectively. The TRI-SCORE was the only surgical risk score associated with in-hospital mortality ($p=0.005$). The area under the receiver operating characteristic curve for the TRI-SCORE was 0.83, much higher than for the logistic EuroSCORE (0.58) or EuroSCORE II (0.61). The TRI-SCORE was also associated with major postoperative complication rates and survival free of readmissions for heart failure.

Conclusion Redo ITVS was rarely performed and was associated with an overall high in-hospital mortality and morbidity, but hiding important individual disparities. The TRI-SCORE accurately predicted in-hospital mortality after redo ITVS and may guide clinical decision-making process (www.tri-score.com).

INTRODUCTION

Contrasting with the high prevalence of tricuspid regurgitation (TR) and its dismal prognosis,^{1–3} most patients with severe TR are conservatively managed with diuretics to relieve their symptoms, while a curative isolated tricuspid valve surgery

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Redo isolated tricuspid valve surgery is reputed to be associated with poor outcome.
- ⇒ The TRI-SCORE has been developed and validated to predict in-hospital mortality after isolated tricuspid valve surgery on native valve.

WHAT THIS STUDY ADDS

- ⇒ Redo isolated tricuspid valve surgery is rarely performed.
- ⇒ In-hospital mortality and outcomes are highly variable after redo isolated tricuspid valve surgery, mainly driven by preoperative presentation.
- ⇒ The TRI-SCORE accurately predicts in-hospital mortality, in-hospital complications and midterm outcomes after redo isolated tricuspid valve surgery, while conventional surgical risk scores do not.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The TRI-SCORE (www.tri-score.com) may inform patients, cardiologists and cardiac surgeons regarding surgical risk and may guide heart team decisions when a redo isolated tricuspid valve surgery is considered.

(ITVS) is seldom performed even in the recent era.^{4,5} Reluctance to perform an ITVS is at least partially explained by the high in-hospital mortality reported in most series, around 10%, remarkably consistent across the literature.^{5–7} However, clinical presentation is the main driver of postoperative outcomes, and the high in-hospital mortality observed after ITVS is due to the advanced disease stage at the time of the intervention.⁵ Following these observations, the TRI-SCORE was recently developed to predict this surgical risk of ITVS. The TRI-SCORE is a simple, dedicated and reliable risk score model for predicting in-hospital mortality after ITVS on native tricuspid valve (TV), based on

eight preoperative parameters divided into three categories: clinical (age, New York Heart Association (NYHA) functional class, right heart failure signs and daily dose of diuretics), biological (glomerular filtration rate and total bilirubin) and echocardiographic (left and right ventricular systolic function).⁸

After prior TV repair or replacement, the situation is even worse, and a redo TV surgery is seldom performed. Only few small monocentric studies spanning over a long period of enrolment have reported the outcome of redo ITVS, and surgical risk scores in this setting are cruelly lacking, especially as tricuspid transcatheter therapies are emerging.^{9–10} The assessment of operative risk usually relies on the EuroSCORE^{11–12} and/or the Society of Thoracic Surgeons (STS) score,¹³ but there is no STS tricuspid-specific score and both logistic EuroSCORE and EuroSCORE II have not been designed and validated in this population. Relying on a multicentre consecutive cohort of patients who underwent a redo ITVS at 12 French tertiary centres, we aimed to assess the accuracy of the TRI-SCORE in the prediction of in-hospital mortality and to compare its predictive value with logistic EuroSCORE and EuroSCORE II.

METHODS

Study design

Using the local PMSI (Programme de Médicalisation des Systèmes d'Information) database,¹⁴ we collected all consecutive TV surgeries performed in adult patients at 12 tertiary French centres between 1 January 2007 and 31 December 2017. The design of the study has been previously reported.⁵ From the overall cohort, we identified all patients who underwent an isolated redo TV surgery and this subset constituted our study population. Clinical presentation, laboratory results, echocardiography, and immediate and midterm outcomes were retrospectively collected locally at each centre. As the study was purely retrospective with only data collection, no written informed consent was required.

Patients' characteristics

The type (repair or replacement) and mechanism of the index TV dysfunction (functional, endocarditis or other organic), as well as the mechanism of the TV repair/replacement dysfunction which led to the redo ITVS (functional for TV repair, deterioration for TV replacement, or thrombosis, infective endocarditis and periprosthetic leak for both), were collected. Right-sided heart failure signs were defined as severe jugular venous distension, ascites and/or marked peripheral oedema. Glomerular filtration rate was calculated using the Cockcroft-Gault formula according to sex. Liver enzymes were considered elevated when above laboratory thresholds. Left ventricular ejection fraction was measured visually or using the biplane method of discs (modified Simpson's rule). Right ventricular (RV) size was visually assessed as normal, mildly, moderately or severely enlarged. RV function was semiquantitatively assessed using an integrative approach based on visual assessment, tricuspid annulus plane systolic excursion and Doppler tissue imaging peak systolic annular velocity S' as recommended.^{15–16} The Charlson Comorbidity Index was used to assess for patients' comorbidities. Logistic EuroSCORE, EuroSCORE II and TRI-SCORE⁸ were calculated.

Outcome

In-hospital mortality was defined as death occurring between the intervention and hospital discharge during the same hospital stay. Major postoperative complications were defined as death, shock,

tamponade, acute renal failure requiring dialysis or prolonged (>72 hours) mechanical ventilation. Lengths of stay (total and in intensive care unit) were calculated as the time duration between admission and hospital discharge. During follow-up, all-cause death and readmissions due to congestive heart failure (CHF) were collected.

Statistics

Variables were expressed as mean \pm SD or median (percentile 25th and 75th) for continuous variables and number of patients (percentage) for categorical variables. Comparisons between groups were performed using analysis of variance, χ^2 or Fisher's exact test for categorical variables, and Student's t-test or non-parametric Wilcoxon test for continuous variables, as appropriate. Logistic regression in univariate analysis was used to assess the determinants of in-hospital death. The performance of risk scores in predicting in-hospital death was assessed through discrimination evaluated by the area under the receiver operating characteristic curve (AUROC). The risks of death and CHF readmission overall and according to the TRI-SCORE grade (≤ 3 points: low risk; 4–5 points: intermediate risk; and ≥ 6 points: high risk, as previously suggested)⁸ were assessed using the Kaplan-Meier method and compared by the log-rank test. Data were analysed using JMP V.9.0 (SAS Institute) and SPSS V.27.0. All tests were two-sided and a p value <0.05 was considered statistically significant.

RESULTS

Study population

Among 5661 consecutive cases of TV surgery performed in adult patients at 12 tertiary French centres between 1 January 2007 and 31 December 2017, we identified 536 patients who underwent an isolated TV surgery. Surgery was performed on native TV in 466 patients (ie, no prior TV surgery), and this subset was used to develop and validate the TRI-SCORE, while 70 patients underwent a redo TV surgery (ie, prior TV surgery) and constituted our study population (figure 1). Three patients were included in both subsets, first when they underwent their index isolated surgery on native TV and later when they were reoperated on, but their respective clinical and echocardiographic characteristics were considered at each time point.

Patients' characteristics

The characteristics of the 70 consecutive patients who underwent a redo ITVS are presented in table 1. Briefly, the mean age was 54 ± 15 years, 63% were female, most patients were severely symptomatic (53% were admitted in the year prior for CHF, 56% were in NYHA functional class III–IV, 63% presented with right heart failure and 76% were treated with loop diuretics), 56% had moderate/severe RV dilatation and 34% had moderate/severe RV dysfunction. The TRI-SCORE was low in 44%, intermediate in 27% and high in 29%.

Prior intervention

Index TV surgery was a TV repair in 36 patients (51%) and a TV replacement in 34 patients (49%). The index TV surgery was concomitant to a left-sided heart valve surgery in 29 patients (41%) (mitral valve surgery in 90% of combined interventions). The index TV repair was mostly performed for functional TR (66%) at the time of left-sided heart valve surgery (56%), using a rigid ring (58%), while the index TV replacement was mostly an isolated TV surgery (74%) performed for organic TR (82%),

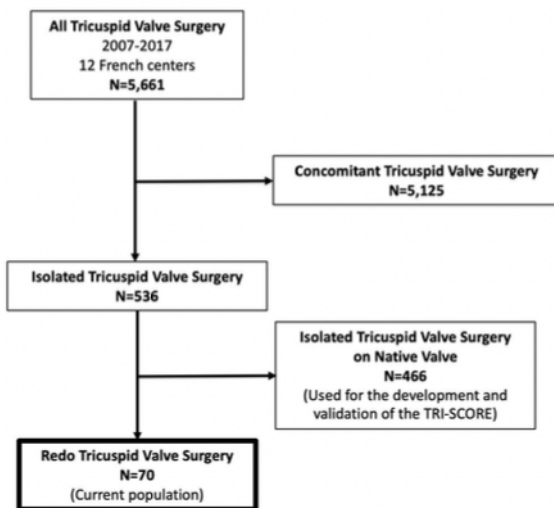


Figure 1 Flow chart of the study population. A total of 5661 adult patients underwent a tricuspid valve surgery at 12 tertiary French centres between 1 January 2007 and 31 December 2017. Among them, 536 underwent an isolated non-congenital surgery, of whom 466 were on native tricuspid valve (who served as the TRI-SCORE development and validation subset) and 70 were redo tricuspid valve surgeries (our study population).

especially due to infective endocarditis (62%), using a bioprosthesis (91%).

Redo intervention

Redo ITVS was performed 10 ± 9 years after the index TV surgery. TV repair/replacement dysfunction was a valve regurgitation in 56%, a valve stenosis in 24% and a mixed disease in 20%. Redo ITVS was almost exclusively performed for functional TR in patients with prior repair (94% had severe TR and 6% had a mixed disease). In contrast, TV prosthetic dysfunction was a regurgitation in 8%, a stenosis in 50% and a mixed disease in 42% (the mean gradient was 11 ± 4 mm Hg, 50% had no or mild TR, and 79% had moderate or less TR), mainly due to valve degeneration. TV prosthetic thrombosis represented 9% of redo ITVS, and infective endocarditis and/or periprosthetic leak 18%. Notably, thrombosis, infective endocarditis and/or periprosthetic leak occurred only on TV prosthetic valve. Compared with patients with prior replacement, those with previous TV repair were older, more often severely symptomatic (NYHA functional class III–IV, right heart failure), in atrial fibrillation, with anaemia, with renal and liver failure with ascites, with significant RV dilatation and with pulmonary hypertension (all $p < 0.05$).

In-hospital outcome

A TV replacement was performed through median sternotomy in all patients, on beating heart for 31% of the population. Most patients received a bioprosthesis (86%) and 21% required a new permanent pacemaker implantation. In-hospital mortality rate was 10% and major postoperative complication rate was 34%. At discharge, TR was absent or mild, and the mean TV gradient normal in all patients. The in-hospital outcomes are summarised in table 2.

Determinants of in-hospital mortality and complications

Factors associated with in-hospital mortality in the univariate analysis are presented in table 3. In-hospital mortality after redo ITVS was associated with severity of symptoms (NYHA class III/IV, right heart failure), daily dose of loop diuretics, and kidney and liver impairment. Patients with prior TV repair tended to incur a worse in-hospital mortality, although it did not reach statistical significance (14% vs 6%, respectively, $p = 0.43$), higher rates of cardiogenic shock (31% vs 6%, $p = 0.01$) and a longer stay in intensive care unit (6 (3–19) days vs 4 (2–6) days, $p = 0.01$) than patients with prior TV replacement.

Predictive values of the surgical risk scores

As shown in table 3, logistic EuroSCORE and EuroSCORE II were not statistically different between patients who died in hospital and those discharged alive ($p = 0.50$ and $p = 0.35$, respectively). In contrast, the TRI-SCORE, calculated in all but two patients, was significantly associated with in-hospital mortality ($p = 0.005$). Observed and predicted in-hospital mortality rates according to TRI-SCORE grade ranged from 0% to 25% and from 3% to 38%, respectively, for a score ≤ 3 and a score ≥ 6 , with marked raise in mortality rates as the TRI-SCORE increased (table 4). Good discrimination performance was found for the TRI-SCORE, with an AUROC of 0.83 for in-hospital death, markedly higher than with the logistic EuroSCORE (AUROC = 0.58) and EuroSCORE II (AUROC = 0.61) (figure 2).

Interestingly, the TRI-SCORE was significantly higher in patients with prior TV repair than replacement (5 (2–7) vs 3 (1–5), $p = 0.05$).

The rate of major postoperative complications (death, shock, tamponade, acute renal failure requiring dialysis or prolonged mechanical ventilation) increased with the TRI-SCORE, with a rate of 10% for a score ≤ 3 , 44% for a score of 4–5 and up to 65% for a score ≥ 6 (table 4).

Midterm outcome

Follow-up was 76% complete, with a mean follow-up duration of 5 ± 3 years. Overall, the estimated rates of survival and survival free of CHF readmission were 85% and 80% at 1 year, and 79% and 71% at 5 years, respectively (figure 3A,B). Survival and survival free of CHF readmission curves according to the TRI-SCORE grades were excellent for patients with TRI-SCORE ≤ 3 (95% and 90% at 5 years, respectively) but markedly worsened as the TRI-SCORE increased (all $p < 0.05$) (online supplemental material).

DISCUSSION

In this study, we collected all consecutive patients who underwent a redo ITVS performed at 12 tertiary French centres between 1 January 2007 and 31 December 2017, assessed their clinical, biological and echocardiographic presentations, and evaluated their in-hospital and midterm outcomes. Redo ITVS was rarely performed, the in-hospital mortality rate was 10% and the rate of major postoperative complications was 34%. The TRI-SCORE was the only risk score associated with in-hospital mortality and provided a good discrimination. The TRI-SCORE was also significantly associated with major postoperative complication rate, as well as survival free of readmissions for heart failure.

Redo ITVS is a rare intervention and was performed only in 70 patients during an 11-year period at 12 tertiary French centres. Among all patients who underwent a TV surgery, 91% were performed combined with a left-sided heart valve surgery and

Valvular heart disease

Table 1 Baseline characteristics of the population overall and according to previous TV repair or replacement

| Characteristics | Overall (n=70) | Previous TV repair (n=36) | Previous TV replacement (n=34) | P value |
|--|----------------|---------------------------|--------------------------------|---------------|
| Clinical | | | | |
| Age, years | 54±15 | 61±13 | 48±14 | 0.0006 |
| Female gender | 44 (63) | 25 (69) | 19 (56) | 0.32 |
| Body mass index, kg/m ² | 26±6 | 25±6 | 26±5 | 0.48 |
| Hypertension | 17 (24) | 11 (31) | 6 (18) | 0.30 |
| Diabetes mellitus | 8 (11) | 4 (11) | 4 (12) | 1.00 |
| Chronic lung disease | 9 (13) | 3 (8) | 6 (18) | 0.30 |
| Peripheral vascular disease | 2 (3) | 1 (3) | 1 (3) | 1.00 |
| Prior stroke | 6 (9) | 5 (14) | 1 (3) | 0.19 |
| Coronary artery disease | 6 (9) | 4 (11) | 2 (6) | 0.67 |
| Chronic kidney disease | 16 (23) | 11 (31) | 5 (15) | 0.16 |
| Chronic liver disease | 12 (17) | 6 (17) | 6 (18) | 1.00 |
| Liver cirrhosis | 6 (9) | 2 (6) | 4 (12) | 0.42 |
| Permanent pacemaker | 15 (21) | 7 (19) | 8 (24) | 0.77 |
| Hospitalisation for congestive heart failure (< 1 year) | 37 (53) | 21 (58) | 16 (47) | 0.47 |
| Number of previous cardiac surgeries | | | | 0.21 |
| 1 | 46 (66) | 21 (58) | 25 (74) | |
| ≥2 | 24 (34) | 15 (42) | 9 (26) | |
| Time between previous TV surgery and redux TV surgery, years | 10±9 | 9±10 | 11±8 | 0.44 |
| NYHA functional class III-IV | 39 (56) | 25 (69) | 14 (41) | 0.03 |
| Right-sided heart failure signs | 44 (63) | 29 (81) | 15 (44) | 0.003 |
| Ascites | 11 (16) | 9 (25) | 2 (6) | 0.046 |
| Loop diuretics | 53 (76) | 30 (83) | 23 (68) | 0.17 |
| Daily dose of loop diuretics, mg | 60(20-250) | 80(40-250) | 40 [0-180] | 0.16 |
| Atrial fibrillation | 33 (47) | 23 (64) | 10 (29) | 0.005 |
| Biological | | | | |
| Haemoglobin, g/l | 130±24 | 123±20 | 137±27 | 0.02 |
| Creatinine, µmol/l | 91±32 | 94±35 | 89±28 | 0.50 |
| Glomerular filtration rate, ml/min | 83±39 | 73±35 | 94±41 | 0.03 |
| Elevated ALT and/or AST | 15/68 (22) | 11 (31) | 4/32 (13) | 0.07 |
| Elevated GGT and/or ALP | 35/68 (51) | 20 (56) | 15/32 (47) | 0.47 |
| Total bilirubin, µmol/l | 14.2±9.1 | 15.7±10.2 | 12.6±7.5 | 0.17 |
| Elevated bilirubin | 22/68 (32) | 13 (36) | 9 (28) | 0.79 |
| Echocardiographic | | | | |
| LV ejection fraction, % | 59±7 | 58±8 | 59±7 | 0.75 |
| Moderate/severe RV dilatation | 39 (56) | 27 (75) | 12 (35) | 0.007 |
| TAPSE, mm | 14±5 | 16±5 | 12±4 | 0.01 |
| Peak systolic annular velocity S', cm/s | 8.9±2.9 | 9.6±2.7 | 7.9±2.9 | 0.10 |
| Moderate/severe RV dysfunction | 24 (34) | 11 (31) | 13 (38) | 0.62 |
| Systolic pulmonary artery pressure, mmHg | 44±13 | 48±14 | 38±10 | 0.02 |
| TV thrombosis | 3 (4) | 0 (0) | 3 (9) | 0.54 |
| Infective endocarditis and/or periprosthetic leak | 6 (9) | 0 (0) | 6 (18) | 0.01 |
| Risk evaluation | | | | |
| Logistic EuroSCORE | 6.7 [3.3-16.3] | 7.2 [5.6-22.5] | 5.2 [3.3-10.3] | 0.06 |
| EuroSCORE II | 4.1 [2.5-6.4] | 4.8 [2.7-9.2] | 4.0 [2.4-5.0] | 0.03 |
| Charlson comorbidity index | 2(1-4) | 3(1-4) | 1 [0-3] | 0.006 |
| Charlson comorbidity index ³ 2 | 43 (61) | 27 (75) | 16 (47) | 0.044 |
| TRI-SCORE | 4(2-6)(n=68) | 5(2-7)(n=36) | 3(1-5)(n=32) | 0.05 |
| ≤3 | 30 (44) | 11 (31) | 19 (59) | |
| 4-5 | 18 (27) | 11 (31) | 7 (22) | |
| ≥6 | 20 (29) | 14 (38) | 6 (19) | |

Values are number of patients (percentage), mean±SD or median (interquartiles).

Bolded results are statistically significant at the p<0.05 level.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LV, left ventricle; NYHA, New York Heart Association; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TV, tricuspid valve.

Table 2 In-hospital outcomes overall and according to previous TV repair or replacement

| Characteristics | Overall (N=70) | Previous TV repair (n=36) | Previous TV replacement (n=34) | P value |
|---|----------------|---------------------------|--------------------------------|-------------|
| Urgent surgery | 12 (17) | 4 (11) | 8 (24) | 0.21 |
| Sternotomy | 70 (100) | 36 (100) | 34 (100) | 1.00 |
| Beating heart | 22 (31) | 14 (39) | 8 (24) | 0.20 |
| TV replacement | 70 (100) | 36 (100) | 34 (100) | 1.00 |
| Bioprosthesis | 60 (86) | 33 (92) | 27 (79) | 0.18 |
| In-hospital death | 7 (10) | 5 (14) | 2 (6) | 0.43 |
| Major postoperative complications | 24 (34) | 15 (42) | 9 (26) | 0.21 |
| Shock | 18 (26) | 13 (36) | 5 (15) | 0.06 |
| Cardiogenic shock | 13 (19) | 11 (31) | 2 (6) | 0.01 |
| Tamponade | 4 (6) | 2 (6) | 2 (6) | 1.00 |
| Acute renal failure | 20 (29) | 12 (33) | 8 (24) | 0.43 |
| Acute renal failure requiring dialysis | 11 (16) | 8 (22) | 3 (9) | 0.19 |
| Prolonged mechanical ventilation | 7 (10) | 5 (14) | 2 (6) | 0.43 |
| New permanent pacemaker implantation | 15 (21) | 9 (25) | 6 (18) | 0.56 |
| Length of stay in intensive care unit, days | 4 (2–8) | 6 (3–19) | 4 (2–6) | 0.01 |
| Length of stay in hospital, days | 17 (11–31) | 23 (11–37) | 16 (11–21) | 0.15 |
| Postoperative TV leak: no/mild | 70 (100) | 36 (100) | 34 (100) | 1.00 |
| Postoperative TV stenosis | 0 (0) | 0 (0) | 0 (0) | 1.00 |
| Postoperative mean TV gradient, mm Hg | 4±2 | 4±2 | 4±2 | 0.62 |

Values are number of patients (percentage), mean±SD or median (interquartiles). Bolded results are statistically significant at the p<0.05 level. Major postoperative complications were defined as death, shock, tamponade, acute renal failure requiring dialysis or prolonged mechanical ventilation (>72 hours). TV, tricuspid valve.

9% were ITVS; redo ITVS represented 1% of all TV surgeries and 13% of all ITVS. It is important to emphasise that these results are representative of the clinical practice at the nationwide level as these 12 centres accounted for approximately 40% of the surgical volume in France.⁷

Reluctance to perform an ITVS on native valve, and even more for a redo ITVS, is mainly related to the wrong belief of a uniformly high in-hospital mortality. As for ITVS on native valve, in-hospital mortality after redo ITVS was highly variable, hiding important individual disparities (from 0% to 25% according to TRI-SCORE grade), and was mainly driven by clinical presentation, including NYHA functional class, right heart failure, and liver or renal impairment. Interestingly, patients with prior TV repair incurred higher event rate than those with prior TV replacement, but also presented with a more advanced disease stage as illustrated by their higher TRI-SCORE. Thus, these results extend to redo ITVS previous results reported for ITVS on native valve that the reputed high in-hospital mortality observed after ITVS is due to the advanced disease stage more than intrinsically due to the surgery itself.

Table 3 Univariate logistic regression for predictors of in-hospital death in adult patients undergoing a redo isolated TV surgery

| Characteristics | In-hospital death (n=7) | Discharged alive (n=63) | P value |
|---|-------------------------|-------------------------|-------------------|
| Age, years | 58±8 | 54±16 | 0.50 |
| Age ≥70 years | 0 (0) | 10 (16) | 0.58 |
| Female gender | 5 (71) | 39 (62) | 1.00 |
| Body mass index, kg/m ² | 30±9 | 25±5 | 0.05 |
| Hypertension | 1 (14) | 16 (25) | 1.00 |
| Diabetes mellitus | 4 (57) | 4 (6) | 0.002 |
| Chronic lung disease | 1 (14) | 8 (13) | 1.00 |
| Peripheral vascular disease | 0 (0) | 2 (3) | 1.00 |
| Prior stroke | 1 (14) | 5 (8) | 0.48 |
| Coronary artery disease | 2 (29) | 4 (6) | 0.11 |
| Chronic kidney disease | 4 (57) | 12 (19) | 0.043 |
| Chronic liver disease | 3 (43) | 9 (14) | 0.09 |
| Liver cirrhosis | 1 (14) | 5 (8) | 0.48 |
| Permanent pacemaker | 3 (43) | 12 (19) | 0.16 |
| Hospitalisation for congestive heart failure (<1 year) | 6 (86) | 31 (49) | 0.11 |
| Functional aetiology of tricuspid regurgitation before prior TV surgery | 5 (71) | 25 (40) | 0.13 |
| Previous TV repair | 5 (71) | 31 (49) | 0.43 |
| ≥2 previous cardiac surgeries | 3 (43) | 21 (33) | 0.68 |
| NYHA functional class III–IV | 7 (100) | 32 (51) | 0.015 |
| Right-sided heart failure signs | 7 (100) | 37 (59) | 0.041 |
| Ascites | 5 (71) | 6 (10) | 0.001 |
| Loop diuretics | 7 (100) | 46 (73) | 0.18 |
| Daily dose of loop diuretics, mg | 500 (250–750) | 40 (0–80) | 0.006 |
| Daily dose of loop diuretics ≥125 mg | 7 (100) | 14 (22) | <0.0001 |
| Atrial fibrillation | 4 (57) | 29 (46) | 0.70 |
| Haemoglobin, g/L | 109±16 | 132±24 | 0.02 |
| Creatinine, µmol/L | 127±35 | 87±29 | 0.006 |
| Glomerular filtration rate, mL/min | 63±30 | 86±40 | 0.16 |
| Glomerular filtration rate <30 mL/min | 0 (0) | 3 (5) | 1.00 |
| Elevated ALT and/or AST | 2 (29) | 13/61 (21) | 0.65 |
| Elevated GGT and/or ALP | 6 (86) | 29/61 (48) | 0.04 |
| Total bilirubin, µmol/L | 18.3±11.9 | 13.8±8.8 | 0.22 |
| Elevated bilirubin | 3 (43) | 19/61 (31) | 1.00 |
| LV ejection fraction, % | 55±8 | 59±7 | 0.13 |
| LV ejection fraction <60% | 4 (57) | 22 (35) | 0.25 |
| Moderate/severe RV dilatation | 5 (71) | 34 (54) | 0.69 |
| TAPSE, mm | 17±4 | 14±5 | 0.22 |
| Peak systolic annular velocity S', cm/s | 10.8±1.9 | 8.5±2.9 | 0.11 |
| Moderate/severe RV dysfunction | 1 (14) | 23 (37) | 0.25 |

Continued

Table 3 Continued

| Characteristics | In-hospital death (n=7) | Discharged alive (n=63) | P value |
|---|------------------------------|-----------------------------|--------------|
| Systolic pulmonary artery pressure, mm Hg | 45 | 44±13 | 0.92 |
| TR grade | 4 (2–5) | 4 (3–4) | 0.60 |
| Logistic EuroSCORE | 14.9±12.5 15.7 (3.3–23.7) | 11.2±12.7 6.6 (3.3–16.0) | 0.50 |
| EuroSCORE II | 6.0±3.7 5.8 (4.1–8.0) | 5.1±3.5 4.0 (2.5–6.1) | 0.35 |
| TRI-SCORE | 6.6±1.5 6 (5–8) | 3.7±2.5 4 (2–6) | 0.005 |
| Urgent surgery | 1 (14) | 11 (17) | 1.00 |
| Beating heart | 3 (43) | 19 (30) | 0.67 |

Values are number of patients (percentage), mean±SD or median (interquartiles). Bolded results are statistically significant at the p<0.05 level. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LV, left ventricle; NYHA, New York Heart Association; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TV, tricuspid valve.

In this cohort, we have evaluated the prognostic value of the TRI-SCORE. The TRI-SCORE was developed and validated in patients who underwent an ITVS on native valve. It relies on eight clinical, biological and echocardiographic parameters that reflect the disease stage and the consequences of the TV disease on the RV, the kidneys and the liver. These parameters were associated with in-hospital mortality, and the TRI-SCORE also reliably predicted in-hospital mortality after redo ITVS. In contrast, neither the logistic EuroSCORE nor the EuroSCORE II was associated with in-hospital mortality. The discrimination of the TRI-SCORE to predict in-hospital mortality was excellent, with an AUROC of 0.83 vs 0.58 and 0.61 for the two other surgical risk scores. If a TRI-SCORE of ≤3 defined a low surgical risk (in-hospital mortality 3% predicted and 0% observed) for native ITVS, an in-hospital mortality markedly raised above this threshold and a TRI-SCORE of 4–5 were associated with a high in-hospital mortality risk (11% predicted and observed) and a score of ≥6 with a very high risk (38% predicted and 25% observed). It is important to highlight that the TRI-SCORE also accurately predicted the rates of in-hospital major complications and survival free of CHF readmission.

Approximately half of patients had a prior TV repair and all redo ITVS consisted of a TV replacement in our cohort. As a retrospective study, the decision was left to the treating team. Although TR was the main mechanism leading to reintervention after a TV repair, tissue thickening/calcification and the high risk of failure of a redo TV repair logically led to a TV replacement in all patients,¹⁷ especially as patients with prior TV repair

Table 4 Predicted and observed in-hospital mortality rates and major complication rates according to the TRI-SCORE divided into three grades

| TRI-SCORE | Patients (n) | Observed in-hospital mortality | Predicted in-hospital mortality | Major postoperative complications |
|-----------|--------------|--------------------------------|---------------------------------|-----------------------------------|
| 0–3 | 30 | 0 (0) | 1 (3) | 3 (10) |
| 4–5 | 18 | 2 (11) | 2 (11) | 8 (44) |
| ≥6 | 20 | 5 (25) | 8 (38) | 13 (65) |

Values are number of patients (percentage). Major postoperative complications were defined as death, shock, tamponade, acute renal failure requiring dialysis or prolonged mechanical ventilation (>72 hours).

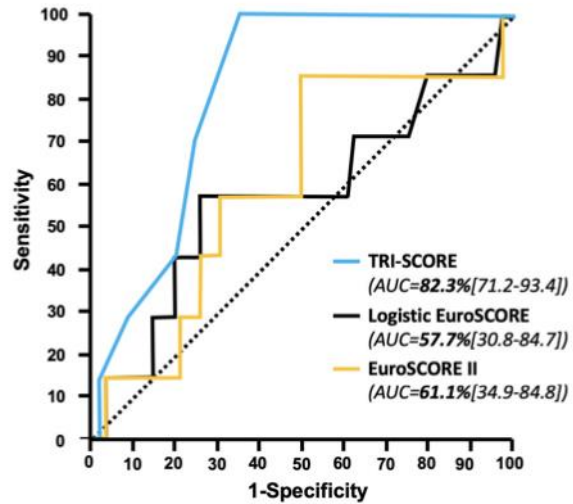


Figure 2 Receiver operating characteristic curve analysis of the risk score models, TRI-SCORE, logistic EuroSCORE and EuroSCORE II, for predicting in-hospital mortality. AUC, area under the curve.

presented with more advanced disease and higher TRI-SCORE than patients with prior TV replacement.

Study limitations

The present study deserves several comments. First, it was a retrospective study. Nevertheless, we were able to collect almost all data and to calculate the TRI-SCORE in all but two patients for whom the bilirubin value was missing, while the two other risk scores were calculated in all 70 patients. Evaluation of the prognostic value of the TRI-SCORE and the comparisons with the other surgical risk scores were thus performed in these 68 patients. Similarly, outcomes were not adjudicated and collected from chart reviews, but our primary endpoint was in-hospital mortality, and the collection of our other outcomes of interest was straightforward with little room for interpretation. Second, our sample size was relatively small. However, we collected all consecutive redo ITVS performed at 12 tertiary French centres during an 11-year period, reflecting real-world practice. Third, as our sample size was small, no meaningful multivariate analysis was performed. However, the aim of the present study was to evaluate the predictive value of the TRI-SCORE for in-hospital mortality. Comparisons with other risk scores should also be considered cautiously as our sample size was small with only seven deaths. Thus, there was a trend towards an association between conventional surgical risk score and in-hospital mortality and we might not have been able to demonstrate a statistical significance due to lack of power. Nevertheless, the AUROC of TRI-SCORE was markedly higher than the AUROC of other surgical risk scores as observed for native ITVS.⁸ Fourth, there is no tricuspid-specific STS score that we could compare with the TRI-SCORE. Fifth, follow-up was complete in only 76% of our population and midterm results should only be regarded as hypothesis-generating. The predictive value of the TRI-SCORE for midterm outcome deserves further validation in this setting. Finally, small single-centre studies have suggested that postoperative mortality and complications might be reduced by minimally invasive techniques.^{18–20} All our patients underwent

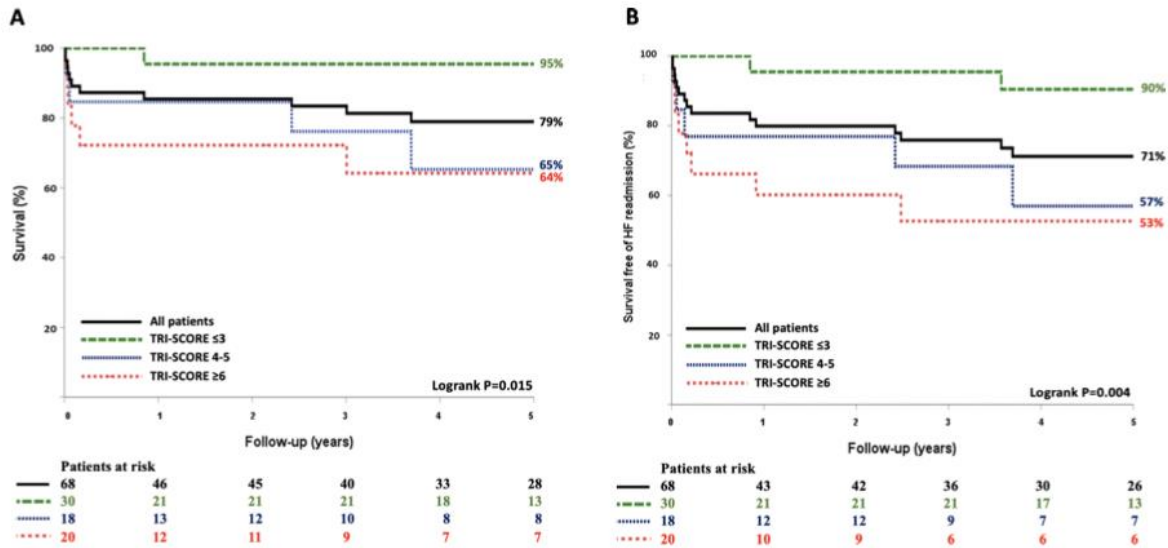


Figure 3 Event rates overall and according to the TRI-SCORE divided into three grades. The figure displays Kaplan-Meier curves of (A) survival rates and (B) survival free of heart failure (HF) readmission rates at 5 years, overall and according to the TRI-SCORE divided into three grades: TRI-SCORE ≤3, TRI-SCORE 4–5 and TRI-SCORE ≥6.

a median sternotomy and we could not comment on the impact of the surgical technique.²¹

Clinical implications

The TRI-SCORE provides an individualised assessment of the operative risk for both native and redo TV interventions. It may be helpful during heart team discussions on the management of patients considered for a redo ITVS to inform patients, cardiologists and cardiac surgeons regarding the expected outcome. The TRI-SCORE should be integrated with other parameters such as the feasibility, safety and efficiency of less invasive transcatheter interventions, acknowledging the fact that infective endocarditis or periprosthetic leak may likely preclude a transcatheter option (observed in 18% of patients who underwent an index TV replacement).^{22–25}

CONCLUSION

In this multicentre series, we collected all consecutive redo ITVS performed at 12 tertiary French centres during an 11-year period. Redo ITVS was rarely performed and was associated with high in-hospital mortality and morbidities, which were hiding important individual disparities, and clinical presentation was the main driver of outcomes. Extending our prior results on native TV, the TRI-SCORE accurately predicted in-hospital mortality, in-hospital complications and midterm outcomes in patients who underwent a redo ITVS, while conventional surgical risk scores did not. The TRI-SCORE (www.tri-score.com) may be helpful during heart team discussion to guide clinical decisions when a redo ITVS is considered, especially as less invasive interventions become available.

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REFERENCES

- Topilsky Y, Maltais S, Medina Inojosa J, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging* 2019;12:433–42.
- Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* 2004;43:405–9.
- Messika-Zeitoun D, Verta P, Gregson J, et al. Impact of tricuspid regurgitation on survival in patients with heart failure: a large electronic health record patient-level database analysis. *Eur J Heart Fail* 2020;22:1803–13.
- Messika-Zeitoun D, Candolfi P, Dreyfus J, et al. Management and outcome of patients admitted with tricuspid regurgitation in France. *Can J Cardiol* 2021;37:1078–85.
- Dreyfus J, Flagiello M, Bazire B, et al. Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes. *Eur Heart J* 2020;41:4304–17.
- Zack CJ, Fender EA, Chandrashekar P, et al. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol* 2017;70:2953–60.
- Dreyfus J, Ghalem N, Garbarz E, et al. Timing of referral of patients with severe isolated tricuspid valve regurgitation to surgeons (from a French nationwide database). *Am J Cardiol* 2018;122:323–6.
- Dreyfus J, Audureau E, Bohbot Y, et al. TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. *Eur Heart J* 2022;43:654–62.
- Jones JM, O'kane H, Gladstone DJ, et al. Repeat heart valve surgery: risk factors for operative mortality. *J Thorac Cardiovasc Surg* 2001;122:913–8.
- Bernal JM, Morales D, Revuelta C, et al. Reoperations after tricuspid valve repair. *J Thorac Cardiovasc Surg* 2005;130:498–503.
- Nashef SA, Roques F, Michel P, et al. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;16:9–13.
- Nashef SAM, Roques F, Sharples LD, et al. EuroSCORE II. *Eur J Cardiothorac Surg* 2012;41:734–44.
- O'Brien SM, Feng L, He X, et al. The society of thoracic surgeons 2018 adult cardiac surgery risk models: part 2—statistical methods and results. *Ann Thorac Surg* 2018;105:1419–28.
- Programme de médicalisation des systèmes d'informations (PMSI). n.d. Available: <http://www.dreessantegouv.fr/redressements-du-programme-de-medicalisation-des-systemes-d-informations-pmsi>
- Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;16:777–802.
- Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;30:303–71.
- McCarthy PM, Bhudia SK, Rajeswaran J, et al. Tricuspid valve repair: durability and risk factors for failure. *J Thorac Cardiovasc Surg* 2004;127:674–85.
- Chen J, Ma W, Ming Y, et al. Minimally invasive valve replacement for late tricuspid regurgitation after left-sided valve surgery. *Ann Thorac Surg* 2021;111:e381–3.
- Hanedan MO, Çiçekçiöğlü F, Aksöyek A, et al. Tricuspid valve replacement through right thoracotomy has better outcomes in redo cases. *Heart Lung Circ* 2017;26:88–93.
- Pfannmüller B, Misfeld M, Borger MA, et al. Isolated reoperative minimally invasive tricuspid valve operations. *Ann Thorac Surg* 2012;94:2005–10.
- Russo MJ, Thourani VH, Cohen DJ, et al. Minimally invasive versus full sternotomy for isolated aortic valve replacement in low-risk patients. *Ann Thorac Surg* 2022;114:2124–30.
- McElhinney DB, Cabalka AK, Aboulhosn JA, et al. Transcatheter tricuspid valve-in-valve implantation for the treatment of dysfunctional surgical bioprosthetic valves: an international, multicenter registry study. *Circulation* 2016;133:1582–93.
- McElhinney DB, Aboulhosn JA, Dvir D, et al. Mid-term valve-related outcomes after transcatheter tricuspid valve-in-valve or valve-in-ring replacement. *J Am Coll Cardiol* 2019;73:148–57.
- Aboulhosn J, Cabalka AK, Levi DS, et al. Transcatheter valve-in-ring implantation for the treatment of residual or recurrent tricuspid valve dysfunction after prior surgical repair. *JACC Cardiovasc Interv* 2017;10:53–63.
- Bouleti C, Juliard J-M, Himbert D, et al. Tricuspid valve and percutaneous approach: no longer the forgotten valve! *Arch Cardiovasc Dis* 2016;109:55–66.

Article 9

First-in-human implantation of the Topaz transcatheter tricuspid valve replacement system

Teiger E, Nejjari M, Lim P, Ruf T, Blanke P, Schäfer U,
Treede H, Gallet R, **Dreyfus J**

EuroIntervention. 2022 Nov 18;18(10):862-864

Article 9 : Première implantation chez l'homme d'un système de remplacement valvulaire tricuspide percutané avec la prothèse TOPAZ

Afin de pouvoir proposer une solution thérapeutique curative aux patients présentant une IT sévère qui sont à haut risque opératoire, le traitement percutané, moins invasif que la chirurgie, est actuellement en plein essor avec de nombreux systèmes en cours de développement et/ou de validation, que ce soit des solutions de réparation ou de remplacement de la VT^{75,101-103}.

La prothèse Topaz (TRiCares) est un nouveau système de remplacement percutané de la VT par voie transfémorale, auto-expansible, orthotopique, conçu avec un cadre à deux stents en nitinol. Le stent externe s'adapte à la morphologie de la VT et à ses variations au cours du cycle cardiaque pour permettre un ancrage étanche au niveau de la VT tout en protégeant le deuxième stent, interne, de toute déformation causée par la contraction du VD. Le stent interne, de morphologie circulaire et rigide, contient la valve avec trois feuillets fabriqués avec du péricarde porcine, et agit indépendamment du stent externe auquel il est relié (Figure 48). Des implantations de cette prothèse ont été réalisées avec succès chez l'animal.

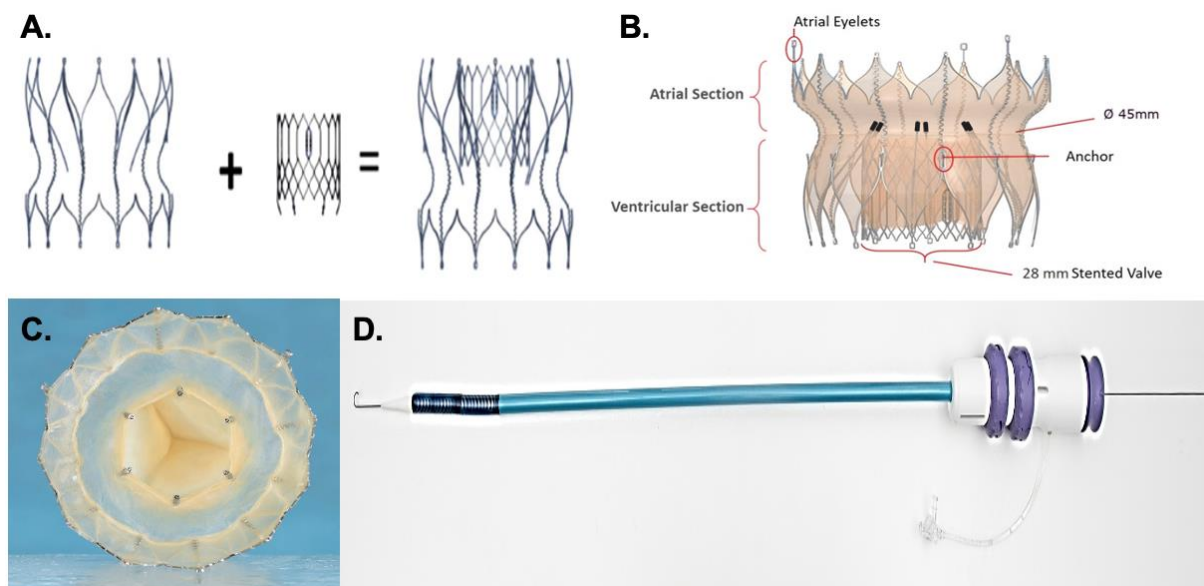


Figure 48. Système de remplacement percutané de la valve tricuspide Topaz

- A. et B. Illustration d'une vue latérale de la prothèse avec les 2 stents, séparés puis assemblés, et les ancres
- C. Vue en face atriale de la prothèse avec les 2 stents et les 3 feuillets valvulaires

D. Cathéter pour l'abord fémoral

L'objectif de cette étude était de réaliser les premières implantations chez l'homme de la prothèse Topaz, nouveau système de remplacement valvulaire tricuspide percutané par voie transfémorale.

Nous rapportons les deux premiers cas d'utilisation compassionnelle du système percutané Topaz pour le traitement d'une IT. Ces deux procédures avaient été approuvées par l'Agence Nationale de Sécurité du Médicament et des produits de santé. Les deux interventions ont été réalisées en juin 2021. Les patients étaient des femmes de 70 ans (patient 1) et de 86 ans (patient 2). Elles présentaient des IT fonctionnelles respectivement massive et torrentielle¹⁹, dont le mécanisme était une dilatation de l'AT secondaire à une FA chronique. Les deux patients avaient été récusés pour un traitement curatif chirurgical devant un risque opératoire considéré élevé avec des TRI-SCORE⁸⁴ à 5 (mortalité hospitalière post-opératoire prédite de 14%) et 6 (mortalité hospitalière post-opératoire prédite de 22%) respectivement, et n'étaient pas éligibles pour une réparation percutanée bord-à-bord de la VT en raison de défauts de coaptation trop larges malgré le traitement médical optimal (Figure 49).

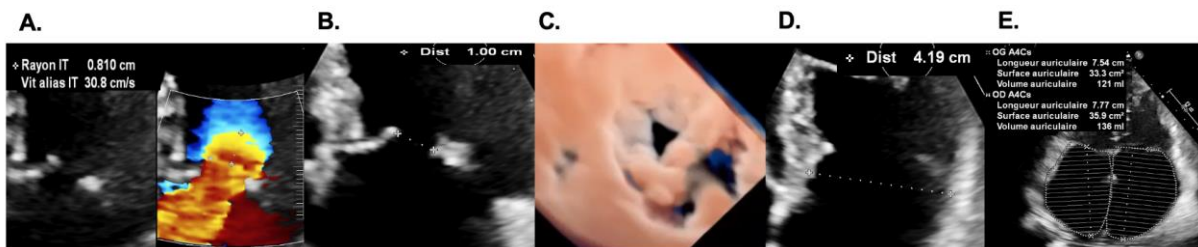


Figure 49. Evaluation pré-procédurale de l'insuffisance tricuspide par échocardiographie transthoracique

- A. Rayon de PISA de l'insuffisance tricuspide
- B. Largeur du défaut de coaptation valvulaire tricuspide en bidimensionnel
- C. Défaut de coaptation valvulaire tricuspide en tridimensionnel
- D. Diamètre de l'anneau tricuspide
- E. Dimensions des oreillettes droite et gauche

Le scanner cardiaque retrouvait une anatomie compatible avec l'implantation d'une

prothèse Topaz (angle entre la veine cave inférieure et l'AT, dimensions de l'AT, taille et morphologie du VD...) (Figure 50), sachant qu'il n'y avait qu'une seule taille de prothèse disponible (45mm).

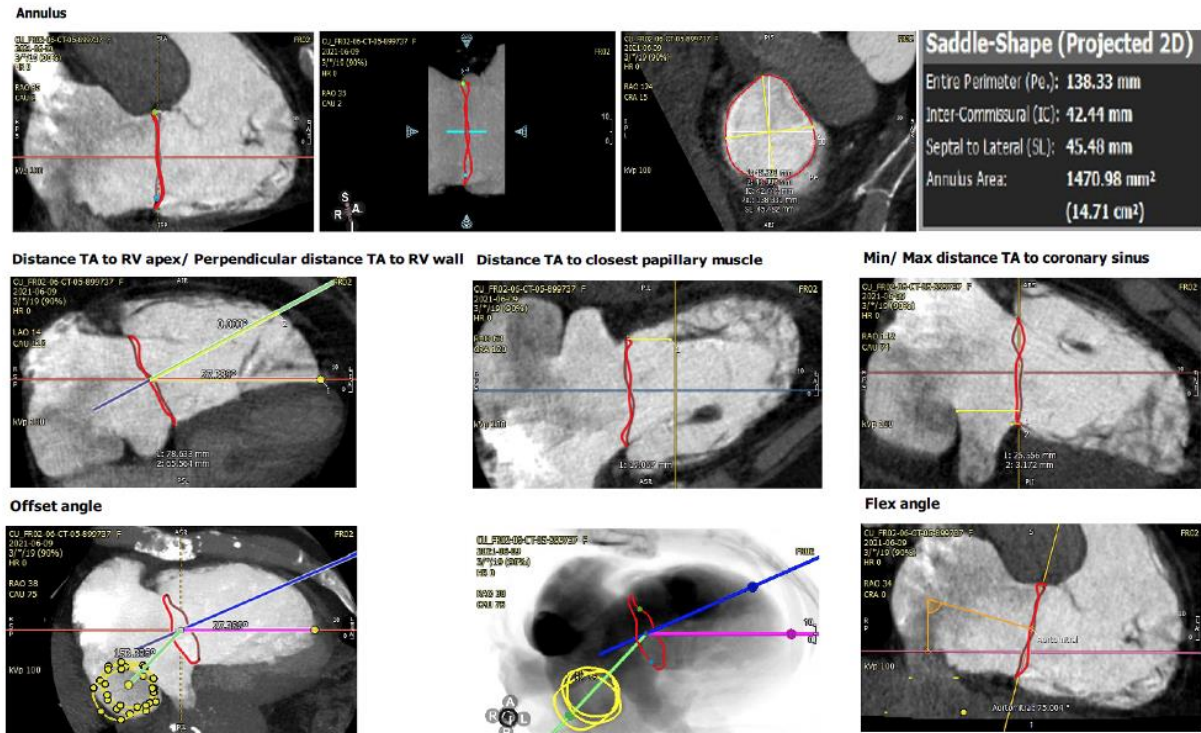


Figure 50. Analyse du scanner cardiaque réalisé dans le cadre du bilan pré-procédural, avec différents plans de coupes et mesures
RV : ventricule droit, TA : anneau tricuspide,

La faisabilité technique avait ensuite été confirmée après impression 3D du cœur des patients et simulation de l'implantation des prothèses (Figure 51).

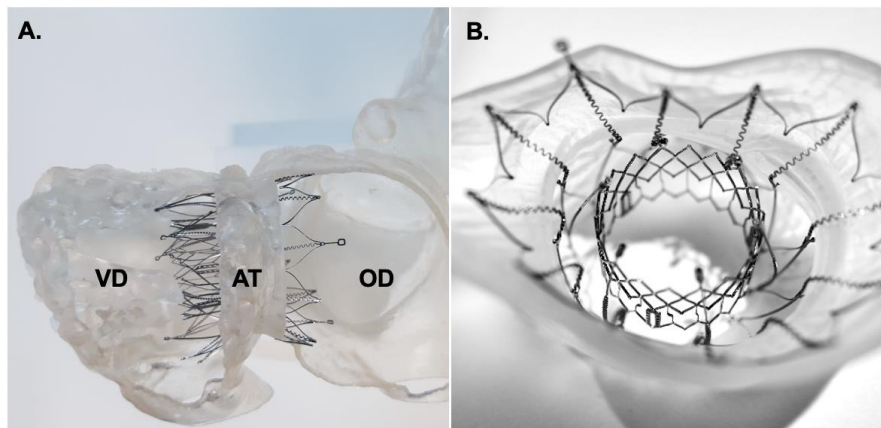


Figure 51. Simulation d'une prothèse Topaz implantée au niveau de la valve tricuspide à partir d'une impression en trois dimensions du cœur du patient

A. Coupe longitudinale des cavités droites

B. Vue en face atriale droite de la valve tricuspide permettant la visualisation des deux stents de la prothèse

AT : anneau tricuspide, OD : oreillette droite, VD : ventricule droit

Les interventions ont été réalisées sous anesthésie générale, avec un abord veineux fémoral, guidées par fluoroscopie et ETO, notamment dans l'incidence transgastrique avec reconstructions multiplanaires (Figure 52).

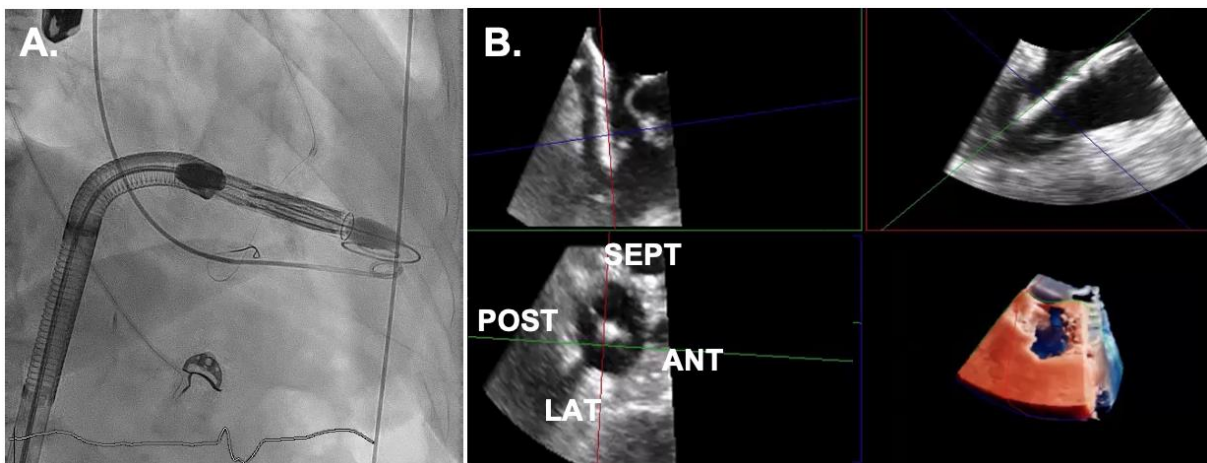


Figure 52. Guidage péri-procédural de l'implantation de la prothèse tricuspide percutanée Topaz

A. Fluoroscopie

B. Echocardiographie trans-oesophagienne dans l'incidence transgastrique avec reconstructions multi-planaires

Ant : antérieur, Lat : latéral, Sept : septal, Post : postérieur

Le succès de la procédure (défini comme l'implantation de la prothèse à la position souhaitée sans migration ni fuite paravalvulaire significative) a été obtenu dans les deux cas, avec une durée de procédure courte (18 et 12 minutes respectivement de l'introduction à la

sortie du système) et sans complications. Les résultats hémodynamiques immédiats étaient excellents, avec un bon déploiement de la prothèse au niveau souhaité, un gradient transvalvulaire antérograde moyen de 2 mmHg chez les deux patients, l'absence d'IT résiduelle et l'absence de régurgitation péri-prothétique (Figure 53).

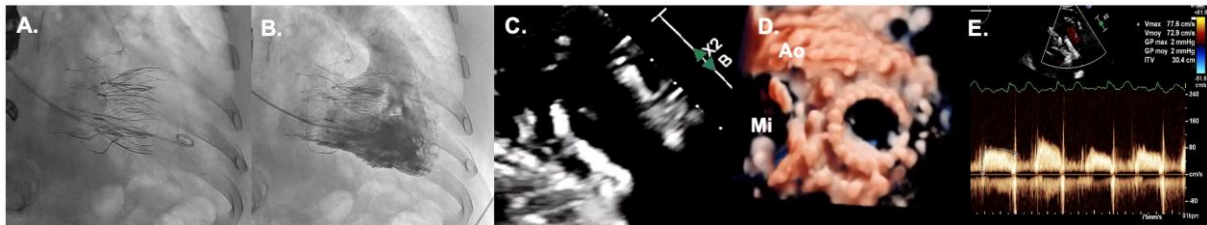


Figure 53. Résultat post-procédural immédiat après implantation de la prothèse Topaz au niveau de la valve tricuspide

A. Prothèse visualisée en fluoroscopie

B. Angiographie du ventricule droit

C. Prothèse visualisée en échocardiographie transthoracique bidimensionnelle

D. Prothèse visualisée en échocardiographie transthoracique tridimensionnelle

E. Gradient moyen antérograde trans-prothétique en échocardiographie transthoracique

Ao : valve aortique, Mi : valve mitrale

Le scanner cardiaque post-procédural avant la sortie d'hospitalisation retrouvait une prothèse parfaitement bien déployée, avec un bon fonctionnement des cusps, sans interaction pathologique avec les autres structures, ni d'autre anomalie (Figure 54).

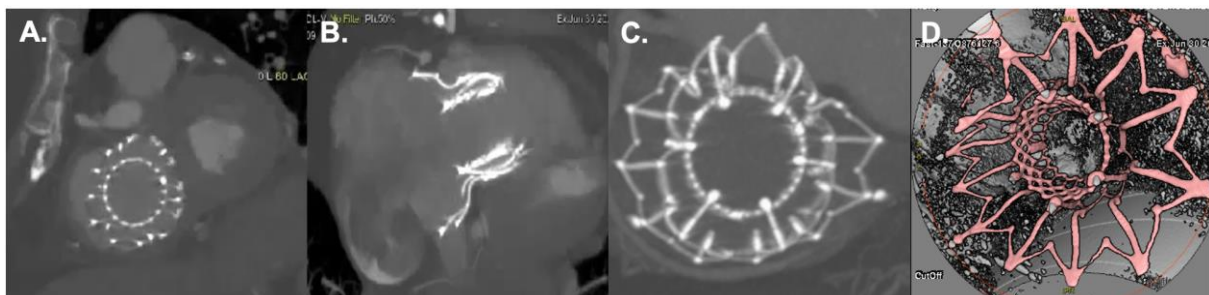


Figure 54. Scanner post-procédural après implantation de la prothèse Topaz au niveau de la valve tricuspide

A., B., C. et D représentent différents plans de coupe et reconstructions

Les deux patients sont sortis le quatrième jour post-procédural, et sont restés sous anticoagulation orale qui était indiquée pour de la FA.

A 3 mois de l'intervention, les deux patients n'ont présenté aucune complication (pas de décès, pas d'anomalie de conduction, pas de ré-hospitalisation, notamment pour IC...) et ont présenté une amélioration clinique rapide et très franche (classe fonctionnelle NYHA passée de III à I et absence de signes cliniques d'IC droite pour les deux patients). Chez le patient 1, le furosémide a été arrêté alors qu'il prenait 500 mg par jour avant l'intervention.

L'ETT réalisée à 3 mois de l'intervention retrouvait un bon résultat hémodynamique, sans fuite résiduelle intra- ou péri-prothétique et un gradient transvalvulaire antérograde moyen inchangé (2 mmHg pour les deux patients) (Figure 55).

Le scanner cardiaque réalisée à 3 mois de l'intervention n'a révélé aucune thrombose de prothèse.

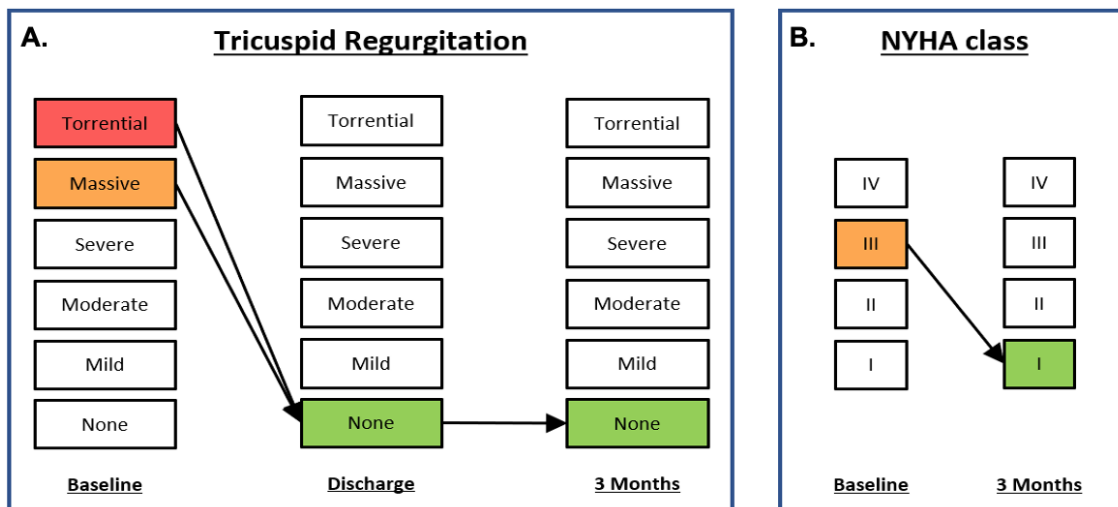


Figure 55. Evolution du degré de sévérité de l'insuffisance tricuspide et du statut fonctionnel des patients avant et 3 mois après remplacement valvulaire tricuspide percutané par la prothèse Topaz

A. Grade de sévérité de l'insuffisance tricuspide

B. Classe fonctionnelle NYHA

Cette première expérience humaine avec le système de remplacement percutané de la VT Topaz montre sa faisabilité et sa sécurité, permettant d'abolir l'IT et d'offrir aux patients une franche amélioration clinique très rapidement après l'intervention.

First-in-human implantation of the Topaz transcatheter tricuspid valve replacement system

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Introduction

Severe tricuspid regurgitation (TR) is frequent and associated with poor outcomes¹. Nevertheless, many patients are declined for surgery because of prohibitive surgical risks. In this setting, transcatheter tricuspid valve (TV) intervention may be a less invasive option. Transcatheter edge-to-edge repair (TEER) has been the most used approach so far²; however, transcatheter tricuspid valve replacement (TTVR) might be a more attractive strategy. Indeed, besides providing an alternative for patients whose anatomies are not suitable for TEER (due to large coaptation gaps or short/retracted septal leaflets), TTVR procedures are likely to be less challenging and more reproducible, as demonstrated in the first-in-human trials³.

Methods

The Topaz transfemoral tricuspid heart valve replacement system (TRiCares) is a novel orthotopic self-expanding TTVR system designed with a two-stent frame made of nitinol. The outer

stent provides a sealed anchoring into the native tricuspid apparatus while protecting the inner stent, which contains the valve, from any deformation caused by the contraction of the right ventricle (RV). The stiffer inner stent houses the three-leaflet valve made from porcine pericardium, which acts independently of the outer stent, thus allowing it to maintain a circular shape and full valve integrity. The system is delivered via the femoral vein through a 29 Fr steerable introducer, currently with no possibility of recapture. The steerable introducer is first brought into the right atrium and oriented toward the tricuspid annulus. The crimped valve is then advanced to the apex of the RV and deployed in a two-step procedure, first the ventricular part of the valve and then the atrial part. The anchoring mechanism does not rely on radial force but on a layer of anchors located below the annulus level. Therefore, no oversizing of the valve is needed. To date, only one size of the valve is available, which allows treatment of an annulus diameter <45 mm based on diastolic computed tomography (CT) scan measurements.

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We herein report the first two cases of compassionate use of the TRiCares Topaz transfemoral tricuspid heart valve replacement system for the treatment of TR. These two cases were

approved by the French authorities (Agence nationale de sécurité du médicament et des produits de santé [ANSM]; Ref. No. 2100459) (Figure 1).

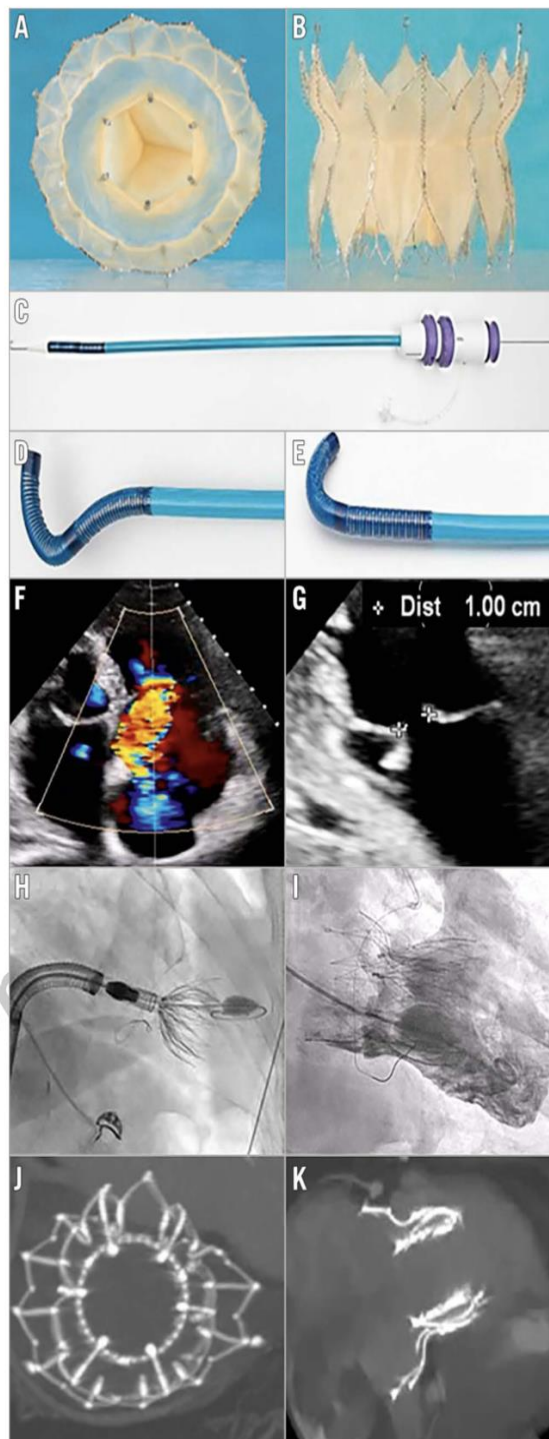


Figure 1. Topaz orthotopic transcatheter tricuspid valve replacement for severe TR. Topaz system: a two-stent design, self-expanding prosthesis with 3 porcine pericardium leaflets; the outer stent adapts to the anatomy while the inner stent is more rigid, thus maintaining a circular shape. A) En face view; B) side view. C, D & E) Double-curve steerable sheath for transvenous femoral access. F) Colour Doppler view of the preprocedural torrential tricuspid regurgitation of patient 2 (all the following images are also for patient 2). G) Two-dimensional echographic view of the tricuspid valve coaptation defect. H) Fluoroscopic view of valve deployment. I) Right ventricular angiography immediately after valve deployment. J & K) Post-procedural CT showing the round inner stent linked to the outer stent that conforms to the patient's anatomy. CT: computed tomography; TR: tricuspid regurgitation

Results

The two procedures were performed in June 2021. The patients were 70-year-old (patient 1) and 86-year-old (patient 2) females. They presented with massive and torrential functional TR¹ due to tricuspid annulus dilatation related to chronic atrial fibrillation. However, both were declined for surgery by the local Heart Teams because of prohibitive surgical risks with TRI-SCOREs of 5 (intermediate risk) and 6 (high risk), respectively⁴, and were not considered suitable for TEER owing to excessive coaptation gaps⁵.

Interventions were performed under general anaesthesia, using a transvenous femoral approach and guided by fluoroscopy and transoesophageal echocardiography. Procedural success (defined as implantation of the valve at the intended position without migration or significant paravalvular leak) was achieved in both cases, with a short procedure time (18 and 12 minutes, respectively, from delivery system in to delivery system out) and with no adverse events. Immediate haemodynamic results were excellent, with good valve deployment at the intended annular position, a mean transvalvular gradient of 2 mmHg in both patients, no residual TR and no paravalvular regurgitation. The two patients were discharged on day four and, given the setting of atrial fibrillation, remained on a non-vitamin K oral anticoagulant.

Discussion

No death or complication and, notably, no rehospitalisation for heart failure occurred before the post-procedure 3-month follow-up. Transthoracic echocardiography at 3 months showed sustained haemodynamics with no residual TR and an unchanged mean transvalvular gradient (2 mmHg for both patients). However, while there was complete resolution of TR, RV function decreased at three months in both patients (tricuspid annular plane systolic excursion [TAPSE]: 18 mm to 11 mm in patient 1 and 14 mm to 11 mm in patient 2). The three-month CT scan did not reveal any valve thrombosis. Clinical improvement was significant, with an improvement in New York Heart Association (NYHA) functional status from Class III to Class I in both patients. Moreover, in patient 1, the furosemide dose was decreased from 500 mg to none, and the right heart failure symptoms (oedema and jugular congestion) present at baseline were not present at 3 months. Finally, no conduction abnormalities were observed during follow-up.

Limitations

As further investigations are needed, the TRICURE first-in-human trial is planned to start soon.

Conclusions

This first-in-human experience with the Topaz TTVR confirms feasibility and safety, abolishing TR with an effective associated short-term clinical improvement.

Conflict of interest statement

T. Ruf is a consultant and proctor for TRiCares, Abbott Laboratories, and Edwards Lifesciences. P. Blanke is a shareholder of TRiCares. U. Schäfer is a shareholder of TRiCares. H. Treede is a shareholder of TRiCares. R. Gallet is a shareholder of TRiCares. P. Lim is the founder and a shareholder of TRiCares. The other authors have no conflicts of interest to declare.

References

- Messika-Zeitoun D, Verta P, Gregson J, Pociock SJ, Boero I, Feldman TE, Abraham WT, Lindenfeld J, Bax J, Leon M, Enriquez-Sarano M. Impact of tricuspid regurgitation on survival in patients with heart failure: a large electronic health record patient-level database analysis. *Eur J Heart Fail.* 2020;22:1803-13.
- Taramasso M, Benfari G, van der Bijl P, Alessandrini H, Attinger-Toller A, Biasco L, Lurz P, Braun D, Brochet E, Connelly KA, de Bruijn S, Denti P, Deuschl F, Estevez-Loureiro R, Fam N, Frerker C, Gavazzoni M, Hausleiter J, Ho E, Juliard JM, Kaple R, Besler C, Kodali S, Kreidel F, Kuck KH, Latib A, Lauten A, Monivas V, Mehr M, Muntané-Carol G, Nazif T, Nickening G, Pedrazzini G, Philippon F, Pozzoli A, Praz F, Puri R, Rodés-Cabau J, Schäfer U, Schofer J, Sievert H, Tang GHL, Thiele H, Topilsky Y, Rommel KP, Delgado V, Vahanian A, Von Bardeleben RS, Webb JG, Weber M, Windecker S, Winkel M, Zuber M, Leon MB, Hahn RT, Bax JJ, Enriquez-Sarano M, Maisano F. Transcatheter Versus Medical Treatment of Patients With Symptomatic Severe Tricuspid Regurgitation. *J Am Coll Cardiol.* 2019;74:2998-3008.
- Fam NP, von Bardeleben RS, Hensey M, Kodali SK, Smith RL, Hausleiter J, Ong G, Boone R, Ruf T, George I, Szerlip M, Nábauer M, Ali FM, Moss R, Bapat V, Schnitzler K, Kreidel F, Ye J, Deva DP, Mack MJ, Grayburn PA, Peterson MD, Leon MB, Hahn RT, Webb JG. Transcatheter Tricuspid Valve Replacement With the EVOQUE System: A Multicenter, Observational, First-in-Human Experience. *JACC Cardiovasc Interv.* 2021;14:501-11.
- Dreyfus J, Audureau E, Bohbot Y, Coisne A, Lavie-Badie Y, Bouchery M, Flaggiello M, Bazire B, Eggenspieler F, Viau F, Riant E, Mbaki Y, Eyharts D, Senage T, Modine T, Nicol M, Doguet F, Nguyen V, Le Tourneau T, Tribouilloy C, Donal E, Tomasi J, Habib G, Selton-Suty C, Raffoul R, Lung B, Obadia JF, Messika-Zeitoun D. TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. *Eur Heart J.* 2022;43:654-62.
- Ruf TF, Hahn RT, Kreidel F, Beiras-Fernandez A, Hell M, Gerdes P, da Roche E Silva JG, Vosseler M, Geyer M, Tamm A, Münzel T, von Bardeleben RS. Short-Term Clinical Outcomes of Transcatheter Tricuspid Valve Repair With the Third-Generation MitraClip XTR System. *JACC Cardiovasc Interv.* 2021;14:1231-40.

Conclusions et perspectives

L'IT, qui a été longtemps négligée, est actuellement considérée comme un problème de santé publique nécessitant une prise en charge adaptée du fait de l'augmentation de sa prévalence liée au vieillissement de la population et de sa gravité puisqu'elle est associée à une morbidité (diminution des capacités fonctionnelles, insuffisance cardiaque) et une mortalité importantes.

Au travers de ces travaux, nous avons abordé cette pathologie de son diagnostic à sa prise en charge.

Nous avons montré qu'une IT significative, qui est le plus souvent fonctionnelle et secondaire à une valvulopathie du cœur gauche, est fréquemment retrouvée chez les patients ayant une valvulopathie mitrale sévère mais beaucoup plus rare chez les patients ayant une valvulopathie aortique sévère.

L'évaluation des grades de sévérité de l'IT, principalement réalisée en ETT^{18,19}, reste débattue (Annexe – Article 12) et un défi en pratique^{14,104} (Annexe – Revue 1) sachant qu'elle doit être basée sur une analyse multiparamétrique dans l'attente de logiciels qui permettront une analyse tridimensionnelle fiable, adaptée à la morphologie de la VT de chaque patient qui est extrêmement variable d'un individu à l'autre¹⁰⁵.

La littérature est consensuelle pour dire que l'IT est un facteur pronostic associé à une morbi-mortalité d'autant plus importante qu'elle est sévère, ce que nous avons également retrouvé chez les patients ayant une valvulopathie sévère du cœur gauche, et ce quel que soit la valvulopathie du cœur gauche.

Pour autant, bien que la mortalité et la morbidité à court terme des patients hospitalisés pour IT pris en charge médicalement soient considérables, la très grande majorité d'entre eux n'a pas de traitement curatif puisque seuls 10% bénéficient d'un traitement chirurgical sur la VT⁸⁵.

Il faut distinguer 2 situations cliniques.

Dans la première situation, le patient est adressé pour une chirurgie valvulaire du cœur gauche. Les recommandations Américaines et Européennes suggèrent alors de réaliser un geste concomitant sur la VT en cas d'IT sévère (indication de classe I) ou lorsque l'AT est dilaté (indication de classe IIa)^{39,40} (Figure 56).

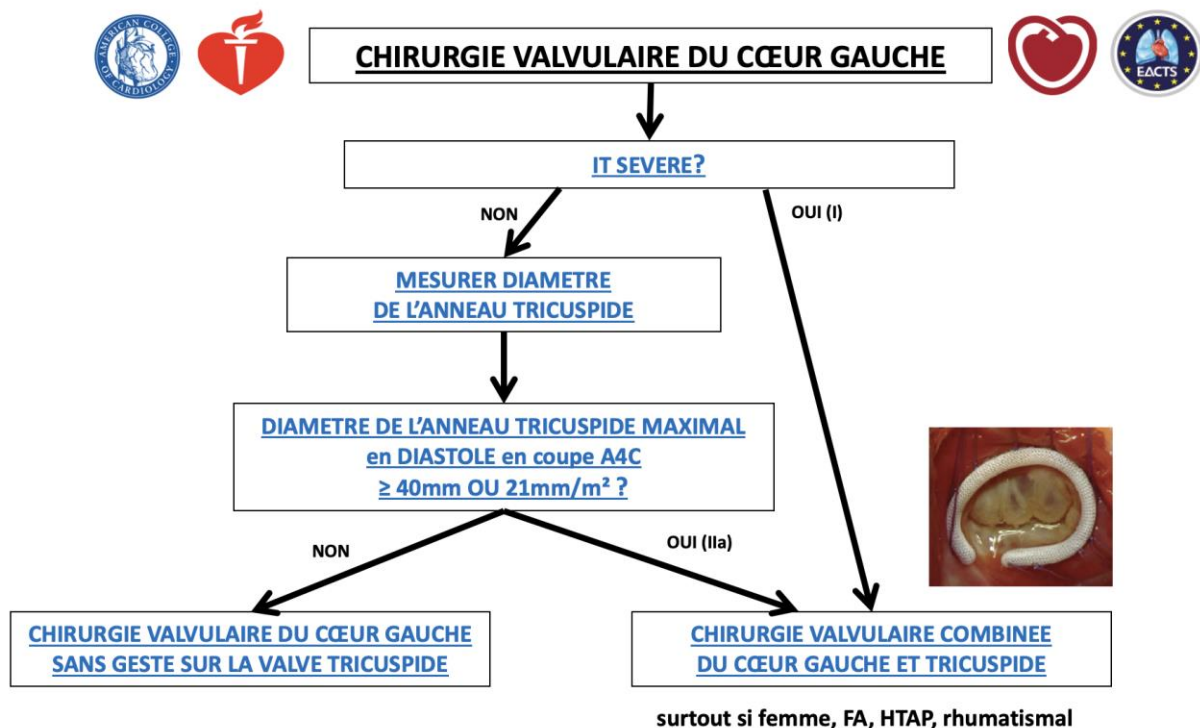


Figure 56. Indications de geste chirurgical sur la valve tricuspide au moment d'une chirurgie valvulaire du cœur gauche

FA : fibrillation atriale, HTAP : hypertension artérielle pulmonaire

Nous avons montré que ces recommandations sont bien respectées en pratique pour les patients ayant une indication de classe I.

Les indications de classe IIa sont basées sur la dilatation de l'AT en ETT avec un seuil de 40 mm ou 21 mm/m², sans préciser l'incidence échocardiographique. Nous avons montré que la mesure du diamètre de l'AT dans l'incidence A4C était la plus facile à réaliser et la plus reproductible des incidences en ETT, et bien que sous-estimant de façon systématique la mesure du grand axe de l'AT comparativement à l'ETO-3D, elle offrait un bon reflet du degré de dilatation de l'AT. Les seuils pathologiques que nous avons obtenus étaient relativement proches de ceux proposés dans les recommandations et actuellement utilisés¹⁰⁵.

En pratique, le nombre de chirurgies de la VT concomitante d'une chirurgie valvulaire du cœur gauche est en constante augmentation et représente actuellement plus de 90% des chirurgies de la VT⁶⁹.

Dans la deuxième situation, le patient présente une IT sévère isolée. Les recommandations Américaines et Européennes suggèrent de réaliser une chirurgie isolée de la VT chez les patients ayant une IT sévère qui sont symptomatiques ou qui ont une dilatation du VD, en l'absence de dysfonction VD ou VG sévère ou d'HTAP^{39,40}.

Chez les patients ayant une IT fonctionnelle isolée, nous avons montré que la dilatation et le remodelage des cavités droites sont bien corrélés avec le degré de sévérité de l'IT fonctionnelle, mais sans altération concomitante des paramètres de fonction ventriculaire droite¹⁰⁴.

Contrairement à sa prévalence et à l'ampleur du problème, la grande majorité des patients avec IT sévère isolée est traitée uniquement médicalement par diurétiques pour soulager les symptômes. Ainsi, nous avons montré qu'un traitement chirurgical curatif isolé de la VT pour IT sévère n'est réalisé que chez environ 120 patients/an en France, ce qui correspond à moins de 10% de toutes les chirurgies de la VT^{69,80}.

Une des raisons pour expliquer la réticence à adresser ces patients en chirurgie est le taux de mortalité hospitalière élevé de cette intervention observé dans toutes les séries, y compris dans notre registre Français ($\approx 10\%$)^{69,79,80}.

Nous avons montré que ce taux moyen cachait d'importantes disparités et était prédit par la sévérité de la présentation préopératoire, tandis que le mécanisme/étiologie de l'IT avait un impact limité⁶⁹.

Afin de pouvoir évaluer ce risque à l'échelon individuel, nous avons développé le TRI-SCORE, premier score de risque spécifiquement dédié à la prédiction de la mortalité hospitalière après chirurgie isolée de la VT pour IT sévère sur valve native, basé sur 8 paramètres cliniques, biologiques et échocardiographiques faciles à évaluer et qui reflètent le retentissement de l'IT sur le VD, le foie et les reins⁸⁴. Ce score, simple et fiable, est valide quel que soit le mécanisme de l'IT.

Nous avons montré que le TRI-SCORE est aussi fiable pour prédire le risque de mortalité hospitalière après chirurgie isolée de la VT chez les patients redx sur la VT et qu'il

est également associé aux taux de complications post-opératoires et à la mortalité à moyen terme, que ce soit pour des interventions sur VT native ou redux⁸⁴.

Afin de faciliter son utilisation en routine, nous avons mis à disposition un calculateur en ligne gratuit de ce score (www.tri-score.com) et une application sera bientôt disponible pour téléphones portables et tablettes sur iOS et android.

L'utilisation du Levosimendan, substance inotrope et vasodilatatrice, semble offrir un bénéfice temporaire chez les patients présentant une IT fonctionnelle sévère compliquée d'IC (Annexe – Article 13). Aussi, dans le but d'essayer de diminuer la mortalité hospitalière après chirurgie de la VT, une étude multicentrique randomisée Française est en cours pour évaluer le bénéfice du LEVOSIMENDAN vs placebo en pré-opératoire de cette intervention (étude LEONARD).

Moins invasif que le traitement chirurgical, le traitement percutané de l'IT est actuellement en plein développement et pourrait permettre d'augmenter le nombre de patients traités. La porte a d'ailleurs été entre-ouverte dans les dernières recommandations Européennes pour le traitement percutané³⁹. Les résultats des études préliminaires semblent prometteurs, que ce soit avec les outils de réparation valvulaire^{55,56}, la technique de réparation bord-à-bord des feuillets valvulaires étant la plus largement répandue actuellement, ou avec les prothèses comme la prothèse Topaz que nous avons implantée^{102,106}. Plusieurs essais contrôlés randomisés sont en cours (TRILUMINATE Pivotal Trial, CLASP II TR, TRISCEND II Pivotal trial)¹⁰⁷ (Annexe – Editorial 2) dont un Français (TRI-FR)⁷⁶ (Annexe – Article 14), visant à évaluer le bénéfice des traitements percutanés par rapport au traitement médical seul et à fournir davantage de preuves concernant le moment et le type d'intervention les plus appropriés pour améliorer le pronostic des patients atteints d'IT sévère. Ces études pourraient permettre de démontrer formellement que l'IT n'est pas un simple marqueur de risque mais que la correction de l'IT améliore le pronostic. Pour d'autres solutions thérapeutiques percutanées qui sont à un stade moins avancé, notamment des prothèses valvulaires⁵³ (Annexe – Revue 2), des études compassionnelles sont en cours ou à venir (dont les études TRINITY avec la prothèse LuX et TRICURE avec la prothèse Topaz auxquels nous participons).

Le TRI-SCORE pourrait servir d'outil unique pour caractériser et comparer les populations incluses dans ces essais sachant que les patients ayant une IT forment une population hétérogène. Cela pourrait permettre d'éviter d'obtenir des résultats divergents entre

ces essais comme pour COAPT et MITRA-FR^{108,109}. Dans cet esprit, nous sommes actuellement en train d'utiliser le TRI-SCORE pour comparer des cohortes de patients avec IT sévère traitées médicalement, chirurgicalement ou par voie percutanée dans un registre multicentrique international (étude TRIGISTRY).

La question du moment de l'intervention reste controversée. Nous avons montré que les patients sont souvent opérés à un stade évolué dans l'histoire naturelle de l'IT (TRI-SCORE ≥ 4 chez la moitié des patients) et que le pronostic est corrélé au TRI-SCORE, avec un excellent pronostic à court et moyen terme pour les patients avec un TRI-SCORE bas (≤ 3) et un pronostic d'autant plus sombre que le TRI-SCORE augmente⁸⁴. Ces résultats sont concordants avec ceux d'autres équipes^{23,25}.

Nos résultats suggèrent d'adopter une approche plus proactive pour les interventions sur la VT, plus précocement dans l'évolution de la maladie chez les patients atteints d'IT sévère isolée, quel que soit le mécanisme/l'étiologie de l'IT, avant l'apparition de conséquences avancées/irréversibles telles qu'une dilatation ou une dysfonction VD sévère, une insuffisance rénale, une insuffisance hépatique ou une IC réfractaire, la réalisation d'une intervention à un stade avancé de la maladie pouvant être considérée comme futile^{110,111} (Figure 57 et Annexe – Editorial 3).

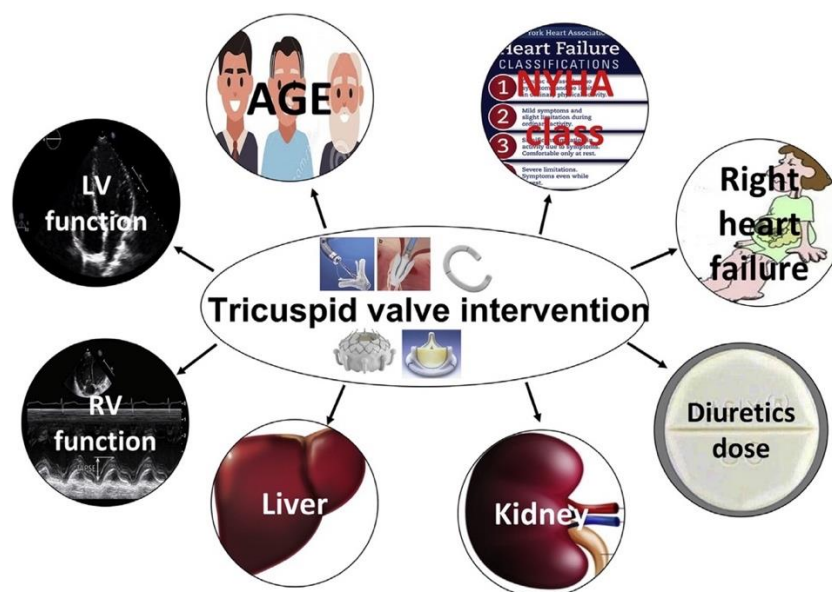


Figure 57. Principaux déterminants du pronostic chez les patients présentant une insuffisance

tricuspide sévère référés pour une intervention, d'après Messika-Zeitoun et al¹¹¹

Le TRI-SCORE pourrait ainsi conduire à des interventions chirurgicales ou percutanées plus précoces et pourrait permettre d'augmenter le nombre de patients traités, avant l'apparition de conséquences graves/irréversibles de l'IT sévère qui affectent considérablement le pronostic.

Comme suggéré dans les recommandations³⁹, les patients présentant une IT sévère doivent être évalués dans des centres experts, où la « Heart Valve Team », équipe multidisciplinaire intégrant des cardiologues (imageurs et interventionnels), des chirurgiens cardiaques, des anesthésistes et d'autres spécialistes, pour discuter la stratégie thérapeutique la plus appropriée à l'échelon individuel¹⁵. Plusieurs paramètres doivent être pris en compte par cette équipe parmi lesquels le risque opératoire évalué par le TRI-SCORE et la faisabilité des procédures en considérant l'anatomie et la qualité de l'imagerie pour les procédures percutanées (Figure 58).

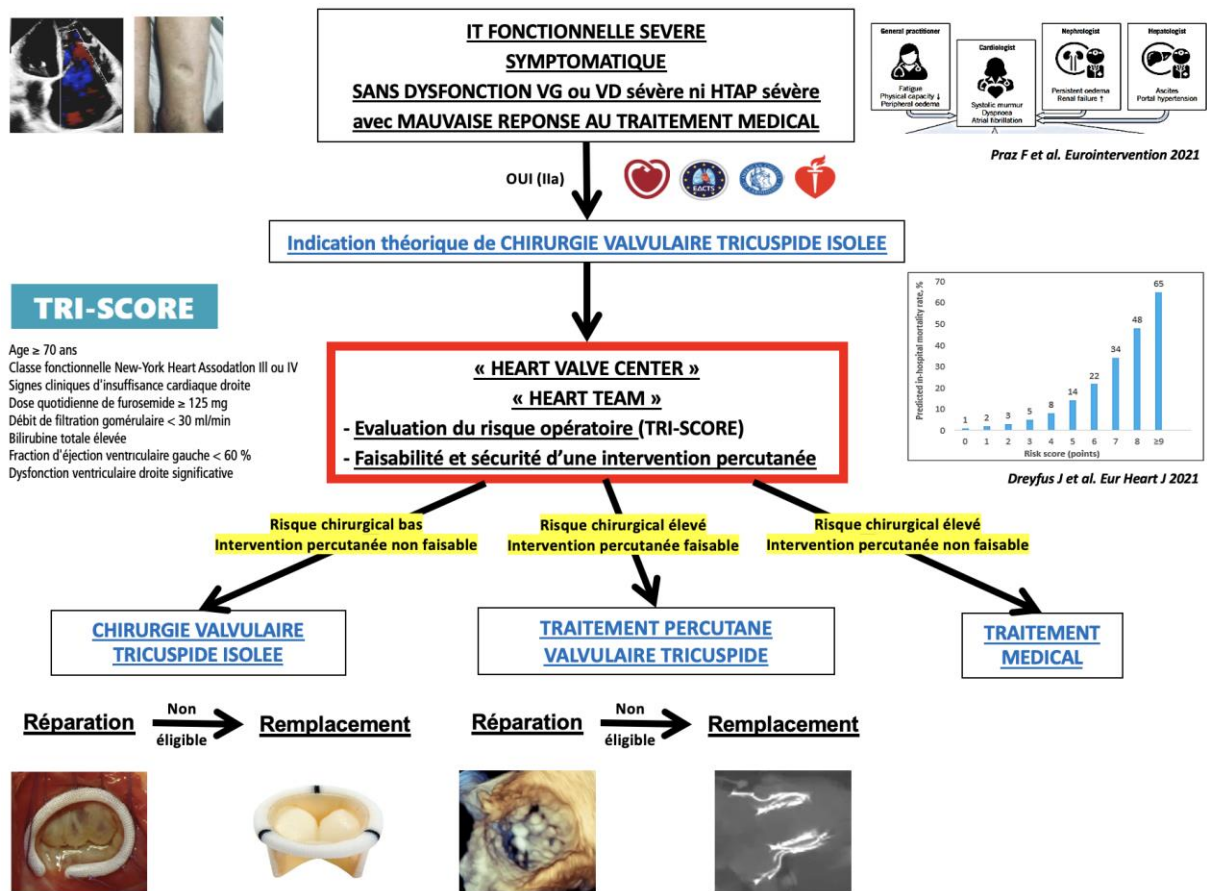


Figure 58. Proposition d'algorithme décisionnel dans la prise en charge des patients ayant une insuffisance tricuspide fonctionnelle sévère

Nous vivons actuellement une révolution dans la prise en charge de l'IT avec la perspective d'augmenter le nombre de patients traités de façon curative, de les traiter plus précocement et d'améliorer leur pronostic, ce qui laisse entrevoir un nouvel horizon...

Références

1. Mascherbauer J, Maurer G. The forgotten valve: lessons to be learned in tricuspid regurgitation. *Eur Heart J* 2010;31(23):2841-3. DOI: 10.1093/eurheartj/ehq303.
2. Hahn RT, Badano LP, Bartko PE, et al. Tricuspid regurgitation: recent advances in understanding pathophysiology, severity grading and outcome. *Eur Heart J Cardiovasc Imaging* 2022;23(7):913-929. DOI: 10.1093/ehjci/jeac009.
3. Joudinaud TM, Flecher EM, Duran CM. Functional terminology for the tricuspid valve. *J Heart Valve Dis* 2006;15(3):382-8. (<https://www.ncbi.nlm.nih.gov/pubmed/16784076>).
4. Hahn RT, Weckbach LT, Noack T, et al. Proposal for a Standard Echocardiographic Tricuspid Valve Nomenclature. *JACC Cardiovasc Imaging* 2021;14(7):1299-1305. DOI: 10.1016/j.jcmg.2021.01.012.
5. Fukuda S, Saracino G, Matsumura Y, et al. Three-dimensional geometry of the tricuspid annulus in healthy subjects and in patients with functional tricuspid regurgitation: a real-time, 3-dimensional echocardiographic study. *Circulation* 2006;114(1 Suppl):I492-8. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16820625).
6. Ton-Nu TT, Levine RA, Handschumacher MD, et al. Geometric determinants of functional tricuspid regurgitation: insights from 3-dimensional echocardiography. *Circulation* 2006;114(2):143-9. DOI: 10.1161/CIRCULATIONAHA.106.611889.
7. Dreyfus GD, Corbi PJ, Chan KM, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? *Ann Thorac Surg* 2005;79(1):127-32. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15620928).
8. Spinner EM, Shannon P, Buice D, et al. In vitro characterization of the mechanisms responsible for functional tricuspid regurgitation. *Circulation* 2011;124(8):920-9. DOI: 10.1161/CIRCULATIONAHA.110.003897.
9. Silver MD, Lam JH, Ranganathan N, Wigle ED. Morphology of the human tricuspid valve. *Circulation* 1971;43(3):333-48. DOI: 10.1161/01.cir.43.3.333.
10. Stuge O, Liddicoat J. Emerging opportunities for cardiac surgeons within structural heart disease. *J Thorac Cardiovasc Surg* 2006;132(6):1258-61. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17140937).
11. Topilsky Y, Maltais S, Medina Inojosa J, et al. Burden of Tricuspid Regurgitation in Patients Diagnosed in the Community Setting. *JACC Cardiovasc Imaging* 2019;12(3):433-442.
12. Prihadi EA, Delgado V, Leon MB, Enriquez-Sarano M, Topilsky Y, Bax JJ. Morphologic Types of Tricuspid Regurgitation: Characteristics and Prognostic Implications. *JACC Cardiovasc Imaging* 2019;12(3):491-499. DOI: 10.1016/j.jcmg.2018.09.027.
13. Shiran A, Sagie A. Tricuspid regurgitation in mitral valve disease incidence, prognostic implications, mechanism, and management. *J Am Coll Cardiol* 2009;53(5):401-8. DOI: 10.1016/j.jacc.2008.09.048.
14. Guerin A, Dreyfus J, Le Tourneau T, et al. Secondary tricuspid regurgitation: Do we understand what we would like to treat? *Arch Cardiovasc Dis*;112(10):642-651. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=31351805).
15. Praz F, Muraru D, Kreidel F, et al. Transcatheter treatment for tricuspid valve disease. *EuroIntervention* 2021;17(10):791-808. DOI: 10.4244/EIJ-D-21-00695.
16. Offen S, Strange G, Playford D, Celermajer DS, Stewart S. Prevalence and prognostic impact of tricuspid regurgitation in patients with cardiac implantable electronic devices: From the

- national echocardiography database of Australia. *Int J Cardiol* 2022. DOI: 10.1016/j.ijcard.2022.10.160.
17. Dreyfus J, Messika-Zeitoun D. Cardiac implantable electronic devices: Leads can lead to tricuspid regurgitation and death! *Int J Cardiol* 2023;372:91-92. DOI: 10.1016/j.ijcard.2022.12.011.
 18. Lancellotti P, Pibarot P, Chambers J, et al. Multi-modality imaging assessment of native valvular regurgitation: an EACVI and ESC council of valvular heart disease position paper. *Eur Heart J Cardiovasc Imaging* 2022;23(5):e171-e232. DOI: 10.1093/ehjci/jeab253.
 19. Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. *Eur Heart J Cardiovasc Imaging* 2017;18(12):1342-1343. DOI: 10.1093/ehjci/jex139.
 20. Taramasso M, Gavazzoni M, Pozzoli A, et al. Tricuspid Regurgitation: Predicting the Need for Intervention, Procedural Success, and Recurrence of Disease. *JACC Cardiovasc Imaging*;12(4):605-621.
 21. Dietz MF, Prihadi EA, van der Bijl P, et al. Prognostic Implications of Right Ventricular Remodeling and Function in Patients With Significant Secondary Tricuspid Regurgitation. *Circulation* 2019;140(10):836-845. DOI: 10.1161/CIRCULATIONAHA.119.039630.
 22. Dietz MF, Prihadi EA, van der Bijl P, Ajmone Marsan N, Delgado V, Bax JJ. Prognostic Implications of Staging Right Heart Failure in Patients With Significant Secondary Tricuspid Regurgitation. *JACC Heart Fail* 2020;8(8):627-636. DOI: 10.1016/j.jchf.2020.02.008.
 23. Sala A, Lorusso R, Zancanaro E, et al. Mid-term outcomes of isolated tricuspid valve surgery according to preoperative clinical and functional staging. *Eur J Cardiothorac Surg* 2022;62(2). DOI: 10.1093/ejcts/ezac172.
 24. Vely M, L'Official G, Galli E, et al. Functional tricuspid regurgitation: A clustering analysis and prognostic validation of three echocardiographic phenotypes in an external cohort. *Int J Cardiol* 2022;365:140-147. DOI: 10.1016/j.ijcard.2022.07.019.
 25. Galloo X, Stassen J, Butcher SC, et al. Staging right heart failure in patients with tricuspid regurgitation undergoing tricuspid surgery. *Eur J Cardiothorac Surg* 2022;62(2). DOI: 10.1093/ejcts/ezac290.
 26. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* 2004;43(3):405-9. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15013122).
 27. Messika-Zeitoun D, Verta P, Gregson J, et al. Impact of tricuspid regurgitation on survival in patients with heart failure: a large electronic health record patient-level database analysis. *Eur J Heart Fail* 2020;22(10):1803-1813. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=32367642).
 28. Chen E, L'Official G, Guerin A, et al. Natural history of functional tricuspid regurgitation: impact of cardiac output. *Eur Heart J Cardiovasc Imaging* 2021;22(8):878-885. DOI: 10.1093/ehjci/jeab070.
 29. Groves PH, Lewis NP, Ikram S, Maire R, Hall RJ. Reduced exercise capacity in patients with tricuspid regurgitation after successful mitral valve replacement for rheumatic mitral valve disease. *Br Heart J* 1991;66(4):295-301. DOI: 10.1136/hrt.66.4.295.
 30. Messika-Zeitoun D, Thomson H, Bellamy M, et al. Medical and surgical outcome of tricuspid regurgitation caused by flail leaflets. *J Thorac Cardiovasc Surg* 2004;128(2):296-302. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15282468).
 31. Wang N, Fulcher J, Abeysuriya N, et al. Tricuspid regurgitation is associated with increased mortality independent of pulmonary pressures and right heart failure: a systematic review and meta-analysis. *Eur Heart J* 2018;40(5):476-484. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=30351406).

32. Peugnet F, Bohbot Y, Chadha G, et al. Improvement of the Prognosis Assessment of Severe Tricuspid Regurgitation by the Use of a Five-Grade Classification of Severity. *Am J Cardiol* 2020;132:119-125. DOI: 10.1016/j.amjcard.2020.06.044.
33. Santoro C, Marco Del Castillo A, Gonzalez-Gomez A, et al. Mid-term outcome of severe tricuspid regurgitation: are there any differences according to mechanism and severity? *Eur Heart J Cardiovasc Imaging* 2019;20(9):1035-1042. DOI: 10.1093/ehjci/jez024.
34. Benfari G, Antoine C, Miller WL, et al. Excess Mortality Associated With Functional Tricuspid Regurgitation Complicating Heart Failure With Reduced Ejection Fraction. *Circulation* 2019;140(3):196-206. DOI: 10.1161/CIRCULATIONAHA.118.038946.
35. Essayagh B, Antoine C, Benfari G, et al. Functional tricuspid regurgitation of degenerative mitral valve disease: a crucial determinant of survival. *Eur Heart J* 2020;41(20):1918-1929. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=32300779).
36. Kalbacher D, Schafer U, von Bardeleben RS, et al. Impact of tricuspid valve regurgitation in surgical high-risk patients undergoing MitraClip implantation: results from the TRAMI registry. *EuroIntervention* 2017;12(15):e1809-e1816. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=28089952).
37. Mascherbauer J, Kammerlander AA, Marzluf BA, Graf A, Kocher A, Bonderman D. Prognostic Impact of Tricuspid Regurgitation in Patients Undergoing Aortic Valve Surgery for Aortic Stenosis. *PLoS One* 2015;10(8):e0136024. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=26291082).
38. Fan J, Liu X, Yu L, et al. Impact of tricuspid regurgitation and right ventricular dysfunction on outcomes after transcatheter aortic valve replacement: A systematic review and meta-analysis. *Clin Cardiol* 2019;42(1):206-212. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=30515860).
39. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2021 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=34453165).
40. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;143(5):e72-e227. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=33332150).
41. Ruel M, Rubens FD, Masters RG, Pipe AL, Bedard P, Mesana TG. Late incidence and predictors of persistent or recurrent heart failure in patients with mitral prosthetic valves. *J Thorac Cardiovasc Surg* 2004;128(2):278-83. DOI: 10.1016/j.jtcvs.2003.11.048.
42. Porter A, Shapira Y, Wurzel M, et al. Tricuspid regurgitation late after mitral valve replacement: clinical and echocardiographic evaluation. *J Heart Valve Dis* 1999;8(1):57-62. (<https://www.ncbi.nlm.nih.gov/pubmed/10096483>).
43. De Bonis M, Lapenna E, Sorrentino F, et al. Evolution of tricuspid regurgitation after mitral valve repair for functional mitral regurgitation in dilated cardiomyopathy. *Eur J Cardiothorac Surg* 2008;33(4):600-6. DOI: 10.1016/j.ejcts.2008.01.011.
44. Van de Veire NR, Braun J, Delgado V, et al. Tricuspid annuloplasty prevents right ventricular dilatation and progression of tricuspid regurgitation in patients with tricuspid annular dilatation undergoing mitral valve repair. *J Thorac Cardiovasc Surg* 2011;141(6):1431-9. DOI: 10.1016/j.jtcvs.2010.05.050.

45. Badano LP, Muraru D, Enriquez-Sarano M. Assessment of functional tricuspid regurgitation. *Eur Heart J* 2013;34(25):1875-85. DOI: 10.1093/eurheartj/ehs474.
46. Chikwe J, Itagaki S, Anyanwu A, Adams DH. Impact of Concomitant Tricuspid Annuloplasty on Tricuspid Regurgitation, Right Ventricular Function, and Pulmonary Artery Hypertension After Repair of Mitral Valve Prolapse. *J Am Coll Cardiol* 2015;65(18):1931-8. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=25936265).
47. Badhwar V, Rankin JS, He M, et al. Performing Concomitant Tricuspid Valve Repair at the Time of Mitral Valve Operations Is Not Associated With Increased Operative Mortality. *Ann Thorac Surg* 2016;103(2):587-593. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=27570159).
48. Gammie JS, Chu MWA, Falk V, et al. Concomitant Tricuspid Repair in Patients with Degenerative Mitral Regurgitation. *N Engl J Med* 2022;386(4):327-339. DOI: 10.1056/NEJMoa2115961.
49. Dreyfus G, Essayagh B, Benfari G, et al. Outcome of consistent guideline-based tricuspid management in patients undergoing degenerative mitral regurgitation correction. *JTCVS Open* 2021.
50. Pagnesi M, Montalto C, Mangieri A, et al. Tricuspid annuloplasty versus a conservative approach in patients with functional tricuspid regurgitation undergoing left-sided heart valve surgery: A study-level meta-analysis. *Int J Cardiol*;240:138-144. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=28499671).
51. Parolari A, Barili F, Pilozzi A, Pacini D. Ring or suture annuloplasty for tricuspid regurgitation? A meta-analysis review. *Ann Thorac Surg* 2014;98(6):2255-63. DOI: 10.1016/j.athoracsur.2014.06.100.
52. Fukuda S, Song JM, Gillinov AM, et al. Tricuspid valve tethering predicts residual tricuspid regurgitation after tricuspid annuloplasty. *Circulation* 2005;111(8):975-9. DOI: 10.1161/01.CIR.0000156449.49998.51.
53. Dreyfus J, Dreyfus GD, Taramasso M. Tricuspid valve replacement: The old and the new. *Prog Cardiovasc Dis* 2022;72:102-113. DOI: 10.1016/j.pcad.2022.06.004.
54. Alkhouli M, Berzinger C, Kowatli A, Alqahtani F, Badhwar V. Comparative early outcomes of tricuspid Valve repair versus replacement for secondary tricuspid regurgitation. *Open Heart* 2018;5(2):e000878.
55. Taramasso M, Alessandrini H, Latib A, et al. Outcomes After Current Transcatheter Tricuspid Valve Intervention: Mid-Term Results From the International TriValve Registry. *JACC Cardiovasc Interv* 2019;12(2):155-165. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=30594510).
56. Nickenig G, Weber M, Lurz P, et al. Transcatheter edge-to-edge repair for reduction of tricuspid regurgitation: 6-month outcomes of the TRILUMINATE single-arm study. *Lancet*;394(10213):2002-2011. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=31708188).
57. Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 2007;28(2):230-68. DOI: 10.1093/eurheartj/ehl428.
58. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*;38(36):2739-2791.
59. Amano M, Izumi C, Taniguchi T, et al. Impact of concomitant tricuspid regurgitation on long-term outcomes in severe aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2018;20(3):353-360.

- (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=30085068).
60. Chancellor WZ, Mehaffey JH, Beller JP, et al. Impact of tricuspid regurgitation with and without repair during aortic valve replacement. *J Thorac Cardiovasc Surg* 2020;162(1):44-50 e2. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=32173103).
 61. Pavasini R, Ruggerini S, Grapsa J, et al. Role of the tricuspid regurgitation after mitralclip and transcatheter aortic valve implantation: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging* 2017;19(6):654-659. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=28586413).
 62. Lung B, Delgado V, Rosenhek R, et al. Contemporary Presentation and Management of Valvular Heart Disease: The EURObservational Research Programme Valvular Heart Disease II Survey. *Circulation* 2019;140(14):1156-1169. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=31510787).
 63. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(23):e521-643.
 64. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012;33(19):2451-96. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22922415).
 65. Geyer M, Keller K, Bachmann K, et al. Concomitant tricuspid regurgitation severity and its secondary reduction determine long-term prognosis after transcatheter mitral valve edge-to-edge repair. *Clin Res Cardiol* 2021;110(5):676-688. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=33433670).
 66. Shamekhi J, Sugiura A, Tabata N, et al. Impact of Tricuspid Regurgitation in Patients Undergoing Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv* 2020;13(9):1135-1137. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=31954675).
 67. Hahn RT, Asch F, Weissman NJ, et al. Impact of Tricuspid Regurgitation on Clinical Outcomes: The COAPT Trial. *J Am Coll Cardiol* 2020;76(11):1305-1314. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=32912445).
 68. Kilic A, Saha-Chaudhuri P, Rankin JS, Conte JV. Trends and outcomes of tricuspid valve surgery in North America: an analysis of more than 50,000 patients from the Society of Thoracic Surgeons database. *Ann Thorac Surg* 2013;96(5):1546-52; discussion 1552.
 69. Dreyfus J, Flagiello M, Bazire B, et al. Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes. *Eur Heart J* 2020;41(45):4304-4317. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=32974668).
 70. Brescia AA, Ward ST, Watt TMF, et al. Outcomes of Guideline-Directed Concomitant Annuloplasty for Functional Tricuspid Regurgitation. *Ann Thorac Surg* 2020;109(4):1227-1232. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=31479635).
 71. Messika-Zeitoun D, Candolfi P, Enriquez-Sarano M, et al. Presentation and outcomes of mitral valve surgery in France in the recent era: a nationwide perspective. *Open Heart* 2020;7(2) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=32788294).

72. Vassileva CM, Shabosky J, Boley T, Markwell S, Hazelrigg S. Tricuspid valve surgery: the past 10 years from the Nationwide Inpatient Sample (NIS) database. *J Thorac Cardiovasc Surg* 2012;143(5):1043-9.
73. Gammie JS CM, Falk V, Overbey JR, Moskowitz AJ, Gillinov M, Mack MJ, Voisine P, Krane M, Yerokun B, Bowdish ME, Conradi L, Bolling SF, Miller MA, Taddei-Peters WC, Jeffries NO, Parides MK, Weisel R, Jessup M, Rose EA, Mullen JC, Raymond S, Moquete EG, O'Sullivan K, Marks ME, Iribarne A, Beyersdorf F, Borger MA, Geirsson A, Bagiella E, Hung J, Gelijns AC, O'Gara PT, Ailawadi G; CTSN Investigators. Concomitant Tricuspid Repair in Patients with Degenerative Mitral Regurgitation. *NEJM* 2021(. doi: 10.1056/NEJMoa2115961. Online ahead of print. PMID: 34767705).
74. Dreyfus J, Audureau E, Bohbot Y, et al. TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. *Eur Heart J* 2021 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=34586392).
75. Taramasso M, Benfari G, van der Bijl P, et al. Transcatheter Versus Medical Treatment of Patients With Symptomatic Severe Tricuspid Regurgitation. *J Am Coll Cardiol* 2019;74(24):2998-3008. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=31568868).
76. Donal E, Leurent G, Ganivet A, et al. Multicentric randomized evaluation of a tricuspid valve percutaneous repair system (clip for the tricuspid valve) in the treatment of severe secondary tricuspid regurgitation Tri.Fr Design paper. *Eur Heart J Cardiovasc Imaging* 2021. DOI: 10.1093/ehjci/jeab255.
77. Mehr M, Karam N, Taramasso M, et al. Combined Tricuspid and Mitral Versus Isolated Mitral Valve Repair for Severe MR and TR: An Analysis From the TriValve and TRAMI Registries. *JACC Cardiovasc Interv* 2020;13(5):543-550. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=31954679).
78. De Meester P, Van De Bruaene A, Voigt JU, Herijgers P, Budts W. Outcome and determinants of prognosis in patients undergoing isolated tricuspid valve surgery: retrospective single center analysis. *Int J Cardiol*;175(2):333-9.
79. Zack CJ, Fender EA, Chandrashekar P, et al. National Trends and Outcomes in Isolated Tricuspid Valve Surgery. *J Am Coll Cardiol* 2017;70(24):2953-2960.
80. Dreyfus J, Ghalem N, Garbarz E, et al. Timing of Referral of Patients With Severe Isolated Tricuspid Valve Regurgitation to Surgeons (from a French Nationwide Database). *Am J Cardiol* 2018;122(2):323-326.
81. LaPar DJ, Likosky DS, Zhang M, et al. Development of a Risk Prediction Model and Clinical Risk Score for Isolated Tricuspid Valve Surgery. *Ann Thorac Surg*;106(1):129-136.
82. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;16(1):9-13. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10456395).
83. Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. *Eur J Cardiothorac Surg* 2012;41(4):734-44; discussion 744-5. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22378855).
84. Dreyfus J, Audureau E, Bohbot Y, et al. TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. *Eur Heart J* 2022;43(7):654-662. DOI: 10.1093/eurheartj/ehab679.
85. Messika-Zeitoun D, Candolfi P, Dreyfus J, et al. Management and Outcome of Patients Admitted with Tricuspid Regurgitation in France. *Can J Cardiol* 2020

- (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=33358751).
86. Jones JM, O'Kane H, Gladstone DJ, et al. Repeat heart valve surgery: risk factors for operative mortality. *J Thorac Cardiovasc Surg* 2001;122(5):913-8. DOI: 10.1067/mtc.2001.116470.
 87. Bernal JM, Morales D, Revuelta C, Llorca J, Gutierrez-Morlote J, Revuelta JM. Reoperations after tricuspid valve repair. *J Thorac Cardiovasc Surg* 2005;130(2):498-503. DOI: 10.1016/j.jtcvs.2004.12.044.
 88. O'Brien SM, Feng L, He X, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 2-Statistical Methods and Results. *Ann Thorac Surg* 2018;105(5):1419-1428. DOI: 10.1016/j.athoracsur.2018.03.003.
 89. Programme de médicalisation des systèmes d'informations (PMSI). (<http://www.dressantegouvfr/redressements-du-programme-de-medicalisation-des-systemes-d-informations-pmsi>).
 90. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;16(7):777-802. DOI: 10.1016/S0894-7317(03)00335-3.
 91. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;30(4):303-371. DOI: 10.1016/j.echo.2017.01.007.
 92. McCarthy PM, Bhudia SK, Rajeswaran J, et al. Tricuspid valve repair: durability and risk factors for failure. *J Thorac Cardiovasc Surg* 2004;127(3):674-85. DOI: 10.1016/j.jtcvs.2003.11.019.
 93. Chen J, Ma W, Ming Y, et al. Minimally Invasive Valve Replacement for Late Tricuspid Regurgitation After Left-Sided Valve Surgery. *Ann Thorac Surg* 2021;111(5):e381-e383. DOI: 10.1016/j.athoracsur.2020.08.091.
 94. Hanedan MO, Cicekioglu F, Aksoyek A, et al. Tricuspid Valve Replacement Through Right Thoracotomy has Better Outcomes in Redo Cases. *Heart Lung Circ* 2017;26(1):88-93. DOI: 10.1016/j.hlc.2016.05.118.
 95. Pfannmuller B, Misfeld M, Borger MA, et al. Isolated reoperative minimally invasive tricuspid valve operations. *Ann Thorac Surg* 2012;94(6):2005-10. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22959578).
 96. Russo MJ, Thourani VH, Cohen DJ, et al. Minimally Invasive Versus Full Sternotomy for Isolated Aortic Valve Replacement in Low-Risk Patients. *Ann Thorac Surg* 2021. DOI: 10.1016/j.athoracsur.2021.11.048.
 97. McElhinney DB, Cabalka AK, Aboulhosn JA, et al. Transcatheter Tricuspid Valve-in-Valve Implantation for the Treatment of Dysfunctional Surgical Bioprosthetic Valves: An International, Multicenter Registry Study. *Circulation* 2016;133(16):1582-93. DOI: 10.1161/CIRCULATIONAHA.115.019353.
 98. McElhinney DB, Aboulhosn JA, Dvir D, et al. Mid-Term Valve-Related Outcomes After Transcatheter Tricuspid Valve-in-Valve or Valve-in-Ring Replacement. *J Am Coll Cardiol* 2019;73(2):148-157. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=30654886).
 99. Aboulhosn J, Cabalka AK, Levi DS, et al. Transcatheter Valve-in-Ring Implantation for the Treatment of Residual or Recurrent Tricuspid Valve Dysfunction After Prior Surgical Repair. *JACC Cardiovasc Interv* 2017;10(1):53-63. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=28057286).
 100. Bouleti C, Juliard JM, Himbert D, et al. Tricuspid valve and percutaneous approach: No longer the forgotten valve! *Arch Cardiovasc Dis* 2016;109(1):55-66.

- (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=26498535).
101. Lurz P, Stephan von Bardeleben R, Weber M, et al. Transcatheter Edge-to-Edge Repair for Treatment of Tricuspid Regurgitation. *J Am Coll Cardiol* 2021;77(3):229-239. DOI: 10.1016/j.jacc.2020.11.038.
 102. Lu FL, Ma Y, An Z, et al. First-in-Man Experience of Transcatheter Tricuspid Valve Replacement With LuX-Valve in High-Risk Tricuspid Regurgitation Patients. *JACC Cardiovasc Interv* 2020;13(13):1614-1616. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=32646711).
 103. Fam NP, von Bardeleben RS, Hensey M, et al. Transfemoral Transcatheter Tricuspid Valve Replacement With the EVOQUE System: A Multicenter, Observational, First-in-Human Experience. *JACC Cardiovasc Interv* 2021;14(5):501-511. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=33582084).
 104. Guerin A, Vabret E, Dreyfus J, et al. Cardiac remodelling in secondary tricuspid regurgitation: Should we look beyond the tricuspid annulus diameter? *Arch Cardiovasc Dis* (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=33446476).
 105. Dreyfus J, Durand-Viel G, Raffoul R, et al. Comparison of 2-Dimensional, 3-Dimensional, and Surgical Measurements of the Tricuspid Annulus Size: Clinical Implications. *Circ Cardiovasc Imaging* 2015;8(7):e003241. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=26156015).
 106. Teiger E, Nejari M, Lim P, et al. First-in-human implantation of the Topaz transcatheter tricuspid valve replacement system. *EuroIntervention* 2022;18(10):862-864. DOI: 10.4244/EIJ-D-22-00277.
 107. Dreyfus J, Obadia JF, Messika-Zeitoun D. Tricuspid regurgitation: Light at the end of the tunnel? *Arch Cardiovasc Dis* 2022;115(3):117-121. DOI: 10.1016/j.acvd.2021.12.008.
 108. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. *N Engl J Med* 2018;379(24):2297-2306. DOI: 10.1056/NEJMoa1805374.
 109. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *N Engl J Med* 2018;379(24):2307-2318. DOI: 10.1056/NEJMoa1806640.
 110. Stolz L, Orban M, Besler C, et al. Cardiohepatic Syndrome Is Associated With Poor Prognosis in Patients Undergoing Tricuspid Transcatheter Edge-to-Edge Valve Repair. *JACC Cardiovasc Interv* 2022;15(2):179-189. DOI: 10.1016/j.jcin.2021.10.033.
 111. Messika-Zeitoun D, Burwash IG, Dreyfus J. Tricuspid Transcatheter Edge-to-Edge Valve Repair: Sooner Rather Than Later. *JACC Cardiovasc Interv* 2022;15(2):190-192. DOI: 10.1016/j.jcin.2021.11.014.

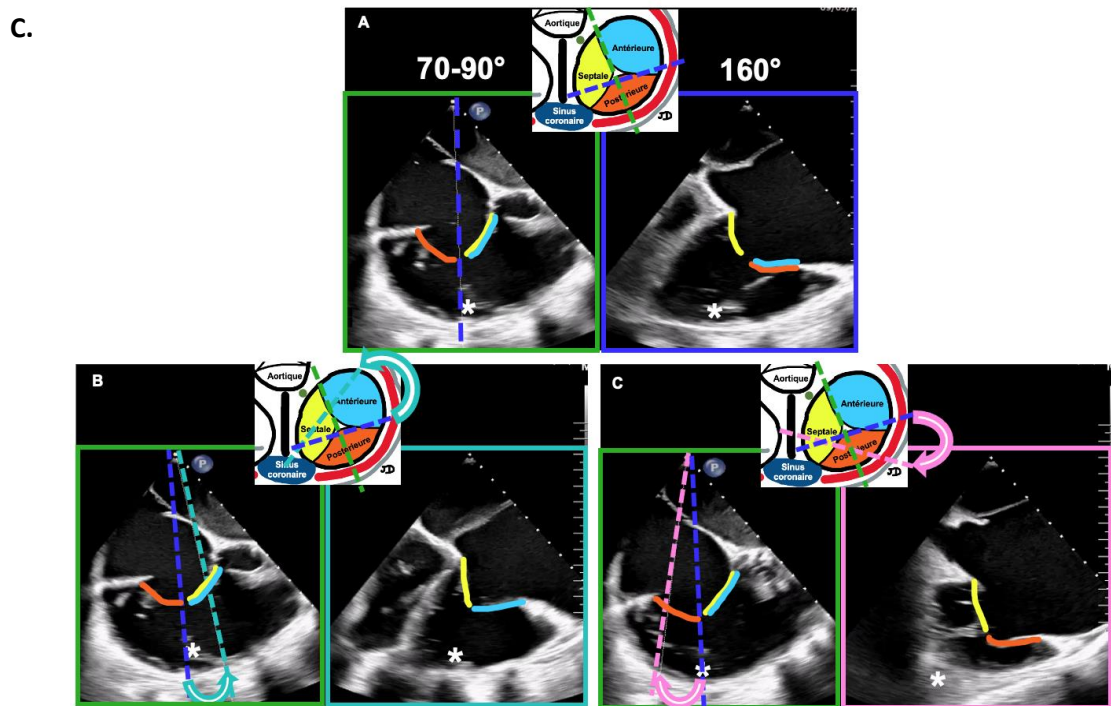
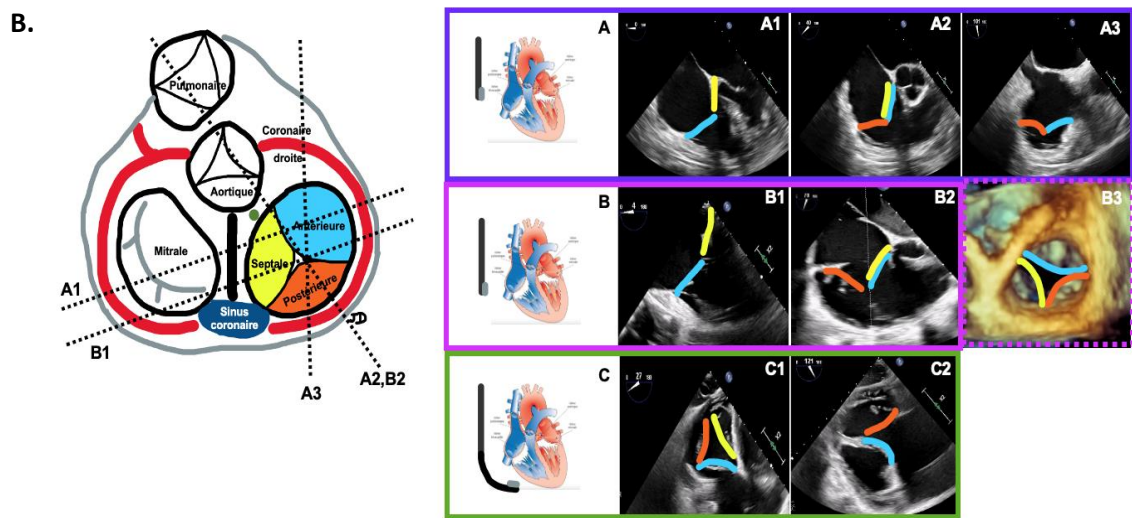
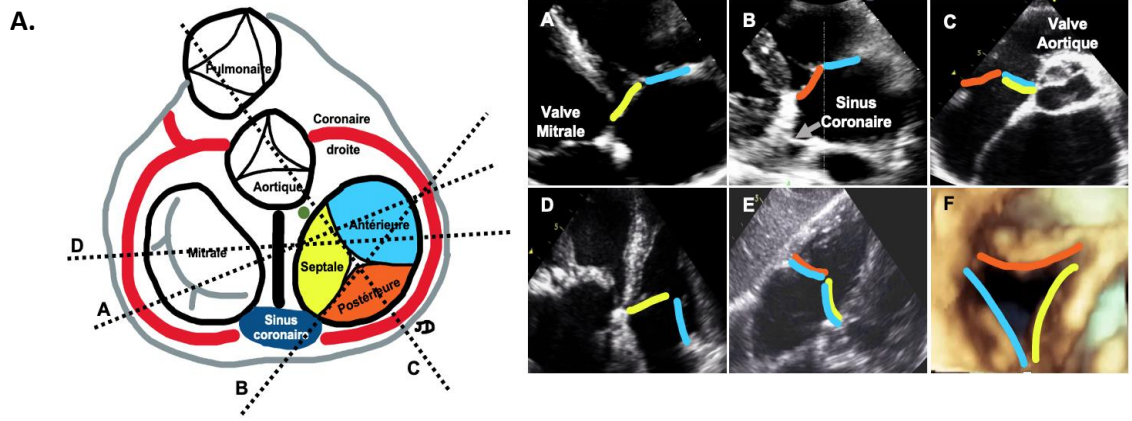
Annexes

Figure S1. Incidences échocardiographiques pour l'analyse de la valve tricuspide, notamment des feuillets valvulaires

- A. En échocardiographie trans-thoracique : incidences parasternale gauche grand axe centrée sur les cavités droites avec visualisation de la valve mitrale (A), même incidence mais avec la sonde béquée plus vers le bas pour visualiser le sinus coronaire (B), parasternale gauche petit axe au niveau de la valve aortique (C), apicale 4 cavités (D), sous-costale (E) et 3D en vue ventriculaire (F)
- B. En échocardiographie trans-oesophagienne : au niveau oesophagien moyen (A) : à 0° équivalente à une apicale 4 cavités en ETT (A1), à 40° équivalente à une parasternale gauche petit axe au niveau de la valve aortique (A2) et à 120° bicavale (A3) ; au niveau oesophagien distal (B) : à 0° (B1), coupe « inflow-outflow » vers 70° (B2) et en 3D (B3) ; au niveau transgastrique (C) : vue « en face » des feuillets vers 40° (C1) et coupe longitudinale vers 130° (C2)
- C. Analyse des feuillets en échocardiographie trans-oesophagienne avec la modalité biplan. En partant d'une coupe oesophagienne distale « inflow-outflow » vers 70° permettant de visualiser le pilier antérieur (A), le balayage du faisceau ultrasonore vers la valve aortique va permettre de visualiser dans un plan orthogonal les feuillets antérieur et septal (B); à l'inverse, le balayage du faisceau ultrasonore s'éloignant de la valve aortique va permettre de visualiser dans un plan orthogonal les feuillets postérieur et septal (C)

Le feuillet antérieur est dessiné en bleu, le feuillet septal en jaune et le feuillet postérieur en orange

L'astérisque correspond au pilier antérieur



Revue 1

Secondary tricuspid regurgitation: Do we understand what we would like to treat?

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REVIEW

Secondary tricuspid regurgitation: Do we understand what we would like to treat?

Régurgitation tricuspide secondaire : comprenons-nous ce que nous voudrions traiter ?

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KEYWORDS

Tricuspid regurgitation;
Quantification;
Pathophysiology;
Treatment

Summary Tricuspid regurgitation has long been a neglected and underestimated entity; its prevalence is significant, and is increasing with the ageing population. Tricuspid regurgitation is often a consequence of chronic left cardiac pathologies or atrial fibrillation. Surgical treatment is recommended for patients with severe symptomatic tricuspid regurgitation or tricuspid annulus dilatation at the time of left heart valve surgery. Secondary tricuspid regurgitation is a complex disease; this review focuses on the need for better understanding of its mechanisms and quantification – mandatory with the advent of new percutaneous treatments.

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Abbreviations: 2D, two-dimensional; 3D, three-dimensional; EROA, effective regurgitant orifice area; PISA, proximal isovelocity surface area; RA, right atrium; RV, right ventricle/ventricular; STR, secondary tricuspid regurgitation; TA, tricuspid annulus; TR, tricuspid regurgitation; TV, tricuspid valve; VC, vena contracta.

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MOTS CLÉS

Insuffisance tricuspidé ;
Quantification ;
Pathophysiologie ;
Traitement

Résumé L'insuffisance tricuspidé a été longtemps négligée. Sa prévalence est importante et augmente avec le vieillissement de la population. C'est souvent la conséquence d'une pathologie chronique du cœur gauche ou d'une fibrillation atriale. Le traitement chirurgical est recommandé pour les patients ayant une régurgitation sévère et symptomatique ou lorsque l'anneau tricuspidé est dilaté au moment d'une chirurgie du cœur gauche. L'insuffisance tricuspidé secondaire est une entité complexe. Cette revue est orientée sur les besoins d'une meilleure compréhension de ses mécanismes et de sa quantification avec l'avènement de nouveaux traitements percutanés.

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Background

Tricuspid regurgitation (TR) is one of the most frequent manifestations of valvular heart disease, and a common echocardiographic finding, the prevalence and severity of which increase with age [1]. It is estimated that moderate or severe TR may affect over 1 million patients in the USA, with higher prevalence in women [2]. The aetiology of TR is divided into two categories (Table 1). TR may be primary (or organic), defined by abnormalities of the tricuspid valve (TV) structure. There are many causes of primary TR, such as endocarditis, rheumatic heart disease, carcinoid syndrome, congenital heart disease (mainly Ebstein's anomaly), endomyocardial fibrosis, myxomatous disease, thoracic trauma or iatrogenic damage (including transvenous pacemaker or defibrillator leads, drug-induced valve disease and radiation) [3,4]. Most cases of TR, however, are

secondary (or functional), as a consequence of deformation of the TV complex with morphologically normal leaflets. Secondary TR (STR) is mainly related to right ventricular (RV) dilatation and/or dysfunction, annular dilatation and/or leaflet tethering, which are usually secondary to left-sided valvular heart disease (especially affecting the mitral valve), atrial fibrillation or pulmonary hypertension [5,6].

TR is an independent prognostic factor associated with significant excess mortality and morbidity that increase with TR grade in various clinical situations (Table 2). Surgery is mostly performed at the time of left-sided valve surgery for STR, whereas isolated TV surgery is rarely performed, but is recommended in patients with severe TR who are either symptomatic or are facing progressive RV dilation/dysfunction. However, the optimal timing for surgery is difficult to determine, as patients may be asymptomatic for a long period of time, symptoms are usually non-specific and RV size and function are difficult to assess in routine clinical practice.

The aim of this review is to look carefully at the determinants of TR.

Table 1 Aetiologies of tricuspid regurgitation.

| |
|--|
| Primary (organic) causes |
| Rheumatic heart disease |
| Congenital heart disease (mainly Ebstein's anomaly) |
| Endocarditis |
| Carcinoid syndrome |
| Endomyocardial fibrosis |
| Myxomatous disease |
| Thoracic trauma |
| Iatrogenic |
| Drug-induced |
| Radiation |
| Pacemaker or defibrillator leads |
| RV biopsy |
| Secondary (functional) causes |
| Left heart disease (valve disease or LV dysfunction) |
| Primary or secondary pulmonary hypertension from any cause |
| Atrial fibrillation |
| Chronic high stroke volume state |
| Any cause of RV dysfunction |

LV: left ventricle; RV: right ventricle.

Anatomy of the TV complex (Fig. 1)

The TV has a more apical position than the mitral valve; it is a dynamic complex structure that separates the right atrium (RA) and the right ventricle (RV), and is generally associated with three leaflets of unequal size (anterior, posterior and septal – in decreasing order of size, and in a clockwise direction as seen by the surgeon) inserted in a fibrous annulus and connected by chordae tendineae to papillary muscles attached to the RV myocardium. TV function depends on the integrity and coordination of all these components.

The number of leaflets can be restricted to only two or extended to four or five. The septal leaflet is located medially, at the level of the septum. The posterior leaflet frequently comprises multiple scallops. Indeed, tricuspid anatomy differs greatly from one patient to another. Papillary muscle anatomy is highly variable: there are generally two or three, but there can be up to nine. The anterior papillary muscle is the most prominent, and arises from the moderator band or from the adjacent myocardial wall. The

Table 2 Prognostic value of secondary tricuspid regurgitation according to clinical situation.

| Clinical situation | Prognostic value | References |
|--|--|---|
| General population | Increased mortality | Nath et al., 2004 [45] |
| Heart failure with preserved ejection fraction | Prognostic marker | Mascherbauer et al., 2017 [46] |
| LV systolic dysfunction | Severe TR: +55% mortality | Koelling et al., 2002 [47] Neuhold et al., 2013 [48] |
| Patients referred for heart transplantation | Severe TR: +50% cardiovascular events | Hung et al., 1998 [49] |
| Significant isolated TR | Increased mortality | Lee et al., 2010 [50] Topilsky et al., 2019 [2] |
| Severe aortic regurgitation | TR $\geq 2/4$; mortality relative risk 1.47 | Varadarajan et al., 2012 [51] |
| Mitral valve disease | Worse survival; increased heart failure; reduced functional capacity | Shiran et al., 2009 [52] Sagie et al., 1997 [53] |
| Aortic valve surgery for aortic stenosis | Worse postoperative survival | Mascherbauer et al., 2015 [54] |

LV: left ventricle; TR: tricuspid regurgitation.

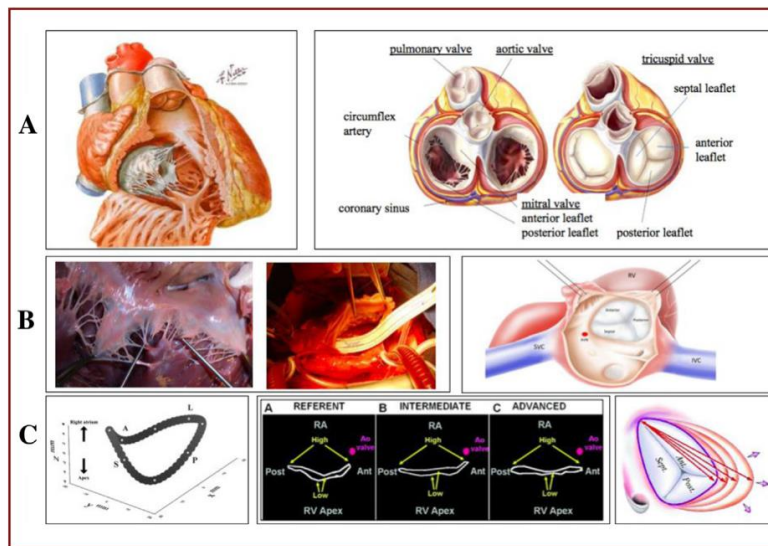


Figure 1. Anatomy of the tricuspid valve complex [12,35,36]. A. Drawings illustrating the anatomy of the tricuspid valve and its relationships with the mitral valve, aortic valve, coronary arteries and veins, displaying the chordae tendineae and papillary muscles. B. Pictures (and drawing illustrating the surgical view) of the complexity of the chordae tendineae, and of measurement of the mitral annular diameter during a surgical intervention. C. Saddle shape of the mitral annulus; the saddle shape is lost when the atrium is enlarged and the tricuspid annulus is enlarged; the enlargement of the tricuspid annulus is mainly in the lateral direction. A, Ant: anterior; Ao: aortic; AVN: atrioventricular node; IVC: inferior vena cava; L: lateral; P, Post: posterior; RA: right atrium; RV: right ventricle; S, Sept: septal; SVC: superior vena cava.

posterior papillary muscle is often bifid or trifid, and arises from the inferior wall. Finally, the septal papillary muscle is the least prominent, and can be absent in 20% of cases. Three types of chordae tendineae can be distinguished: the primary or marginal, attached to the free leaflet margin; the secondary or intermediary, attached to the body of leaflets; and the tertiary or basal. Some chordae tendineae arise directly from the myocardial wall.

The tricuspid annulus (TA) has a non-planar three-dimensional (3D) elliptical "saddle shape" in healthy

individuals. The "lowest point" from the RA (towards the RV apex) is the posteroseptal segment where the coronary sinus ends, whereas the anterosseptal and posterolateral segments are closer to the RA; the "highest point" of the TA is located at the anterosseptal segment, close to the RV outflow tract and aortic valve. The shape and size of the annulus change during the cardiac cycle and breathing. The TA size decreases by up to 25% during systole in healthy individuals. The TA becomes more planar and more circular when it dilates. Dilatation of the TA occurs mainly in the direction of

its free wall, meaning at the level of the anterior and posterior leaflets, but not the septal leaflet, because the septal annulus is part of the cardiac fibrous skeleton.

The TV is closely related to two important structures that can be injured at the time of intervention. First, the bundle of His crosses the septal segment of the TA approximately 5 mm from the anteroseptal commissure. Secondly, the right coronary artery runs in the right atrioventricular groove, a few millimetres from the anteroposterior segment of the TA.

The challenging anatomy, the importance of the interactions between each of the components (septum, RV, RA, pericardium, etc.), and variations in the cardiac cycle and breathing make assessment of the mechanisms and severity of STR difficult [7].

Do we understand the mechanisms of STR?

The TV is the largest orifice among the four cardiac valves. STR is not a disease of the leaflets, but the consequence of loading conditions and right chamber remodelling [8]. Two main processes seem to lead to STR. The first mechanism relies on valvular leaflet tethering and restricted motion induced by RV dilatation (most often as a consequence of increased afterload caused by pulmonary hypertension), leading to papillary muscle displacement and then chordal traction. The second mechanism relies on TA dilatation as a result of the enlargement of the RA extending to the RV, which may result in loss of coaptation or malalignment of the leaflets [6]. Atrial fibrillation is known to enlarge the RA, as patients with STR and atrial fibrillation have a larger TA diameter and a smaller tethering angle compared with patients with STR in sinus rhythm [9]. Thus, annular dilatation is a fundamental condition for STR onset [10] (Fig. 2). It has been shown that STR cannot develop when the TA diameter is < 33 mm [11]. However these two mechanisms, annular dilatation and leaflet tethering, can be associated [12]. Indeed, ventricular volume overload occurring in patients with TR may lead to progression of myocardial dysfunction and right chamber enlargement. This process of RV remodelling affects the structure and function of the tricuspid apparatus, and further increases the magnitude of STR through a vicious cycle.

It is mandatory to assess the characteristics of right chamber remodelling and the two types of STR mechanisms for a better understanding of the pathological process leading to STR and, further, for individualizing therapeutic management. As data on these two mechanisms were scarce, we initiated a French registry (TRAP) looking at the mechanisms of STR and their consequences for prognosis.

How to assess STR?

Clinical evaluation

Patients with STR remain asymptomatic for a long period of time; then, they develop non-specific symptoms, such as asthenia, or symptoms that reflect low cardiac output, dyspnoea as a consequence of elevated pulmonary or LV filling pressures and, finally, signs of right heart failure (peripheral lower limb oedema, ascites, etc.). Murmur

(soft pansystolic murmur at the lower sternal border that increases in intensity during inspiration) is also not easily audible. Unfortunately, STR is mostly diagnosed very late in the course of the disease, when there is end-stage organ damage with RV dysfunction and renal and liver failure.

Echocardiography

Two-dimensional (2D) transthoracic echocardiography is the cornerstone for assessing TV morphology, TA dilatation and/or leaflet tethering and the grade of TR in routine practice. However, only two leaflets can be seen simultaneously using 2D echocardiography, and the use of 3D echocardiography (either transthoracic or transoesophageal) is mandatory to see the entire TA with all leaflets at the same time. Thus, assessment of the TA diameter using 2D transthoracic echocardiography is difficult, especially as it has a non-circular, non-planar shape. It is recommended to measure the TA diameter in the apical four-chamber view (septal-lateral) at the time of maximum TV diastolic opening between the two hinge points at the junction between the valvular leaflets and the TA, but we should keep in mind that this measurement systematically underestimates the long axis of the TA compared with 3D echocardiography [13] and cardiac magnetic resonance imaging (Fig. 3). The normal TA diameter is 28 ± 5 mm in the apical four-chamber view in diastole in healthy adults. Current guidelines from the European Society of Cardiology/European Association for Cardio-Thoracic Surgery and the American College of Cardiology/American Heart Association suggest a threshold diameter of > 40 mm or 21 mm^2 to recommend combined TV annuloplasty at the time of left-sided valve surgery.

Leaflet tethering is the consequence of the displacement of the papillary muscles with RV dilatation, and can be assessed by measuring the coaptation height (the distance between the annulus plane and the point of coaptation) and the tenting area (the area between the atrial surface of the leaflets and the annulus plane) in the apical four-chamber view at maximal systolic closure. 3D echocardiography allows measurement of tenting volume. A coaptation height > 10 mm, a tenting area > 16 mm^2 and a tenting volume > 2.3 mL are associated with severe TR and TV repair failure immediately after surgery [14], consequently favouring TV replacement.

The grade of TR can change according to the cardiac cycle, notably during respiration. Indeed, inspiration is associated with an increase in right cardiac chamber volumes and TA size that can worsen TR. A decreased peak of TR velocity during inspiration of > 0.6 m/s compared with expiration is associated with severe TR (sensitivity of 66% and specificity of 94%) [15].

TR grade can be assessed by qualitative, semiquantitative and quantitative variables (Fig. 4). Visual evaluation using colour flow Doppler is a good qualitative approach for moderate-to-severe TR, but is insufficient to accurately quantify the leak [16]. To assess TR, guidelines [17,18] recommend 2D and colour Doppler echocardiography in all standard views (parasternal tricuspid inflow view and short-axis view at the level of the aortic valve, apical view and subcostal view). Several variables have been proposed, and should be used in a multivariable approach to assess TR, because no single variable is ideal for STR quantification.

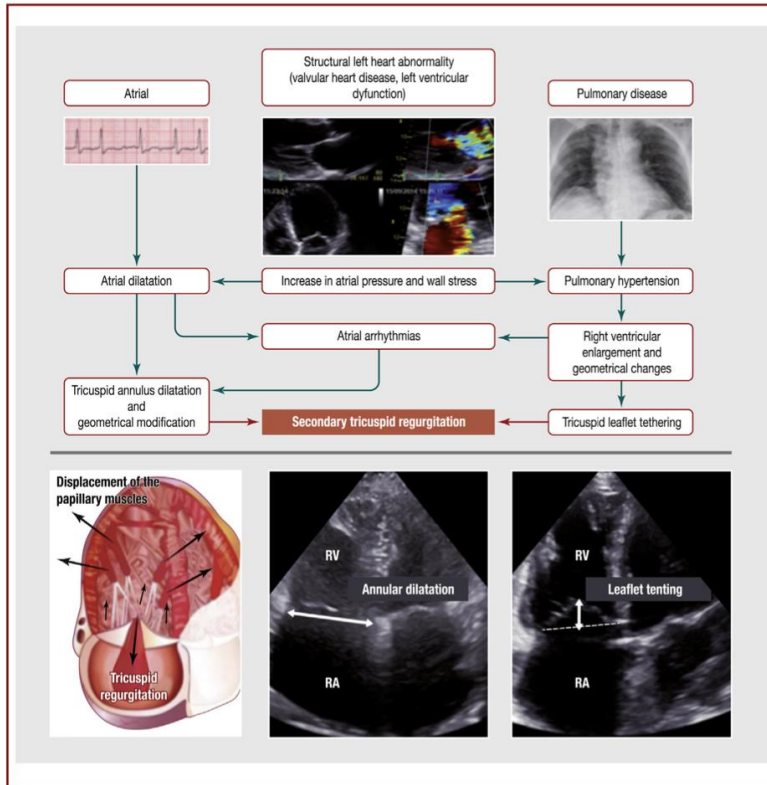


Figure 2. Mechanisms of secondary tricuspid regurgitation [37].

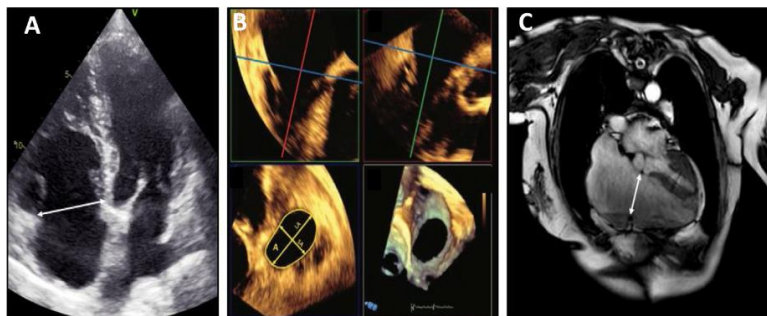


Figure 3. Measurement of the tricuspid annulus diameter. A. Using two-dimensional transthoracic echocardiography. B. Using three-dimensional transoesophageal echocardiography. C. Using cardiac magnetic resonance imaging [13].

In addition, TR grade is influenced by loading conditions that vary from time to time (for instance, a change in the patient’s position or diuretic treatment), RV compliance and respiratory cycle.

The TR jet area in the RA does not correlate well with TR severity, unlike vena contracta (VC) width and proximal isovelocity surface area (PISA) measurements. A VC width ≥ 6.5 mm is correlated with severe TR [19]; this variable is relatively unaffected by loading conditions, but

one limitation is its reliance on the complex regurgitant orifice geometry, which is not necessarily circular. A TR PISA radius > 9 mm at a Nyquist limit of 28 cm/s has been associated with severe TR (corresponding to an effective regurgitant orifice area [EROA] ≥ 40 mm² and a regurgitant volume ≥ 45 mL). The PISA method has several specific limitations. First, alignment with the beam of ultrasound may be difficult for eccentric jets. Second, leaflets are tenting, and the outer angle formed by leaflets should be accounted for

| Parameters | Mild | Moderate | Severe |
|----------------------------|--------------------|-------------------|--|
| Qualitative | | | |
| Tricuspid valve morphology | Normal / abnormal | Normal / abnormal | Abnormal / flail / large coaptation defect |
| Color flow TR jet | Small, central | Intermediate | Very large central jet or eccentric wall impinging jet |
| CW signal of TR jet | Faint / parabolic | Dense / parabolic | Dense / triangular with early peaking (< 2m/s in massive TR) |
| Semi-quantitative | | | |
| VC width (mm) | Not defined | < 6.5 | > 6.5 |
| PISA radius (mm) | ≤ 5 | 6.9 | > 9 |
| Hepatic vein flow | Systolic dominance | Systolic blunting | Systolic flow reversal |
| Tricuspid inflow | Normal | Normal | E-wave dominant (≥ 1 cm/s) |
| Quantitative | | | |
| EROA (mm ²) | Not defined | Not defined | ≥ 40 |
| R Vol (ml) | Not defined | Not defined | ≥ 45 |

Figure 4. Echocardiographic assessment of tricuspid regurgitation (TR) severity [17]. CW: continuous wave; EROA: effective regurgitant orifice area; PISA: proximal isovelocity surface area; R Vol: regurgitant volume; VC: vena contracta.

| | Trace | Mild | Moderate | Severe | Massive | Torrential |
|------------------------------|-------|------|----------|---------|---------|------------|
| VCW (mm) | - | < 3 | 3 – 6.9 | 7 - 13 | 14 – 20 | ≥ 20 |
| EROA (mm²) | - | < 20 | 20 - 39 | 40 - 59 | 60 - 79 | ≥ 80 |

Figure 5. New classification of tricuspid regurgitation grades, proposed by Hahn and Zamorano [22]. EROA: effective regurgitant orifice area; VCW: vena contracta width.

in the calculation of the regurgitant volume. Peak E velocity > 1 m/s on antegrade tricuspid flow (in the absence of TV stenosis) and systolic flow reversal in the hepatic vein are also markers of severe TR. Assessment of pulmonary pressure level (with maximal velocity of TR) as well as right chamber volumes and RV function (with tricuspid annular plane systolic excursion [TAPSE], tricuspid annular systolic velocity, fractional area change, etc.) are mandatory.

Other imaging methods

Cardiac magnetic resonance imaging is considered as the gold standard technique for evaluating the size (volumes) of the right chambers and RV function. Cine cardiac magnetic resonance sequences and 3D reconstructions can be useful for assessing TV morphology and TA motion. Regurgitant tricuspid volume can also be quantified [20].

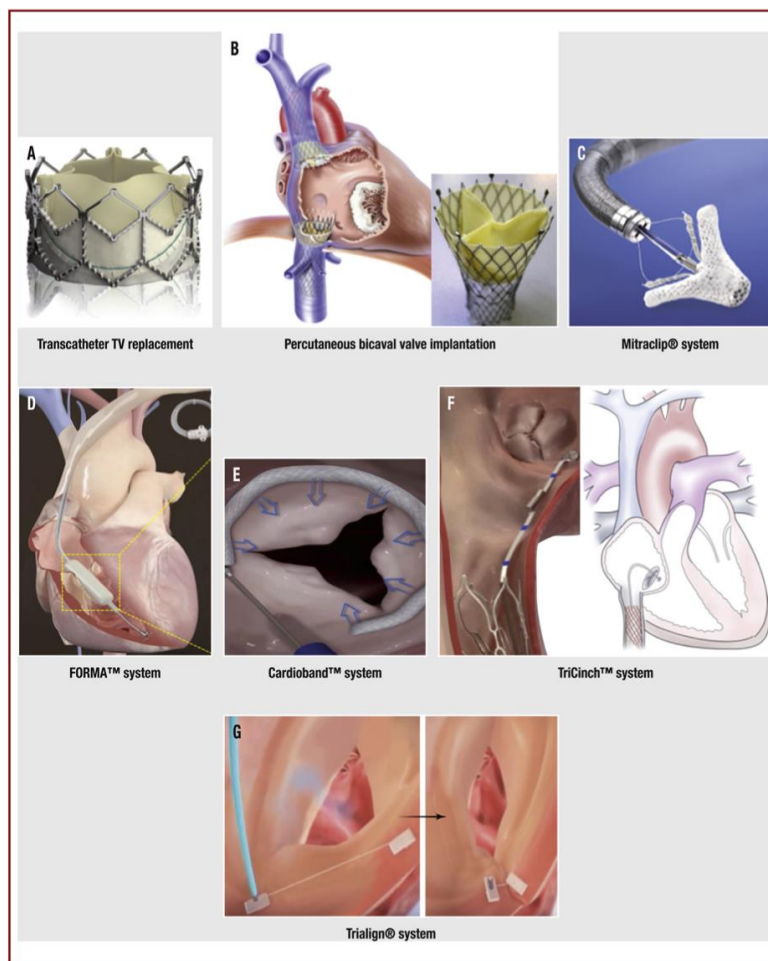


Figure 6. Percutaneous treatment of tricuspid valve (TV) regurgitation [38–44]. A. Prosthetic approach on the TV. B. Prosthetic approach in the vena cava. C. Mitraclip® system (Abbott, Abbott Park, IL, USA): the clip can be used as for the mitral valve, trying to grasp the anterior and septal leaflets. D. The FORMA™ system (Edwards Lifesciences, Irvine, CA, USA): a balloon is positioned in the middle of the regurgitant TV to decrease the defect between leaflets. E. The Cardioband™ system (Edwards Lifesciences, Irvine, CA, USA): the percutaneous annulus placed on the tricuspid annulus is trying to mimic surgical tricuspid annuloplasty, which is the current gold standard technique for treating tricuspid regurgitation. G. The Trialign™ system (Mitralign, Inc., Tewksbury, MA, USA) is a technique for achieving bicuspidization of the TV, and trying to decrease and change the geometry of the tricuspid annulus. F. The TriCinch™ system (4Tech Cardio Ltd., Galway, Ireland) acts on the tricuspid annulus shape and size (F). None of these techniques has been validated as yet, but some are under investigation.

Multislice computed tomography only informs about static anatomy, but can be relevant for measuring tethering height, tethering angle, annular diameter and the distance between each commissure before tricuspid annuloplasty [21]. This technique also reveals the right coronary artery anatomy, providing a landmark before a percutaneous intervention.

Right heart catheterization is essential in the clinical work-up of TR, not for TR quantification, but rather for measuring pulmonary artery pressures, especially when laminar TR precludes reliable assessment, as severe pulmonary

hypertension can be a contraindication for surgical intervention.

Evolution of TR gradation

The development of percutaneous or transcatheter solutions to treating severe TR highlighted the limited value of guidelines for assessing TR grade. Not only were mild and moderate TR not defined clearly on a quantitative basis, but the need to define very severe (massive) or worse than massive (torrential) grades has emerged, in order to

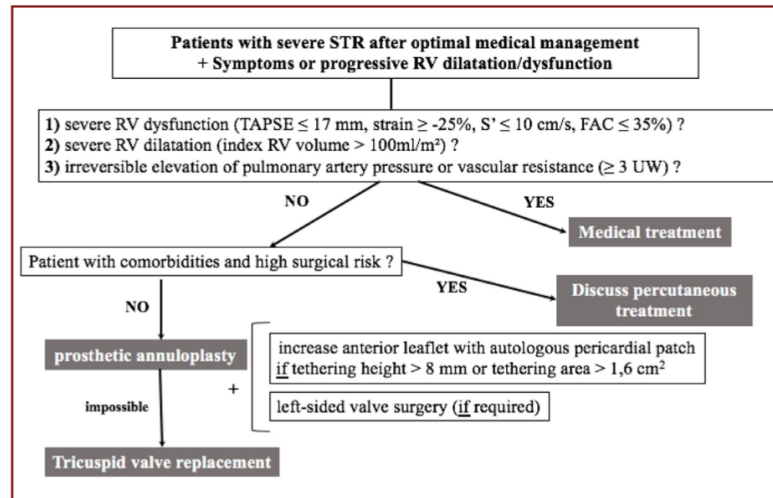


Figure 7. Proposal for management of severe secondary tricuspid regurgitation (STR). FAC: fractional area change; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion; UW: Wood units.

objectively evidence the severity of TR and the decrease in severity after percutaneous interventions [22]. Hence, Hahn and Zomorano proposed a new classification for severe-to-torrential TR. Severe TR was defined as a VC diameter of 7–13 mm or an EROA of 40–59 mm², massive TR was defined as a VC diameter of 14–20 mm or an EROA of 60–79 mm², and torrential TR was defined as a VC diameter ≥ 21 mm or an EROA ≥ 80 mm². Although this classification adds new information about TR magnitude, and will help clinicians to explain to their patients that percutaneous interventions are actually effective in reducing TR (e.g. torrential or massive to severe, rather than severe to severe), the most important aspect is the absolute need for a quantitative approach to TR rather than the qualitative approach used by most clinicians (Fig. 5).

Therapeutic management

Intervention is the only curative treatment for severe TR, as medical therapy – mainly with diuretics – has only a palliative effect, by decreasing volume overload. Although significant TR with progressive RV dilatation and dysfunction may remain clinically silent for a prolonged period, it compromises individual patient outcome. In addition, the timing of surgical intervention for TR remains controversial, and surgery is commonly undertaken at a late stage.

Recent international guidelines on valvular heart disease contain sparse recommendations regarding the management of STR. The guidelines from both Europe [23] and the USA [24] state that isolated TV surgery should be considered after previous left-sided valve surgery in patients with severe STR who are symptomatic or have progressive RV dilatation/dysfunction in the absence of severe RV or LV dysfunction and severe pulmonary hypertension (Class IIaC in the European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines and class IIbC in the

American College of Cardiology/American Heart Association guidelines). Isolated TV surgery may also be considered for those patients, even if there was no previous left-sided valve surgery [25].

The mortality rate for isolated TV surgery is still high (between 8% and 10% in the most recent studies) because patients are referred to the surgeon too late after congestive heart failure, RV dysfunction, liver disease and/or renal failure onset [26,27]; surgery should be performed earlier in the course of the disease, before irreversible RV dysfunction.

TV surgery for STR should be a repair whenever possible. TV replacement (almost exclusively a biological prosthesis) will be performed only when the TV leaflets are significantly tethered and the annulus is severely dilated, because it is associated with poorer perioperative and long-term outcome than TV repair [28]. TV surgery is mostly performed via median sternotomy under cardioplegia, although beating-heart surgery may prevent atrioventricular block and reduce ischaemic time. High mortality (around 10% at 1 year), and high rates of permanent pacemaker implantation remain a matter of concern [29,30]. Several surgical techniques have been proposed for TV repair, with either plication suture of the annulus (De Vega's annuloplasty), suture bicuspidization (Kay's annuloplasty), suture of the leaflets ("clover") or a ring around the annulus (flexible or rigid). The aim of these techniques is to narrow the valve orifice to achieve leaflet coaptation. The best option is still a matter of debate, but annuloplasty with an open prosthetic oval-shaped ring (to avoid injury to the bundle of His) is usually associated with the best early and long-term results [31]. To take into account both tethering leaflet and annular dilatation, Dreyfus et al. suggested a technique for treating severe STR, increasing anterior leaflet size with an autologous pericardial patch and annuloplasty [32].

New transcatheter solutions are now emerging for high-risk patients with severe STR; they are still in development or in the initial phase of clinical application to demonstrate

their safety and efficacy, but seem really promising (Fig. 6) [33,34].

STR remains poorly understood, and we have to separate isolated STR and STR associated with left-valve disease to reflect upon it. The identification of prognostic factors and characterization of the population seems essential for clinical decision making, including the possibility of correcting STR surgically or percutaneously. The optimal therapeutic strategy is still to be defined, although many technical advances are already showing promise (Fig. 7).

Conclusions

STR is frequent, significantly influences outcome and needs specific management, but is often diagnosed late in the course of the disease and poorly quantified. The TV is no more the forgotten valve, but identification of the mechanisms and accurate grading of STR are still challenging. As a consequence, we need to improve understanding of this disease through dedicated studies, such as the TRAP registry, with the ultimate goal of offering the most appropriate treatment to patients.

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Disclosure of interest

The authors declare that they have no competing interest.

References

- [1] Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol* 1999;83:897–902.
- [2] Topilsky Y, Maltais S, Medina Inojosa J, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging* 2019;12:433–42.
- [3] Hauck AJ, Freeman DP, Ackermann DM, Danielson GK, Edwards WD. Surgical pathology of the tricuspid valve: a study of 363 cases spanning 25 years. *Mayo Clin Proc* 1988;63:851–63.
- [4] Waller BF. Etiology of pure tricuspid regurgitation. *Cardiovasc Clin* 1987;17:53–95.
- [5] Mutlak D, Aronson D, Lessick J, Reisner SA, Dabbah S, Agmon Y. Functional tricuspid regurgitation in patients with pulmonary hypertension: is pulmonary artery pressure the only determinant of regurgitation severity? *Chest* 2009;135:115–21.
- [6] Spinner EM, Shannon P, Buice D, et al. In vitro characterization of the mechanisms responsible for functional tricuspid regurgitation. *Circulation* 2011;124:920–9.
- [7] Topilsky Y, Khanna A, Le Tourneau T, et al. Clinical context and mechanism of functional tricuspid regurgitation in patients with and without pulmonary hypertension. *Circ Cardiovasc Imaging* 2012;5:314–23.
- [8] Kim HK, Kim YJ, Park JS, et al. Determinants of the severity of functional tricuspid regurgitation. *Am J Cardiol* 2006;98:236–42.
- [9] Utsunomiya H, Itabashi Y, Mihara H, et al. Functional tricuspid regurgitation caused by chronic atrial fibrillation: a real-time 3-dimensional transesophageal echocardiography study. *Circ Cardiovasc Imaging* 2017;10, <http://dx.doi.org/10.1161/CIRCIMAGING.116.004897> [pii: e004897].
- [10] Tei C, Pilgrim JP, Shah PM, Ormiston JA, Wong M. The tricuspid valve annulus: study of size and motion in normal subjects and in patients with tricuspid regurgitation. *Circulation* 1982;66:665–71.
- [11] Sugimoto T, Okada M, Ozaki N, Hatakeyama T, Kawahira T. Long-term evaluation of treatment for functional tricuspid regurgitation with regurgitant volume: characteristic differences based on primary cardiac lesion. *J Thorac Cardiovasc Surg* 1999;117:463–71.
- [12] Fukuda S, Gillinov AM, Song JM, et al. Echocardiographic insights into atrial and ventricular mechanisms of functional tricuspid regurgitation. *Am Heart J* 2006;152:1208–14.
- [13] Dreyfus J, Durand-Viel G, Raffoul R, et al. Comparison of 2-dimensional, 3-dimensional, and surgical measurements of the tricuspid annulus size: clinical implications. *Circ Cardiovasc Imaging* 2015;8:e003241.
- [14] Fukuda S, Song JM, Gillinov AM, et al. Tricuspid valve tethering predicts residual tricuspid regurgitation after tricuspid annuloplasty. *Circulation* 2005;111:975–9.
- [15] Mutlak D, Carasso S, Lessick J, Aronson D, Reisner SA, Agmon Y. Excessive respiratory variation in tricuspid regurgitation systolic velocities in patients with severe tricuspid regurgitation. *Eur Heart J Cardiovasc Imaging* 2013;14:957–62.
- [16] Rivera JM, Vandervoort PM, Morris E, Weyman AE, Thomas JD. Visual assessment of valvular regurgitation: comparison with quantitative Doppler measurements. *J Am Soc Echocardiogr* 1994;7:480–7.
- [17] Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;14:611–44.
- [18] Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;30:303–71.
- [19] Tribouilloy CM, Enriquez-Sarano M, Bailey KR, Tajik AJ, Seward JB. Quantification of tricuspid regurgitation by measuring the width of the vena contracta with Doppler color flow imaging: a clinical study. *J Am Coll Cardiol* 2000;36:472–8.
- [20] Huttin O, Voilliot D, Mandry D, Venner C, Juilliere Y, Selton-Suty C. All you need to know about the tricuspid valve: tricuspid valve imaging and tricuspid regurgitation analysis. *Arch Cardiovasc Dis* 2016;109:67–80.
- [21] Gopalan D. Right heart on multidetector CT. *Br J Radiol* 2011;84(Spec No. 3):S306–23.
- [22] Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. *Eur Heart J Cardiovasc Imaging* 2017;18:1342–3.

- [23] Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739–91.
- [24] Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:e57–185.
- [25] Badano LP, Muraru D, Enriquez-Sarano M. Assessment of functional tricuspid regurgitation. *Eur Heart J* 2013;34:1875–85.
- [26] Dreyfus J, Ghalem N, Garbarz E, et al. Timing of referral of patients with severe isolated tricuspid valve regurgitation to surgeons (from a French nationwide database). *Am J Cardiol* 2018;122:323–6.
- [27] Zack CJ, Fender EA, Chandrashekar P, et al. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol* 2017;70:2953–60.
- [28] Guenther T, Noebauer C, Mazzitelli D, Busch R, Tassani-Prell P, Lange R. Tricuspid valve surgery: a thirty-year assessment of early and late outcome. *Eur J Cardiothorac Surg* 2008;34:402–9 [discussion 9].
- [29] Alqahtani F, Berzingi CO, Aljohani S, Hijazi M, Al-Hallak A, Alkhouli M. Contemporary trends in the use and outcomes of surgical treatment of tricuspid regurgitation. *J Am Heart Assoc* 2017;6.
- [30] Kundi H, Popma JJ, Cohen DJ, et al. Prevalence and outcomes of isolated tricuspid valve surgery among medicare beneficiaries. *Am J Cardiol* 2019;123:132–8.
- [31] Tang GH, David TE, Singh SK, Maganti MD, Armstrong S, Borger MA. Tricuspid valve repair with an annuloplasty ring results in improved long-term outcomes. *Circulation* 2006;114:1577–81.
- [32] Dreyfus GD, Raja SG, John Chan KM. Tricuspid leaflet augmentation to address severe tethering in functional tricuspid regurgitation. *Eur J Cardiothorac Surg* 2008;34:908–10.
- [33] Hahn RT, Meduri CU, Davidson CJ, et al. Early feasibility study of a transcatheter tricuspid valve annuloplasty: SCOUT Trial 30-Day Results. *J Am Coll Cardiol* 2017;69:1795–806.
- [34] Taramasso M, Pozzoli A, Guidotti A, et al. Percutaneous tricuspid valve therapies: the new frontier. *Eur Heart J* 2017;38:639–47.
- [35] Dreyfus GD, Corbi PJ, Chan KM, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? *Ann Thorac Surg* 2005;79:127–32.
- [36] Ton-Nu TT, Levine RA, Handschumacher MD, et al. Geometric determinants of functional tricuspid regurgitation: insights from 3-dimensional echocardiography. *Circulation* 2006;114:143–9.
- [37] Mascherbauer J, Maurer G. The forgotten valve: lessons to be learned in tricuspid regurgitation. *Eur Heart J* 2010;31:2841–3.
- [38] Besler C, Orban M, Rommel KP, et al. Predictors of procedural and clinical outcomes in patients with symptomatic tricuspid regurgitation undergoing transcatheter edge-to-edge repair. *JACC Cardiovasc Interv* 2018;11:1119–28.
- [39] Corno AF, Zhou J, Tozzi P, von Segesser LK. Off-bypass implantation of a self-expandable valved stent between inferior vena cava and right atrium. *Interact Cardiovasc Thorac Surg* 2003;2:166–9.
- [40] Latib A, Agricola E, Pozzoli A, et al. First-in-man implantation of a tricuspid annular remodeling device for functional tricuspid regurgitation. *JACC Cardiovasc Interv* 2015;8:e211–4.
- [41] Laule M, Stangl V, Sanad W, Lembcke A, Baumann G, Stangl K. Percutaneous transfemoral management of severe secondary tricuspid regurgitation with Edwards Sapien XT bioprosthesis: first-in-man experience. *J Am Coll Cardiol* 2013;61:1929–31.
- [42] Lauten A, Ferrari M, Hekmat K, et al. Heterotopic transcatheter tricuspid valve implantation: first-in-man application of a novel approach to tricuspid regurgitation. *Eur Heart J* 2011;32:1207–13.
- [43] Perlman G, Praz F, Puri R, et al. Transcatheter tricuspid valve repair with a new transcatheter coaptation system for the treatment of severe tricuspid regurgitation: 1-year clinical and echocardiographic results. *JACC Cardiovasc Interv* 2017;10:1994–2003.
- [44] Schofer J, Bijuklic K, Tiburtius C, Hansen L, Groothuis A, Hahn RT. First-in-human transcatheter tricuspid valve repair in a patient with severely regurgitant tricuspid valve. *J Am Coll Cardiol* 2015;65:1190–5.
- [45] Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* 2004;43:405–9.
- [46] Mascherbauer J, Kammerlander AA, Zotter-Tufaro C, et al. Presence of isolated tricuspid regurgitation should prompt the suspicion of heart failure with preserved ejection fraction. *PLoS One* 2017;12:e0171542.
- [47] Koelling TM, Aaronson KD, Cody RJ, Bach DS, Armstrong WF. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. *Am Heart J* 2002;144:524–9.
- [48] Neuhold S, Huelsmann M, Pernicka E, et al. Impact of tricuspid regurgitation on survival in patients with chronic heart failure: unexpected findings of a long-term observational study. *Eur Heart J* 2013;34:844–52.
- [49] Hung J, Koelling T, Semigran MJ, Dec GW, Levine RA, Di Salvo TG. Usefulness of echocardiographic determined tricuspid regurgitation in predicting event-free survival in severe heart failure secondary to idiopathic-dilated cardiomyopathy or to ischemic cardiomyopathy. *Am J Cardiol* 1998;82:1301–3 [A10].
- [50] Lee JW, Song JM, Park JP, Lee JW, Kang DH, Song JK. Long-term prognosis of isolated significant tricuspid regurgitation. *Circ J* 2010;74:375–80.
- [51] Varadarajan P, Pai RG. Prognostic implications of tricuspid regurgitation in patients with severe aortic regurgitation: results from a cohort of 756 patients. *Interact Cardiovasc Thorac Surg* 2012;14:580–4.
- [52] Shiran A, Sagie A. Tricuspid regurgitation in mitral valve disease incidence, prognostic implications, mechanism, and management. *J Am Coll Cardiol* 2009;53:401–8.
- [53] Sagie A, Freitas N, Chen MH, Marshall JE, Weyman AE, Levine RA. Echocardiographic assessment of mitral stenosis and its associated valvular lesions in 205 patients and lack of association with mitral valve prolapse. *J Am Soc Echocardiogr* 1997;10:141–8.
- [54] Mascherbauer J, Kammerlander AA, Marzluf BA, Graf A, Kocher A, Bonderman D. Prognostic impact of tricuspid regurgitation in patients undergoing aortic valve surgery for aortic stenosis. *PLoS One* 2015;10:e0136024.

Editorial 1

**Cardiac implantable electronic devices: Leads can
lead to tricuspid regurgitation and death!**

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Editorial

Cardiac implantable electronic devices: Leads can lead to tricuspid regurgitation and death!

Cardiac implantable electronic device (CIED) associated tricuspid regurgitation (TR) is an increasingly prevalent condition. Its diagnosis is often difficult due to the presence of the lead and to several mechanisms, its impact is not well understood and its management remains often challenging [1–5].

In this issue of *International Journal of Cardiology*, Offen et al. [6] report a “real-world” experience on the prevalence and outcome of TR associated with CIED leads. From the National Echocardiography Database Australia (NEDA), the authors retrospectively included 18,797 adult patients with a CIED and 439,558 individuals without CIED who underwent an echocardiography across 25 centers in Australia over a 20 year-period. As more and more permanent pacemakers (PPM) and intra-cardiac defibrillators (ICD) are implanted over time, this is a highly relevant topic.

Main findings of the study are that CIED-associated moderate or greater TR was 1) highly prevalent (23.8%), 2-fold greater than in individuals without devices, 2) linked with a 1.6 to 2.5-fold increase in all-cause mortality compared to individuals with no TR, after adjustment for age, sex, atrial fibrillation or left-heart disease, especially among younger individuals, and 3) that mortality was more related to the TR grade than to the cause of the TR as observed mortality was similar irrespective of the presence or absence of a device lead.

These results are important and shed light on the high prevalence of CIED-associated TR and its impact on outcome although no causative relationship can be inferred from this observational study. In addition, several other limitations deserve discussion:

- This was a retrospective study, not specifically designed for TR assessment, and the NEDA registry captures only limited clinical, echocardiographic and mortality data. It therefore lacks the granularity regarding patient location (inpatient vs outpatient), cardiovascular risk factors and comorbid conditions. The type of device-lead implantation could not be differentiated (PPM, ICD, cardiac resynchronization therapy) while the underlying disease, which portends important prognostic information, may play a confounder role.
- The mechanism of TR could not be defined, and assessment of TR severity was not centralized with possible important inter-individual and centers variations. TR induced by a CIED is considered as a new entity by itself, to be set apart from both secondary/functional or primary/organic TR [7], and its mechanisms are complex and often multiple (leaflet impingement, leaflet/chordal entanglement/chordal rupture, leaflet adherence, leaflet perforation...). It is critical to distinguish between TR induced by a CIED lead and TR associated but not specifically

related to a CIED lead. Three-dimensional echocardiography has a valuable role to understand the location of the lead and TR mechanism (Fig. 1). In addition, assessment of TR severity is often challenging due to the presence of a CIED as the lead can prevent usual quantitative assessment of TR and eccentric jets due to leaflet impingement or damage may lead to underestimation of TR severity. Moreover, despite being an echocardiographic registry, the quantitative data related to chamber quantification was scarce. This is a cross sectional study with no longitudinal follow-up and lack of data regarding delay between device-implantation and echocardiography. TR severity usually progresses over time but time course of new onset or worsening TR following right ventricular lead implantation was not available. A referral bias in the cohort of patients with CIED toward reporting more significant TR could not be excluded as patients with more severe diseases might be more easily referred for an echocardiogram. In that regard, the median duration of study follow-up was 4.1 years (interquartile range [IQR] 2.1–6.9 years) for the cohort without CIED leads but only 2.6 years (interquartile range [IQR] 1.1–4.6 years) for the group of patients with CIED leads.

The first question is how to prevent or at least mitigate the occurrence of CIED-induced TR? There is no consensual answer but, as the location of the lead could be responsible for the leak, implanters should favor the center of the valve or commissural areas and make sure that the lead does not interfere with the mobility of leaflets. Echocardiographic guiding during the implantation of the CIED has been proposed but would be complicated to implement in real world practice and the position can sometimes change over time. Performance of a transthoracic echocardiography immediately after the implantation and regularly during the follow-up could identify CIED-induced TR early in the disease course before development of fibrosis. Leadless pacemaker, coronary sinus lead, epicardial stimulation or subcutaneous ICD represent attractive alternatives.

The second question is how to manage the challenging group of patients with TR induced by a CIED? Transvenous extraction of PPM or ICD lead is rarely performed and may not be efficient to reduce TR, as if fibrosis as settled, impairing the mobility of the leaflets even once the lead is removed. Moreover, this procedure can worsen the leak by tearing a part of the subvalvular apparatus or the valve. As those patients usually have a high surgical risk [8], a surgical correction of TR, either a repair or a replacement, is seldom performed [9]. Transcatheter repair, currently mostly an edge-to-edge repair, can only be performed in selected patients and transcatheter replacement may represent an interesting option in the future but we lack experience for those patients.

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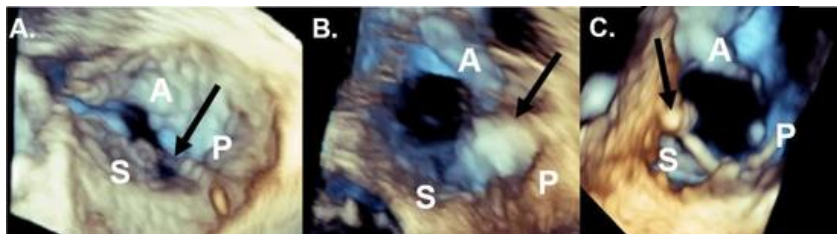


Fig. 1. Different types and locations of cardiac implantable electronic devices leads crossing the tricuspid valve. A. Pacemaker lead in the postero-septal commissure. B. Defibrillator lead in the center of the valve. C. Impingement of the septal leaflet by a pacemaker lead. A = Anterior leaflet, P = Posterior leaflet, S = Septal leaflet. The black crosses indicate the pacemaker or defibrillator leads.

In conclusion, this study raises awareness regarding the importance of assessing TR after CIED and on the altered prognosis of those who developed TR. Future prospective cohorts with thorough echocardiographic assessment of TR mechanism and grade at different time points will better define the natural history of CIED-induced TR and strategies to mitigate the risk of new-onset or worsening TR as well as the management of this challenging subset of patients.

Disclosures

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References

- [1] K. Addetia, S.C. Harb, R.T. Hahn, S. Kapadia, R.M. Lang, Cardiac implantable electronic device Lead-induced tricuspid regurgitation, *JACC Cardiovasc. Imaging* 12 (2019) 622–636.
- [2] K. Anvardeen, R. Rao, S. Hazra, et al., Prevalence and significance of tricuspid regurgitation post-endocardial lead placement, *JACC Cardiovasc. Imaging* 12 (2019) 562–564.
- [3] E.A. Prihadi, P. van der Bijl, E. Gursoy, et al., Development of significant tricuspid regurgitation over time and prognostic implications: new insights into natural history, *Eur. Heart J.* 39 (2018) 3574–3581.
- [4] J. Gelves-Meza, R.M. Lang, M.D. Valderrama-Achury, et al., Tricuspid regurgitation related to cardiac implantable electronic devices: an integrative

- review, *J. Am. Soc. Echocardiogr.* 35 (2022) 1107–1122.
- [5] N. Papageorgiou, D. Falconer, N. Wyeth, et al., Effect of tricuspid regurgitation and right ventricular dysfunction on long-term mortality in patients undergoing cardiac devices implantation: > 10-year follow-up study, *Int. J. Cardiol.* 319 (2020) 52–56.
- [6] S. Offen, G. Strange, D. Playford, D.S. Celermajer, S. Stewart, Prevalence and prognostic impact of tricuspid regurgitation in patients with cardiac implantable electronic devices: from the national echocardiography database of Australia, *Int. J. Cardiol.* (2022).
- [7] F. Praz, D. Muraru, F. Kreidel, et al., Transcatheter treatment for tricuspid valve disease, *EuroIntervention* 17 (2021) 791–808.
- [8] J. Dreyfus, E. Audureau, Y. Bohbot, et al., TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery, *Eur. Heart J.* (2021).
- [9] J. Dreyfus, N. Ghalem, E. Garbarz, et al., Timing of referral of patients with severe isolated tricuspid valve regurgitation to surgeons (from a French Nationwide Database), *Am. J. Cardiol.* 122 (2018) 323–326.

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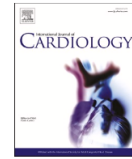
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Article 10

Functional tricuspid regurgitation: A clustering analysis and prognostic validation of three echocardiographic phenotypes in an external cohort

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Functional tricuspid regurgitation: A clustering analysis and prognostic validation of three echocardiographic phenotypes in an external cohort

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ABSTRACT

Background: Functional tricuspid regurgitation (FTR) is an independent risk factor for morbidity and mortality. New pathophysiological concepts but also new therapeutic options are justifying new knowledges for characterizing FTRs and their prognoses. Aim: To study echocardiographic criteria associated with prognosis in FTR-patients using a clustering method in two cohorts.

Methods and results: Two hundred forty-one patients with at least severe (\geq grade 3) TR were enrolled: 92 in the retrospective cohort (mean age 77.9 ± 13 years) and 149 in the prospective validation cohort. Hierarchical clustering analysis was conducted. Four parameters explained the clustering categorization according to a multinomial regression (right ventricular (RV) end-diastolic mid-cavity diameter, RV free-wall strain, right atrial (RA) volume index, RA strain; $p = 0.0039$). Three clusters were identified in the retrospective cohort: Cluster 1 had better right ventricular, left ventricular, and right atrial function than Cluster 2 (reduced RV and RA strain despite similar sizes). Cluster 3 included patients with severely dilated heart chambers associated to RV and RA dysfunctions. When applying the model in the validation (external) cohort, the rate of the primary endpoint (hospitalization for heart failure and/or death from any cause) was lowest in Cluster 1 (30.8% versus 48% and 58.8% in Clusters 2 and 3, respectively; $p < 0.05$).

Conclusion: In FTR patients, different profiles of RV and RA remodeling are associated with different outcomes. Therefore, the diagnostic work-up in this clinical setting should include RV and RA characteristics. Under noninterventive management, the phenotype corresponding to preserved RV size and preserved RA and RV functions appears to have a better prognosis.

1. Introduction

Although it has been neglected for years, the diagnosis of a moderate to severe functional (or secondary) tricuspid regurgitation (TR) has been consistently reported as an independent risk factor for morbidity and mortality [1–4]. Its management remains an unresolved issue. Cardiorenal syndrome, a straightforward consequence of TR, affects the sustained efficacy of medical treatment [5], and surgery might not be

the solution for many of these patients with chronic atrial arrhythmias, comorbidities and sometimes an advanced age [6–8]. The advent of percutaneous procedures as potential alternative to surgery [9,10] has led to increasing interest in better understanding and selecting patients eligible for intervention.

TR is characterized by complex pathophysiology [11,12]. Prihadi et al. [13] suggested distinguishing two categories among functional TRs: TR with atrial dilatation secondary to atrial fibrillation and TR with

Abbreviations: AF, atrial fibrillation; AF-TR, atrial functional tricuspid regurgitation; EROA, effective regurgitant orifice area; FAC, fraction area change; FTR, functional tricuspid regurgitation; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; PISA, proximal isovelocity surface area; RA, right atrial; RV, right ventricle; RVFWLS, right ventricular free wall longitudinal strain; TAPSE, tricuspid annular plane systolic excursion; TEE, transesophageal echocardiography; TR, tricuspid regurgitation; TTE, transthoracic echocardiography.

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right ventricular remodeling and valvular tethering [14]. Patients with a pacemaker lead crossing the valve are reported in a separate category of TR. Muraru et al. [15,16] nicely described the determinants of tricuspid annulus dilation (and of TR severity), but the question arises whether this characterization of functional TR has any clinical importance.

In view of the suboptimal outcomes of the currently practiced management of patients with TR [17], the improvement in risk stratification would facilitate decision-making about treatment strategies in each individual case.

Accordingly, we aimed to use echocardiographic characteristics that could be associated with the prognosis in patients with severe TR using a clustering approach in a retrospective single-center cohort (derivation cohort). The defined clusters were thereafter tested for their prognostic significance in an external validation cohort (the prospective multi-center TRicuspid Analysis Project “TRAP”) [17–19]. This is a multi-center prospective French cohort of patients with isolated secondary TR explored by echocardiography and followed.

2. Methods

2.1. Population selection

For this single-center retrospective observational study, we recruited patients who were referred from November 2019 to February 2021 to the tertiary center of Rennes University Hospital to evaluate and discuss the management of severe TR.

The inclusion criteria were the presence of severe secondary TR (EROA ≥ 40 mm² and/or vena contracta width ≥ 7 mm), a 3-dimensional echocardiographic analysis available for the tricuspid apparatus, and at least one echocardiogram performed at the University Hospital of Rennes (transthoracic echocardiography (TTE) potentially completed by a transesophageal echocardiography (TEE)). This 3D analysis was possible in atrial arrhythmic patients for the annular characteristics but was not accessible to the 3D analysis of the right ventricular volumes and ejection fraction (volume/rate issue). These patients had to be euolemic and were equally inpatients and outpatients referred for an evaluation. They should have at least grade 3 TR (i.e., severe, massive or torrential TR), and the other cardiac or extracardiac diseases should not be the principal cause of the symptoms or of the referral for an echocardiographic evaluation. The principal diagnosis of the patients from this retrospective cohort was “functional TR”.

We excluded patients with heart disease in which prognosis was not predominantly related to TR (advanced arrhythmogenic right ventricular dysplasia (ARVD), laminopathies, very severe biventricular dysfunction with LVEF $< 20\%$) and patients in whom TR was not isolated but associated with any other significant valve diseases (mitral regurgitation or aortic stenosis but also any degree of significant mitral valve stenosis). Patients with un-controlled cardio-renal syndrome were excluded.

One hundred eighty patients with severe TR were initially considered for inclusion; 3-dimensional echocardiographic analysis of the tricuspid annulus was performed and was interpretable for 109 of them. Of these 109 patients, 17 patients were excluded during the follow-up (because of the occurrence of a significant left heart disease concomitant with TR in 9 patients and regression of TR after treatment in 8 patients). Finally, 92 patients were included in the analysis.

Demographic, clinical, and biological data were collected at the same time as the echocardiogram and included age, sex, main medical history, the presence of other associated heart disease (atrial fibrillation, coronary artery disease, another associated valve disease), symptoms and clinical signs of heart failure, the occurrence of hospitalization or death, the dosage of diuretics, biology composed blood ionogram, blood cell count, NT-proBNP, and liver enzymes. This study was conducted in accordance with the “Good Clinical Practice” Guidelines in the Declaration of Helsinki. All patients provided their consent for participation in this study.

2.2. Echocardiography analysis

All transthoracic echocardiograms were performed at rest using a Vivid E9, or E95 ultrasound system (GE Healthcare, Horten, Norway) equipped with a 4Vc-D transducer, color Doppler, pulsed-wave, and continuous-wave Doppler. All exams were analyzed in a Core Laboratory (CIC-IT 1414, Rennes, France).

Parasternal, subcostal, and apical views were used. Left ventricular function was assessed using LVEF and global longitudinal strain by two-dimensional speckle-tracking echocardiography according to the current guidelines [20]. Right ventricular function was assessed using several parameters: RV free-wall speckle-tracking strain, RV free-wall and septum speckle-tracking strain, maximal lateral tricuspid annulus velocity measured by TDI (S-wave tric), tricuspid annular plane systolic excursion (TAPSE), and RV fractional area change (FAC). Quantitation of TR was performed using the proximal Isovelocity Surface Area (PISA) method as previously validated [21]. The severity of TR is defined according to recommendations [22], along with the new classification of severe TR by adding a 5th severity grade (torrential) [23]. Severe TR (grade 3/5) was defined by an EROA ≥ 40 mm² and/or vena contracta width ≥ 7 mm (single-planed), and torrential TR (grade 5/5) was defined by an EROA ≥ 80 mm² and/or vena contracta width ≥ 20 mm. Significant tricuspid annular dilatation was defined by an end-diastolic diameter of > 21 mm/m² (or > 35 mm) on an RV-focused four-chamber view. For 3D analysis, the parasternal long-axis view was used in TTE, and the mid-esophageal oblique short-axis view focused on the TV in TEE (inflow-outflow for TV). In view of the lack of specific software dedicated to the tricuspid valve, we used the mitral module to carry out the measurements of the TA. We used 5 landmarks to delimit the annulus (the anterior-posterior direction, the septal-lateral direction, and the coaptation point) (Fig. 1).

2.3. Endpoint

The primary outcome was hospitalization for heart failure or death from any cause until June 2021 in the derivation (external) cohort. Then, this primary outcome was analyzed in the TRAP cohort [17,18].

2.4. External validation cohort using the TRAP cohort

The TRAP cohort is an observational prospective study [17,18,19] including 160 patients between January 2017 and August 2019 from 13 French centers. The goal of TRAP was to analyze the natural history of patients having a significant secondary TR and no other cardiac disease. The inclusion criteria were very close to the Rennes-cohort: severe functional TR and age ≥ 18 years. The exclusion criteria were primary TR, LVEF $< 40\%$, significant left valvular heart disease (i.e., aortic and mitral regurgitation $\geq 2/4$, aortic stenosis > 1.5 cm², or mitral stenosis < 2 cm²), primary pulmonary hypertension, and congenital cardiopathy. Patients underwent echocardiography and clinical and biological analysis annually for 2 years.

2.5. Statistical analysis

Histogram, skewness, and kurtosis calculus were used to assess the normality of the distribution and to detect outliers. We imputed missing values with a Markov chain Monte Carlo (MCMC) method and generated 5 complete datasets (MI procedure, SAS 15.1). We checked for multivariate outliers and multicollinearity (with an arbitrary cutoff at 0.70 for the correlation coefficient between parameters). We performed hierarchical clustering (Ward’s method) based on Euclidian standardized distance data. This was done blinded to the clinical outcome using 23 echo parameters, which were selected a priori on expert advice. The pseudo-F statistic helped to identify the number of clusters (CLUSTER and TREE procedures, SAS 15.1). Hence, we reported three clusters. We then compared the distributions of echo parameters across clusters.

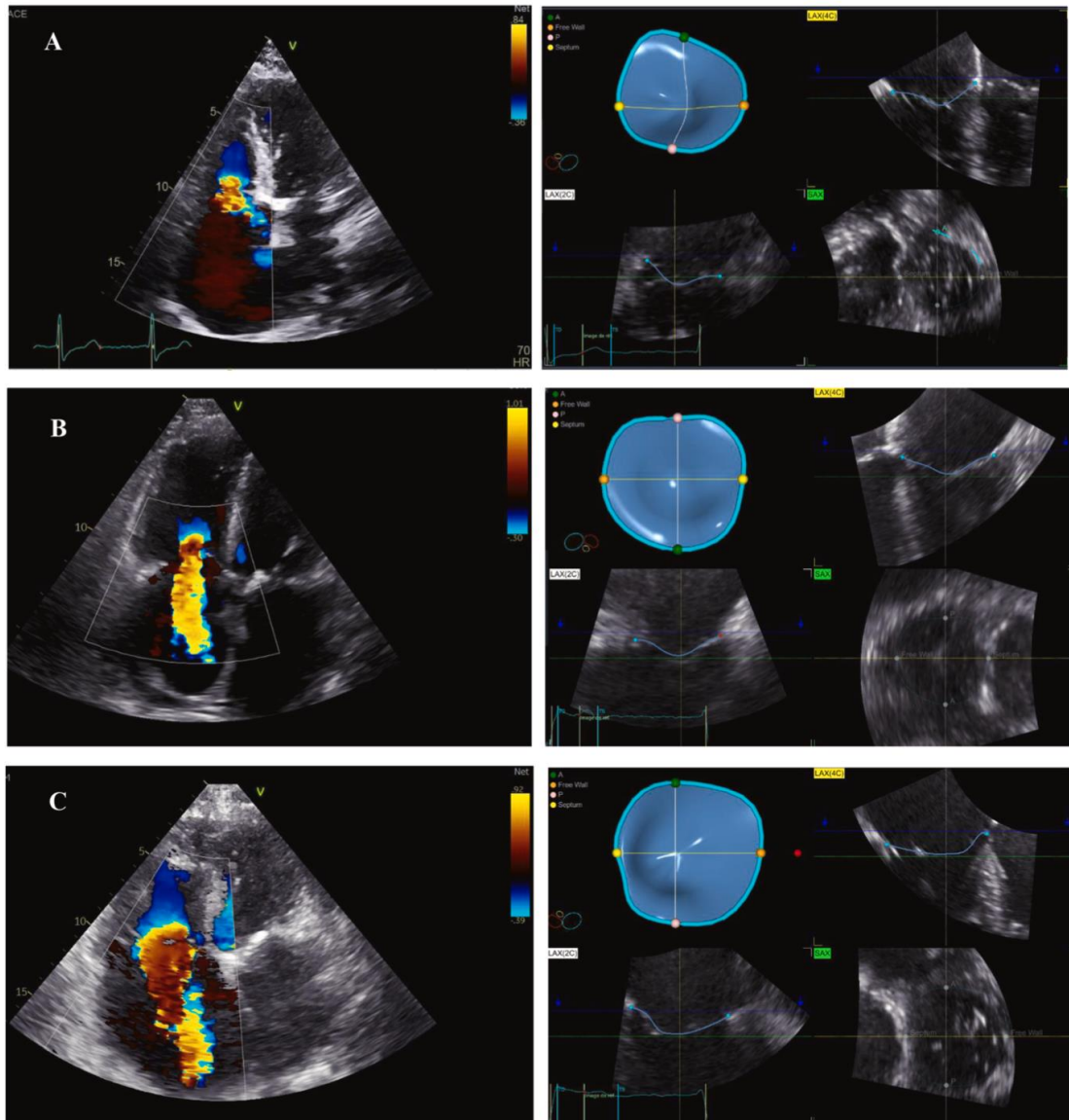


Fig. 1. 3D echocardiographic analysis of the tricuspid annulus (TA) according to the 3 clusters. A = Cluster 1, B = Cluster 2, C = Cluster 3. The TA is more dilated in Cluster 3. There was no significant difference between Clusters 1 and 2 in terms of measurements and shapes.

Descriptive statistics are the median \pm interquartile range. To compare the distributions of parameters across phenotypes, we used the Kruskal–Wallis test for continuous parameters and Fisher’s exact test for categorical variables. We presented nominal p values, as well as multiplicity-adjusted p values, using the Holm method (also known as the step-down Bonferroni method), which controls for the familywise error rate without assuming independence.

Using a multinomial regression model with stepwise backward selection, we found that 4 parameters (namely, RV end-diastolic mid-

cavity diameter, RA volume index, RA strain, and RV strain-free wall), handled as continuous variables, adequately explained the cluster categorization (LOGISTIC procedure, SAS 15.1). As an output, the procedure generated a dataset that contained sufficient information about the fitted model to score new data (i.e., the TRAP data) without having to refit the model.

3. Results

3.1. Study population characteristics

The baseline characteristics are presented in Table 1-A. The median age of this population was 77.9 ± 13 years. Of the 92 patients in this study, 45 (48.9%) were women. Most patients had permanent AF (63 patients, 68.5%). Regarding associated valve disease, 24 patients (26.1%) had mitral regurgitation (MR) grade II-III, and 7 patients (7.61%) had an aortic stenosis (moderate). Thirty-two patients (36.8%) had associated coronary artery disease, and 13 patients (14.6%) had a pacemaker or automatic implantable defibrillator. Clinically, 37 patients (40.2%) had signs and symptoms of isolated left ventricular failure, 6 patients (6.52%) had isolated right ventricular failure, and 42 patients (45.6%) had biventricular heart failure symptoms. Most patients were classified as NYHA stage II (60.9%) versus 36 patients (39.1%) who were classified as stage III or IV. Regarding the biological data, the median NT-proBNP was 2098 pg/ml, the median creatinine was $99 \mu\text{mol/L}$, and the median total bilirubin was 16 mmol/L .

Annex 1 and Annex 2 are providing the characteristics of the validation cohort.

Echocardiographic parameters are presented in Table 1-B. Fifty-six patients (60.9%) had massive TR (grade 4), and 31 patients (33.7%) had torrential TR (grade 5). The median LVEF was 55%, the median RV end-diastolic mid-cavity diameter was 41 mm (norm <35 mm), the median TAPSE was 16 mm, the median indexed RA volume was large to 73.3 ml/m^2 , and the median right atrial strain was reduced to 9.3%. The 3D tricuspid annulus assessment parameters led to a median sphericity index of 87%, and the median tenting volume was 3.4 mL. The tricuspid annulus remodeling was important with a spherization and lost of the physiological saddle shape of th annulus but some degree of tethering according to the RV-remodeling. (See Table 2.)

3.2. Echocardiographic parameters: differences in the cluster analysis

3.2.1. Cluster 1 (n = 53) = corresponding to "preserved RV size and functions"

34 patients (64.2%) had massive TR (grade 4), and 17 patients (32.1%) had torrential TR (grade 5). Right ventricular function was preserved with a s' tricuspid annular velocity of 0.12 m/s ($p = 0.0039$),

TAPSE of 17 mm ($p = 0.0039$), and RV free-wall speckle-tracking strain of -21.5% ($p = 0.0039$), all of which were higher than those in the other clusters. Similar to the right ventricle, the right atrial function was also better than in the other clusters, with an RA strain of -11.9% ($p = 0.0039$). The RA was large. Concerning the left-sided cavities, the median LVEF was 57%, and the left atrial strain (-9.53%) was better than in the other clusters ($p = 0.0039$).

3.2.2. Cluster 2 (n = 25) = corresponding to a "depressed ventricular function"

TR was massive (grade 4) in 20 patients (80%); 3 patients (12%) had severe TR (grade 3), and 2 patients (8%) had torrential TR (grade 5). Right ventricular function was significantly worse in this cluster than in Cluster 1, with a s' tricuspid velocity of 0.08 m/s, a reduced TAPSE of 13 mm, and RV-free wall strain of -13.7% . Left ventricular function was significantly lower than in the other clusters, with a moderately reduced LVEF of 45% ($p = 0.0039$) and a significantly lower GLS of -10.5% ($p = 0.0039$). Left ventricular filling pressures were significantly higher in Cluster 2 than in the other 2 clusters (E/e' of 15.4, $p = 0.0039$).

3.2.3. Cluster 3 (n = 14) = "severe dilatation and dysfunction of RV and RA"

This cluster comprised 12 patients (85.7%) with massive TR and 2 patients (14.3%) with torrential TR. The RV was significantly more dilated (the median RV end-diastolic mid-cavity diameter was 55 mm, $p = 0.0039$). Right atrium (the median RA indexed volume was 120 ml/m^2 , $p = 0.0039$) and the tricuspid annulus (the median TA area was 20.2 cm^2 , $p = 0.0046$, the median TA diameter was 51.5 mm, $p = 0.0039$) were bigger as well. Right atrial function (RA reservoir strain) was more impaired than in Cluster 1 but similar to that in Cluster 2 (RA strain -6.9% , $p = 0.0039$). The right ventricular function was worse than in Cluster 1 (S' tricuspid annular wave: 0.10 m/s, TAPSE: 16 mm, RV free-wall strain: -13.5% ; $p = 0.0039$).

There was no significant difference in any of the clinical parameters reported in Table 1-A across the clusters separated on the basis of hierarchical clustering, except for NT-proBNP and total bilirubin ($p = 0.0308$ and $p = 0.0039$, respectively).

3.2.4. Outcomes across clusters

For the outcomes, 21 patients (Cluster 1: 39.62%), 10 patients

Table 1-A
Population description (clinical and biological parameters), overall and according to the clustering.

| Variable | Missing N (%) | Overall N = 92 | Cluster-1 N = 53 | Cluster-2 N = 25 | Cluster-3 N = 14 | Nominal P value | adjusted P value |
|----------------------------------|---------------|----------------|---------------------|---------------------|---------------------|-----------------|------------------|
| Age, years | 0 | 77.9 (13.0) | 79.1 (13.2) | 73.1 (11.2) | 77.9 (13.0) | 0.3216 | |
| Sex, female | 0 | 45 (48.9) | 29 (54.7) | 10 (40.0) | 6 (42.9) | 0.4243 | |
| Heart rate, bpm | 2 | 75.0 (20.0) | 75.0 (13.5) | 80.0 (26.0) | 73.0 (21.0) | 0.0419 | 0.6704 |
| Rhythm sinus | 0 | 22 (23.9) | 17 (32.1) | 2 (8.00) | 3 (21.4) | 0.1096 | |
| Atrial fibrillation | 0 | 63 (68.5) | 31 (58.5) | 21 (84.0) | 11 (78.6) | | |
| Electrodriven | 0 | 7 (7.61) | 5 (9.4) | 2 (8.00) | - | | |
| MR None | 0 | 14 (15.2) | 9 (17.0) | 2 (8.00) | 3 (21.4) | 0.2093 | |
| Grade I-II | 0 | 54 (58.7) | 31 (58.5) | 13 (52.0) | 10 (71.4) | | |
| Grade II-III | 0 | 24 (26.1) | 13 (24.5) | 10 (40.0) | 1 (7.14) | | |
| Non severe Aortic stenosis | 0 | 7 (7.61) | 3 (5.66) | 3 (12.0) | 1 (7.14) | 0.6467 | |
| Coronary artery disease | 5 | 32 (36.8) | 16 (31.4) | 11 (50.0) | 5 (35.7) | 0.3164 | |
| PM or def | 3 | 13 (14.6) | 6 (11.5) | 4 (16.7) | 3 (23.1) | 0.4819 | |
| Symptoms None | 0 | 6 (6.52) | 6 (11.3) | - | - | 0.5588 | |
| LV failure | 0 | 37 (40.2) | 21 (39.6) | 11 (44.0) | 5 (35.7) | | |
| RV failure | 0 | 6 (6.52) | 4 (7.55) | 2 (8.00) | - | | |
| Both | 0 | 42 (45.6) | 21 (39.6) | 12 (48.0) | 9 (64.3) | | |
| Palpitations | 0 | 1 (1.09) | 1 (1.89) | - | - | | |
| NYHA Class III or IV | 0 | 36 (39.1) | 16 (30.2) | 13 (52.0) | 7 (50.0) | 0.1217 | |
| Creatinine, $\mu\text{mol/L}$ | 7 | 99 (41) | 96.0 (41.0) | 115 (87.5) | 99.0 (26.0) | 0.0447 | 0.6704 |
| Bilirubin total, mmol/L | 49 (53.3) | 16.0 (11.0) | 11.0 (4.50) | 20.5 (5.50) | 22.5 (14.0) | 0.0001 | 0.0039 |
| γ GT, U/L | 31 (33.7) | 130 (185) | 134 (190) | 106 (145) | 169 (252) | 0.5173 | |
| NT-pro-BNP, pg/mL | 13 (14.1) | 2098 (3134) | 1627 (1918) | 4012 (4429) | 2243 (1953) | 0.0014 | 0.0308 |

Values are median (interquartile range) or frequency (percentage). Nominal P values are based on the Kruskal-Wallis test or Fisher's exact test, and multiplicity-adjusted p values are based on the Holm method.

Table 1-B
Population description (echo parameters), overall and according to the clustering.

| Variable | Missing N (%) | Overall N = 92 | Cluster-1 N = 53 | Cluster-2 N = 25 | Cluster-3 N = 14 | Nominal P value | Adjusted P value |
|---------------------------------------|---------------|----------------|---------------------|---------------------|---------------------|-----------------|------------------|
| LV end-diastolic diameter, mm | 0 | 48.0 (10.0) | 47.0 (10.0) | 50.0 (10.0) | 47.0 (10.0) | 0.0441 | 0.6704 |
| LVEF, % | 0 | 55.0 (12.0) | 57.0 (9.00) | 45.0 (16.0) | 57.5 (10.0) | <0.0001 | 0.0039 |
| GLS, % | 14 (15.2) | 13.0 (4.80) | 15.0 (5.00) | 10.5 (4.80) | 12.2 (3.94) | <0.0001 | 0.0039 |
| LAVI, ml/m ² | 2 (2.17) | 63.4 (37.0) | 53.7 (30.0) | 83.0 (42.7) | 70.0 (21.2) | 0.0051 | 0.1071 |
| LA Strain, % PALS | 4 (4.35) | 7.35 (4.89) | 9.53 (6.79) | 6.62 (3.31) | 6.07 (2.19) | <0.0001 | 0.0039 |
| E/e' | 27 (29.3) | 9.52 (5.62) | 8.00 (5.17) | 15.4 (7.68) | 12.1 (11.4) | <0.0001 | 0.0039 |
| Cardiac output, L/min | 2 (2.17) | 4.23 (1.60) | 4.40 (1.31) | 4.10 (2.10) | 3.24 (1.42) | 0.0278 | 0.4726 |
| RV end-diastolic mid-cavity diam., mm | 3 (3.26) | 41.0 (12.0) | 41.0 (11.5) | 39.4 (8.00) | 55.0 (6.00) | <0.0001 | 0.0039 |
| FAC, % | 4 (4.35) | 35.6 (16.4) | 38.1 (12.3) | 31.8 (16.1) | 28.7 (15.1) | 0.0105 | 0.2020 |
| RA volume index, ml/m ² | 3 (3.26) | 73.3 (47.7) | 68.0 (40.8) | 64.9 (18.7) | 120 (107) | <0.0001 | 0.0039 |
| RA Strain, % PALS | 6 (6.52) | 9.30 (7.65) | 11.9 (8.28) | 6.40 (5.28) | 6.90 (6.06) | <0.0001 | 0.0039 |
| Tricuspid annular s'-wave, m/s | 15 (16.3) | 0.11 (0.05) | 0.12 (0.04) | 0.08 (0.02) | 0.10 (0.05) | <0.0001 | 0.0039 |
| RV Strain free wall, % | 9 (9.78) | 17.4 (9.00) | 21.5 (6.30) | 13.7 (4.60) | 13.5 (9.50) | <0.0001 | 0.0039 |
| TAPSE, mm | 7 (7.61) | 16.0 (6.00) | 17.0 (6.00) | 13.0 (4.00) | 16.0 (8.95) | <0.0001 | 0.0039 |
| Annular tricuspid diam, mm | 1 (1.09) | 45.0 (10.0) | 44.5 (9.00) | 44.0 (7.00) | 51.5 (9.00) | 0.0001 | 0.0039 |
| TR severity 3 | 0 | 5 (5.43) | 2 (3.77) | 3 (12.0) | — | <0.0001 | 0.0039 |
| 4 | | 56 (60.9) | 34 (64.2) | 20 (80.0) | 2 (14.3) | | |
| 5 | | 31 (33.7) | 17 (32.1) | 2 (8.00) | 12 (85.7) | | |
| Vena contracta, mm | 4 (4.35) | 8.00 (3.00) | 8.00 (2.50) | 7.60 (2.00) | 14.5 (5.50) | <0.0001 | 0.0039 |
| TR V max, m/s | 3 (3.26) | 3.10 (0.80) | 3.10 (0.80) | 3.20 (0.80) | 2.20 (1.62) | 0.0155 | 0.2790 |
| TR volume, mL | 7 (7.61) | 60.4 (29.0) | 61.0 (26.0) | 51.3 (17.8) | 94.8 (13.0) | <0.0001 | 0.0039 |
| VCI, mm | 16 (17.4) | 22.0 (5.50) | 21.0 (5.00) | 22.0 (7.27) | 34.1 (7.34) | <0.0001 | 0.0039 |
| Annular area 3D, cm ² | 0 | 16.0 (6.35) | 15.1 (4.60) | 15.9 (7.50) | 20.2 (4.00) | 0.0002 | 0.0046 |
| Sphericity index, % | 1 (1.09) | 87.0 (10.0) | 88.0 (10.0) | 86.0 (11.0) | 86.0 (14.0) | 0.7393 | |
| Tenting volume, mL | 0 | 3.40 (3.70) | 3.00 (2.70) | 3.40 (3.50) | 6.65 (4.50) | 0.0101 | 0.2020 |
| Systolic PAP | | 47.8 (17.5) | 50.9 (15.9) | 51.0 (20.9) | 37.6 (16.9) | 0.1009 | |
| Right atrial pressure | 37 (40.2) | 11.0 (8.00) | 10.0 (6.00) | 13.0 (7.50) | 15.0 (8.00) | 0.3335 | |
| EROA, mm ² | 8 (8.69) | 60.0 (36.0) | 60.0 (32.0) | 50.0 (19.0) | 109 (110) | <0.0001 | 0.0039 |

Table 2
Crosstabulation of the outcome (31 hospitalizations and 10 deaths) by cluster.

| Outcome | Cluster | | | Total |
|-----------|---------|-------|-------|-------|
| | 1 | 2 | 3 | |
| Frequency | | | | |
| Percent | | | | |
| No | 32 | 15 | 4 | 51 |
| | 60.38 | 60.00 | 28.57 | |
| Yes | 21 | 10 | 10 | 41 |
| | 39.62 | 40.00 | 71.43 | |
| Total | 53 | 25 | 14 | 92 |

Chi-square test p value = 0.0896.

(Cluster 2: 40%) and 10 patients (Cluster 3: 71.43%) in the three clusters presented with death (10 patients) and/or hospitalization for heart failure (31 patients), respectively, without a significant difference among the groups (chi-square p value = 0.0896).

3.3. External validation of the model in the TRAP cohort

First, we demonstrated the validity of cluster categorization by using 4 criteria that best explained the distribution of patients across the subsets (RV end-diastolic mid-cavity diameter, RA volume index, RA strain, and RV strain-free wall). We then used these 4 parameters to recreate the 3 clusters in the TRAP cohort. As shown in Table 3, the

Table 3
Summary of the number of censored and uncensored values in the validation dataset (149 patients).

| Summary of the Number of Censored and Uncensored Values | | | | | |
|---|---------|-------|--------|----------|------------------|
| Stratum | Cluster | Total | Failed | Censored | Percent Censored |
| 1 | 1 | 107 | 33 | 74 | 69.16 |
| 2 | 2 | 25 | 12 | 13 | 52.00 |
| 3 | 3 | 17 | 10 | 7 | 41.18 |
| Total | | 149 | 55 | 94 | 63.09 |

primary endpoint was present in 33 out of 107 patients (30.8%) in Cluster 1, 12 out of 25 patients (48%) in Cluster 2, and 10 out of 17 patients (58.8%) in Cluster 3. There was a significant difference among these 3 clusters regarding the occurrence of the primary endpoint, as shown by the survival curves in Fig. 2 (p < 0.05).

4. Discussion

In this study, using a hierarchical cluster analysis, we identified 3 subsets of patients with functional TR of grade ≥ 3 that were characterized by different profiles of RV and RA functional and structural remodeling and different outcomes. Patients with preserved RV but enlarged right atrium were associated with a more favorable clinical course.

TR is becoming a frequent and complex clinical challenge. An expert consensus, supposed to guide for interventions, has been established; however, the evidence is still scarce [16]. The current recommendations suggest surgery for symptomatic patients when their RV function is not impaired (grade IIa–B) [22], but most patients are asymptomatic for a long time, and RV function characterization may be challenging when TR is severe (stage 3) or more [22–25]. Therefore, most patients are managed with diuretics and undergo medical follow-up without any intervention. The natural history of FTR managed pharmacologically is the matter of our work. Regular follow-up is required to avoid cardio-renal syndrome. We have to take attention to remodeling and progressive dysfunction of the RV. The recommendations encourage a multiparametric approach, including RV-strain [26,27].

We currently demonstrated that a combination of 4 echo-derived parameters could be relevant to characterize TR patients with different profiles and prognoses. Based on the clustering analysis and no a priori assumption, three distinct phenogroups, differing in terms of pathophysiology and clinical risk, were separated. The difference among the 3 clusters for the primary endpoint did not reach statistical significance in the derivation cohort of 92 patients because this analysis was underpowered. However, the prognostic significance of this stratification was demonstrated in the validation cohort: there were fewer hospitalizations for heart failure or all-cause death in Cluster 1 than in

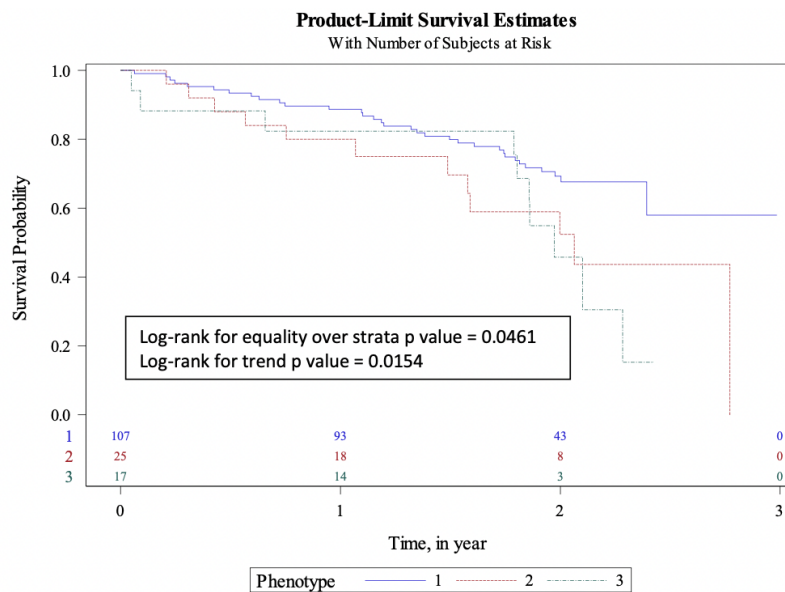


Fig. 2. Time to outcome (55 events, 18 hospitalizations or 37 deaths) according to the clustering in the validation dataset (149 observations without missing data).

Clusters 2 and 3.

Cluster 1 had a phenotype with preserved RV size and preserved RV function. Cluster 2 had a phenotype with RA and RV dysfunction, and Cluster 3 had an advanced TR, mostly torrential, with RV and RA dilatation and dysfunction. Our phenotyping characterization resembles, with more details, the recently proposed pathophysiological categories of atrial and ventricular functional TR. Muraru et al. [15] suggested that AF-TR could be more severe than VF-TR, as the TA is more dilated in this category. Indeed, in our study, TR in Cluster 1 seemed to exceed TR in Cluster 2 (torrential TR represented 32% in Cluster 1 versus 8% in Cluster 2); however, the TA anatomy analyzed by 3D echocardiography did not significantly differ between Clusters 1 and 2. More data are needed but the patients with preserved RV function seems to have a better prognosis even if the RA is very large. Utsunomiya et al. [28] reported similar data.

To date, no study has compared the prognosis of FTR that are related to enlarged RV to the ones related to mainly sick RA. Our analysis suggests that RA related TR might have better outcome under conservative management. Cluster 1 is prevalent and is associated with a lower clinical risk than the Cluster 2. In subjects included in Cluster 3, remodeling was greater for the RA and RV but also for the left-sided heart chambers, and almost 60% of them reached the primary endpoint over 2 years. These results are globally consistent with the study of Dietz et al., in which 70% of patients who had severe TR with RV dilatation and/or dysfunction were hospitalized for HF or died within 5 years [29].

AF is ubiquitous in the TR population (68.5% of patients were in AF during TTE, not counting patients with paroxysmal AF), partially explaining the atrial dilatation found in all clusters. This indicates that patients admitted to a tertiary center are too advanced according to the endpoint occurrence. More priority should be given to treating TR before the development of permanent AF? The present report could not answer to the question but our observation makes even more relevant upcoming studies reporting on patients “interventionally” treated for their TR.

We still have a lot to learn about “functional” TR. Our results

reinforce the significance of the RA and RV size and function that can be easily assessed by the longitudinal strain. It confirms the prognostic value of multiparametric assessment in TR patients based not exclusively on the regurgitant jet characteristics but also the integration of RV and RA morphological and functional features. The value of clustering analysis is that it allows to generate hypotheses and it provides an approach combining many parameters from multiple domains. Specifically, in the case of TR, it was possible to look at parameters related to the regurgitation itself, but also, related to ventricular and atrial remodelings, or loading conditions. All can contribute to a better characterization and stratification of the risk related to the disease entity. A clear distinction between AF-TR and VF-TR may sometimes be problematic because RV and RA remodeling progresses, and in more advanced stages, both these categories may overlap in terms of the consequences of TR for the right-sided heart chambers. Using the clustering method allows the selection of subjects with homogenous profiles of RV and RA derangements, irrespective of the preceding trajectories of changes. Moreover, this approach permitted the identification of parameters crucial for the prognostic stratification of TR patients.

4.1. Clinical implications

Our analysis indicates that both RV and RA remodeling should be taken into account when assessing patient prognosis and planning treatment strategies in TR. The disadvantage of clustering – the approach used in our study – is that it does not provide specific thresholds to permit translation into clinical practice. Limited evidence exists on the prognostic cutoff values for RV parameters in TR, and no data in this regard can be found for RA indices. Among RV function metrics, TAPSE <16 mm and RV free-wall longitudinal strain (RVFWLS) < 17% have been demonstrated to confer a poor prognosis for patients with high-grade TR [25,33]. Indeed, further studies involving broader populations are needed to establish the cutoff points for RV and RA parameters to define the prognostic algorithm that could be used as a clinical tool.

Despite a relatively better clinical course, AF-TR is not a benign

disease [30–32] and, similar to VF-TR, interventional management should be considered in these patients to avoid RV over-remodeling, as in Cluster 3.

4.2. Limitations

Several study limitations should be acknowledged. First, despite external validation, the recruitment of patients from a single academic center might constrain the generalizability of our results. Second, the differences in the clinical profiles between the derivation and validation cohorts, especially the presence of less severe TR in the validation subset, might have affected the accuracy of prognostic assessment. Third, the cohorts remain small but it is a first work using these methods and we believe that is provided hypothesis and great reasons to continue, to explore and to report on more patients coming from

different healthcare systems.

5. Conclusion

Among patients with severe functional TR, clustering approach distinguished three clusters with distinct characteristics that reflected the recently proposed pathophysiological categories. The diagnostic work-up in patients with significant TR should not be limited to the quantification of tricuspid valve characteristics. The phenotype corresponding to AF-TR appears to have a better prognosis than that of VF-TR.

Declaration of Competing Interest

None

Appendix

Table Annex-1 Baseline clinical characteristics in the validation cohort and according to events

| | Missing values | All patients N = 160 | No event N = 95 | Event N = 56 | p value |
|-------------------------------------|----------------|-------------------------|--------------------|-----------------|---------|
| Age, years | 1 | 78 [71–83] | 77 [67–82] | 80 [75–83] | 0.019 |
| Female | 0 | 99 (61.9) | 63 (66.3) | 32 (57.1) | 0.260 |
| Body Mass Index, kg/m ² | 1 | 26.1 ± 4.6 | 26.2 ± 4.5 | 26.3 ± 4.8 | 0.910 |
| Hypertension | 1 | 103 (64.8) | 58 (61.7) | 41 (73.2) | 0.150 |
| Systolic blood pressure, mm Hg | 6 | 128 ± 20 | 130 ± 21 | 125 ± 18 | 0.162 |
| Diastolic blood pressure, mm Hg | 6 | 73 ± 13 | 74 ± 13 | 71 ± 13 | 0.195 |
| Diabetes | 1 | 35 (22.0) | 20 (21.3) | 13 (23.2) | 0.782 |
| Dyslipidaemia | 1 | 58 (36.5) | 42 (44.7) | 14 (25.0) | 0.016 |
| Chronic Obstructive Pulmonary | 1 | 16 (10.1) | 7 (7.45) | 7 (12.5) | 0.303 |
| Malignancy | 1 | 31 (19.5) | 18 (19.1) | 13 (23.2) | 0.552 |
| Ischaemic heart disease | 2 | 32 (20.2) | 16 (17.0) | 11 (20.0) | 0.649 |
| Prior stroke | 1 | 16 (10.1) | 7 (7.45) | 7 (12.5) | 0.303 |
| History of atrial fibrillation | 1 | 127 (79.9) | 73 (77.6) | 48 (85.7) | 0.227 |
| Atrial fibrillation at baseline | 8 | 93 (61.2) | 51 (57.3) | 37 (68.5) | 0.050 |
| Aortic surgery | 1 | 10 (6.29) | 7 (7.45) | 3 (5.36) | 0.744 |
| Mitral surgery | 1 | 10 (6.29) | 8 (8.51) | 2 (3.57) | 0.322 |
| NYHA, Class I | 5 | 19 (12.3) | 17 (18.9) | 2 (3.57) | 0.002 |
| Class II | | 76 (49.0) | 47 (52.2) | 26 (46.4) | 0.002 |
| Class III or IV | | 60 (38.7) | 26 (28.9) | 28 (50.0) | 0.002 |
| Anticoagulant Vitamin K antagonists | 1 | 67 (42.1) | 38 (40.4) | 27 (48.2) | 0.437 |
| Direct oral anticoagulation | | 57 (35.8) | 33 (35.1) | 20 (35.7) | |
| ACE inhibitor | 1 | 41 (25.8) | 24 (25.5) | 15 (26.8) | 0.865 |
| ARB | 2 | 21 (13.3) | 16 (17.2) | 5 (8.93) | 0.156 |
| Betablocker | 1 | 103 (64.8) | 62 (66.0) | 38 (67.9) | 0.811 |
| Diuretic Potassium sparing diuretic | 1 | 49 (30.8) | 25 (26.6) | 24 (42.9) | 0.040 |
| Loop diuretic | 1 | 124 (78.0) | 65 (69.1) | 51 (91.1) | 0.002 |

Events were hospitalization for heart failure (n = 18) and death (n = 38); COPD, chronic obstructive pulmonary disease; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

Table Annex-2 Baseline echo parameters of the validation cohort and according to events

| | Missing values | All patients N = 160 | No event N = 95 | Event N = 56 | p value |
|--|----------------|-------------------------|--------------------|-----------------|---------|
| Cardiac index, L/min/m ² | 17 | 2.58 ± 0.81 | 2.61 ± 0.77 | 2.54 ± 0.89 | 0.663 |
| LVEF, % | 3 | 60.8 ± 8.77 | 62.3 ± 7.71 | 59.4 ± 9.32 | 0.038 |
| Global longitudinal Strain, % | 22 | 16.6 ± 3.70 | 17.2 ± 3.20 | 16.1 ± 4.25 | 0.116 |
| Right atrial strain, % | 17 | 10.2 [6.72–17.2] | 12.0 [7.50–18.6] | 8.0 [6.60–13.3] | 0.023 |
| TAPSE, mm | 6 | 18.8 ± 5.10 | 19.6 ± 5.27 | 17.5 ± 4.55 | 0.019 |
| SPAP | 35 | 44.0 [35.0–54.0] | 40 [34–50] | 50 [38–55] | 0.012 |
| TAPSE/sPAP | 39 | 0.46 ± 0.21 | 0.50 ± 0.22 | 0.40 ± 0.16 | 0.019 |
| End diastolic RV diameter, mm | 12 | 42.0 ± 9.07 | 40.5 ± 8.41 | 44.4 ± 10.0 | 0.018 |
| Right atrial volume index, ml/m ² | 11 | 68.6 [49.4–99.8] | 64.7 [43.7–94.0] | 73.0 [63.3–117] | 0.017 |
| Strain RV free wall, % | 19 | 21.1 ± 6.88 | 22.3 ± 6.50 | 19.8 ± 7.22 | 0.042 |
| Tricuspid s wave | 11 | 10.9 ± 3.11 | 11.4 ± 2.94 | 10.2 ± 3.10 | 0.02 |
| Regurgitant Orifice Area, mm ² | 13 | 47 [30–77] | 47 [28–70] | 51 [32–100] | 0.16 |
| Moderate to severe (30–39 mm) | 13 | 42 (31.6) | 27 (32.9) | 11 (25.6) | 0.34 |
| | | 32 (24.1) | 22 (26.8) | 9 (20.9) | 0.34 |

(continued on next page)

(continued)

| | Missing values | All patients N = 160 | No event N = 95 | Event N = 56 | p value |
|---|----------------|-------------------------|--------------------|-----------------|---------|
| Severe (40–59 mm ²) | | | | | |
| Massive or torrential (≥ 60 mm ²) | | 59 (44.4) | 33 (40.2) | 23 (53.5) | 0.34 |

LVEF stands for left ventricular ejection fraction; TAPSE for tricuspid annular plane systolic excursion; SPAP for systolic pulmonary arterial pressure; RV for right ventricle.

References

- [1] J. Nath, E. Foster, P.A. Heidenreich, Impact of tricuspid regurgitation on long-term survival, *J. Am. Coll. Cardiol.* 43 (3) (2004 Feb 4) 405–409.
- [2] E. Chorin, Z. Rozenbaum, Y. Topilsky, M. Konigstein, T. Ziv-Baran, E. Richert, et al., Tricuspid regurgitation and long-term clinical outcomes, *Eur. Heart J. Cardiovasc. Imaging* 21 (2) (2020 Feb 1) 157–165.
- [3] G. Benfari, C. Antoine, W.L. Miller, P. Thapa, Y. Topilsky, A. Rossi, et al., Excess mortality associated with functional tricuspid regurgitation complicating heart failure with reduced ejection fraction, *Circulation*. 140 (3) (2019 Jul 16) 196–206.
- [4] N. Wang, J. Fulcher, N. Abeyuriya, M. McGrady, I. Wilcox, D. Celermajer, et al., Tricuspid regurgitation is associated with increased mortality independent of pulmonary pressures and right heart failure: a systematic review and meta-analysis, *Eur. Heart J.* 40 (5) (2019 Feb 1) 476–484.
- [5] J.C. Jentzer, A. Bihorac, S.B. Brusca, G. Del Rio-Pertuz, K. Kashani, A. Kazory, et al., Contemporary management of severe acute kidney injury and refractory cardiorenal syndrome: JACC Council perspectives, *J. Am. Coll. Cardiol.* 76 (9) (2020 Sep 1) 1084–1101.
- [6] F. Alqahtani, C.O. Berzinger, S. Aljohani, M. Hijazi, A. Al-Hallak, M. Alkhouli, Contemporary trends in the use and outcomes of isolated treatment of tricuspid regurgitation, *J. Am. Heart Assoc.* 6 (12) (2017 Dec 22).
- [7] A.L. Axtell, V. Bhambhani, P. Moonsamy, E.W. Healy, M.H. Picard, T.M. Sundt, et al., Surgery does not improve survival in patients with isolated severe tricuspid regurgitation, *J. Am. Coll. Cardiol.* 74 (6) (2019 Aug 13) 715–725.
- [8] D.J. LaParo, D.S. Likosky, M. Zhang, P. Theurer, C.E. Fonner, J.A. Kern, et al., Development of a risk prediction model and clinical risk score for isolated tricuspid valve surgery, *Ann. Thorac. Surg.* 106 (1) (2018 Jul 1) 129–136.
- [9] J. Rodés-Cabau, R.T. Hahn, A. Latib, M. Laule, A. Lauten, F. Maisano, et al., Transcatheter therapies for treating tricuspid regurgitation, *J. Am. Coll. Cardiol.* 67 (15) (2016 Apr 19) 1829–1845.
- [10] M. Taramasso, G. Benfari, P. van der Bijl, H. Alessandrini, A. Attinger-Toller, L. Biasco, et al., Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation, *J. Am. Coll. Cardiol.* 74 (24) (2019 Dec 17) 2998–3008.
- [11] L.P. Badano, S. Caravita, V. Rella, V. Guida, G. Parati, D. Muraru, The added value of 3-dimensional echocardiography to understand the pathophysiology of functional tricuspid regurgitation, *JACC Cardiovasc. Imaging* 14 (3) (2021 Mar 1) 683–689.
- [12] R.T. Hahn, L.T. Weckbach, T. Noack, N. Hamid, M. Kitamura, R. Bae, et al., Proposal for a standard echocardiographic tricuspid valve nomenclature, *JACC Cardiovasc. Imaging* 14 (7) (2021 Jul 1) 1299–1305.
- [13] E.A. Prihadi, V. Delgado, M.B. Leon, M. Enriquez-Sarano, Y. Topilsky, J.J. Bax, Morphologic types of tricuspid regurgitation: characteristics and prognostic implications, *JACC Cardiovasc. Imaging* 12 (3) (2019 Mar) 491–499.
- [14] Y. Topilsky, A. Khanna, T. Le Tourneau, S. Park, H. Michelena, R. Suri, et al., Clinical context and mechanism of functional tricuspid regurgitation in patients with and without pulmonary hypertension, *Circ Cardiovasc. Imag.* 5 (3) (2012 May 1) 314–323.
- [15] D. Muraru, K. Addetia, A.C. Guta, R.C. Ochoa-Jimenez, D. Genovesi, F. Veronesi, et al., Right atrial volume is a major determinant of tricuspid annulus area in functional tricuspid regurgitation: a three-dimensional echocardiographic study, *Eur. Heart J. Cardiovasc. Imaging* 22 (6) (2021 May 10) 660–669.
- [16] F. Praz, D. Muraru, F. Kreidel, P. Lurz, R.T. Hahn, V. Delgado, et al., Transcatheter treatment for tricuspid valve disease, *EuroIntervention*. 17 (10) (2021 Nov 19) 791–808.
- [17] J. Dreyfus, M. Flagiello, B. Bazire, F. Eggenpieler, F. Viau, E. Riant, et al., Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes, *Eur. Heart J.* 41 (45) (2020 Dec 1) 4304–4317.
- [18] A. Guérin, E. Vabret, J. Dreyfus, Y. Lavie-Badie, C. Sportouch, J.-C. Eicher, et al., Cardiac remodelling in secondary tricuspid regurgitation: should we look beyond the tricuspid annulus diameter? *Arch Cardiovasc Dis.* 114 (4) (2021 Apr) 277–286.
- [19] E. Chen, G. L'official, A. Guérin, J. Dreyfus, Y. Lavie-Badie, C. Sportouch, et al., Natural history of functional tricuspid regurgitation: impact of cardiac output, *Eur. Heart J. Cardiovasc. Imaging* 22 (8) (2021 Jul 20) 878–885.
- [20] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, *Eur. Heart J. Cardiovasc. Imaging* 16 (3) (2015 Mar) 233–270.
- [21] C.M. Tribouilloy, M. Enriquez-Sarano, M.A. Capps, K.R. Bailey, A.J. Tajik, Contrasting effect of similar effective regurgitant orifice area in mitral and tricuspid regurgitation: a quantitative Doppler echocardiographic study, *J. Am. Soc. Echocardiogr.* 15 (9) (2002 Sep) 958–965.
- [22] A. Vahanian, F. Beyersdorf, F. Praz, M. Milojevic, S. Baldus, J. Bauersachs, et al., ESC/EACTS Guidelines for the management of valvular heart disease, *Eur. Heart J.* 43 (7) (2022) 561–632.
- [23] Y.Y. Go, R. Dulgheru, P. Lancellotti, The conundrum of tricuspid regurgitation grading, *Front Cardiovasc. Med.* (5) (2018 Nov 9) 164.
- [24] S.-H. Hsiao, S.-K. Lin, W.-C. Wang, S.-H. Yang, P.-L. Gin, C.-P. Liu, Severe tricuspid regurgitation shows significant impact in the relationship among peak systolic tricuspid annular velocity, tricuspid annular plane systolic excursion, and right ventricular ejection fraction, *J. Am. Soc. Echocardiogr.* 19 (7) (2006 Jul 1) 902–910.
- [25] F. Ancona, F. Melillo, F. Calvo, N. Attalla El Halabieh, S. Stella, C. Capogrosso, et al., Right ventricular systolic function in severe tricuspid regurgitation: prognostic relevance of longitudinal strain, *Eur. Heart J. Cardiovasc. Imaging* 22 (8) (2021 Jul 20) 868–875.
- [26] M. Tadic, C. Cuspidi, D.A. Morris, W. Rottbauer, Functional tricuspid regurgitation, related right heart remodeling, and available treatment options: good news for patients with heart failure? *Heart Fail. Rev.* 27 (4) (2022) 1301–1312.
- [27] F. Ancona, S. Stella, M. Taramasso, C. Marini, A. Latib, P. Denti, et al., Multimodality imaging of the tricuspid valve with implication for percutaneous repair approaches, *Heart.* 103 (14) (2017 Jul) 1073–1081.
- [28] H. Utsunomiya, Y. Harada, H. Susawa, Y. Ueda, K. Izumi, K. Itakura, et al., Tricuspid valve geometry and right heart remodelling: insights into the mechanism of atrial functional tricuspid regurgitation, *Eur. Heart J. Cardiovasc. Imaging* 21 (10) (2020 Oct 1) 1068–1078.
- [29] M.F. Dietz, E.A. Prihadi, P. van der Bijl, L. Goedemans, B.J.A. Mertens, E. Gursøy, et al., Prognostic implications of right ventricular remodeling and function in patients with significant secondary tricuspid regurgitation, *Circulation*. 140 (10) (2019 Sep 9) 836–845.
- [30] E. Agricola, C. Marini, S. Stella, A. Monello, A. Fiscaro, V. Tufaro, et al., Effects of functional tricuspid regurgitation on renal function and long-term prognosis in patients with heart failure, *J. Cardiovasc. Med. (Hagerstown)* 18 (2) (2017 Feb) 60–68.
- [31] J.J. Silbiger, Atrial functional tricuspid regurgitation: an underappreciated cause of secondary tricuspid regurgitation, *Echocardiography*. 36 (5) (2019) 954–957.
- [32] N. Prapan, N. Ratanasit, K. Karaketklang, Significant functional tricuspid regurgitation portends poor outcomes in patients with atrial fibrillation and preserved left ventricular ejection fraction, *BMC Cardiovasc. Disord.* 20 (1) (2020 Oct 6) 433.
- [33] Y. Abe, K. Akamatsu, K. Ito, Y. Matsumura, K. Shimeno, T. Naruko, et al., Prevalence and prognostic significance of functional mitral and tricuspid regurgitation despite preserved left ventricular ejection fraction in atrial fibrillation patients, *Circ. J.* 82 (5) (2018) 1451–1458.

Article 11

Natural history of functional tricuspid regurgitation: impact of cardiac output

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Natural history of functional tricuspid regurgitation: impact of cardiac output

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Aims

Tricuspid regurgitation (TR) was long forgotten until recent studies alerting on its prognostic impact. Cardiac output (CO) is the main objective of heart mechanics. We sought to compare clinical and echocardiographic data of patients with TR from inclusion to 1-year follow-up according to initial CO.

Methods and results

Patients with isolated secondary TR and left ventricular ejection fraction (LVEF) $\geq 40\%$ were prospectively included. All patients had a clinical and echocardiographic evaluation at baseline and after 1 year. Echocardiographic measurements were centralized. The patients were partitioned according to their CO at baseline. The primary outcome was all-cause death. Ninety-five patients completed their follow-up. The majority of patients had normal CO ($n = 64$, 67.4%), whereas 16 (16.8%) patients had low-CO and 12 (12.6%) had high-CO. right ventricular function was worse in the low-CO group but with improvement at 1 year (30% increase in tricuspid annular plane systolic excursion). LVEF and global longitudinal strain were significantly worse in the low-CO group. Overall, 18 (19%) patients died during follow-up, of which 10 (55%) patients had abnormal CO. There was a U-shaped association between CO and mortality. Normal CO patients had significantly better survival (87.5% vs. 62.5% and 66.67%) in the low- and high-CO groups, respectively, even after adjustment (heart rate 2.23 for the low-CO group and 9.08 for high-CO group; $P = 0.0174$).

Conclusion

Significant isolated secondary TR was associated with 19% of mortality. It is also associated with higher long-term mortality if CO is abnormal, suggesting a possible role for evaluating better and selecting patients for intervention.

Keywords

tricuspid regurgitation • cardiac output • right ventricular function • prognosis

Introduction

Secondary (or functional) tricuspid regurgitation (TR) is one of the most common valvular heart disease.¹ TR has been forgotten for a long time, as it was believed to be secondary to left heart disease and to regress after treating the underlying cause. It has long been seen as a prognostic marker when associated to other valvular heart dis-

eases.² We know now that TR increases the risk of death independently of anything else.³

The management of TR remains challenging. Treatment is essentially medical (symptomatic and palliative) and based on diuretics that decreases volume overload. Guidelines recommend tricuspid surgery in limited circumstances: surgery is recommended on tricuspid valve (TV) only if left valvular heart disease surgery is needed; or if there is

significant symptomatic TR with progressive right ventricular (RV) dilatation and/or dysfunction in those with left valvular heart disease that have previously been operated on.^{4,5} In fact, TV surgery is not often performed because of high mortality, ranging from 18% to 36% at 1 year in different studies.^{3,6,7} It may be explained by the delayed occurrence of surgery at the stage of irreversible RV dilatation and dysfunction associated with multiorgan failure.^{8,9}

In these last years, in regard to left valvular diseases successfully being treated with percutaneous devices, many similar techniques are developed for TR as an alternative to surgery, with promising results. Several innovative approaches, mimicking surgical techniques, are still under-investigation.^{9,10} As a consequence, many uncertainties and challenges are to be solved before eventually integrating these interventions in daily practice. The selection criteria and timing of intervention of patients are some of the main questions still under investigation. Right heart function is involved in the success of the intervention as expected, but few studies have taken interest in haemodynamic parameters.

Cardiac output (CO) is the main objective of heart mechanics, and the impact of significant TR on that main function remains a question. Severe TR can be compared to a state of low-CO with a possible inverse relationship implied.^{11,12} Low-CO is known to be a prognostic marker, especially in heart failure (HF).^{13,14} Hence, CO has been suggested as additional tools in the assessment of HF, besides left ventricular ejection fraction (LVEF).¹⁴ Recently, high-output HF has been proposed as a separate entity and in the differential diagnosis of HF with preserved ejection fraction.¹⁵ Severe TR shares similar features, such as a frequent association with liver and renal diseases.¹⁶

We sought to compare the clinical and echocardiographic data of patients with significant TR from inclusion to 1 year later looking specifically at the main heart goal, the output.

Methods

Population selection

In our observational prospective study (TRAP), patients were recruited in 13 French hospitals between January 2017 and August 2019.¹⁷ Criteria for inclusion were age ≥ 18 years, significant TR (at least moderate), and optimized volaemic status. Patients were excluded if they had one of the following features: primary TR, significant left valvular heart disease (i.e. aortic and mitral regurgitation $\geq 2/4$, aortic stenosis >1.5 cm², or mitral stenosis <2 cm²), LVEF $<40\%$, congenital cardiopathy, primary pulmonary hypertension, life expectancy shorter than 1 year apart from valve disease, or poor acoustic window.

Follow-up

Patients were evaluated at baseline by a physical examination along with an electrocardiogram, a blood test, and echocardiography at distance from the initial diagnosis after optimal medical treatment. Medical background [including history of chronic obstructive pulmonary disease (COPD), malignancy, renal dysfunction, anaemia, ischaemic cardiomyopathy, atrial fibrillation (AF), and prior stroke] and cardiovascular risk factors were collected from medical files, self-reporting, and physical examination before echocardiographic examination, as well as functional New York Heart Association (NYHA) status. All tests were repeated at 1 year along with a physical examination. All data were reported in an on-line case report form dedicated to TRAP.¹⁷

Echocardiography analysis

Details on echocardiography equipment and measures have already been described in a previous work.¹⁸ Briefly, all patients underwent standard transthoracic echocardiography using essentially a Vivid 7, a Vivid E9, or an E95 ultrasound system (GE Healthcare, Horten, Norway) equipped with a 3S or M5S 3.5 MHz transducer for 2D, colour, pulsed-wave, and continuous-wave Doppler. Data were stored on a dedicated workstation for off-line analysis (EchoPAC version 112.99. Research Release. GE Healthcare, Horten, Norway). All exams were analysed in a core laboratory (CIC-IT 1414, Iso9001).

Left ventricle (LV), as well as the volumes and functions of the right cavities, was measured according to guidelines.¹⁹ RA volume was indexed to body surface. LV function was assessed by LVEF and global longitudinal strain (GLS). The ratio of early transmitral flow velocity to mean tissue Doppler imaging (TDI) annular velocity (E/e') was considered an index of mean LV filling pressure and diastolic function by measuring the septal and lateral mitral annulus velocities with TDI. The tricuspid annulus was measured according to guidelines too.²⁰ RV function was estimated by seven performance indices: tricuspid annular plane systolic excursion (TAPSE), maximal lateral tricuspid annulus velocity measured by TDI (RV S'), RV free wall speckle-tracking strain, RV free wall, and septum speckle-tracking strain, RV onset to peak isovolumic acceleration (IVA), Tei index, and RV fraction area change. The assessment of TR severity was defined according to the recommendations along with the new classification of severe TR, adding a fifth grade of severity corresponding to torrential TR.^{21,22} Moderate TR was defined by an effective regurgitant orifice area (EROA) of 20–39 mm², severe TR as an EROA of 40–59 mm², and massive and torrential TR were regrouped as an EROA ≥ 60 mm².

CO was estimated in the apical five-chamber view by calculating systolic volume using the velocity time integral (VTI) of the flow through the left ventricular outflow tract (LVOT) by placing the Doppler sample volume 5 mm below the aortic valve, the LVOT diameter measured on the long parasternal axis, and heart rate (HR) during the imaging study. CO was calculated using the following formula: CO = HR (bpm) \times stroke volume, with stroke volume = LVOT area (cm²) \times LVOT VTI (cm) = π (LVOT diameter/2)² \times LVOT VTI (cm³ or mL), so CO (mL/min) = HR (bpm) \times LVOT VTI (cm) \times π \times (LVOT diameter/2)² (cm²).

Measures were all repeated over three cardiac cycles in sinus rhythm and over five cardiac cycles in patients with AF to obtain mean values and limit the variability caused by different heart cycle lengths.

Statistical analysis

Patients were partitioned according to their CO at baseline as follows ('low' CO <3.28 , 'normal' CO 3.28–6.22, and 'high' CO >6.22 L/min), with cut-offs being the mean (4.75) ± 1 SD (1.47).

Clinical characteristics and measurements of echocardiographic parameters at baseline were described according to CO at baseline. The association between these characteristics or measurements of echocardiographic parameters and CO at baseline was assessed through Wilcoxon or Spearman tests, as CO was a continuous variable.

The primary outcome was all-cause death in the current state-of-monitoring. The Kaplan–Meier estimator was used to describe the survival in the three different subgroups according to CO at baseline; the log-rank test was used to test for differences across the three different subgroups, ignoring the underlying order. Cox regression analysis was performed to adjust the baseline covariates associated with CO (univariate $P < 0.20$, pending $<5\%$ of missing values and prevalence for binary variable greater than 10%).

Ethics

Our observational multicentre study (TRAP) was conducted in accordance with the 'Good Clinical Practice' guidelines of the Declaration of Helsinki and reviewed by an independent regional ethics committee on 28 June 2016. All patients gave their written informed consent for study participation. The National Commission for Information Technology and Privacy approved the data collection conducted by the TRAP investigators on 7 November 2016 (N^o 20050960v0).

Results

Baseline characteristics of the population

A total of 95 patients with complete follow-up were included and analysed, although three patients were not classified in any group due to missing CO appropriate measurement. Baseline clinical characteristics are described in Table 1. Mean (standard deviation, SD) CO was 4.75 (1.47), median CO was 4.60 L/min, and ranging from 2 to 10. The majority of patients had normal CO ($n = 64$, 67.4%), whereas 16 (16.8%) patients had low-CO (defined as below 3.28 which was the mean -1 SD) and 12 (12.6%) had high-CO (defined as above 6.22 which was the mean $+1$ SD). To summarize, the three groups were comparable with no significant differences identified. Mean age was 76.9 ± 10.5 years, with an inverse relationship between age and CO,

the low-CO-group being the oldest, although not significantly. There was a majority of female patients (60%), with an elevated mean body mass index of 26 ± 4.4 kg/m². Of note, two-thirds of the cohort had hypertension and known AF at baseline. Malignancy, known ischaemic heart disease, and left valvular heart disease surgery were present in all groups in comparable proportions. No patient in the high-CO group had COPD, renal dysfunction, or a history of prior stroke. No anaemia was reported, as the mean haemoglobin level was 12 g/dL, thus not explaining the high-CO in the respective group. Approximately 60% of the patients were mildly symptomatic with class NYHA I or II. Notably, an inverse relationship between the HF marker NT-proBNP (N terminal pro Brain Natriuretic peptide) and CO was suggested, but it was not significant ($P = 0.67$).

Echocardiographic characteristics and evolution

Echocardiographic parameters at baseline are presented in Table 2. Importantly, there was no difference in the different grades of TR severity proportion in each group. Overall, RV function was worse in the low-CO group, as TAPSE and RV S' were significantly lower ($P < 0.01$). As CO increased, so did these parameters, from a mean TAPSE of 16.3 mm in the low-CO group to 18.7 mm, and 20.5 mm in the normal and high-CO groups, respectively. Similarly, mean RV S'

Table 1 Population baseline clinical characteristics

| | Missing values | All patients N = 95 | Cardiac output ^a | | | P-value |
|------------------------------------|----------------|------------------------|--------------------------------|---------------------------------------|---------------------------------|---------|
| | | | 'Low' <3.28 L/min N = 16 | 'Normal' 3.28–6.22 L/min N = 64 | 'High' >6.22 L/min N = 12 | |
| Age, years | | 76.9 ± 10.5 | 79.9 ± 10.1 | 76.8 ± 10.3 | 72.3 ± 12.5 | 0.07 |
| Female | | 57 (60.0) | 11 (68.7) | 38 (59.4) | 6 (50.0) | 0.24 |
| Body mass index, kg/m ² | | 26 ± 4.4 | 27 ± 4.1 | 26 ± 4.1 | 27 ± 6.6 | 0.65 |
| Hypertension | | 64 (67.4) | 10 (62.5) | 45 (70.3) | 8 (66.7) | 0.64 |
| Systolic blood pressure, mmHg | 3 | 129 ± 20 | 127 ± 18 | 130 ± 21 | 126 ± 14 | 0.56 |
| Diastolic blood pressure, mmHg | 3 | 75 ± 13 | 70 ± 16 | 75 ± 14 | 76 ± 7 | 0.39 |
| Diabetes | | 20 (21.0) | 4 (25.0) | 11 (17.2) | 4 (33.3) | 0.85 |
| Dyslipidaemia | | 38 (40.0) | 4 (25.0) | 29 (45.3) | 4 (33.3) | 0.95 |
| COPD | | 9 (9.47) | 2 (12.5) | 7 (10.9) | — | 0.28 |
| Malignancy | | 16 (16.8) | 3 (18.7) | 10 (15.6) | 3 (25.0) | 0.47 |
| Renal insufficiency | 1 | 2 (2.13) | 1 (6.25) | 1 (1.59) | — | 0.23 |
| Creatinine level, μmol/L | 3 | 99 ± 39 | 100 ± 19 | 98 ± 43 | 103 ± 39 | 0.30 |
| Haemoglobin level, G/dL | 8 | 12 ± 1.9 | 12 ± 1.6 | 13 ± 1.9 | 12 ± 2.5 | 0.21 |
| NT-proBNP, ng/L | 26 | 1166 [1329] | 1498 [1538] | 1165 [1115] | 733 [2205] | 0.67 |
| Ischaemic heart disease | | 17 (17.9) | 5 (31.2) | 9 (14.1) | 2 (16.7) | 0.33 |
| Prior stroke | | 11 (11.6) | 5 (31.2) | 4 (6.25) | — | 0.10 |
| AF at baseline | | 61 (64.2) | 8 (50.0) | 44 (68.7) | 6 (50.0) | 0.36 |
| Aortic/mitral surgery | | 15 (15.8) | 1 (6.25) | 12 (18.7) | 2 (16.7) | 0.79 |
| NYHA, class I or II | 1 | 56 (59.6) | 9 (56.2) | 37 (58.7) | 8 (66.7) | 0.53 |
| TR severity, massive | 0 | 37 (38.9) | 8 (50.0) | 24 (37.5) | 4 (33.3) | |
| TR severity, severe | | 17 (17.9) | 3 (18.7) | 10 (15.6) | 4 (33.3) | 0.54 |
| TR severity, moderate | | 41 (43.2) | 5 (31.2) | 30 (46.9) | 4 (33.3) | |

^aThere were three missing values; values are mean ± SD, median [interquartile range], or n (%); COPD stands for chronic obstructive pulmonary disease; and P -values were based on either Wilcoxon or Spearman tests as CO was a continuous variable.

Table 2 Population baseline echocardiographic characteristics

| | Missing values | All patients N = 95 | Cardiac output ^a | | | P-value |
|--|----------------|------------------------|--------------------------------|---------------------------------------|----------------------------------|---------|
| | | | 'Low' <3.28 L/min N = 16 | 'Normal' 3.28–6.22 L/min N = 64 | 'High' > 6.22 L/min N = 12 | |
| LVEF, % | 0 | 61.4 ± 8.22 | 57.9 ± 7.31 | 62.1 ± 8.52 | 61.5 ± 7.32 | 0.02 |
| E/e' | 11 | 11.9 ± 4.77 | 11.8 ± 5.04 | 12.3 ± 5.00 | 10.7 ± 3.01 | 0.30 |
| Longitudinal global strain, % | 4 | 17.0 ± 3.63 | 15.7 ± 3.34 | 16.9 ± 3.75 | 18.9 ± 2.75 | <0.01 |
| TAPSE, mm | 0 | 18.5 ± 4.71 | 16.3 ± 4.41 | 18.7 ± 4.62 | 20.5 ± 5.08 | <0.01 |
| RV s', cm/s | 2 | 10.7 ± 2.85 | 8.90 ± 2.43 | 10.9 ± 2.92 | 12.0 ± 1.89 | <0.01 |
| Onset to peak IVA | 7 | 41.8 ± 11.2 | 47.9 ± 16.0 | 39.6 ± 8.64 | 46.4 ± 14.2 | 0.77 |
| Tricuspid annulus diameter, mm | 0 | 46.4 ± 6.33 | 48.3 ± 5.70 | 46.2 ± 6.53 | 45.3 ± 5.04 | 0.45 |
| End diastolic RV diameter, mm | 0 | 52.7 ± 8.68 | 56.8 ± 8.12 | 51.7 ± 8.46 | 52.4 ± 9.62 | 0.18 |
| Right atrial volume index, mL/m ² | 46 | 85.3 ± 46.4 | 108 ± 53.6 | 82.0 ± 46.9 | 71.3 ± 38.1 | 0.21 |
| Strain RV free wall + septum, % | 5 | 18.3 ± 4.69 | 16.4 ± 3.85 | 18.8 ± 4.83 | 18.3 ± 5.27 | 0.06 |
| Strain RV free wall, % | 4 | 22.0 ± 5.95 | 19.3 ± 5.21 | 22.9 ± 6.00 | 21.7 ± 6.43 | 0.10 |
| RV fractional area change, % | 0 | 0.42 ± 0.09 | 0.37 ± 0.08 | 0.44 ± 0.09 | 0.39 ± 0.11 | 0.30 |
| Tricuspid regurgitant peak velocity, m/s | 0 | 2.81 ± 0.61 | 2.72 ± 0.69 | 2.85 ± 0.62 | 2.74 ± 0.39 | 0.97 |

^aThere were three missing values; values are mean ± SD or n (%); TAPSE stands for Tricuspid annular plane systolic excursion; RV stands for right ventricle; and P-values were Spearman tests as CO was a continuous variable.

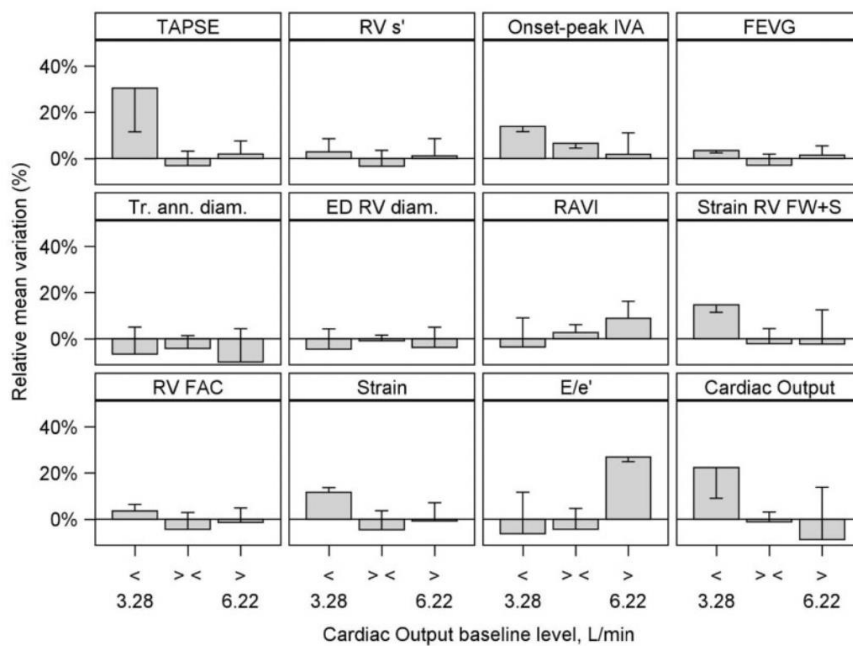


Figure 1 Echographic parameters evolution according to output.

was measured at 8.9 cm/s in the low-CO group, suggesting the possible appearance of RV dysfunction according to recommendations,²³ whereas it normalized to 10.9 and 12 cm/s, respectively. The other parameters were not significantly different, although RV strain (free wall \pm septum) tended to be lower in this category in terms of absolute value, which is in line with a more impaired RV function. Evaluation at 1 year (Figure 1) suggested an improvement in RV function in the low-CO group, with TAPSE increasing by nearly 30%, as well as improvement in the RV free wall and septum strain, along with CO. RV S' and the other RV-function parameters did not vary significantly.

Moreover, right cavities tended to be more dilated in the low-CO group, although it was not significant (108 ± 53.6 vs. 82 ± 46.9 and 71.3 ± 38.1 mL/m², $P = 0.21$ for right atrial volume; 56.8 ± 8.12 vs. 51.7 ± 8.46 and 52.4 ± 9.62 mm, $P = 0.18$ for end-diastolic RV diameter; and 48.3 ± 5.7 vs. 46.2 ± 6.53 and 45.3 ± 5.04 , $P = 0.45$ for tricuspid annulus diameter). There was a trend suggesting an inverse relationship between CO and RA volume, with the latter being more dilated as the CO was lower. At 1 year, these parameters tended to decrease except for the increase in RA volume in the high-CO group, suggesting possible positive remodelling of the RV after therapeutic optimization or invasive intervention.

As far as the left cavities are concerned, LVEF was significantly lower in the low-CO group ($P = 0.02$) and GLS ($P < 0.01$). The latter increased significantly along with CO. No difference was noted regarding diastolic function and left ventricular filling pressures at baseline, but the E/e' ratio was higher at 1 year in the high-CO group, suggesting higher left ventricular filling pressures.

Outcome

Overall, 18 (19%) patients died (HF-related death for all) during follow-up, of which 10 (55%) patients had abnormal CO (Table 3). At 1 year, 11 patients had TV intervention: 6 had tricuspid annuloplasty, 3 had bioprosthetic TV replacement, and 2 had percutaneous TV repair with edge-to-edge technique. All had normal CO at baseline, except for two patients in the surgical annuloplasty group.

The normal CO group had significantly better survival rate (87.5% vs. 62.5% and 66.67% in the low- and high-CO groups, respectively). In fact, all-cause death was significantly associated with both low and high-CO, with a three-fold higher risk of mortality ($P = 0.049$) compared to the normal CO group when not adjusted (Table 4 and Figure 2). This U-shaped association was still significant after adjustment for age, gender, TAPSE, RV S', end-diastolic RV diameter, RV strain free wall, and septum or free wall alone, with an HR of 2.23 for the low-CO group and as high as 9.08 in the high-CO group

($P = 0.017$). Of note, multivariate analysis after adjustment was performed on 85 patients, as there was missing data for 7 patients.

The Kaplan–Meier curve shows significantly higher long-term mortality in patients with abnormal baseline CO compared to those with normal CO (log-rank $P = 0.034$) (Figure 3). The probability of 2-year survival drastically dropped to 60% in the high-CO group and 40% in the low-CO group, whereas the survival of the normal CO group was estimated at 80%.

Discussion

Main results

This is the first study, to our knowledge, that takes interest in the relationship between TR and CO. The main findings are (i) significant isolated functional TR is characterized by high mortality at 1-year follow-up, with 19% of deaths, despite the absence of significant LV and RV dysfunction; (ii) abnormal CO is relatively common, as it was found in one-third of this specific population; (iii) there is a U-shaped relationship between CO and mortality in our population, with abnormal CO being significantly associated with higher long-term mortality compared to normal CO, with an estimated three-fold risk of mortality.

TR and CO

Maintaining an adapted CO for optimal oxygen supply to the organs constantly is the main goal of the heart mechanics. It corresponds to the product of HR and stroke volume, the latter also depending on pre-load, afterload, and inotropy. It can be impaired by many different aetiologies including most of heart diseases.

Low-CO and high-CO (or hypo- and hyper-circulatory states) are associated with higher mortality in HF.^{13,15} In fact, low CO involves less oxygenation to all organs, resulting in multiorgan failure secondary to chronic or acute ischaemia. LVEF is usually impaired, but it can also be normal or moderately reduced, as in our cohort. In this case, RV and LV interdependence plays an important role. Significant TR leads to RV-dilatation by increasing diastolic volume and RV-dilatation increases TR by increasing tricuspid leaflet tethering and coaptation defects and so on. The atrial TR is another fundamental mechanism. AF leads to the RA dilatation, leading to annulus dilatation and TR and RV-dilatation and...^{22,24} RV-dilatation leads to RV dysfunction with an increase in RV filling pressures transmitted to the interventricular septum, resulting in a paradoxical septum that reduces LV diastolic filling and thus impacting CO.²⁵ Additionally, RV afterload is secondarily chronically elevated because of impaired LV end diastolic pressure, thus decreasing RV output, consequently resulting in low global CO.

Contrarily, the hyper circulatory state is not as known to this day. It is thought to be related to higher metabolic demand and systemic vasodilatation, leading to reduced afterload and decrease in arterial volume, which provokes renal hypoperfusion, thus activating the neurohormonal system and plasma volume expansion.¹⁵ The aetiology reported are essentially liver, pulmonary, and renal diseases, especially end-stage renal failure needing an arteriovenous fistula. Significant TR is known to be associated with hepatic disorders.²⁶ It is hypothesized that increased 'backward' pressure induced by TR leads to hepatic venule congestion and perivenular fibrosis with decreased

Table 3 Patients dead or alive at 1-year follow-up

| Group | Total | Death | Alive | Percent alive (%) |
|-----------------------------|-------|-------|-------|-------------------|
| Below 3.28 L/min | 16 | 6 | 10 | 62.50 |
| Between 3.28 and 6.22 L/min | 64 | 8 | 56 | 87.50 |
| Above 6.22 L/min | 12 | 4 | 8 | 66.67 |
| Total | 92 | 18 | 74 | 80.43 |

Table 4 Association between baseline CO and all-cause death based on 92 patients (18 deaths) and 85 patients (15 deaths) when adjusted

| Cardiac output | | HR | 95% CL | P-value | Adjusted HR | 95% CL | P-value |
|----------------|-----------------|------|-----------|---------|-------------|-----------|---------|
| 'Normal' | 3.28–6.22 L/min | 1.00 | | | 1.00 | — | |
| 'Low' | <3.28 L/min | 3.31 | 1.15–9.55 | 0.0493 | 2.23 | 0.62–8.08 | 0.0174 |
| 'High' | >6.22 L/min | 3.03 | 0.91–10.1 | — | 9.08 | 1.97–41.8 | — |

P-values were based on Type 3 Wald chi-square tests; adjustment on age, gender, TAPSE, RV s', End diastolic RV-diameter, and either Strain RV free wall + septum, or Strain RV free wall; of note, only Strain RV free wall + septum was significantly associated with all-cause death.

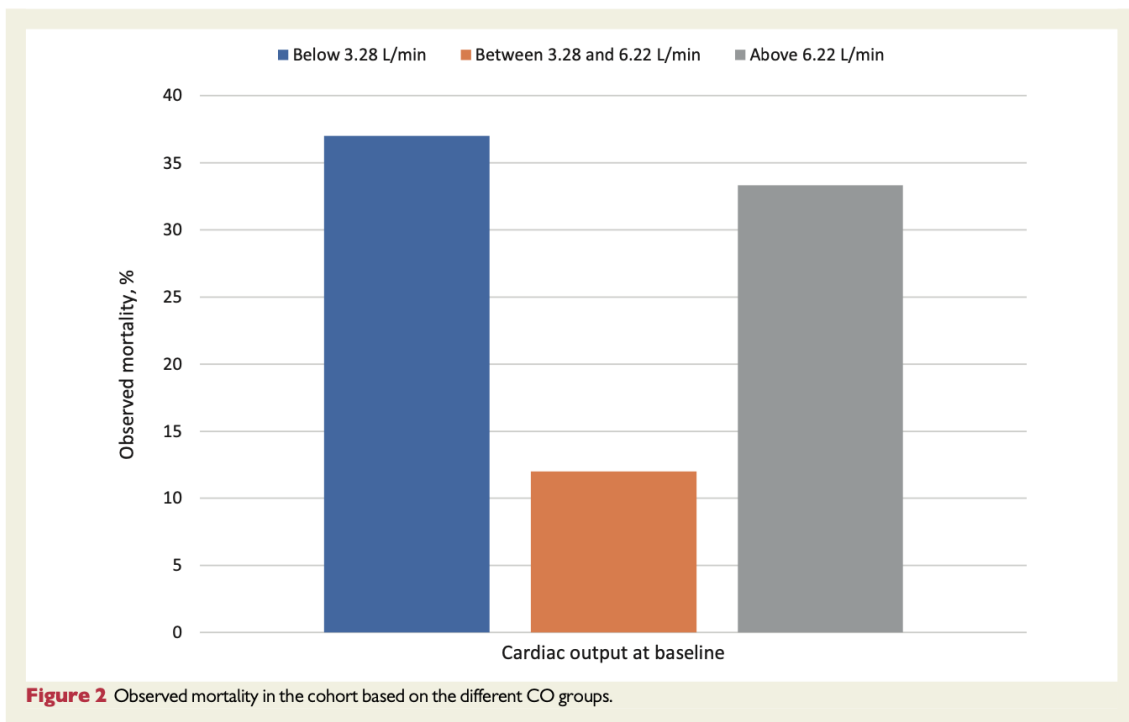


Figure 2 Observed mortality in the cohort based on the different CO groups.

synthetic liver function, resulting in cholestatic liver disorders and hypoalbuminemia, ultimately leading to cardiac cirrhosis.²⁷ Mirroring this fact, cirrhotic cardiomyopathy is caused by liver-derived toxic factors leading to arterial dilation and hyperdynamic circulation, resulting in high CO.²⁷ Hepatic vasoactive substances can also cause splanchnic vasodilatation, eventually leading to relative hypovolemia. It then activates the renin–angiotensin–aldosterone system with renal sodium retention and results in hypervolemia contributing to the hyper circulatory state by increasing cardiac pre-load.¹⁸ However, significant TR with a high CO mechanism has not yet been clarified. We need to confirm our results working on the hepato-cardiac relationship as well as on the cardio-renal interactions. Interestingly, we found no significant correlation between TR severity grade and CO, thus implying other complex mechanisms not elucidated to this day.

In our cohort, we found a U-shaped correlation between mortality and CO in this specific population. This relation has been previously

hinted at.¹³ Wehner *et al.*²⁸ found that supra-normal LVEF is associated with higher mortality. High CO was thought to be associated with better survival, but as Reddy *et al.*¹⁵ observed, it was contrarily linked to worse prognosis. Accordingly, our study shows that abnormal CO is significantly associated with higher long-term mortality, in at least moderate isolated functional TR with preserved or mid-range LVEF.

Prognosis of isolated functional TR

Mortality at 1-year in our cohort is as high as 19%. Similar results were found by Topilsky *et al.*²³ in a cohort of 353 patients with isolated TR. Among them, 68 patients had severe TR that they defined by EROA ≥ 40 mm² with a similar mortality rate of 19% at 2 years. In a more recent retrospective study in a large population, yearly mortality of isolated TR was of 12.1% and 5-year survival was only at 51.7%.²⁹ More recently, an analysis of an electronic health record

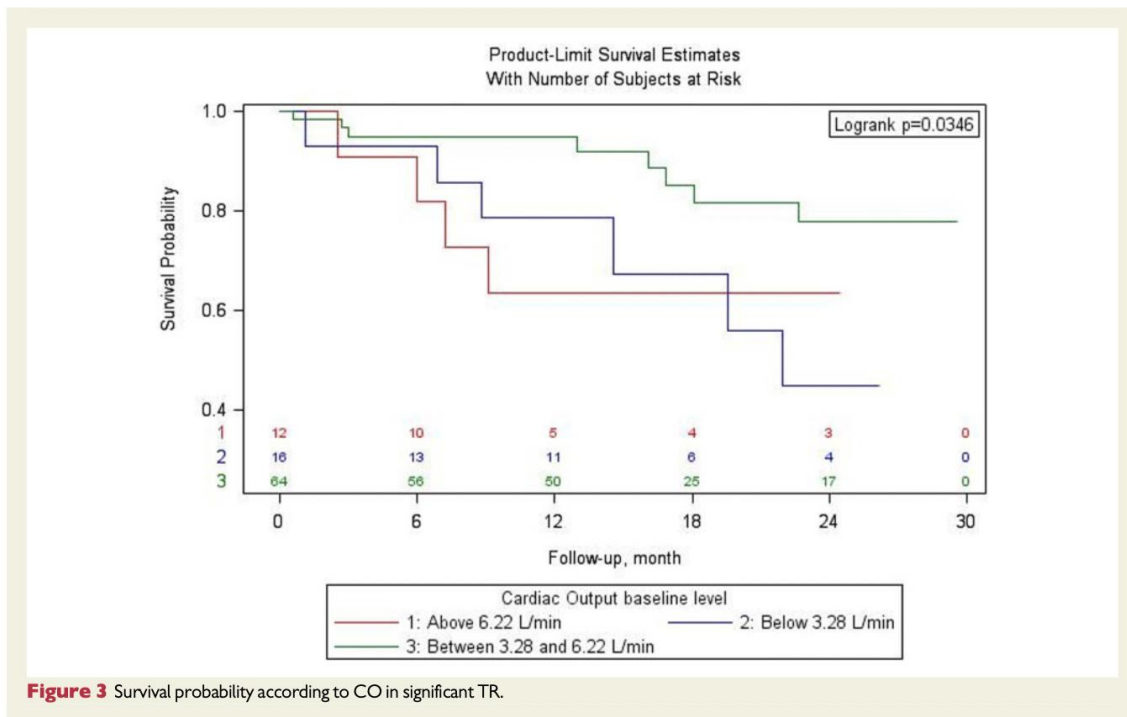


Figure 3 Survival probability according to CO in significant TR.

database in the USA also showed similar results with a mortality of 21% in at least moderate TR in HF, although it did not exclude primary TR.³⁰ Overall, literature shows that mortality increases with TR severity, with significantly worse prognosis from the moderate stage of TR and worse.^{23,29,30} We did not stratify mortality according to TR severity but we confirmed that at least moderate TR was indeed associated with impaired prognosis independently from LV function and RV function or other comorbidities, although we cannot affirm if TR is the cause or a marker of mortality. Thus, close attention should be paid to this specific population with rigorous follow-up and monitoring.

Impact on clinical practice

Functional TR plays an important role in prognosis stratification in patients and should no longer be overshadowed by the other valve diseases. It should be systematically assessed when performing echocardiography and follow-up should be done according to its severity. At the same time, CO should also be systematically estimated as our work suggests that it has an important role in the natural history of TR. It would be interesting to further investigate our findings in larger dedicated studies to determine whether CO is a relevant parameter to monitor and to take into account to better select patients for interventional treatment. In fact, recent positive results with aortic and mitral percutaneous treatment paved the way to rapid development of similar devices for TR. Thus far, percutaneous treatment of TR shows encouraging results with good outcomes.⁸ But many questions remain, especially selection criteria of patients and CO could be one of them. This specific population should be closely monitored

with regular echocardiographic and physical examination to determine the best timing of intervention when needed. In fact, significant isolated TR may benefit from early intervention when CO is normal and RV is still preserved, with low-CO possibly suggesting the appearance of RV dysfunction (lower TAPSE and RV S' in this group of our cohort), which is known to be related to worse outcome,³¹ and high-CO possibly reflecting the liver consequences of severe TR with higher mortality.³²

Perspective

It would be interesting to assess our results in surgical or percutaneous treatment cohorts by comparing outcomes according to pre-operative CO. Ongoing randomized controlled trials will evaluate the impact of TR correction on clinical outcome and determine whether there is a causal relationship with mortality.

Limitations

First, our population is relatively small, limited to 95 patients. These patients were medically managed with dosages of diuretics that are not all reported and they were changing over time (all where at least treated by 40 mg/day of furosemide). The medical management of the patients was not among the objectives of the study. However, the strength of the TRAP cohort is its prospective and multicentric design.¹⁷ Secondly, the cut-offs for normal and abnormal output were adapted for the studied population and might differ from previous reports.⁹ Thirdly, CO was estimated by echocardiography only and index was not reported because of the weight variations observed in this population that can gain several kilograms according

to the volume status.³³ Estimation of CO by echocardiography has been well correlated with the thermodilution technique, which can be considered the actual gold standard.³⁴ Of note, severe TR may underestimate CO by the thermodilution technique, whereas it may be overestimated by TTE.¹⁵ Finally, no data on liver function, on albumin and on precise renal function assessment were systematically collected in the original design of the study. It could have been informative as we know liver function is impacted by TR and HF and could possibly play a role on CO adaptations.

Conclusion

Significant isolated secondary TR was associated with 19% of mortality. It is also associated with higher long-term mortality if CO is abnormal, suggesting a possible role to explore to better monitor, and select patients for intervention.

Conflict of interest: none declared.

References

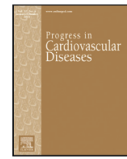
- Dahou A, Levin D, Reisman M, Hahn RT. Anatomy and physiology of the tricuspid valve. *JACC Cardiovasc Imaging* 2019;**12**:458–68.
- Dahou A, Magne J, Clavel MA, Capoulade R, Bartko PE, Bergler-Klein J et al. Tricuspid regurgitation is associated with increased risk of mortality in patients with low-flow low-gradient aortic stenosis and reduced ejection fraction: results of the multicenter TOPAS Study (True or Pseudo-Severe Aortic Stenosis). *JACC Cardiovasc Interv* 2015;**8**:588–96.
- Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* 2004;**43**:405–9.
- Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a Report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol* 2017;**70**:252–89.
- Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ et al.; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–91.
- Moraca RJ, Moon MR, Lawton JS, Guthrie TJ, Aubuchon KA, Moazami N et al. Outcomes of tricuspid valve repair and replacement: a propensity analysis. *Ann Thorac Surg* 2009;**87**:83–8; discussion 8–9.
- Axtell AL, Bhambhani V, Moonsamy P, Healy EW, Picard MH, Sundt TM III et al. Surgery does not improve survival in patients with isolated severe tricuspid regurgitation. *J Am Coll Cardiol* 2019;**74**:715–25.
- Chang CC, Veen KM, Hahn RT, Bogers A, Latib A, Oei FBS et al. Uncertainties and challenges in surgical and transcatheter tricuspid valve therapy: a state-of-the-art expert review. *Eur Heart J* 2020;**41**:1932–40.
- Orban M, Besler C, Braun D, Nabauer M, Zimmer M, Orban M et al. Six-month outcome after transcatheter edge-to-edge repair of severe tricuspid regurgitation in patients with heart failure. *Eur J Heart Fail* 2018;**20**:1055–62.
- Orban M, Rommel KP, Ho EC, Unterhuber M, Pozzoli A, Connelly KA et al. Transcatheter edge-to-edge tricuspid repair for severe tricuspid regurgitation reduces hospitalizations for heart failure. *JACC Heart Fail* 2020;**8**:265–76.
- Hansing CE, Rowe GG. Tricuspid insufficiency. A study of hemodynamics and pathogenesis. *Circulation* 1972;**45**:793–9.
- Andersen MJ, Nishimura RA, Borlaug BA. The hemodynamic basis of exercise intolerance in tricuspid regurgitation. *Circ Heart Fail* 2014;**7**:911–7.
- Opotowsky AR, Hess E, Maron BA, Brittain EL, Baron AE, Maddox TM et al. Thermodilution vs estimated fick cardiac output measurement in clinical practice: an analysis of mortality from the Veterans Affairs Clinical Assessment, Reporting, and Tracking (VA CART) Program and Vanderbilt University. *JAMA Cardiol* 2017;**2**:1090–9.
- Fincke R, Hochman JS, Lowe AM, Menon V, Slater JN, Webb JG et al. Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. *J Am Coll Cardiol* 2004;**44**:340–8.
- Reddy YNV, Melenovsky V, Redfield MM, Nishimura RA, Borlaug BA. High-output heart failure: a 15-year experience. *J Am Coll Cardiol* 2016;**68**:473–82.
- Sundaram V, Fang JC. Gastrointestinal and liver issues in heart failure. *Circulation* 2016;**133**:1696–703.
- Guerin AV, Dreyfus J, Lavie-Badie Y, Sportouch C, Eicher JC, Marechaux S et al. Cardiac remodeling in secondary tricuspid regurgitation: should we look beyond the tricuspid annulus diameter? *Arch Cardiovasc Dis* 2021. Available online 11 January 2021
- Bolognesi M, Di Pascoli M, Verardo A, Gatta A. Splanchnic vasodilation and hyperdynamic circulatory syndrome in cirrhosis. *World J Gastroenterol* 2014;**20**:2555–63.
- Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233–70.
- Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA et al.; Scientific Document Committee of the European Association of Cardiovascular Imaging Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;**14**:611–44.
- Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. *Eur Heart J Cardiovasc Imaging* 2017;**18**:1342–3.
- Guerin A, Dreyfus J, Le Tourneau T, Sportouch C, Lairez O, Eicher JC et al. Secondary tricuspid regurgitation: do we understand what we would like to treat? *Arch Cardiovasc Dis* 2019;**112**:642–51.
- Topilsky Y, Nkomo VT, Vatury O, Michelena HI, Letourneau T, Suri RM et al. Clinical outcome of isolated tricuspid regurgitation. *JACC Cardiovasc Imaging* 2014;**7**:1185–94.
- Donal E, Galli E, Bidaut A. Advocacy for more consideration of the secondary tricuspid regurgitation. *Heart* 2019;**105**:1221–2.
- Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK et al.; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; and Council on Cardiovascular Surgery and Anesthesia. Evaluation and management of right-sided heart failure: a scientific statement from the American Heart Association. *Circulation* 2018;**137**:e578–e622.
- Anand IS, Florea VG. High output cardiac failure. *Curr Treat Options Cardiovasc Med* 2001;**3**:151–9.
- Xanthopoulos A, Starling RC, Kitai T, Triposkiadis F. Heart failure and liver disease: cardiohepatic interactions. *JACC Heart Fail* 2019;**7**:87–97.
- Wehner GJ, Jing L, Haggerty CM, Suever JD, Leader JB, Hartzel DN et al. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? *Eur Heart J* 2020;**41**:1249–57.
- Topilsky Y, Maltais S, Medina Inojosa J, Oguz D, Michelena H, Maalouf J et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging* 2019;**12**:433–42.
- Messika-Zeitoun D, Verta P, Gregson J, Pocock SJ, Boero I, Feldman TE et al. Impact of tricuspid regurgitation on survival in patients with heart failure: a large electronic health record patient-level database analysis. *Eur J Heart Fail* 2020;**22**:1803–13.
- Dietz MF, Prihadi EA, van der Bijl P, Goedemans L, Mertens BJA, Gursøy E et al. Prognostic implications of right ventricular remodeling and function in patients with significant secondary tricuspid regurgitation. *Circulation* 2019;**140**:836–45.
- Lau GT, Tan HC, Kritharides L. Type of liver dysfunction in heart failure and its relation to the severity of tricuspid regurgitation. *Am J Cardiol* 2002;**90**:1405–9.
- Robson SC, Murray A, Peart I, Heads A, Hunter S. Reproducibility of cardiac output measurement by cross sectional and Doppler echocardiography. *Br Heart J* 1988;**59**:680–4.
- Dericbourg C, Tribouilloy C, Kugener H, Avinee P, Rey JL, Lesbre JP. Noninvasive measurement of cardiac output by pulsed Doppler echocardiography. Correlation with thermodilution. *Arch Mal Coeur Vaiss* 1990;**83**:237–44.

Revue 2

Tricuspid valve replacement: The old and the new

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Tricuspid valve replacement: The old and the new

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ABSTRACT

Tricuspid regurgitation is a frequent and serious condition but tricuspid valve (TV) surgery, that may be a valve replacement when a repair is not feasible, is rarely performed. Recent development of transcatheter TV interventions offers new options for those high-surgical risk patients, especially TV replacement for patients who are not eligible for transcatheter TV repair. In this review, we describe indications and outcome after surgical TV replacement, and devices available or in development for transcatheter TV replacement.

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Abbreviations: AF, atrial fibrillation; CaHD, carcinoid heart disease; CAVI, Caval Valve Implantation; HF, heart failure; LV, left ventricle or ventricular; NYHA, New York Heart Association; PPI, permanent pacemaker implantation; RA, right atrium or atrial; RV, right ventricle or ventricular; TR, tricuspid regurgitation; TS, tricuspid stenosis; TTVI, transcatheter tricuspid valve intervention; TTVR, transcatheter tricuspid valve replacement; TV, tricuspid valve; TVIE, tricuspid valve infective endocarditis; TVR, tricuspid valve replacement; TVr, tricuspid valve repair.

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Introduction

Tricuspid valve (TV) disease is mostly a tricuspid regurgitation (TR) issue, which is a frequent condition that has been often overlooked in the past.¹⁻³ Despite its high prevalence and its dismal prognosis with a critical need for a curative treatment, most patients are undertreated as medical treatment remains the mainstay of therapy and a TV surgery is seldom performed, mostly at the time of left-sided heart valve surgery^{3,4} owing to the lack of solid data, especially randomized studies, to demonstrate that surgical management of TV disease is beneficial when compared to medical management and to suggest the best timing for intervention. Among operated patients, a TV replacement (TVR), which can be either a biological or a mechanical prosthesis, is currently rarely considered, only when a TV repair (TVr) is not feasible.^{5,6} In observational studies, TVR suffers a bad reputation, with poor early and long-term outcome, that may be related to a late referral of patients at an advanced stage of the TV disease, with right ventricular (RV) dysfunction and end-organ damage (hepatic or renal dysfunction), rather than the intervention itself knowing that TV disease is usually well tolerated during a long period of time. With the development of less invasive transcatheter interventions, there is currently a growing interest for the management of TV disease. The aim of this review is to describe current management of TV disease using a surgical TVR and to look at the devices available or in development for transcatheter TVR (TTVR).

Mechanism/etiologies of TR and tricuspid stenosis (TS)

TR can be divided into “primary” / “organic” and “secondary” / “functional”. Approximately 80% of cases of significant TR are “secondary”, without intrinsic lesion of the TV itself, related to tricuspid annular dilation and/or leaflet tethering in the setting of RV and/or right atrial (RA) remodeling due to pressure and/or volume overload induced by left-sided heart diseases (valve disease and/or left ventricular/LV dysfunction), pulmonary hypertension, RV dysfunction or atrial fibrillation (AF). Conversely, primary TR is relatively rare and is the consequence of a primitive lesion of the TV that affects the leaflets and/or the chordal structures due to a variety of causes/contexts including congenital disorders such as Ebstein's anomaly or acquired diseases of the TV, such

as myxomatous disease, infective endocarditis (especially in intravenous drug addicts), carcinoid syndrome, rheumatic disease, radiation, thoracic trauma, drug-induced, endomyocardial fibrosis or iatrogenic.

TS is rare and often combined with TR most frequently of rheumatic origin, and therefore almost always associated with left-sided valve lesions, particularly mitral stenosis. Other causes are rare, including congenital, drug-induced valve diseases, endocarditis, Whipple's disease and large right atrial tumor.

TV Surgery

Indications and timing

TV surgery can be performed either isolated or at the time of left-sided valve surgery. Clinical practice guidelines are based on expert opinion and limited data because of the lack of high quality randomized controlled trials.

TR

Timing

The timing of surgical intervention for patients with TR remains controversial, mostly due to the limited data available and their heterogeneous nature⁷ but surgery should be carried out sufficiently early to avoid irreversible RV dysfunction.

TV surgery at the time of left-sided valve intervention. Surgery is recommended at the time of left-sided valve surgery for patients with severe TR (either primary or secondary) (Class of Recommendation (COR) I, Level of Evidence (LOE) B in the American College of Cardiology (ACC)/American Heart Association (AHA) and in the European Society of Cardiology (ESC) guidelines), and should be considered in patients with moderate primary TR (COR IIa LOE C in ESC guidelines), or in patients with mild or moderate secondary TR with a dilated annulus (≥ 40 mm or > 21 mm/m² by bidimensional transthoracic echocardiography) (COR IIa LOE B in ACC/AHA and in ESC guidelines) or prior evidence of right heart failure (HF; COR IIa LOE B in ACC/AHA guidelines).^{5,6}

Isolated TV surgery. Surgery is indicated in symptomatic patients with severe isolated primary TR without severe RV dysfunction (COR I LOE C in ESC guidelines and COR IIa LOE B in ACC/AHA guidelines) and should be considered in asymptomatic or mildly symptomatic patients with severe isolated primary TR and progressive RV dilatation or deterioration of RV function (COR IIa LOE C in ESC guidelines and COR IIb LOE C in ACC/AHA guidelines). Surgery could also be beneficial for symptomatic patients with severe isolated secondary TR attributable to annular dilation who are poorly responsive to medical therapy (COR IIa LOE B in ESC guidelines and in ACC/AHA guidelines) and for asymptomatic patients with RV dilatation (COR IIa LOE B in ESC guidelines) in the absence of severe pulmonary hypertension or severe left ventricular (LV) or RV dysfunction.

After previous left-sided valve surgery and in absence of recurrent left-sided valve dysfunction, surgery should be considered in patients with severe TR who are symptomatic (COR IIa LOE B in ESC guidelines and COR IIb LOE B in ACC/AHA guidelines) or have progressive RV dilatation (COR IIa LOE B in ESC guidelines), in the absence of severe LV or RV dysfunction or severe pulmonary hypertension.^{5,6}

Repair or replacement

TVr remains the preferred technique that should be performed whenever possible for the management of TV disease requiring surgery.^{5,6} However, TVR may be required in a specific situation in which repair is not feasible or with a failed repair/replacement.

Patients with functional TR. TVR should be considered when the TV leaflets are significantly tethered or the annulus is severely dilated. Indeed, a tethering height (the distance between the coaptation of the septal and anterior leaflets and the tricuspid annular plane) >0.5 cm and a tethering area (the area enclosed by the annular plane and septal and anterior leaflets) >0.8 cm² are predictive of moderate to severe TR early postoperatively and 1 year after TV annuloplasty.³ Moreover, in a recent study, TVR was associated with an improved survival over TVr in the subgroup of patients with tricuspid annular diameter > 44 mm.⁹

Patients with organic TR. TVR may be required because of the extent and severity of the underlying pathology.

Patients with failing repair/replacement. TVR is always performed for a redo TV surgery when previous intervention was a TVR and mostly implanted after a TVr as a redo-repair is usually not feasible.

TS

Timing

Surgery is recommended for patients with severe TS undergoing left-sided valve intervention (COR I LOE C in ESC guidelines) or for patients with isolated symptomatic severe TS (COR I LOE C in ESC guidelines).⁶

Repair or replacement

A TVR is often necessary for surgical treatment of TS as a TVr is not adequate or not feasible due to valve destruction or multiple levels of pathological involvement.

Technique for tv surgery

TVR procedures are usually performed through a median sternotomy with a beating or arrested heart approach depending on the surgeon's preference.

Mini-invasive

Small non randomized single-center studies have suggested that minimally invasive techniques could be interesting to decrease post-

operative mortality and complications, especially for redo surgery. Indeed, minimally invasive techniques for TVR would generate less surgical trauma, with less operative time and postoperative bleeding and possibly lower mortality rates than a median reoperative sternotomy.¹⁰⁻¹²

Types of surgical prostheses in the tv position

There are two types of surgical prostheses that can be implanted in the TV position: biological and mechanical. All types of surgical prostheses are presented in Fig. 1.

Biological prosthesis

Bioprosthetic valves are stented and manufactured from native porcine valve or bovine pericardium. They do not require a long-term anti-thrombotic treatment. Porcine bioprostheses have been considered the valves of choice for TVR because of their higher thromboresistance, usually without anticoagulation, which renders such devices ideal for the low-pressure right-sided atrio-ventricular position. Moreover, bioprosthetic valves allow secondary pacemaker implantation in the RV and right heart catheterization.

Durability of bioprosthesis

The risk of long-term valve dysfunction is a major concern related to bioprosthetic TVR but assessment of durability is difficult as there is no clear definition of biological valve dysfunction in the TV position (mean gradient? reoperation, knowing that patients could be reoperated for a multiple valve surgery?). There are only small single center series and life-expectancy of patients who underwent a TVR was shortened by comorbidities and impact on the RV.

Mechanisms of TVR dysfunction. TVR dysfunction can be caused by structural valve deterioration and non-structural dysfunction. Non-structural dysfunction caused by fibrous pannus formation (host tissue overgrowth) on the cusps of the RV side and valve infection is the most common cause of the dysfunction. Pannus formation is a serious problem that also results in commissure fusion, leading to restricted opening of the valves and bioprosthetic dysfunction.^{13,14} On the contrary, evaluation of the explanted valves showed that structural valve deterioration, such as significant calcification or degeneration, was rare.^{13,14}

Durability of bioprostheses is better in the TV than in mitral position for same patients. It has been shown that porcine bioprostheses (such as the Hancock valve and the Carpentier-Edwards bioprostheses) in the TV position yield significantly better long-term results than those in the mitral position when the same bioprostheses were implanted in both mitral and TV positions in the same patient.¹⁵ Differences in pressure and velocity at the two valve locations with a lower pressure in the right side of the heart and a greater mechanical stress on the cusps at the mitral position are a more likely explanation for a longer durability of bioprosthetic valves and a lower rate of reoperation in the TV position.¹⁶

Lifespan. First studies published in the nineties reported a durability of bioprostheses in the TV position between 7 and 9 years, with a steeper increased rate of bioprosthetic valve degeneration after 7 years.¹⁷ Most recent studies have reported excellent long-term durability of the bioprostheses in the TV position as freedom rates from valve deterioration ranged from 68% to 97% at >10 years.^{17,18} Thus, the 15-year freedom from bioprosthetic valve deterioration was 83% in a large recent study. Reoperation was performed in 64% of the patients with valve deterioration while the remaining patients did not receive re-replacement because of either stable and clinically tolerated valve dysfunction or excessive reoperative risk.¹⁹ As the present series cover a large time span, one may assume that the most recent bioprostheses used for TVR would perform even better. Of note, younger age at implantation

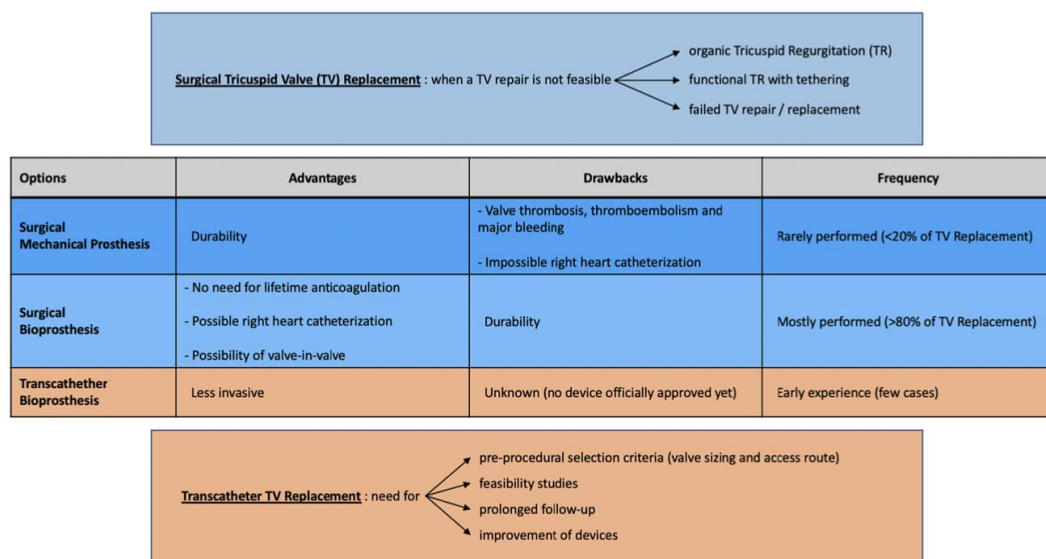


Fig. 1. Current surgical and transcatheter options for tricuspid valve replacement, and future needs for development of tricuspid valve replacement.

and smaller size of the implanted prosthesis are major determinants of early valve deterioration.²⁰

Mechanical prosthesis

Nowadays, mechanical prostheses implanted in the TV position are always bileaflet valves. Only patients without contra-indication for anticoagulation therapy can receive a mechanical prosthesis. Indeed, mechanical valves in the TV position are durable with a low reoperation rate but they are associated with an intrinsic risk of thrombosis and thromboembolic events (pulmonary embolism) requiring a lifetime anticoagulation treatment, especially as they are more prone to valve thrombosis than mechanical valves in the aortic or mitral position due to a lower level of prostacyclin (a powerful inhibitor of platelet aggregation) and a lower velocity of blood in the right-sided heart.²¹ Those complications usually have an insidious onset but with possible catastrophic consequences.^{22,23} Mechanical valve thrombosis occurs more frequently in the first years post-operatively and its incidence significantly declines 5 to 7 years after the operation. Several studies demonstrated that freedom rates from thromboembolism ranged from 80% to 93% in mechanical TVR,^{20,24,25} knowing that many retrospective reports included earlier-generation mechanical prostheses, such as cage ball, tilting disc, or monoleaflet valves, which showed higher thrombogenicity compared with the current bileaflet valves. Valve thromboses and thromboembolic complications are affected by several factors such as ventricular function, rhythm, valve position, prosthetic valve type, coagulation status and patient compliance, which may be the most important factor. Anticoagulation measures should be strictly regulated even with low thrombogenic bileaflet prostheses and the patient should be educated about both risks of thrombo-embolic and bleeding events.

Trends

TV surgeries share <10% of overall cardiac valve surgery volume.²⁶

Isolated versus concomitant TV surgery

Overall, in adult patients, the number of TV surgery is steadily increasing over time, mainly related to a marked increase in the number of combined TV surgery (concomitant with other major cardiac surgical procedures, mostly mitral valve surgery), which represent >80% of all TV surgery.²⁶⁻³⁰ Conversely, the number of isolated TV surgery is very low and barely increasing over time (approximately 700 procedures per year in the United States and 120 per year in France).^{29,31} Thus, in the United States, <1% of surgical centers performed >5 isolated TV surgeries per year.³² This could be explained by the fact that management of TV disease at the time of left-sided heart valve surgery is relatively well codified in recent guidelines while the management of patients with isolated TR is less established.^{5,6}

Surgery for severe TS is most often performed at the time of operation for left-sided valve disease, chiefly rheumatic mitral stenosis or regurgitation.

TVr versus TVR

Overall, TVR is performed in only 10–15% of patients as the majority of TV surgery are TVr (85–90%). Notably, during combined TV surgery, almost all patients have a repair (>90%).³³ On the contrary, during isolated TV surgery, most patients have a TVR (approximately 60%), probably because of a later referral with more severe TV disease at the time of surgery.^{27,28,34}

Bioprosthetic versus mechanical TVR

Mechanical prostheses were frequently implanted several decades ago as few data about durability of bioprostheses were available at this time. Subsequently, the policies for valve choice evolved toward a more systematic use of bioprostheses with an increasing rate over time.¹⁹ Thus, most TVR are now performed using bioprostheses (>80%) while mechanical prostheses currently represent <20% of TVR worldwide and <3% in France after exclusion of congenital heart disease.^{28,29}

Patient characteristics

Overall, characteristics of patients who undergo TVR cannot be easily detailed as it is a heterogeneous population with variable etiologies but those patients are usually younger (mean age of 50–60 years, depending on etiology), with more previous left-heart valve surgery (15–27%), more congestive HF (26%), more liver disease (11%) and more cirrhosis (6%), with no sex difference (54–58% women) in comparison with patients who undergo TVr.^{27,31,34,35} As expected, patients with bioprostheses are generally older than patients with mechanical prostheses.^{36,37}

Outcome after TV surgery

Post-operative/early outcome

Death

Reported early mortality rates after isolated TVR have ranged from 1.4% to 26.6%.¹⁸ After an initial decrease in the last decades due to careful patient selection and the improved pre- and peri-operative management, including the myocardial protection method and modified ultrafiltration, as well as post-operative intensive care,^{19,38,39} early post-operative mortality rate after TVR is now approximately 10% both in the USA and in Europe, with no difference between bioprostheses and mechanical prosthesis.^{28,32,34} Nevertheless, it has been shown that this rate is markedly variable and that post-operative death is predicted by the severity of the clinical presentation while TR mechanism / etiology has a limited impact.²⁸ Determinants of post-operative mortality are older age, New-York Heart Association (NYHA) functional class 3 or 4, right-sided heart failure signs, high daily dose of furosemide, low glomerular filtration rate, elevated total bilirubin level, lower blood haemoglobin level, larger TR jet area and elevated RA pressure, LV and RV dysfunction, and pulmonary hypertension.^{9,28,40} Consequently, late referral is the main issue in the management of those patients and TV surgery should be performed earlier in the course of the disease before the occurrence of irreversible consequences, in particular RV dysfunction. A dedicated score (TRI-SCORE) is now available to predict in-hospital mortality after isolated TV surgery (www.tri-score.com).⁴¹

Need for permanent pacemaker implantation (PPI)

TVR carries a significant risk of conduction disorders requiring PPI explained by the mechanical compression of the prosthesis over the conduction tissue at the level of the antero-septal commissure of the TV. Thus, TV surgery doubled the risk of post-operative PPI in patients with multivalve surgery,⁴² and around one-third of patients undergoing a TVR receive a PPI prior to discharge.^{35,43} Unfortunately, this risk is unpredictable as no pre-operative clinical or ECG characteristics were identified to predict postoperative PPI after TVR.⁴⁴ As most patients who undergo TV surgery are in permanent AF (76%), the vast majority of them are implanted with a single-chamber VVI/VVIR device.⁴³

Data regarding timing and type of device implantation are scarce. In the STS database, 5.6% of the patients with TVR received permanent epicardial pacemaker at the operative time.²⁹ This strategy is debatable as first, epicardial systems are less reliable than endocardial leads and second, half of patients with PPI after cardiac surgery are no longer pacemaker-dependent at long-term follow-up.^{44,45} Conversely, in comparison to transvalvular leads implantation, this approach avoids both crossing the TV prosthesis and permanently leaving a lead through the TV prosthesis that could harm and generate prosthesis dysfunction by leaflet perforation or restrictive closure. Transvalvular leads implantation cannot be performed in patients with mechanical prosthesis but may be acceptable for patients after a bioprosthetic TV as there was no clear evidence of increased risk of post-operative severe TR in a cohort of 58 patients who underwent a bioprosthetic TV implantation prior to PPI.⁴⁶ Coronary sinus lead may be an alternative, especially for patients with mechanical TV prosthesis, but lead placement is often

challenging in patients with RA dilatation. Leadless pacemaker may also be an interesting alternative but only for patients in chronic AF who require a single-chamber ventricular pacing and only for patients with bioprosthesis, as the system has to cross the TV prosthesis. Thus, the approach for device implantation will be performed accordingly to the type of prosthesis and the need for dual-chamber pacing. Eventually, permanent epicardial leads seem reasonable at least in case of complete atrioventricular block with low-rate of escape rhythm at the time of TVR and general guidelines recommendation on PPI indications after cardiac surgery should be applied after TVR regarding the timing, with a period of clinical observation up to 7 days to assess whether the rhythm disturbance is transient and spontaneously resolves. Temporary epicardial leads should be maintained during this observation period. However, in case of complete atrioventricular block with low-rate of escape rhythm, this observation period can be shortened since resolution is unlikely (COR I LOE C in ESC guidelines).⁴⁷ Surprisingly, patients with PPI following TVR experienced a higher life expectancy that was offset by impaired morbidity with a significantly higher rate of thromboembolic complications and an impaired quality of life in comparison with patients who did not receive PPI.⁴³

Other post-operative complications

Main other post-operative complications are shock, congestive heart failure, respiratory complications, tamponade, acute renal failure requiring dialysis, postoperative bleeding requiring reoperation, stroke, valve thrombosis and mediastinitis, with no difference between bioprosthesis and mechanical prosthesis.³⁶

Long-term outcome

Long-term outcome was initially difficult to assess as in-hospital post-operative death rate was very high and most patients undergoing TV replacement had a high-risk profile with a shortened life-expectancy.

Long-term survival

Long-term survival rate significantly raised over time. In a recent study, the 10- and 15-year overall survival rates were 65% and 56% respectively and the 10- and 15-year rates of freedom from cardiac death were 72% and 69% respectively, with no difference between the mechanical and the bioprostheses groups.³⁶

Long-term freedom from valve deterioration

Porcine bioprostheses such as the Hancock valve and the Carpentier-Edwards pericardial valve have provided good long-term results in the TV position with a low incidence of structural valve deterioration.^{13,15,48} Freedom from structural valve deterioration rates ranged from 68% to 97% at >10 years in several studies and were 96% and 78% at 5 and 10 years respectively in a recent one³⁶ but it suffers the lack of a standard definition according to symptoms of right-HF and echocardiographic examination. It has been notified that bioprosthetic TV degeneration increases at a steeper rate after seven years.^{49,50} Predictors of early valve deterioration are younger age at implantation and smaller size of the implanted prosthesis.²⁰

Long-term freedom from valve thrombosis, thromboembolism and major bleeding

Mechanical TVR is associated with a higher incidence of valve thrombosis, thromboembolism and bleeding due to anticoagulation than bioprosthetic TV. Observed rates of mechanical valve thrombosis ranged from 3% to 18%.^{16,20,25,36,39,51,52} In a recent study, 10- and 15-year rates of freedom from thromboembolism and major bleeding were 78% and 66%, respectively (84% and 68% respectively in the bioprosthetic TV group versus 72% and 63% respectively in the mechanical TV group). In the subgroup of patients with bioprosthetic TV and no need for lifelong anticoagulation, no valve thrombosis,

thromboembolism and major bleeding was observed. In the remaining 80% of patients with bioprosthetic TV requiring anticoagulation for reasons other than the TV prosthesis itself such as atrial fibrillation or the presence of other mechanical prosthetic valves, freedom rates from valve thrombosis, thromboembolism and major bleeding at 5 and 10 years were 93% and 84% respectively and significantly higher than in the group of patients with mechanical TV (82% and 75% respectively).

Long-term freedom from reoperation

Rates of freedom from TV reoperation of 76–96% at 10 years are reported.^{53–55} In a recent study, 10- and 15-year rates of freedom from TV reoperation were 95% and 89% respectively.³⁶ The risk of TV reoperation was significantly lower for patients with mechanical than bioprosthetic TV in this study (10- and 15-year rates of freedom from TV reoperation were 91% and 79% respectively in the group of patients with bioprosthetic TV versus 98% and 97% respectively in the group of patients with mechanical TV),³⁶ contrary to a recent meta-analysis that suggested an equal risk of reoperation in patients with mechanical versus biological TVR.³⁷

Determinants of long-term outcome

Long-term outcome is, like post-operative mortality, predicted by the severity of the pre-operative clinical (age, New-York Heart Association functional class, right-sided HF signs, daily dose of furosemide), biological (glomerular filtration rate, total bilirubin level) and echocardiographic presentation (LV and RV dysfunction, pulmonary hypertension).^{9,28}

Bioprosthesis versus mechanical prosthesis

The optimal prosthesis for TVR is still controversial and should be individualized (Fig. 1). The literature lacks a randomized trial comparing mechanical to bioprosthetic valves in the tricuspid position that could be attributed to the small number of patients who require TVR. Moreover, all the available studies are retrospective and several risk factors other than the type of prosthesis used could have affected the outcome of patients requiring a TVR.³⁶

On one hand, mechanical heart valves are durable and have low reoperation rates but non-structural mechanical valve dysfunction, bleeding, thrombosis and thrombo-embolic events with long-term anticoagulation have been problematic; in addition, they preclude the use of trans-venous pacing. On the other hand, bioprosthetic valves do have the advantage of avoiding the need for long-term anticoagulation therapy and its bleeding risk but are associated with the limited durability of a tissue valve, even if degeneration is expected to be slower than the left-sided valve. The need for reoperation is usually considered to be inversely related to the patient's age at the time of implantation. A meta-analysis by Rizzoli et al. showed that despite the belief that mechanical valves have a longer durability, the reoperation rate was similar in both groups due to structural valve degeneration for bioprostheses and to thrombosis and thrombo-embolic events (pulmonary embolism) for mechanical valves.⁵⁰ Kang et al. recently reported that clinical outcomes of bioprosthetic TVR were comparable with those of mechanical TVR in terms of long-term survival and TV related events over a 15-year postoperative follow-up, with higher reoperation rates but lower thrombosis and thrombo-embolic events in the group of patients with bioprosthetic TVR.³⁶ A recent meta-analysis by Negms et al., including 23 retrospective studies involving 945 mechanical and 1332 biological tricuspid prostheses between 2002 and 2019, suggested an equal risk of 30-day and late mortality, reoperation, and 5-year valve failure in patients with mechanical versus biological TVR.³⁷

As there is no superiority of one valve over the other in this position regarding short- and long-term outcomes, the tradeoff between the risk of reoperation for bioprosthetic valve degeneration and the risk associated with long-term anticoagulation, the choice of prosthesis should be discussed in detail with the patient. Bioprosthesis offers a higher quality

of life and is preferred for patients with contraindications for anticoagulation such as pregnancy or older age. Additionally, the possibility of a future transcatheter TV-in-valve replacement, which is simple to perform and involves negligible invasiveness, should be considered in the decision making for prosthetic devices as the risk of long-term structural valve deterioration and limited durability that was the biggest barrier to choose a biological prosthesis is much less a major concern. Finally, there is no “gold standard” for prosthetic TVR and the European guidelines suggest that the prosthetic valve be chosen according to the risks and benefits associated with the patients' lifestyle and personal preference as well as their age.⁶ Unlike aortic or mitral valve, there is no specific cut-off based on age but bioprosthetic TVR may be a valid option regardless of patient age. Multidisciplinary Heart Team decision-making is crucial and the availability of tricuspid valve-in-valve procedures should enter such a discussion.

TVr versus TVR

There is no randomized study that would allow to compare TVr to TVR. Meta-analysis as well as observational studies with propensity-matched groups indicate that TVr is more beneficial in comparison with TVR regarding all-cause mortality.^{26,57,58} Those results are probably related to patient selection (patients who undergo a TVR are usually referred later to surgery) rather than the TVR itself as it is not an independent predictor of both early and long-term outcome contrary to the pre-operative presentation,²⁸ especially parameters that reflect the impact on the RV which are usually not detailed and therefore could not be used for group-matching in those studies.

However, the need for PPI is probably one of major concern after TVR. Indeed, major postoperative complications were not significantly different between the two groups except for the rate of PPI, which was threefold higher following TVR versus TVr.

As a result, TVr should be performed for all patients whenever successfully feasible to avoid the need for life-anticoagulation with mechanical prosthesis or redo-intervention with bioprosthesis.

Follow-up for prosthetic valves

Patients who undergo TVR are not cured but still have serious heart disease and must be followed with the same care as those with native valve disease. There are no dedicated guidelines for follow-up of patients with valve replacement in the tricuspid position. An initial transthoracic echocardiographic study is recommended for patients after prosthetic valve implantation to assess valve hemodynamics (COR I LOE B in ACC/AHA guidelines).⁵ The interval between routine follow-up visits depends on the patient's valve type, residual heart disease, comorbid conditions, and other clinical factors. The asymptomatic uncomplicated patient is usually seen at 1-year intervals for a cardiac history and physical examination. Echocardiograms will be performed according to symptoms or clinical evidence of prosthetic valve or ventricular dysfunction or dysfunction of other heart valves. (COR I LOE C in ACC/AHA guidelines).⁵ Patients who receive bioprostheses must be carefully evaluated with periodic echocardiograms, especially after 7 to 10 years, for detecting clinical and subclinical signs of valve deterioration. A bioprosthetic TS is defined by a mean TV gradient >5 mmHg.

Antithrombotic therapy for prosthetic valves

There are neither dedicated guidelines about the duration of anticoagulation for patients with bioprosthetic TV nor about the INR target according to the type of prosthesis. Anticoagulation with a vitamin K antagonist seems reasonable for at least the first 3 months after bioprosthetic TVR to achieve an INR of 2.5 (range 2.0 to 3.0) and prevent the risk of thrombo-embolism owing to the defective endothelialisation of the prosthetic material.⁵⁹ Effective antithrombotic therapy in patients with mechanical valve requires continuous and lifelong effective

anticoagulation with a vitamin K antagonist and INR in the target range to decrease the incidence of thrombosis and thromboembolism. A regular education of the patients is mandatory and management of anticoagulation should be supervised and monitored frequently by an experienced healthcare professional to prevent both thrombotic complications and bleeding events.

Primary TR with specific issues

Carcinoid

Carcinoid heart disease (CaHD) of the TV occurs in about 20–50% of patients with carcinoid tumors.^{60–62} TR is usually the predominant lesion in CaHD with thickened, retracted and reduced mobility leaflets. The TV is rarely involved in isolation, but rather together with the pulmonary valve. Moreover if there is a patent foramen ovale, left sided valves may also be involved. Valve surgery, which primarily consists of TVR in patients with severe cardiac involvement and well-controlled systemic disease, is the most effective treatment option for advanced CaHD reducing right HF, increasing functional capacity, allowing for more aggressive oncological treatment and improving long-term prognosis.^{63–67} In the largest series from Mayo Clinic with 240 patients who underwent cardiac surgery for CaHD during a 30-year timespan, 30-day mortality rate after surgery had significantly decreased from 29% between 1985 and 1994 to 5% from 2005 onward and overall survival estimates at 1, 3, and 5 years were 69%, 48%, and 34%, respectively with most patients succumbing to progressive tumor burden.⁶⁸ They have also shown that TVR is usually performed alone but replacement of pulmonary, aortic and mitral valves can be associated concomitantly with success, if necessary. An expert statement has been published by Davar J et al. to manage CaHD in patients with neuroendocrine tumors,⁶⁹ insisting on the critical need of an experienced medical (cardiologists and neuro-endocrine tumors specialists), surgical, and anesthetic team approach. The optimal timing for TVR has not been identified. Patients with CaHD are mostly referred for valve surgery when they develop symptoms or RV dysfunction and rarely in anticipation of hepatic surgery.⁷⁰ By consensus, patients with CaHD and severe TR should be referred for cardiac surgery when they develop symptoms or evidence of early RV dysfunction according to echocardiography with at least 12 months of anticipated post-operative survival from their carcinoid tumor. The choice of valve prosthesis should be individually tailored on the basis of the patient's bleeding risk, the specific tumor-related life expectancy and possible future therapeutic interventions. Biological valve prostheses are the preferred option to avoid the need for anticoagulation therapy, especially in patients with liver metastases who have an increased risk of bleeding, and to avoid the increased risk of thrombosis of mechanical prostheses in the tricuspid position⁷¹ that can be worsened by invasive procedures requiring temporary discontinuation of anticoagulation therapy. For the pulmonary valve the most appropriate is homograft replacement. Moreover, the optimization of treatment of carcinoid syndrome after cardiac surgery may protect bioprosthetic valves from the adverse effects of vasoactive peptides by decreasing carcinoid activity.⁷¹ The management of patients undergoing valvular surgery for CaHD is complex and requires a knowledgeable multidisciplinary team with broad experience in the field.^{60,63} as patients with carcinoid syndrome are at risk of a potential life-threatening carcinoid crisis when undergoing surgery, as well as when receiving anesthesia and other perioperative pharmacological agents, such as vasopressors and opioids. Octreotide is given to counteract the serotonin storm originated from the small bowel initial tumor. Patients who have successfully undergone valve replacement surgery should be under the surveillance of a cardiology team experienced in the management of patients with CaHD. As bioprosthetic valve thrombosis on explanted dysfunctional TV bioprostheses in patients with CaHD has been shown recently,⁶⁵ patients with bioprostheses should receive anticoagulation therapy for 3 to 6 months post-

operatively. Transthoracic echocardiographic surveillance should be performed early after surgery, at 3–6 months after surgery (at cessation of anticoagulation therapy) and then at 6 to 12-month intervals.

Endocarditis

TV infective endocarditis (TVIE) is most commonly associated with a history of intravenous drug use (41%), infected pacemaker leads (19%) and congenital defects (17%).⁷² TV surgery for IE is rarely performed,⁷³ in approximately 20% of patients with TVIE,⁷⁴ as it is recommended only for patients with right heart failure secondary to severe TR with poor response to diuretic therapy, IE caused by organisms that are difficult to eradicate (fungi) or bacteraemia for at least 7 days (*Staphylococcus aureus*, *Pseudomonas aeruginosa*) despite adequate antimicrobial therapy, and TV vegetations >20 mm that persist after recurrent pulmonary emboli with or without concomitant right HF (COR IIa LOE C in ESC guidelines).⁷⁵ Conversely, TV surgery should generally be avoided in intravenous drug users with right-sided native infective endocarditis given the high recurrence rate of infective endocarditis due to continued drug abuse.

In TVIE, ACC/AHA guidelines have stated that TVr is preferred whenever possible to TVR to avoid the risk of prosthetic valve deterioration and to reduce the risk of recurrent IE on artificial material, particularly in patients with a history of intravenous drug use (COR I LOE C in ACC/AHA guidelines).⁷⁶ In practice, the indication for TVR is based on the surgeon's discretion when extensive valve damages preclude repair, which is particularly frequent for patients referred late to tertiary care centers. Thus, the largest multicenter studies reported a majority of TVR (51% in the United States,⁷³ 51% in Italy⁷⁷ and 55% in France²⁸). The majority of patients with TVR received a bioprosthetic valve (83%),⁷² notably because of the lower likelihood to adhere to anticoagulation therapy in the intravenous drug use population.

In-hospital post-operative mortality after isolated TV surgery for TVIE was 5% in the most recent study. This low mortality rate was explained by a younger age, less cardiovascular risk factors, less comorbidities and an earlier surgical management with less impact of the TV disease on the RV function than patients with functional TR.²⁸

In a recent meta-analysis with 1165 patients who underwent a TV surgery for TVIE, there was no difference in short- or long-term mortality between TVr versus TVR. However, TVR was associated with more PPI (due to extension of infection into the region of the cardiac conduction system or as a complication of TVR itself), recurrent IE and reoperation but less postoperative and recurrent moderate to severe TR than repair knowing that patients undergoing TVR had a higher burden of disease and a higher preoperative functional status.⁷²

TTVR

Tricuspid valve implantation after previous TVR and ring annuloplasty: valve-in-valve and valve-in-ring

Encouraged by the good results of valve-in-valve implantation in the aortic and mitral position and by the feasibility of valve-in-ring in mitral, several authors have jumped into the tricuspid position and tried the valve-in-valve and valve-in-ring concept (Fig. 2).

The Melody stented bovine jugular vein conduit (Medtronic, Inc.) and the Edwards Sapien XT and Sapien 3 balloon expandable valve (Edwards Lifesciences, Irvine, CA) have been used in the right atrioventricular position. In all these reports, the behavior of the valve seems to be appropriate although the follow-up is still short, with no reports reaching the mark of 5 years. After initial report through transjugular and direct atrial access, nowadays the transfemoral route represents the standard percutaneous access for tricuspid valve-in-valve and valve-in-ring. The procedure is not demanding from a technical standpoint, can be easily performed under conscious sedation and rapid pacing is optional (Fig. 3). In some cases, the angle between the inferior

TRICUSPID VALVE REPLACEMENT

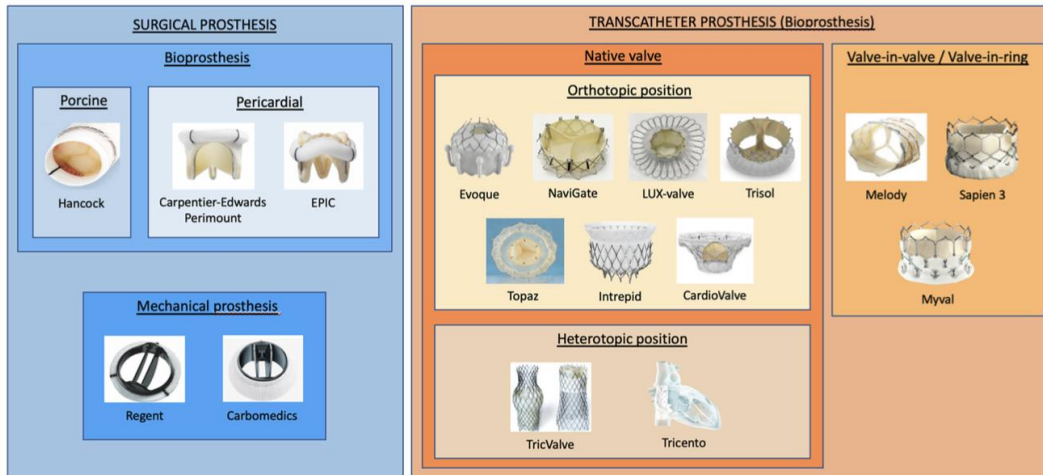


Fig. 2. Main types of surgical and transcatheter tricuspid valve prostheses.

vena cava and the tricuspid annular plane could be really steep and reaching perfect coaxiality during the implantation could be challenging. Contralateral snaring of the tip of the delivery system could help to improve the coaxiality.⁷⁸ Tricuspid valve-in-valve has been shown to be feasible even in presence of pacemaker or implantable cardioverter defibrillator lead through the surgical prostheses, which can be safely jailed between the transcatheter and the surgical valves without increased risk of complications or lead malfunction.⁷⁹

McElhinney et al. reported a procedural success rate of 98.6%, few serious complications, symptom improvement to New York Heart Association functional class I or II in 77% patients (13.3-months median follow-up), and no differences in outcomes irrespective of surgical valve size or transcatheter valve type.⁸⁰ Another study reported a cumulative 3-year incidence of death, reintervention, and valve-related adverse outcomes at 17%, 12%, and 8%, respectively.⁸¹

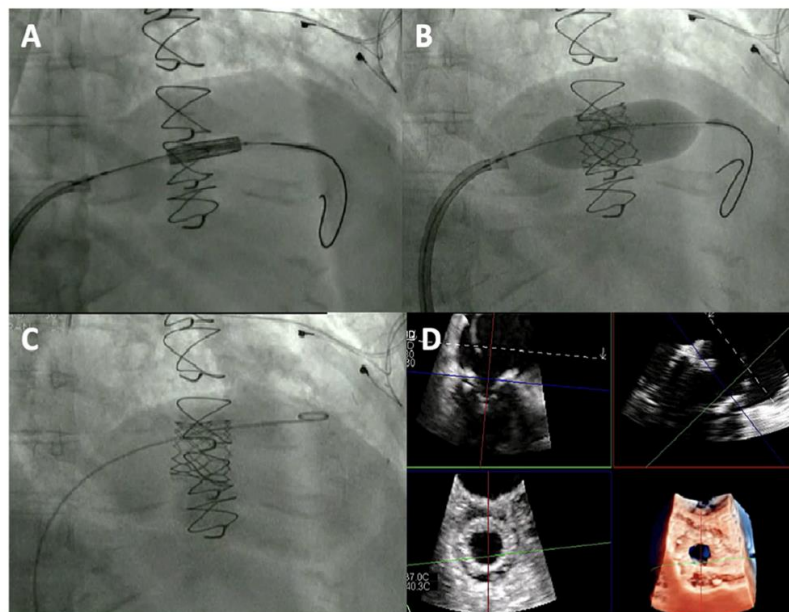


Fig. 3. Transcatheter tricuspid valve-in-valve implantation. Fluoroscopy of the valve deployment (A to C) and intra-procedural transesophageal echocardiography assessing the good deployment of the valve using multiview mode (D).

While tricuspid valve-in-valve is from a technical standpoint a relative straight-forward intervention, valve-in-ring presents several challenges, since in tricuspid position surgical rings usually have an open configuration, and a non-circular and non-planar shape. Therefore, an integrated approach for the accurate sizing of the ring is mandatory using the three available techniques: computed tomography, 3D-transoesophageal echocardiography and fluoroscopy. On the other hand, unlike the mitral position, the risk of RV outflow obstruction is absent, and residual perivalvular leak and risk of embolisation are less of an issue as a result of the low-pressure RV system.

As for valve-in-valve, two types of valves have been implanted so far for valve-in-ring in the TV position, the Melody valve (Medtronic, Minneapolis, MN, USA) and the Edwards SAPIEN valve (Edwards Lifesciences). Both valve devices seem to give promising results, but, given the small sizes available for the Melody valve (maximal diameter of 22 mm), it has been used mainly in children or young adults with congenital heart disease.

Several reports have been published concerning the Edwards SAPIEN valve, using transatrial and transfemoral approaches. Bouleti et al. reported their experience with three valve-in-ring implantations with an Edwards SAPIEN XT valve through a transfemoral approach. On pre-discharge echocardiographic examination, paravalvular leak was absent in one, mild in one and moderate to severe in one. The paravalvular leak was always at the level of the open portion of the ring. At one year, all the patients were alive, with a stable improvement in their functional status (NYHA Class I or II), even in the patient with severe paravalvular regurgitation, and there were no significant gradients (from 3 to 5 mmHg).⁸²

As there is limited information on the long-term follow-up after these procedures, it is also to be expected that some problems could develop over time, including valve thrombosis, early degeneration and endocarditis after valve-in-valve implantation.

Transcatheter tricuspid valve implantation (TTVI) in native anatomy

TTVI presents several technical challenges, mainly due to the tricuspid anatomy (large annulus, thin tissue, 3-leaflets configuration, steep angle between the inferior vena cava and the annular plane) and its proximity of several vital structures (right coronary artery, aortic valve, atrioventricular node, coronary sinus, the free wall of the RV). Moreover, being the most anterior valve of the heart, TV is difficult to be visualized with trans-oesophageal echocardiography and intraprocedural guidance represents often a major challenge due to lack of optimal echo-window.

The most used approach for TTVI is transcatheter repair, with many devices under different phases of investigation, and with 3 of them being recently approved for commercial use in Europe (Triclip, Pascal and Cardioband). Although different studies from real world registries in high-risk population showed feasibility and promising initial results in different clinical settings,^{44,83-88} there are many patients who do not qualify for repair strategy and who could benefit from a catheter based TVR.

Different replacement devices are under clinical and preclinical investigation (Figs. 1 and 2). TTVR has the potential to abolish TR and to fulfill the unmet clinical need for patients who are not suitable for transcatheter repair, usually due to extreme annular dilatation with large coaptation gaps, short or extremely retracted septal leaflets or with inadequate imaging. Due to the complete abolishment of TR, the risk of afterload mismatch of the RV, especially in presence of pulmonary hypertension, represents the main concern in TTVR. Careful evaluation of the RV function is therefore crucial in the patient selection process.

There are two categories of TTVR:

- heterotopic valve replacement: the valve (or the valves) is/are deployed in one or both vena cava, in order to reduce the backflow in the venous system and relief of the venous congestion at the visceral

level; this approach is also known as Caval Valve Implantation (CAVI);

- orthotopic valve replacement: where the valve is deployed at the TV annulus, at the native position.

Heterotopic valve replacement

Heterotopic TV implantation is a palliative approach which is usually reserved when repair or orthotopic implantation are not feasible, with the aim to reduce venous congestion in the visceral system, improve visceral perfusion and relief of the TR-related symptoms (anasarca, ascites, hepatic congestion and dysfunction, kidney congestion, and exertional dyspnea to some degree).⁸⁹ Due to the dilated anatomy of inferior and superior vena cava and the difficult of sealing, specifically dedicated CAVI devices have been developed, like self-expanding valves TricValve (TricValve, P&F Products Features Vertriebs) and the Tricento (NVT).^{90,91} Since this approach basically induces a ventricularization of the RA (leaving the TV severely insufficient), the clinical value of the CAVI approach is debatable and has to be further investigated and validated. One of the main concerns is that a failing RV may not tolerate the acute increase of pressure in the RA after CAVI (especially in case of implantation in both inferior and superior vena cava), therefore patients selection plays a crucial role.

Orthotopic TVR

Different replacement devices are currently under investigation.

Gate Valve

The Gate (NaviGate Cardiac Structures, Inc.) is a biological valved stent which consists of conical-shaped Nitinol alloy stent into which is mounted a trileaflet equine pericardium valve. Currently, four sizes are available (40, 44, 48, 52 mm in diameter) covering an annular range from 36 to 52 mm of diameter. After an initial phase where the Gate was implanted through venous transjugular access, this approach has been abandoned. Most of the human implantations have been performed transatrially through a minimally invasive right thoracotomy directly through the free wall of the RA (Fig. 4).

Initial data from 30 patients with severe or greater TR have been reported: technical success was 87%, with an in-hospital mortality of 10%. Procedural complications included malpositioning requiring surgical conversion, pacemaker implantation due to conduction abnormalities and RV perforation.⁹²

EVOQUE TVR system

The EVOQUE TVR system (Edwards Lifesciences LLC, Irvine, CA, USA) consists of a self-expanding nitinol frame, bovine pericardial leaflets, an intra-annular sealing skirt designed to minimize paravalvular leak and anchors for optimal valve placement. It is available in 44, 48 and 52 mm size which are all delivered through a 28Fr delivery system via transfemoral access. First in human 30-day follow-up outcomes on 25 patients treated under compassionate use were reported, with a very high technical success rate (92%), effective in reducing TR (88% with 0 or 1+ residual TR, 96% < 2+), providing significant clinical improvement (76% were in NYHA functional class I or II) and an excellent safety profile with no procedural deaths.⁹³

The recently presented interim 30-day results from the TRISCEND study confirmed the safety and technical feasibility of the EVOQUE valve in high-risk patients with symptomatic moderate or greater TR (severe in 46%, massive in 29%, and torrential in 15%). The study enrolled 56 high-risk patients (84% in NYHA functional class III-IV) with relevant TR (68%, functional, 11% had degenerative and the rest had mixed/other origins). Nearly half (43%) had undergone a prior valve surgery or intervention. Thirty-day follow-up showed significant

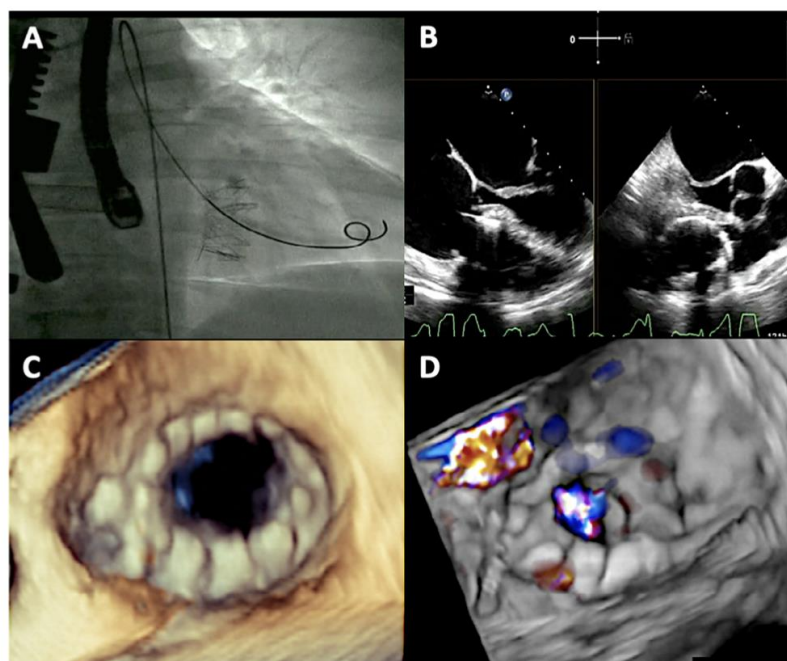


Fig. 4. Transcatheter tricuspid valve replacement with the GATE system. Deployment of the valve guided by fluoroscopy (A). Intra-procedural transesophageal echocardiography assessing the good deployment of the valve using X-plane (B), 3D mode (C), and color-Doppler (D).

reduction in TR severity with 98% of the patients having mild or none/trace TR, with significant improvements in NYHA class, 6-min walk distance and Kansas City Cardiomyopathy Questionnaire score.

Major adverse events at 30-day follow-up revealed that one patient (1.9%) had died of a cardiovascular cause (with an all-cause mortality of 3.8%). There were no strokes or myocardial infarction. The most frequent complication was severe bleeding (none were life-threatening or fatal), which occurred in 12 patients (22.6%), while two (3.8%) required non-elective tricuspid valve reintervention and one (1.9%) had major access-site/vascular complications.

Lux-Valve

The Lux-Valve (Jenscare Biotechnology, Ningbo, China) is a self-expanding bovine pericardial tissue valve mounted on a nitinol stent covered by a layer of polyethylene terephthalate.⁹⁴ Interestingly and different from the other devices, the Lux-Valve does not rely on radial forces in order to secure its position and sealing. Two anterior leaflet clampers attach to the native valve and an interventricular anchor attaches to the interventricular septum. A 32Fr system is required to deliver the valve, under direct right atrial access, through a minimally invasive right thoracotomy. Lux-Valve has been used mostly in China on a compassionate-use basis, with an early feasibility trial in Canada also underway. In 12 patients reported, implantation success rate was 100%, and with a 8.3% 30-day mortality.⁹⁵ Recently, promising data have been reported in 5 patients who reached 1 year follow-up.⁹⁶

Others

Other devices are under pre-clinical evaluation for use in native tricuspid position, including Intrepid (Medtronic), CardioValve (Mitraltch), Topaz (TriCares SAS, Paris, France) and TriSol (Trisol

Medical, Yokneam, Israel). In particular, early feasibility trials with Intrepid and Cardiovalve have been approved in United States.

Conclusion

Despite high frequency of TV disease, tricuspid valve replacement is seldom performed owing to high-surgical risk for those patients referred late in the course of the disease. As a less-invasive alternative to surgery, transcatheter tricuspid valve replacement, which is currently under investigation, is likely a promising option to improve the outcome of this population and may further push for an extension of the number of patients treated if proven to be safe and efficient.

Disclosures

Julien Dreyfus has no conflict of interest to declare.

Gilles Dreyfus has reported teaching courses for Edwards Lifesciences.

Maurizio Taramasso has served as consultant for Abbott Vascular, Edwards Lifesciences, Boston Scientific, 4tech, Shenqi Medical, Simulands, MTEch, Occlufit, CoreMedic.

References

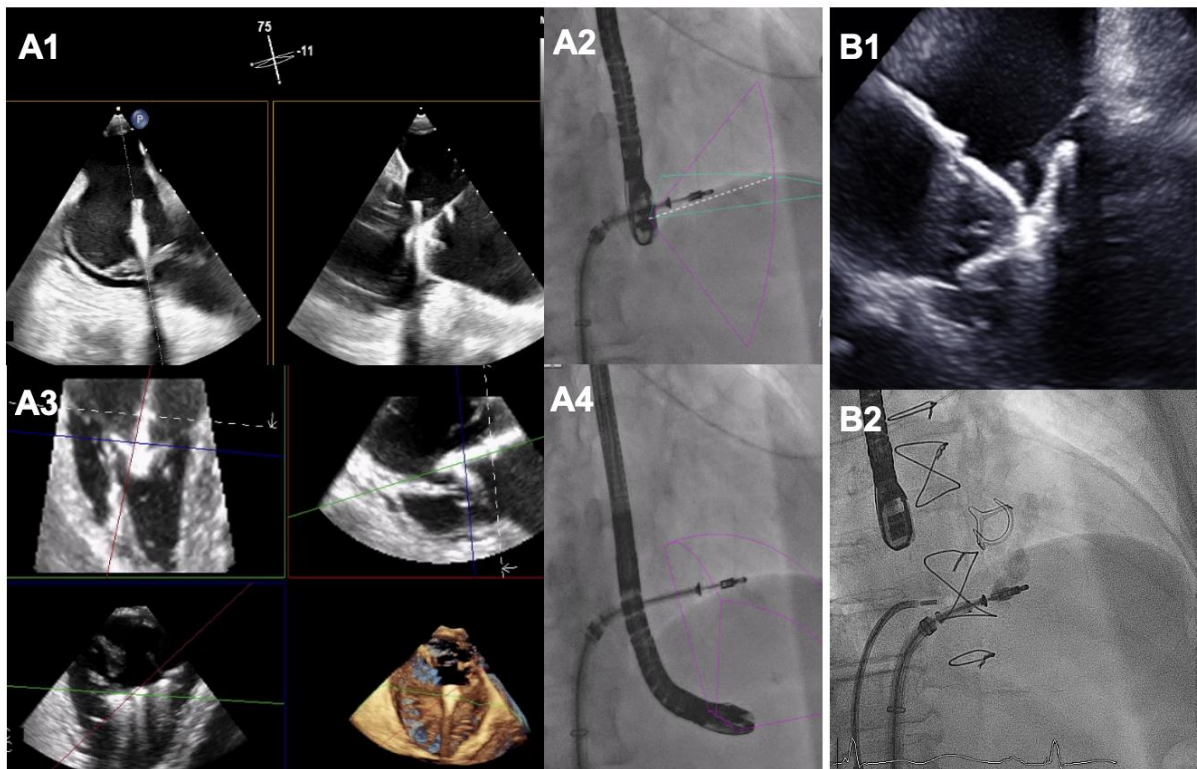
1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;368:1005-1011.
2. Stuge O, Liddicoat J. Emerging opportunities for cardiac surgeons within structural heart disease. *J Thorac Cardiovasc Surg* 2006;132:1258-1261.
3. Topilsky Y, Maltais S, Medina Inojosa J, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging* 2019;12:433-442.

4. Messika-Zeitoun D, Candolfi P, Dreyfus J, et al. Management and outcome of patients admitted with tricuspid regurgitation in France. *Can J Cardiol* 2020;37:1078-1085.
5. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the Management of Patients with Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation* 2021;143:e72-e227.
6. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2021;43:561-632.
7. Dreyfus GD, Corbi PJ, Chan KM, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? *Ann Thorac Surg* 2005;79:127-132.
8. Fukuda S, Saracino G, Matsumura Y, et al. Three-dimensional geometry of the tricuspid annulus in healthy subjects and in patients with functional tricuspid regurgitation: a real-time, 3-dimensional echocardiographic study. *Circulation* 2006;114:1492-1498.
9. Park SJ, Oh JK, Kim SO, et al. Determinants of clinical outcomes of surgery for isolated severe tricuspid regurgitation. *Heart* 2021;107:403-410.
10. Chen J, Ma W, Ming Y, et al. Minimally invasive valve replacement for late tricuspid regurgitation after left-sided valve surgery. *Ann Thorac Surg* 2020;111:e381-e383.
11. Hanedan MO, Cicekcioglu F, Aksoyek A, et al. Tricuspid valve replacement through right thoracotomy has better outcomes in redo cases. *Heart Lung Circ* 2017;26:88-93.
12. Pfanmuller B, Misfeld M, Borger MA, et al. Isolated reoperative minimally invasive tricuspid valve operations. *Ann Thorac Surg* 2012;94:2005-2010.
13. Nakano K, Eishi K, Kosaki Y, et al. Ten-year experience with the Carpentier-Edwards pericardial xenograft in the tricuspid position. *J Thorac Cardiovasc Surg* 1996;111:605-612.
14. Nakano K, Ishibashi-Ueda H, Kobayashi J, Sasako Y, Yagihara T. Tricuspid valve replacement with bioprostheses: long-term results and causes of valve dysfunction. *Ann Thorac Surg* 2001;71:105-109.
15. Guerra F, Bortolotti U, Thiene G, et al. Long-term performance of the Hancock porcine bioprosthesis in the tricuspid position. A review of forty-five patients with fourteen-year follow-up. *J Thorac Cardiovasc Surg* 1990;99:838-845.
16. Carrier M, Hebert Y, Pellerin M, et al. Tricuspid valve replacement: an analysis of 25 years of experience at a single center. *Ann Thorac Surg* 2003;75:47-50.
17. Rizzoli G, De Perini L, Bottio T, Minutolo G, Thiene G, Casarotto D. Prosthetic replacement of the tricuspid valve: biological or mechanical? *Ann Thorac Surg* 1998;66:562-567.
18. Hwang HY, Kim KH, Kim KB, Ahn H. Propensity score matching analysis of mechanical versus bioprosthetic tricuspid valve replacements. *Ann Thorac Surg* 2014;97:1294-1299.
19. Anselmi A, Ruggieri VG, Harmouche M, et al. Appraisal of long-term outcomes of tricuspid valve replacement in the current perspective. *Ann Thorac Surg* 2016;101:863-871.
20. Kaplan M, Kut MS, Demirtas MM, Cimen S, Ozler A. Prosthetic replacement of tricuspid valve: bioprosthetic or mechanical. *Ann Thorac Surg* 2002;73:467-473.
21. Peterffy A, Szentkiralyi I. Mechanical valves in tricuspid position: cause of thrombosis and prevention. *Eur J Cardiothorac Surg* 2001;19:735-736.
22. Jugdutt BI, Fraser RS, Lee SJ, Rossall RE, Callaghan JC. Long-term survival after tricuspid valve replacement. Results with seven different prostheses. *J Thorac Cardiovasc Surg* 1977;74:20-27.
23. Thorburn CW, Morgan JJ, Shanahan MX, Chang VP. Long-term results of tricuspid valve replacement and the problem of prosthetic valve thrombosis. *Am J Cardiol* 1983;51:1128-1132.
24. Chang BC, Lim SH, Yi G, et al. Long-term clinical results of tricuspid valve replacement. *Ann Thorac Surg* 2006;81:1317-1323.discussion 1323-4.
25. Filsoofi F, Anyanwu AC, Salzberg SP, Frankel T, Cohn LH, Adams DH. Long-term outcomes of tricuspid valve replacement in the current era. *Ann Thorac Surg* 2005;80:845-850.
26. Wong WK, Chen SW, Chou AH, et al. Late outcomes of valve repair versus replacement in isolated and concomitant tricuspid valve surgery: a Nationwide cohort study. *J Am Heart Assoc* 2020;9, e015637.
27. Alqahtani F, Berzingi CO, Aljohani S, Hijazi M, Al-Hallak A, Alkhouli M. Contemporary Trends in the use and outcomes of surgical treatment of tricuspid regurgitation. *J Am Heart Assoc* 2017;6.
28. Dreyfus J, Flagiello M, Bazire B, et al. Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes. *Eur Heart J* 2020;41:4304-4317.
29. Kilic A, Saha-Chaudhuri P, Rankin JS, Conte JV. Trends and outcomes of tricuspid valve surgery in North America: an analysis of more than 50,000 patients from the Society of Thoracic Surgeons database. *Ann Thorac Surg* 2013;96:1546-1552.[discussion 1552].
30. Vassileva CM, Shabosky J, Boley T, Markwell S, Hazelrigg S. Tricuspid valve surgery: the past 10 years from the Nationwide Inpatient Sample (NIS) database. *J Thorac Cardiovasc Surg* 2021;143:1043-1049.
31. Dreyfus J, Ghalem N, Garbarz E, et al. Timing of referral of patients with severe isolated tricuspid valve regurgitation to surgeons (from a French Nationwide database). *Am J Cardiol* 2018;122:323-326.
32. Kundi H, Popma JJ, Cohen DJ, et al. Prevalence and outcomes of isolated tricuspid valve surgery among medicare beneficiaries. *Am J Cardiol* 2019;123:132-138.
33. LaPar DJ, Mulloy DP, Stone ML, et al. Concomitant tricuspid valve operations affect outcomes after mitral operations: a multistitutional, statewide analysis. *Ann Thorac Surg* 2012;94:52-57.discussion 58.
34. Zack CJ, Fender EA, Chandrashekar P, et al. National Trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol* 2017;70:2953-2960.
35. Alkhouli M, Berzingi C, Kowati A, Alqahtani F, Badhwar V. Comparative early outcomes of tricuspid valve repair versus replacement for secondary tricuspid regurgitation. *Open Heart* 2018;5, e000878.
36. Kang Y, Hwang HY, Sohn SH, Choi JW, Kim KH, Kim KB. Fifteen-year outcomes after bioprosthetic and mechanical tricuspid valve replacement. *Ann Thorac Surg* 2020;110:1564-1571.
37. Negm S, Arafat AA, Alatafy EE, Fawzy HF. Mechanical versus bioprosthetic valve replacement in the tricuspid valve position: a systematic review and Meta-analysis. *Heart Lung Circ* 2020;30:362-371.
38. Buzzatti N, Iaci G, Taramasso M, et al. Long-term outcomes of tricuspid valve replacement after previous left-side heart surgery. *Eur J Cardiothorac Surg* 2014;46:713-719. discussion 719.
39. Garatti A, Nano G, Bruschi G, et al. Twenty-five year outcomes of tricuspid valve replacement comparing mechanical and biologic prostheses. *Ann Thorac Surg* 2012;93:1146-1153.
40. Garatti A, Canziani A, Mossuto E, et al. Tricuspid valve replacement with mechanical prostheses: long-term results. *J Heart Valve Dis* 2010;19:194-200.
41. Dreyfus J, Audureau E, Bohbot Y, et al. TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. *Eur Heart J* 2021;43:654-662.
42. Koplan BA, Stevenson WG, Epstein LM, Aranki SF, Maisel WH. Development and validation of a simple risk score to predict the need for permanent pacing after cardiac valve surgery. *J Am Coll Cardiol* 2003;41:795-801.
43. Jokinen JJ, Turpeinen AK, Pitkanen O, Hippelainen MJ, Hartikainen JE. Pacemaker therapy after tricuspid valve operations: implications on mortality, morbidity, and quality of life. *Ann Thorac Surg* 2009;87:1806-1814.
44. Mar PL, Angus CR, Kabra R, et al. Perioperative predictors of permanent pacing and long-term dependence following tricuspid valve surgery: a multicentre analysis. *Europace* 2017;19:1988-1993.
45. Esperer HD, Mahmoud FO, von der Emde J. Is epicardial dual chamber pacing a realistic alternative to endocardial DDD pacing? Initial results of a prospective study. *Pacing Clin Electrophysiol* 1992;15:155-161.
46. Eleid MF, Blauwet LA, Cha YM, et al. Bioprosthetic tricuspid valve regurgitation associated with pacemaker or defibrillator lead implantation. *J Am Coll Cardiol* 2012;59:813-818.
47. Brignole M, Auricchio A, Baron-Esquivias G, et al. ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European heart rhythm association (EHRA). *Eur Heart J* 2013;34:2281-2329.
48. Kawachi Y, Tominaga R, Hisahara M, Nakashima A, Yasui H, Tokunaga K. Excellent durability of the Hancock porcine bioprosthesis in the tricuspid position. A sixteen-year follow-up study. *J Thorac Cardiovasc Surg* 1992;104:1561-1566.
49. Hirata K, Tengan T, Wake M, et al. Bioprosthetic tricuspid valve stenosis: a case series. *Eur Heart J Case Rep* 2019;3.
50. Rizzoli G, Vendramin I, Nesseris G, Bottio T, Guglielmi C, Schiavon L. Biological or mechanical prostheses in tricuspid position? A meta-analysis of intra-institutional results. *Ann Thorac Surg* 2004;77:1607-1614.
51. Hwang HY, Kim KH, Kim KB, Ahn H. Mechanical tricuspid valve replacement is not superior in patients younger than 65 years who need long-term anticoagulation. *Ann Thorac Surg* 2012;93:1154-1160.
52. Nakano K, Koyanagi H, Hashimoto A, Ohtsuka G, Nojiri C. Tricuspid valve replacement with the bileaflet St. Jude Medical valve prosthesis. *J Thorac Cardiovasc Surg* 1994;108:888-892.
53. Glover DD, White WD, Smith LR, et al. In-hospital and long-term outcome after porcine tricuspid valve replacement. *J Thorac Cardiovasc Surg* 1995;109:877-883. discussion 883-4.
54. Guenther T, Noebauer C, Mazzitelli D, Busch R, Tassani-Prell P, Lange R. Tricuspid valve surgery: a thirty-year assessment of early and late outcome. *Eur J Cardiothorac Surg* 2008;34:402-409.discussion 409.
55. Ohata T, Kigawa I, Tohda E, Wanibuchi Y. Comparison of durability of bioprostheses in tricuspid and mitral positions. *Ann Thorac Surg* 2001;71:S240-S243.
56. Civelek A, Ak K, Akgun S, Isbir SC, Arsan S. Tricuspid valve replacement: an analysis of risk factors and outcomes. *Thorac Cardiovasc Surg* 2008;56:456-460.
57. Choi JW, Jang MJ, Kim KH, Hwang HY. Repair versus replacement for the surgical correction of tricuspid regurgitation: a meta-analysis. *Eur J Cardiothorac Surg* 2018;53:748-755.
58. Wang TKM, Griffin BP, Miyasaka R, et al. Isolated surgical tricuspid repair versus replacement: meta-analysis of 15 069 patients. *Open Heart* 2020;7, e001227.
59. Chesebro JH, Adams PC, Fuster V. Antithrombotic therapy in patients with valvular heart disease and prosthetic heart valves. *J Am Coll Cardiol* 1986;8:41B-56B.
60. Bernheim AM, Connolly HM, Hobday TJ, Abel MD, Pellikka PA. Carcinoid heart disease. *Prog Cardiovasc Dis* 2007;49:439-451.
61. Bhattacharyya S, Toumpanakis C, Caplin ME, Davar J. Usefulness of N-terminal pro-brain natriuretic peptide as a biomarker of the presence of carcinoid heart disease. *Am J Cardiol* 2008;102:938-942.
62. Gustafsson BI, Hauso O, Drozdov I, Kidd M, Modlin IM. Carcinoid heart disease. *Int J Cardiol* 2008;129:318-324.
63. Bhattacharyya S, Raja SG, Toumpanakis C, Caplin ME, Dreyfus GD, Davar J. Outcomes, risks and complications of cardiac surgery for carcinoid heart disease. *Eur J Cardiothorac Surg* 2011;40:168-172.
64. Connolly HM, Nishimura RA, Smith HC, Pellikka PA, Mullany CJ, Kvolis LK. Outcome of cardiac surgery for carcinoid heart disease. *J Am Coll Cardiol* 1995;25:410-416.
65. Connolly HM, Schaff HV, Abel MD, et al. Early and late outcomes of surgical treatment in carcinoid heart disease. *J Am Coll Cardiol* 2015;66:2189-2196.
66. Mokhles P, van Herwerden LA, de Jong PL, et al. Carcinoid heart disease: outcomes after surgical valve replacement. *Eur J Cardiothorac Surg* 2012;41:1278-1283.

67. Moller JE, Pellikka PA, Bernheim AM, Schaff HV, Rubin J, Connolly HM. Prognosis of carcinoid heart disease: analysis of 200 cases over two decades. *Circulation* 2005;112:3320-3327.
68. Nguyen A, Schaff HV, Abel MD, et al. Improving outcome of valve replacement for carcinoid heart disease. *J Thorac Cardiovasc Surg* 2019;158(99-107), e2.
69. Davar J, Connolly HM, Caplin ME, et al. Diagnosing and managing carcinoid heart disease in patients with neuroendocrine tumors: an expert statement. *J Am Coll Cardiol* 2017;69:1288-1304.
70. Askew JW, Connolly HM. Carcinoid valve disease. *Curr Treat Options Cardiovasc Med* 2013;15:544-555.
71. Raja SG, Bhattacharyya S, Davar J, Dreyfus GD. Surgery for carcinoid heart disease: current outcomes, concerns and controversies. *Future Cardiol* 2010;6:647-655.
72. Yanagawa B, Elbatarny M, Verma S, et al. Surgical management of tricuspid valve infective endocarditis: a systematic review and meta-analysis. *Ann Thorac Surg* 2018;106:708-714.
73. Gaca JG, Sheng S, Daneshmand M, et al. Current outcomes for tricuspid valve infective endocarditis surgery in North America. *Ann Thorac Surg* 2013;96:1374-1381.
74. Akinosgiou K, Apostolakis E, Koutsogiannis N, Leivaditis V, Gogos CA. Right-sided infective endocarditis: surgical management. *Eur J Cardiothorac Surg* 2012;42:470-479.
75. Habib G, Lancellotti P, Antunes MJ, et al. ESC guidelines for the management of infective endocarditis: the task force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;36:3075-3128.
76. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation* 2015;132:1435-1486.
77. Di Mauro M, Foschi M, Dato GMA, et al. Surgical treatment of isolated tricuspid valve infective endocarditis: 25-year results from a multicenter registry. *Int J Cardiol* 2019;292:62-67.
78. Taramasso M, Nietlispach F, Dvir D, et al. Transfemoral tricuspid valve-in-valve implantation: snare it to make it simpler! *EuroIntervention* 2016;12:402.
79. Anderson JH, McElhinney DB, Aboulhosen J, et al. Management and outcomes of transvenous pacing leads in patients undergoing transcatheter tricuspid valve replacement. *JACC Cardiovasc Interv* 2020;13:2012-2020.
80. McElhinney DB, Aboulhosen JA, Dvir D, et al. Mid-term valve-related outcomes after transcatheter tricuspid valve-in-valve or valve-in-ring replacement. *J Am Coll Cardiol* 2019;73:148-157.
81. Aboulhosen J, Cabalka AK, Levi DS, et al. Transcatheter valve-in-ring implantation for the treatment of residual or recurrent tricuspid valve dysfunction after prior surgical repair. *JACC Cardiovasc Interv* 2017;10:53-63.
82. Bouleti C, Juliard JM, Himbert D, et al. Tricuspid valve and percutaneous approach: no longer the forgotten valve! *Arch Cardiovasc Dis* 2016;109:55-66.
83. Miura M, Alessandrini H, Alkhdair A, et al. Impact of massive or torrential tricuspid regurgitation in patients undergoing transcatheter tricuspid valve intervention. *JACC Cardiovasc Interv* 2020;13:1999-2009.
84. Muntane-Carol G, Taramasso M, Miura M, et al. Transcatheter tricuspid valve intervention in patients with right ventricular dysfunction or pulmonary hypertension: insights from the TriValve registry. *Circ Cardiovasc Interv* 2021;14, e009685.
85. Muntane-Carol G, Taramasso M, Miura M, et al. Transcatheter tricuspid valve intervention in patients with previous left valve surgery. *Can J Cardiol* 2021;37:1094-1102.
86. Taramasso M, Alessandrini H, Latib A, et al. Outcomes after current transcatheter tricuspid valve intervention: mid-term results from the international TriValve registry. *JACC Cardiovasc Interv* 2019;12:155-165.
87. Taramasso M, Benfari G, van der Bijl P, et al. Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation. *J Am Coll Cardiol* 2019;74:2998-3008.
88. Taramasso M, Gavazzoni M, Pozzoli A, et al. Outcomes of TTVI in patients with pacemaker or defibrillator leads: data from the TriValve registry. *JACC Cardiovasc Interv* 2020;13:554-564.
89. Lauten A, Figulla HR, Willich C, et al. Percutaneous caval stent valve implantation: investigation of an interventional approach for treatment of tricuspid regurgitation. *Eur Heart J* 2010;31:1274-1281.
90. Cruz-Gonzalez I, Gonzalez-Ferreiro R, Amat-Santos IJ, Carrasco-Chinchilla F, Alonso Briaies JH, Estevez-Loureiro R. TRICENTO transcatheter heart valve for severe tricuspid regurgitation. Initial experience and mid-term follow-up. *Rev Esp Cardiol (Engl Ed)* 2021;74:351-354.
91. Lauten A, Figulla HR, Unbehaun A, et al. Interventional treatment of severe tricuspid regurgitation: early clinical experience in a multicenter, observational, first-in-man study. *Circ Cardiovasc Interv* 2018;11, e006061.
92. Hahn RT, Kodali S, Fam N, et al. Early multinational experience of transcatheter tricuspid valve replacement for treating severe tricuspid regurgitation. *JACC Cardiovasc Interv* 2020;13:2482-2493.
93. Fam NP, von Bardeleben RS, Hensey M, et al. Transfemoral transcatheter tricuspid valve replacement with the EVOQUE system: a multicenter, observational, first-in-human experience. *JACC Cardiovasc Interv* 2021;14:501-511.
94. Goldberg YH, Ho E, Chau M, Latib A. Update on transcatheter tricuspid valve replacement therapies. *Front Cardiovasc Med* 2021;8, 619558.
95. Lu FL, Ma Y, An Z, et al. First-in-man experience of transcatheter tricuspid valve replacement with LuX-valve in high-risk tricuspid regurgitation patients. *JACC Cardiovasc Interv* 2020;13:1614-1616.
96. Sun Z, Zhang Z, Li H, et al. Twelve-month outcomes of the LuX-valve for transcatheter treatment of severe tricuspid regurgitation. *EuroIntervention* 2021;17:818-826.

Figure S2. Guidage péri-procédural pendant une procédure de correction d'une insuffisance tricuspide par réparation bord-à-bord percutanée

- A. Echocardiographie trans-oesophagienne avec les incidences oesophagiennes distales et transgastriques biplan (A1, A3) associées à la scopie (A2, A4)
- B. Echographie intra-cardiaque (B1) associée à la scopie (B2)



Article 12

Comparison of effective regurgitant orifice area by the PISA method and tricuspid coaptation gap measurement to identify very severe tricuspid regurgitation and stratify mortality risk

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Article soumis

Comparison of effective regurgitant orifice area by the PISA method and tricuspid coaptation gap measurement to identify very severe tricuspid regurgitation and stratify mortality risk

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ABSTRACT

Introduction: Various definitions of very severe (VS) tricuspid regurgitation (TR) have been proposed based on the effective regurgitant orifice area (EROA) or tricuspid coaptation gap (TCG). Because of the inherent limitations associated with the EROA, we hypothesized that the TCG would be more suitable for defining VSTR and predicting outcomes.

Materials and methods: In this French multicentre retrospective study, we included 606 patients with \geq moderate-to-severe isolated functional TR (without structural valve disease or an overt cardiac cause) according to the recommendations of the European Association of Cardiovascular Imaging. Patients were further stratified into VSTR according to the EROA (≥ 60 mm²) and then according to the TCG (≥ 10 mm). The primary endpoint was all-cause mortality and the secondary endpoint was cardiovascular mortality.

Results: The relationship between the EROA and TCG was poor ($R^2=0.22$), especially when the size of the defect was large. Four-year survival was comparable between patients with an EROA < 60 mm² vs. ≥ 60 mm² ($68\pm 3\%$ vs. $64\pm 5\%$, $p=0.89$). A TCG ≥ 10 mm was associated with lower four-year survival than a TCG < 10 mm ($53\pm 7\%$ vs. $69\pm 3\%$, $p<0.001$). After adjustment for covariates, including comorbidity, symptoms, dose of diuretics, and right ventricular dilatation and dysfunction, a TCG ≥ 10 mm remained independently associated with higher all-cause mortality (adjusted HR[95%CI]=1.47[1.13-2.21], $p=0.019$) and cardiovascular mortality (adjusted HR[95%CI]=2.12[1.33-3.25], $p=0.001$), whereas an EROA ≥ 60 mm² was not associated with all-cause or cardiovascular mortality (adjusted HR[95%CI]:1.16[0.81-1.64], $p=0.416$, and adjusted HR[95%CI]:1.07[0.68-1.68], $p=0.784$, respectively)

Conclusion: The correlation between the TCG and EROA is weak and decreases with increasing defect size. A TCG ≥ 10 mm is associated with increased all-cause and cardiovascular mortality and should be used to define VSTR in isolated functional TR.

Keywords: very severe tricuspid regurgitation, survival, coaptation gap, effective regurgitant orifice area, mortality.

INTRODUCTION

Tricuspid regurgitation (TR) is a frequent valvular condition that affects approximately 0.8% of the general population (1). Its prevalence increases significantly in elderly patients, especially women, and in cases of atrial fibrillation (AF). (2) Although mild TR is generally considered to be benign, severe TR is systematically associated with a poor prognosis (3-6). Recent data also suggest that even moderate TR is associated with an adverse outcome (7-8). Therefore, accurate quantification of TR severity by Doppler echocardiography is essential. Over the past few years, with the development of transcatheter therapies, the concept of very severe tricuspid regurgitation (VSTR) has emerged (9,10). Massive and torrential TR were thus added to the TR grading scheme using empirical thresholds for effective regurgitant orifice area (EROA) measurements (11). Subsequently, a study reported that patients with \geq massive TR, using this definition, experienced greater mortality than those with “only severe” TR, with no difference between massive and torrential forms (12). Thus, the distinction between massive and torrential TR does not appear to be relevant for risk stratification in clinical practice, but a grade in addition to severe TR (very severe TR, VSTR) had to unquestionably be added to the classification.

Various definitions of VSTR have been proposed since, using EROA or tricuspid coaptation gap (TCG) (13-15). Because of the inherent limitations associated with the EROA (16), the definition of VSTR is a matter of debate. We hypothesized that the TCG would be more suitable for defining VSTR and predicting outcomes. Therefore, we compared the EROA, measured by the PISA method, and the TCG measurement to identify VSTR and stratify mortality risk in a multicentre French cohort of patients with isolated functional TR.

MATERIALS AND METHODS

Study Protocol

This retrospective study was conducted in seven French tertiary centers (Amiens, Lille, Nancy, Nantes, Rennes, Saint Denis, and Toulouse) and included consecutive patients with a diagnosis of significant (\geq moderate-to-severe) isolated TR between 2013 and 2020. Isolated functional TR was defined by structurally normal tricuspid valves with no overt organic cause of TR, no > mild left-sided valvular heart disease, no pulmonary hypertension, preserved (>50%) left ventricular ejection fraction (LVEF), and no previous cardiac surgery. (17) Baseline clinical and demographic characteristics were collected. The Charlson comorbidity index, comprising the sum of individual comorbidities, was calculated for each patient. (18) This study was conducted in accordance with local institutional policies, French legislation, and the revised Declaration of Helsinki and was approved by each local institutional review board. The data underlying this article will be shared upon reasonable request to the corresponding author.

Echocardiography

A complete evaluation by Doppler echocardiography was performed on all patients by experienced echocardiographers using commercially available ultrasound systems. TR was graded as moderate-to-severe and severe by the principal investigator of each center based on the European association of cardiovascular imaging (EACVI) recommendations using the integrative multiparametric approach, including morphological, semi-quantitative, and quantitative parameters (19). Patients were reclassified as VSTR based on an EROA ≥ 60 mm² (11) and then a TCG ≥ 10 mm. The PISA radius was measured in mid-systole using a color baseline shift between 20 and 40 cm/s in the regurgitation direction with a zoom to the convergence zone (19-21) but the ratio of the aliasing velocity to the orifice jet velocity was maintained, as recommended, <10 % whenever feasible. EROA correction for leaflet angles was performed by clinicians when the angle appeared much larger than 180 degrees. The tricuspid coaptation gap was evaluated by 2D echocardiography and measured in end-systole in each available view to identify the largest defect of coaptation. The size of the gap between

leaflets was measured at the tip of the leaflets. RV assessment was performed on multiple views. RV function was assessed using M-mode analysis of the tricuspid annulus systolic excursion (TAPSE) and S' wave velocity at the lateral tricuspid annulus obtained by pulsed wave tissue Doppler imaging. RV dilation was defined by a RV basal diameter >42 mm in an apical four-chamber view (22). Moderate/severe RV dysfunction was defined by either a TAPSE <14mm and/or an S' <10cm/s (22). Tricuspid annulus diameter was measured in diastole in four-chamber view. Low flow was defined by a stroke volume <46 ml for women and <51 ml for men (23).

Follow-up and endpoints

During follow-up, events were collected based on hospital chart reviews, direct patient interviews and/or repeated follow-up letters, questionnaires, and telephone calls to physicians, patients, and (if necessary) family members. The primary endpoint was all-cause mortality and the secondary endpoint cardiovascular mortality, including sudden death, Heart failure related death and deaths attributable to other cardiovascular causes (such as myocardial infarction, stroke...). Decisions on medical or surgical management were made by each heart team based on European Society of Cardiology guidelines and patient comorbidities (10).

Statistical analysis

Baseline continuous variables are expressed as means \pm standard deviations and categorical variables as numbers and percentages. The differences between the three groups (moderate-to-severe TR, severe TR, and VSTR) based on baseline continuous variables were explored using the Student t test. The χ^2 or Fisher exact test were used to compare categorical variables between groups. The significance between the referent group (moderate-to-severe TR) and the other groups was examined when a significant difference between categories was observed. Individual differences were compared using Mann-Whitney U tests (with a Bonferroni correction for multiple comparisons) and Tukey tests for normally distributed data. The

presence of VSTR was assessed in each centre, prior to that study, by the physician's overall judgement of the regurgitation severity and consequences. After integration of all these parameters, the echocardiographer graded TR as severe or VSTR. Using ROC curve analysis, we compared the ability of the TCG and the EROA to diagnose VSTR as defined above. The correlation between EROA and TCG was tested by linear regression. Interobserver reproducibility for EROA and TCG measurements was evaluated using Pearson correlation coefficient and intraclass correlation coefficient (ICC) analysis using a randomly chosen subset of 20 patients with severe TR. Event rates \pm standard errors were estimated using the Kaplan-Meier method and compared by two-sided log-rank tests. Multivariable analyses for all-cause and cardiovascular mortality in the overall study population and in patients with a tricuspid coaptation gap \geq 10 mm, were performed using Cox proportional hazard models. Clinical and echocardiographic covariates considered to have a potential prognostic impact were tested in univariate analysis. All significant variables in univariate analysis with $p < 0.1$ were included in the multivariate cox analyses. The limit of statistical significance was $p < 0.05$ and all tests were two-tailed. Data were analyzed using SPSS 25.0 (SPSS Inc. Chicago, IL).

RESULTS

Comparison of the EROA and TCG to define VSTR

The study population consisted of 606 patients (234 males [38.6%]; mean age: 75 years). TR was graded, using a multiparametric approach, as moderate-to-severe for 212 patients (35%) and severe for 394 patients (65%). The area under the curve (AUC) to predict VSTR graded using a multiparametric approach was only 0.74 for EROA and 0.95 for TCG (*Supplemental Figure 1*). A TCG of 10 mm ($n=104$, 17%) was the best cutoff with a sensitivity of 83% and a specificity of 100% to predict VSTR whereas an EROA of 0.6 cm² ($n=215$, 35%) had a sensitivity of 75% and a specificity of 52% to predict VSTR. Interobserver reproducibility was quite good for the EROA measurement (ICC: 0.89[95%CI:0.73-0.95], $r=0.87$), but better for

TCG measurement (ICC: 0.95 [95% CI:0.85-0.98], $r=0.92$). The correlation between EROA and TCG was poor ($R^2=0.22$), especially when the size of the defect increased (*Figure 1*). Among patients with a TCG ≥ 10 mm ($n=104$, 17%), 73% ($n=76$) had an EROA ≥ 60 mm² and 27% ($n=28$) an EROA between 40 and 60 mm². Correlations between TCG and basal RV diameter and between TCG and tricuspid annular diameter were weak ($R^2=0.17$ and 0.19 respectively).

Baseline Clinical Characteristics according to TR grade

Baseline characteristics of the patients according to TR grade (moderate-to-severe or severe TR defined using a multiparametric approach, then reclassified as VSTR for a TCG ≥ 10 mm) are presented in *Table 1*. Patients with severe and VSTR had more RHF signs, a higher incidence of ascites, used higher doses of loop diuretics, and were more frequently in AF than patients with moderate-to-severe TR (all $p<0.05$) (*Table 1*). Patients with VSTR were more likely to have liver cirrhosis ($p<0.001$) than patients with moderate-to-severe TR (*Table 1*).

In terms of echocardiographic parameters, the area of the left and right atria, TR EROA, and tricuspid annulus diameter increased with TR severity, whereas the TR peak jet velocity decreased. Patients with severe and VSTR were more likely to have inferior vena cava and subhepatic vein dilatation and subhepatic vein flow reversal than patients with moderate-to-severe TR (*Table 1*).

Comparison of the EROA and TCG to predict outcome

In total, 172 (28.4%) deaths occurred during follow-up (median 24 [IQR:11-41] months, mean 28.5 ± 23 months), of which 100 were attributed to cardiovascular causes (58%). When using an EROA ≥ 60 mm² to define VSTR, estimated four-year survival rates were $70\pm 4\%$ for moderate-to-severe TR, $65\pm 5\%$ for severe TR, and $64\pm 5\%$ for VSTR (Log rank $p=0.289$), with no significant difference between patients with an EROA <60 mm² and those with an EROA ≥ 60 mm² ($68\pm 3\%$ vs. $64\pm 5\%$, respectively, Log rank $p=0.899$) (*Figure 2*). When a TCG ≥ 10 mm

was used to define VSTR, estimated four-year survival rates were 70±4% for moderate-to-severe TR, 68±4% for severe TR, and 53±7% for VSTR (Log rank p=0.022), with a significant difference between patients with a TCG <10 mm and those with a TCG ≥10 mm (69±3% vs. 53±7% respectively, Log rank p<0.001) (**Figure 3**).

By multivariate analysis, after adjustment for all variables associated with all-cause mortality on univariate analysis (p<0.1, **Table 2**), the EROA (as a continuous variable) was not associated with all-cause mortality (adjusted HR [95%CI]:1.00 [0.99-1.01], p=0.186 per mm² increase), whereas the TCG was (adjusted HR [95%CI]:1.04 [1.01-1.12], p=0.035 per mm increase). After adjustment to the same variables, a TCG ≥10 mm remained independently associated with all-cause mortality (adjusted HR [95%CI]:1.47 [1.13-2.21], p=0.019), whereas an EROA ≥60 mm² did not (adjusted HR [95%CI]:1.16 [0.81-1.64], p=0.416) (**Table 2, Figure 4**). The results were comparable for cardiovascular mortality (adjusted HR [95%CI]:1.07 [0.68-1.68], p=0.784 for EROA ≥60 mm² and adjusted HR [95%CI]:2.08 [1.33-3.25], p=0.001 for TCG ≥10 mm) after adjustment for the all variables associated with cardiovascular mortality on univariate analysis (**Table 2, Figure 5**).

Prognostic factors in VSTR

For patients with a TCG ≥10 mm, clinical factors associated with all-cause mortality in multivariate analysis were male sex (adjusted HR [95%CI]:2.45 [1.36-5.17], p=0.004), NYHA class III-IV (adjusted HR [95%CI]:2.37 [1.15-4.87], p=0.019), and a Charlson comorbidity index >2 (adjusted HR [95%CI]:1.85 [1.07-3.80], p=0.044), whereas those associated with cardiovascular mortality were male sex (adjusted HR [95%CI]:2.24 [1.08-4.68], p=0.030), NYHA class III-IV (adjusted HR [95%CI]:2.25 [1.03-4.88], p=0.042), and ascites (adjusted HR [95%CI]:2.21 [1.05-4.99], p=0.041) (**Table 2**).

For patients with a TCG ≥ 10 mm, only moderate or severe RV dilatation (adjusted HR [95% CI]: 2.61 (1.25-5.41); $p=0.010$) was associated with all-cause mortality in multivariate analysis. A LVEF between 50 and 60% (adjusted HR [95% CI]: 2.30 [1.09-4.84], $p=0.028$) and moderate or severe RV dilatation (adjusted HR [95% CI]: 3.61 [1.60-8.13], $p=0.002$) were independently associated with cardiovascular mortality (*Table 3*).

DISCUSSION

The prevalence of VSTR in patients with significant isolated functional TR was variable, ranging from 17 to 33% of patients, depending on the parameter used to define it. The correlation between EROA and TCG was poor and decreased with increasing TCG. Risk stratification was significantly improved using the TCG but not EROA. Indeed, after adjustment for established prognostic factors, a TCG ≥ 10 mm was associated with a >2.1 -fold increase in the relative risk of cardiovascular death, whereas an EROA ≥ 60 mm² was not associated with excess mortality. Therefore, a TCG ≥ 10 mm should be used to define VSTR in isolated functional TR.

The latest European guidelines mentioned that a new grading scheme that includes massive and torrential TR has been proposed by certain authors (10), but to date, there is no official recommendation on the interest of using this classification nor on the definition of "more-than-severe" TR (10). Definitions of massive TR and torrential TR using the EROA and vena contracta have been proposed in the context of transcatheter tricuspid valve repair or replacement (24). Indeed, in the first studies assessing the efficacy of transcatheter tricuspid valve therapies or compared these therapies with medical treatment, TR reduction was only moderate, often leaving patients with significant residual TR (9,25). In a population of patients with a baseline TR EROA of 0.85 ± 0.22 mm², the mean residual EROA 30 days after treatment was 0.63 ± 0.29 mm² (9). Thus, according to the current classification of the guidelines, these patients would not change in severity grade because they started from a grade of severe TR and

still had severe TR after treatment (10,19,20,21). However, a significant improvement was observed in terms of stroke volume and quality-of-life scores in these studies (9,25), highlighting the need to revise TR severity grading. Consequently, it has been proposed to add the massive and torrential grades to the TR classification grading scheme using empirical thresholds for vena contracta and the EROA. (11) However, although the current classification is undeniably useful for the assessment of the results of percutaneous treatment, the inclusion of two additional grades has not yet demonstrated its usefulness in the risk stratification of these patients. Indeed, no study has found a difference between massive and torrential forms in terms of outcome prediction (13-15). However, there is now growing evidence (13-15) that adding an additional grade allows risk stratification of all patients with TR (not only those undergoing percutaneous treatment).

Both the EROA and vena contracta present certain limitations. First, interobserver agreement is poor in mitral regurgitation (26,27) and these parameters are even more difficult to assess in TR because of the particular and variable geometry of this valve and the fact that it is often difficult to be perpendicular to the jet to accurately measure vena contracta. (16) It should be noted that although a number of reports have validated thresholds of EROA $>40 \text{ mm}^2$ (28) and EROA is a reliable parameter to identify severe versus non-severe TR with numerous robust data reported. (8,17,19,20,29). Nevertheless, it may not be well suited for the most severe cases of TR. Indeed, the use of EROA assessed by the PISA method relies on geometric hypotheses, which are true for primary mitral regurgitation but not necessarily for TR, in particular, very severe functional secondary TR. Indeed, most PISA assumptions are often not respected in secondary very severe TR, as there is temporal and respiratory variability in TR, the flow convergence zone is rarely hemispheric, and the surface is not flat, as tethering of the leaflets is often present. Therefore, the PISA method faces several limitations and could significantly underestimate the severity of TR by up to 30%. (30,31) With increasing coaptation defect, the

geometry of the orifice becomes less circular and therefore the PISA becomes less reliable. Accordingly, in our population, the relationship between the TCG and EROA was poor ($r^2=0.21$), especially for patients with a large TCG. Indeed, among patients with a TCG ≥ 10 mm, those with the lowest EROA (<40 mm²) had the largest TCG (mean 17.9 mm). Conversely, TCG measurements are relatively easy to perform when TCGs are present. We found a better reproducibility for the TCG measurement than for the EROA probably because the TCG requires only one measurement whereas the calculation of the EROA by the PISA technique requires several parameters (PISA radius, Vmax, VTI), which increases the risk of error and is more technically challenging to obtain. Thus, to summarize, the shape of the regurgitant orifice as well as the frequent not flat surface due to the tethering of the leaflets and the fact that the PISA method is less reliable due to greater variability are our main hypotheses to explain the superiority of TCG over PISA EROA in very severe TRs. Rapid developments in three-dimensional transthoracic echocardiography will soon allow routine measurement of anatomical EROA, which will certainly be more accurate because it will assess the true coaptation defect in all three dimensions but will require clinical validation. Pending the widespread adoption of these new techniques, the two-dimensional measurement in end-systole in the view where the TCG is the largest is simple and present good interobserver reproducibility ($r=0.93$, intraclass correlation coefficient=0.96 [0.86-0.99]). (14) We found that the two-dimensional measurement of TCG was better than the EROA for patient risk stratification, which was markedly improved for a TCG ≥ 10 mm but not an EROA ≥ 60 mm². Therefore, a TCG ≥ 10 mm should be used to define VSTR.

Limitations

Our study had several limitations. First, it was retrospective and suffered from the inherent limitations of this type of analysis. Echocardiograms were not analysed in a central corelab but at each institution separately. The definition of RV dysfunction was based on TAPSE and S'

measurements, despite the limitations of these parameters in the presence of severe TR. Nevertheless, although normal RV systolic function cannot be determined with certainty when the values are normal, the presence of a dysfunction is clear when these parameters are altered. While the extent of TCG is a reflect of the anatomic ERO, TCG might also reflect RV enlargement and/or dysfunction and tricuspid annular dilatation especially when RV dilatation contributes significantly to the severity of TR. However, in isolated functional (or atrial) TR, RV dilatation is not the cause of the disease but rather a late consequence of the regurgitation (32,33). Actually, TCG in our study remained independently associated with all-cause and cardiovascular mortality after adjustment for RV dilatation and dysfunction and the relationship between TCG and basal RV diameter and between TCG and tricuspid annular diameter were weak ($R^2=0.17$ and 0.19 respectively). We did not include the laminar character of the TR and the inversion of the hepatic vein flow in the definition of VSTR, contrary to our previous study (14) because we had some missing data for these parameters and we wanted to propose a simple definition. In patients with these parameters available (82% for the laminar character of the flow and 77% for the hepatic vein flow), they were always present in case of $TCG \geq 10\text{mm}$ (**Table 1**). We believe that these are both important criteria that should be investigated systematically for the quantification of TR. Unfortunately, data on aliasing velocity (V_a) were not collected in our database and we cannot multiply the calculated flow rate by $V_{\text{max}}/(V_{\text{max}} - V_a)$ to yield the correct regurgitant flow rate. (34) However, to avoid this underestimation, the ratio of the aliasing velocity to the tricuspid regurgitant jet velocity in our study was maintained, as recommended, $<10\%$ whenever feasible (92% of patients). (20) Measurement of the TCG may be challenging after percutaneous tricuspid valve edge-to-edge repair, but this is also true of the PISA and vena contracta methods, which have never been validated in these patients. Finally, our results are only valid for patients with isolated functional TR and may not be applicable to other TR etiologies. Indeed, we chose to study isolated TR to have a

homogeneous group and evaluate the true impact of the severity of TR on the prognosis, without interference from other valvular heart diseases, pulmonary hypertension, or left ventricular dysfunction, which could have affected the outcome and biased the results.

Conclusions

The correlation between the TCG and the EROA is weak and decreases with increasing defect size due to limitations inherent to the PISA technique. A TCG ≥ 10 mm is associated with a significant increase in all-cause and cardiovascular mortality and should be used to define VSTR in isolated functional TR.

Disclosure: none

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REFERENCES

1. Topilsky Y, Maltais S, Medina Inojosa J, Oguz D, Michelena H, Maalouf J, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging* (2019) 12:433–442. doi: 10.1016/j.jcmg.2018.06.014.
2. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol* (1999) 83:897-902. doi: 10.1016/s0002-9149(98)01064-9.
3. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* (2004) 43:405–409. doi: 10.1016/j.jacc.2003.09.036.
4. Bohbot Y, Chadha G, Delabre J, Landemaine T, Beyls C, Tribouilloy C. Characteristics and prognosis of patients with significant tricuspid regurgitation. *Arch Cardiovasc Dis* (2019) 112:604–614. doi: 10.1016/j.acvd.2019.06.011.
5. Sadeghpour A, Hassanzadeh M, Kyavar M, Bakhshandeh H, Naderi N, Ghadrdoost B, et al. Impact of severe tricuspid regurgitation on long term survival. *Res Cardiovasc Med* (2013) 2:121–126. doi: 10.5812/cardiovascmed.10686.
6. Prihadi EA, Delgado V, Leon MB, Enriquez-Sarano M, Topilsky Y, Bax JJ. Morphologic types of tricuspid regurgitation: characteristics and prognostic implications. *JACC Cardiovasc Imaging* (2019) 12:491–499. doi: 10.1016/j.jcmg.2018.09.027.
7. Enriquez-Sarano M, Messika-Zeitoun D, Topilsky Y, Tribouilloy C, Benfari G, Michelena H. Tricuspid regurgitation is a public health crisis. *Prog Cardiovasc Dis* (2019) 62:447–451. doi: 10.1016/j.pcad.2019.10.009.
8. Benfari G, Antoine C, Miller WL, Thapa P, Topilsky Y, Rossi A, et al. Excess mortality associated with functional tricuspid regurgitation complicating heart failure with

- reduced ejection fraction. *Circulation* (2019) 140:196–206. doi: 10.1161/CIRCULATIONAHA.118.038946.
9. Taramasso M, Benfari G, van der Bijl P, Alessandrini H, Attinger-Toller A, Biasco L, et al. Transcatheter Versus Medical Treatment of Patients With Symptomatic Severe Tricuspid Regurgitation. *J Am Coll Cardiol* (2019) 74:2998–3008. doi: 10.1016/j.jacc.2019.09.028
 10. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J et al; ESC/EACTS Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. (2022) 43:561-632. doi: 10.1093/eurheartj/ehab395.
 11. Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. *Eur Heart J Cardiovasc Imaging* (2017) 18:1342–1343. doi: 10.1093/ehjci/jex139.
 12. Santoro C, Marco Del Castillo A, González-Gómez A, Monteagudo JM, Hinojar R, Lorente A, et al. Mid-term outcome of severe tricuspid regurgitation: are there any differences according to mechanism and severity? *Eur Heart J Cardiovasc Imaging* (2019) 20:1035–1042. doi: 10.1093/ehjci/jez024.
 13. Kebed KY, Addetia K, Henry M, Yamat M, Weinert L, Besser SA, Mor-Avi V, et al. Refining Severe Tricuspid Regurgitation Definition by Echocardiography with a New Outcomes-Based "Massive" Grade. *J Am Soc Echocardiogr* (2020) 33:1087-1094. doi: 10.1016/j.echo.2020.05.007.
 14. Peugnet F, Bohbot Y, Chadha G, Delpierre Q, Kubala M, Delabre J, et al. Improvement of the Prognosis Assessment of Severe Tricuspid Regurgitation by the Use of a Five-Grade Classification of Severity. *Am J Cardiol* (2020) 132:119-125. doi: 10.1016/j.amjcard.2020.06.044

15. Fortuni F, Dietz MF, Prihadi EA, van der Bijl P, De Ferrari GM, Knuuti J, et al. Prognostic Implications of a Novel Algorithm to Grade Secondary Tricuspid Regurgitation. *JACC Cardiovasc Imaging* (2021) 14:1085-1095. doi: 10.1016/j.jcmg.2020.12.011.
16. Badano LP, Hahn R, Zanella H, Araiza Garaygordobil D, Ochoa- Jimenez RC, et al. Morphological Assessment of the Tricuspid Apparatus and Grading Regurgitation Severity in Patients With Functional Tricuspid Regurgitation: Thinking Outside the Box. *JACC Cardiovasc Imaging* (2019) 12:652-664. doi: 10.1016/j.jcmg.2018.09.029.
17. Topilsky Y, Nkomo VT, Vatury O, Michelena HI, Letourneau T, Suri RM, et al. Clinical outcome of isolated tricuspid regurgitation. *JACC Cardiovasc Imaging* (2014) 7:1185-94. doi: 10.1016/j.jcmg.2014.07.018.
18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* (1987) 40:373–383. doi: 10.1016/0021-9681(87)90171-8.
19. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al; Scientific Document Committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* (2013) 14:611–644. doi: 10.1093/ehjci/jet105.
20. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* (2017) 30:303–371. doi: 10.1016/j.echo.2017.01.007

21. Writing Committee Members, Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* (2021) 77:e25-e197. doi: 10.1016/j.jacc.2020.11.018.
22. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* (2015) 16:233–270. doi: 10.1093/ehjci/jev014.
23. Rusinaru D, Bohbot Y, Djelaili F, Delpierre Q, Altes A, Serbout S, et al. Normative Reference Values of Cardiac Output by Pulsed-Wave Doppler Echocardiography in Adults. *Am J Cardiol* (2021) 140:128-133. doi: 10.1016/j.amjcard.2020.10.046.
24. Lancellotti P, Pibarot P, Chambers J, La Canna G, Pepi M, Dulgheru R, et al; Scientific Document Committee of the European Association of Cardiovascular Imaging. Multi-modality imaging assessment of native valvular regurgitation: an EACVI and ESC council of valvular heart disease position paper. *Eur Heart J Cardiovasc Imaging* (2022) 23:e171-e232. doi: 10.1093/ehjci/jeab253.
25. Hahn RT, Meduri CU, Davidson CJ, Lim S, Nazif TM, Ricciardi MJ et al. Early feasibility study of a transcatheter tricuspid valve annuloplasty: SCOUT trial 30-day results. *J Am Coll Cardiol* (2017) 69:1795–1806. doi: 10.1016/j.jacc.2017.01.054.
26. Biner S, Rafique A, Rafii F, Tolstrup K, Noorani O, Shiota T, et al. Reproducibility of proximal isovelocity surface area, vena contracta, and regurgitant jet area for assessment of mitral regurgitation severity. *JACC Cardiovasc Imaging*. (2010) 3:235–43. doi: 10.1016/j.jcmg.2009.09.029.

27. Coisne A, Aghezzaf S, Edmé JL, Bernard A, Ma I, Bohbot Y, et al. Reproducibility of reading echocardiographic parameters to assess severity of mitral regurgitation. Insights from a French multicentre study. *Arch Cardiovasc Dis.* (2020) 113:599-606. doi: 10.1016/j.acvd.2020.02.004.
28. Tribouilloy CM, Enriquez-Sarano M, Bailey KR, Tajik AJ, Seward JB. Quantification of tricuspid regurgitation by measuring the width of the vena contracta with Doppler color flow imaging: a clinical study. *J Am Coll Cardiol* (2000) 36:472-478. doi: 10.1016/s0735-1097(00)00762-2.
29. Tribouilloy CM, Enriquez-Sarano M, Capps MA, Bailey KR, Tajik AJ. Contrasting effect of similar effective regurgitant orifice area in mitral and tricuspid regurgitation: a quantitative Doppler echocardiographic study. *J Am Soc Echocardiogr* (2002) 15:958-65. doi: 10.1067/mje.2002.117538.
30. Rivera JM, Vandervoort P, Mele D, Weyman A, Thomas JD. Value of proximal regurgitant jet size in tricuspid regurgitation. *Am Heart J* (1996) 131:742-7 doi: 10.1016/s0002-8703(96)90281-1.
31. Topilsky Y, Tribouilloy C, Michelena HI, Pislaru S, Mahoney DW, Enriquez-Sarano M. Pathophysiology of tricuspid regurgitation: quantitative Doppler echocardiographic assessment of respiratory dependence. *Circulation* (2010) 122:1505-13. doi: 10.1161/CIRCULATIONAHA.110.941310.
32. Florescu DR, Muraru D, Volpato V, Gavazzoni M, Caravita S, Tomaselli M, et al. Atrial Functional Tricuspid Regurgitation as a Distinct Pathophysiological and Clinical Entity: No Idiopathic Tricuspid Regurgitation Anymore. *J Clin Med.* (2022);11:382. doi: 10.3390/jcm11020382.
33. Naser JA, Pislaru C, Roslan A, Ciobanu AO, Jouni H, Nkomo VT, Kane GC, Pislaru SV. Unfavorable Tricuspid Annulus Dynamics: A Novel Concept to Explain

Development of Tricuspid Regurgitation in Atrial Fibrillation. *J Am Soc Echocardiogr.* (2022) 35:664-666. doi: 10.1016/j.echo.2022.02.009.

34. Rodriguez L, Anconina J, Flachskampf FA, Weyman AE, Levine RA, Thomas JD. Impact of finite orifice size on proximal flow convergence. Implications for Doppler quantification of valvular regurgitation. *Circ Res.* (1992) 70:923-30. doi: 10.1161/01.res.70.5.923.

FIGURE LEGENDS

Figure 1. Scatter plot representing the relationship between TR EROA and TCG. *EROA: effective regurgitant orifice area, TCG: tricuspid coaptation gap, TR: tricuspid regurgitation.*

Figure 2. Kaplan-Meier survival curves of patients with TR, with VSTR defined by an EROA ≥ 60 mm², in three groups (A) and in two groups (B).

EROA: effective regurgitant orifice area, TCG: tricuspid coaptation gap, TR: tricuspid regurgitation.

Figure 3. Kaplan-Meier survival curves of patients with TR, with VSTR defined by TCG ≥ 10 mm, in three groups (A) and in two groups (B).

TCG: tricuspid coaptation gap, TR: tricuspid regurgitation.

Figure 4. Cox-adjusted survival curves of patients with TR according to the definition of very severe TR using EROA (B) or TCG (B)

EROA: effective regurgitant orifice area, TCG: tricuspid coaptation gap, TR: tricuspid regurgitation.

Figure 5. Cox-adjusted curves of freedom from cardiac death for patients with TR according to the definition of very severe TR using EROA (B) or TCG (B)

EROA: effective regurgitant orifice area, TCG: tricuspid coaptation gap, TR: tricuspid regurgitation.

Table 1: Baseline characteristics according to TR severity with very severe TR defined using coaptation gap>10mm

| Characteristics | Moderate to severe TR (N=212) | Severe TR (N=290) | Very severe TR (N=104) | P-Value |
|---|-------------------------------|-------------------|------------------------|------------------|
| Clinical | | | | |
| Age, years | 75 ± 13 | 74 ± 13 | 75 ± 11 | 0.582 |
| Female gender (% , n) | 64.2 (134) | 60.3 (175) | 58.7 (61) | 0.564 |
| Body surface area, m ² | 1.77 ± 0.20 | 1.81 ± 0.21 | 1.83 ± 0.21 | 0.060 |
| Hypertension (% , n) | 68.4 (145) | 59.7 (173) | 65.4 (68) | 0.122 |
| Diabetes mellitus (% , n) | 21.7 (46) | 25.2 (73) | 21.2 (22) | 0.565 |
| Liver cirrhosis (% , n) | 2.4 (5) | 4.8 (14) | 12.5 (13) † | 0.001 |
| Charlson index | 3.1 ± 2.3 | 2.9 ± 2.1 | 3.2 ± 2.1 | 0.473 |
| NYHA functional class III-IV (% , n) | 38.7 (82) | 39.7 (115) | 40.4 (42) | 0.953 |
| Right-sided heart failure signs (% , n) | 46.2 (98) | 59.3 (172) † | 86.5 (90) † | <0.001 |
| Ascites (% , n) | 4.2 (9) | 8.6 (25) * | 14.4 (15) * | 0.007 |
| Loop diuretics (% , n) | 71.7 (152) | 82.1 (238) † | 87.5 (91) † | 0.001 |
| Daily dose of loop diuretics, mg | 165 ± 231 | 164 ± 221 | 190 ± 231 | 0.623 |
| Atrial fibrillation (% , n) | 75.9 (161) | 81.4 (236) * | 91.3 (95) * | 0.004 |
| Biological | | | | |
| Hemoglobin, g/dl | 12.1 ± 2.1 | 12.2 ± 2.0 | 11.8 ± 2.0 | 0.311 |
| Serum creatinine (µmol/l) | 111 ± 73 | 118 ± 95 | 116 ± 68 | 0.690 |
| Echocardiographic | | | | |
| LV ejection fraction, % | 60 ± 7 | 59 ± 7 | 59 ± 7 | 0.169 |
| LV stroke volume (ml) | 66 ± 21 | 62 ± 21 | 63 ± 23 | 0.153 |
| Left atrial area (cm ²) | 27 ± 10 | 29 ± 10 * | 31 ± 10 * | 0.004 |
| Right atrial area (cm ²) | 28 ± 10 | 34 ± 11 † | 42 ± 13 † | <0.001 |
| TR ERO (mm ²) | 28 ± 6 | 63 ± 26 † | 111 ± 60 † | <0.001 |
| Laminar TR (% , n) | 0 (0) | 31.4 (90) † | 100 (104) † | <0.001 |
| Moderate/severe RV dilatation (% , n) | 59.9 (127) | 79.3 (230) † | 84.6 (88) † | <0.001 |
| TAPSE, mm | 19 ± 4 | 18 ± 5 | 19 ± 6 | 0.508 |
| Peak systolic annular velocity S', cm/s | 10.9 ± 2.7 | 10.9 ± 3.2 | 10.8 ± 3.3 | 0.967 |
| RV FAC (%) | 41 ± 11 | 41 ± 11 | 40 ± 9 | 0.572 |
| RV free wall strain (%)** | -21 ± 7 | -20 ± 7 | -22 ± 5 | 0.173 |
| Tricuspid annulus diameter (mm) | 42 ± 6 | 46 ± 6 † | 51 ± 7 † | <0.001 |
| TR peak jet velocity (m/s) | 2.9 ± 0.5 | 2.7 ± 0.6 † | 2.2 ± 0.6 † | <0.001 |
| Dilated inferior vena cava (% , n) | 59.0 (125) | 79.0 (229) † | 95.2 (99) † | <0.001 |
| Dilated subhepatic veins (% , n) | 25.5 (54) | 54.1 (157) † | 100 (104) † | <0.001 |
| Subhepatic vein flow reversal (% , n) | 20.3 (43) | 46.2 (134) † | 100 (104) † | <0.001 |

Continuous variables are expressed as mean ±1 standard deviation and categorical variables are expressed as percentages and numbers.

*: $p < 0.05$ versus moderate-to-severe TR

†: $p < 0.001$ versus moderate-to-severe TR

** available for 317/606 patients

Abbreviations: ERO: effective regurgitant orifice; FAC: fractional area change; LV: left ventricular; NYHA= New York Heart Association; RHF = right heart failure; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation;

Table 2: Clinical factors associated with all cause and cardiovascular mortality in patients with a tricuspid coaptation gap ≥ 10 mm

| Variable | All-cause mortality | | | | Cardiovascular mortality | | | |
|--|--------------------------------------|------------------|--|--------------|--------------------------------------|--------------|--|--------------|
| | Univariable analysis HR (CI[95%]) | P-Value | Multivariable analysis HR (CI[95%]) | P-Value | Univariable analysis HR (CI[95%]) | P-Value | Multivariable analysis HR (CI[95%]) | P-Value |
| Age>75 years | 1.55 (1.12-2.99) | 0.041 | 1.47 (0.81-2.84) | 0.202 | 1.42 (0.69-2.91) | 0.341 | - | - |
| Male sex | 2.08 (1.10-3.93) | 0.010 | 2.45 (1.36-5.17) | 0.004 | 1.81 (0.90-3.64) | 0.095 | 2.24 (1.08-4.68) | 0.030 |
| NYHA (3-4 vs 1-2) | 2.64 (1.34-5.23) | 0.005 | 2.37 (1.15-4.87) | 0.019 | 2.54 (1.20-5.36) | 0.014 | 2.25 (1.03-4.88) | 0.042 |
| Right heart failure | 1.45 (0.56-3.76) | 0.440 | - | - | 1.21 (0.46-3.18) | 0.706 | - | - |
| Ascites | 1.89 (1.17-4.00) | 0.034 | 1.70 (0.75-3.89) | 0.204 | 2.48 (1.14-5.39) | 0.022 | 2.21 (1.05-4.99) | 0.041 |
| Charlson comorbidity index>2 (without age) | 2.01 (1.16-4.04) | 0.039 | 1.85 (1.07-3.80) | 0.044 | 1.51 (0.73-3.14) | 0.269 | - | - |
| Atrial fibrillation | 1.45 (0.49-4.30) | 0.501 | - | - | 1.18 (0.39-3.59) | 0.763 | - | - |
| Diuretics dose ≥ 125 mg/day | 2.25 (1.19-4.25) | <0.001 | 1.33 (0.62-2.71) | 0.479 | 2.37 (1.17-4.79) | 0.016 | 1.56 (0.71-3.38) | 0.263 |

Abbreviations: NYHA= New York Heart Association

Table 3: Echocardiographic factors associated with all cause and cardiovascular mortality in patients with a tricuspid coaptation gap ≥ 10 mm

| Variable | All-cause mortality | | | | Cardiovascular mortality | | | |
|--------------------------------|--------------------------------------|--------------|--|---------|--------------------------------------|--------------|--|--------------|
| | Univariable analysis HR (CI[95%]) | P-Value | Multivariable analysis HR (CI[95%]) | P-Value | Univariable analysis HR (CI[95%]) | P-Value | Multivariable analysis HR (CI[95%]) | P-Value |
| LVEF 50-60% | 1.73 (0.92-3.27) | 0.089 | 1.71 (0.90-3.26) | 0.103 | 1.92 (0.95-3.68) | 0.070 | 2.30 (1.09-4.84) | 0.028 |
| Low flow | 1.33 (0.70-2.51) | 0.387 | - | - | 1.34 (0.66-2.72) | 0.410 | - | - |
| LA area > 30 cm ² | 1.39 (0.73-2.63) | 0.317 | - | - | 1.17 (0.58-2.37) | 0.664 | - | - |
| RA area >30 cm ² | 1.55 (0.81-2.97) | 0.186 | - | - | 1.70 (0.84-3.47) | 0.142 | - | - |
| TR ERO> 60 mm ² | 0.62 (0.32-1.19) | 0.151 | - | - | 0.56 (0.28-1.14) | 0.110 | - | - |
| Moderate/severe RV dilatation | 2.46 (1.19-5.08) | 0.015 | 1.07 (0.56-2.04) | 0.812 | 2.88 (1.39-6.27) | 0.008 | 3.61 (1.60-8.13) | 0.002 |
| Moderate/severe RV dysfunction | 1.19 (0.63-2.23) | 0.597 | - | - | 1.41 (0.70-2.83) | 0.338 | - | - |

Abbreviations: ERO: effective regurgitant orifice; LA: left atrial; LVEF: left ventricular ejection fraction; RA: right atrial, RV: right ventricular; TR: tricuspid regurgitatio

Figure 1.

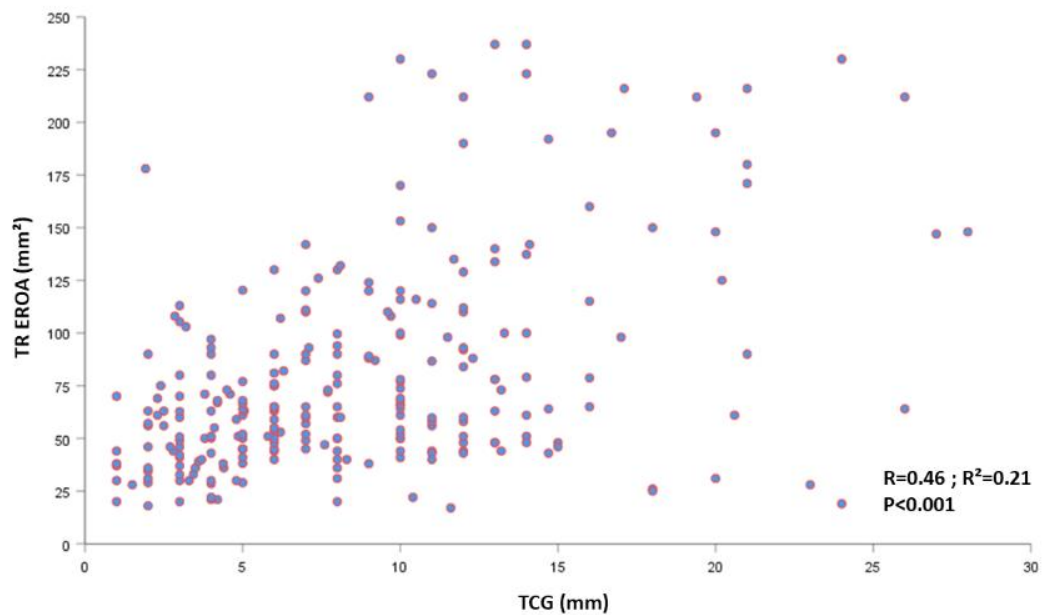


Figure 2.

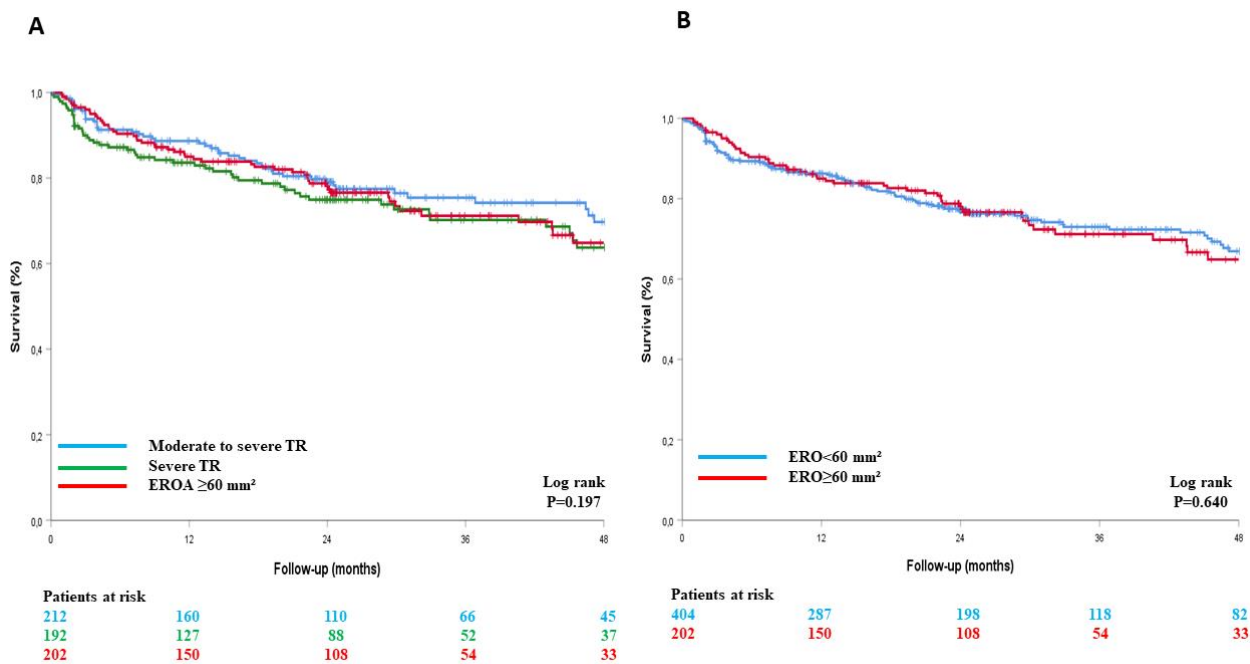


Figure 3.

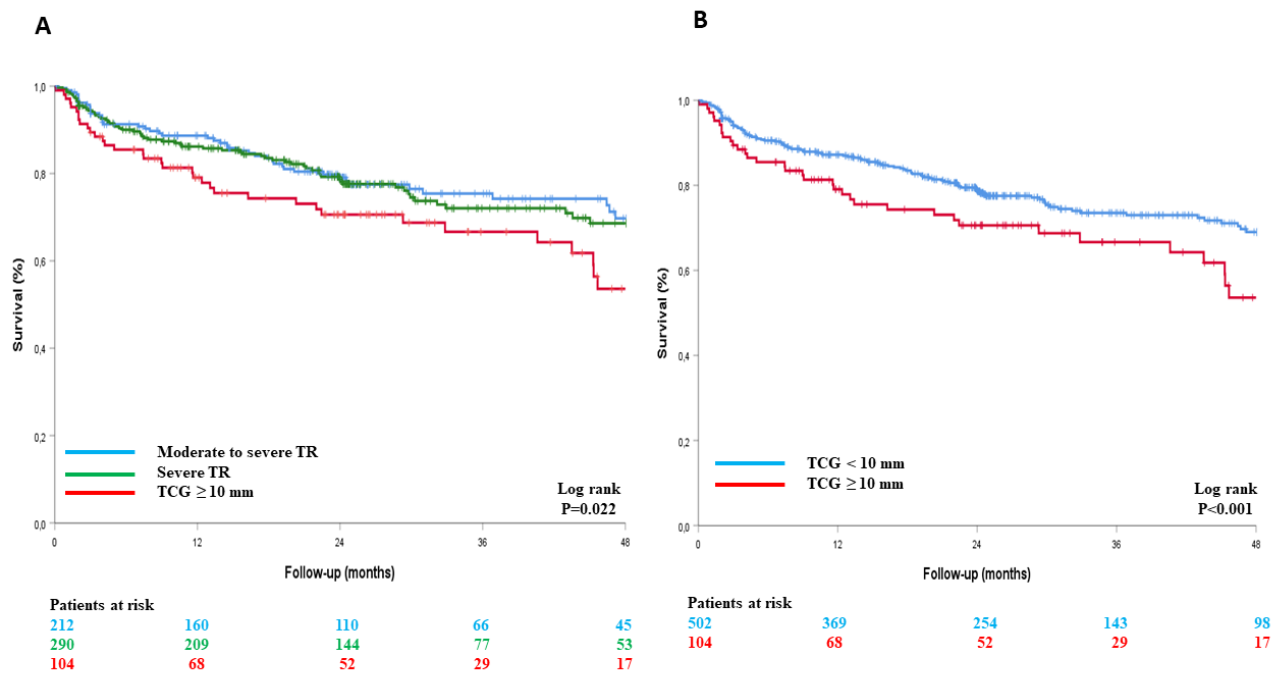


Figure 4.

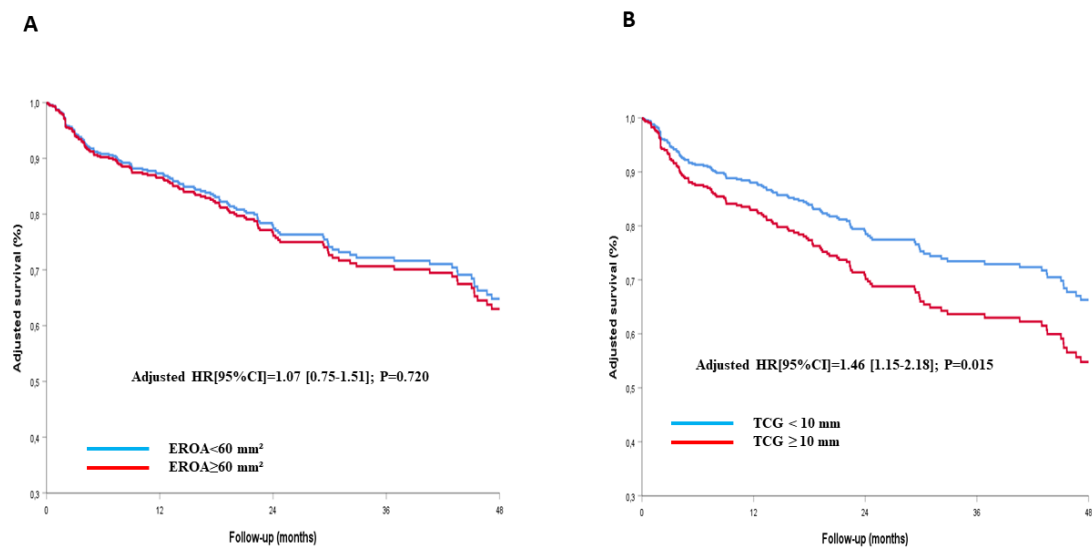
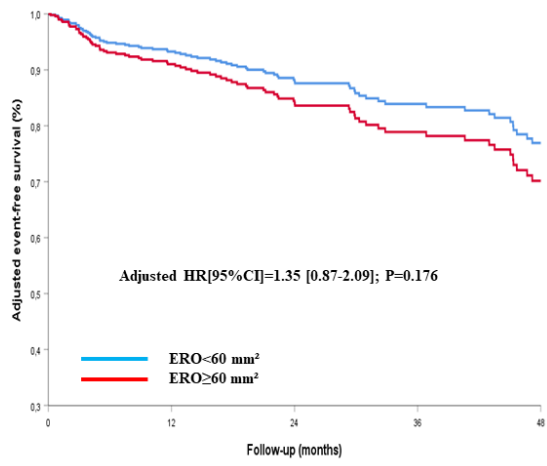
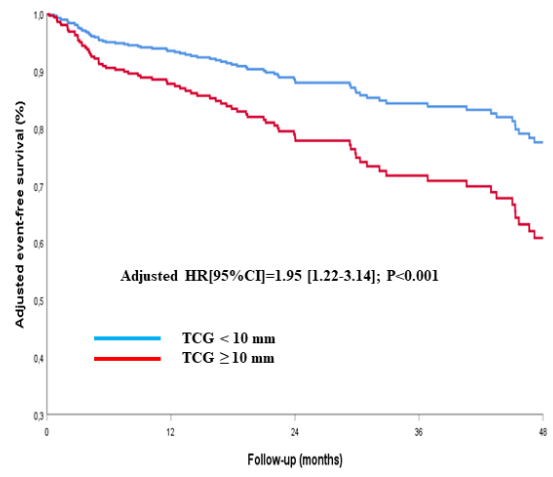


Figure 5.

A



B



Article 13

Repetitive Use of Levosimendan in Severe Functional Tricuspid Regurgitation

Lim P, Sharifi J, Huguet R, **Dreyfus J**, Gallet R, Aouate D

Article soumis

Title: Repetitive Use of Levosimendan in Severe Functional Tricuspid Regurgitation

Short title: Levosimendan in Functional Tricuspid Regurgitation

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Classifications: Research letter

WC=785 without legend and references

1 figure and 4 references

Functional tricuspid regurgitation (FTR) has a very poor outcome and few patients are referred for surgery due to the important peri-operative mortality which averages 15% (1). Edge-to-edge percutaneous repair has been proposed as an alternative to cardiac surgery and preliminary results showed improvement in patient's functional status and outcome. However, the feasibility is limited in patients with advanced FTR disease, i.e. in case of a large gap of leaflet coaptation (2). Levosimendan is a calcium sensitizer agent which enhances cardiac contractility and has a strong vasodilatation effect. Levosimendan seems particularly efficient in improving right ventricular (RV) function. The benefit of repetitive use of levosimendan in chronic heart failure (HF) has been demonstrated (3) but no study has been conducted in patients with severe FTR. In this preliminary clinical study, we reported the clinical and echocardiography impacts of repetitive use of levosimendan in HF patients with severe FTR.

We prospectively included 33 consecutive patients (77±7 years, 48.5% of women) admitted for HF with severe FTR (73% graded as massive or torrential, mean EROA=100±56m²). All patients signed informed consent. Most of the patients were in NYHA class III-IV (91%) with a median dose of furosemide at 250 mg daily [95; 500]. The majority were in chronic atrial fibrillation (92%), 51.5% had history of cardiac surgery and 42.4% had a pacemaker or defibrillator lead. Surgery was denied by the Heart Team because of the operative risk (mean Triscore=25±17%) and percutaneous approach was first excluded because of inappropriate anatomy or imaging. Levosimendan was delivered without bolus by intravenous perfusion (0.2 γ/kg/min over 24 hours) and repeated at least one time after 2 or 3 weeks. The severity of TR was graded according to effective regurgitation orifice area (EROA) using the PISA (Proximal Isovelocity Surface Area) method (3) by transthoracic echocardiography. Tricuspid annulus diameter, tricuspid leaflet tenting and coaptation, RV and right atrial (RA) dimensions were quantified from 4-chamber view and inferior vena cava (IVC) diameter was assessed in subcostal view. RV function was assessed using TAPSE (tricuspid annular plane systolic excursion).

Levosimendan infusion was repeated 3 times [median, range, 2 to 4 times] with no serious events reported. After levosimendan infusion, most patients were functionally improved with NYHA in class I-II in 64% (n=21/33). There was a decrease in NT-pro-BNP levels (2960 pg/mL [1473-5023 vs. 1874 pg/ml [800-2872], p=0.03) and total bilirubin (19±13 μM/L vs. 12±6 μM/L, p=0.003). Maximum improvement in EROA (104±56mm² vs. 53±26mm², p<0.001), TAPSE (14.9±4.7mm vs. 17.4±4.4mm, p=0.005) and IVC size (29±6mm vs. 26±6mm, p=0.006) were obtained after the first infusion, while changes in coaptation gap, tricuspid annulus diameter and RA (38±13 cm² vs. 34±12cm², p=0.001) were

maximal at the last infusion (Figure). During the follow-up [4 months, 1 to 17] after the last infusion, edge-to-edge repair became feasible in 6 patients because of improvement in coaptation gap (from $7.33\pm 6.2\text{mm}$ to $2.1\pm 3.5\text{mm}$) and 3 patients were referred for tricuspid valve replacement (n=2 percutaneous and one surgical valve replacements). All patients were functionally improved (in NYHA I-II class) but the severity of FTR remained graded as severe in 2 patient following the edge to edge repair and 2 patients died, one by stroke the day after edge to edge intervention and one by septicemia 8 months after percutaneous valve replacement. In patients without tricuspid intervention (n=24), 10 (41.7%) died after a median period of 15.7 months following the last levosimendan infusion (5 from septicemia and 5 from heart failure). The remaining patients (n=14) were all in NYHA class I or II and the majority had mild to moderate FTR (n=8/14).

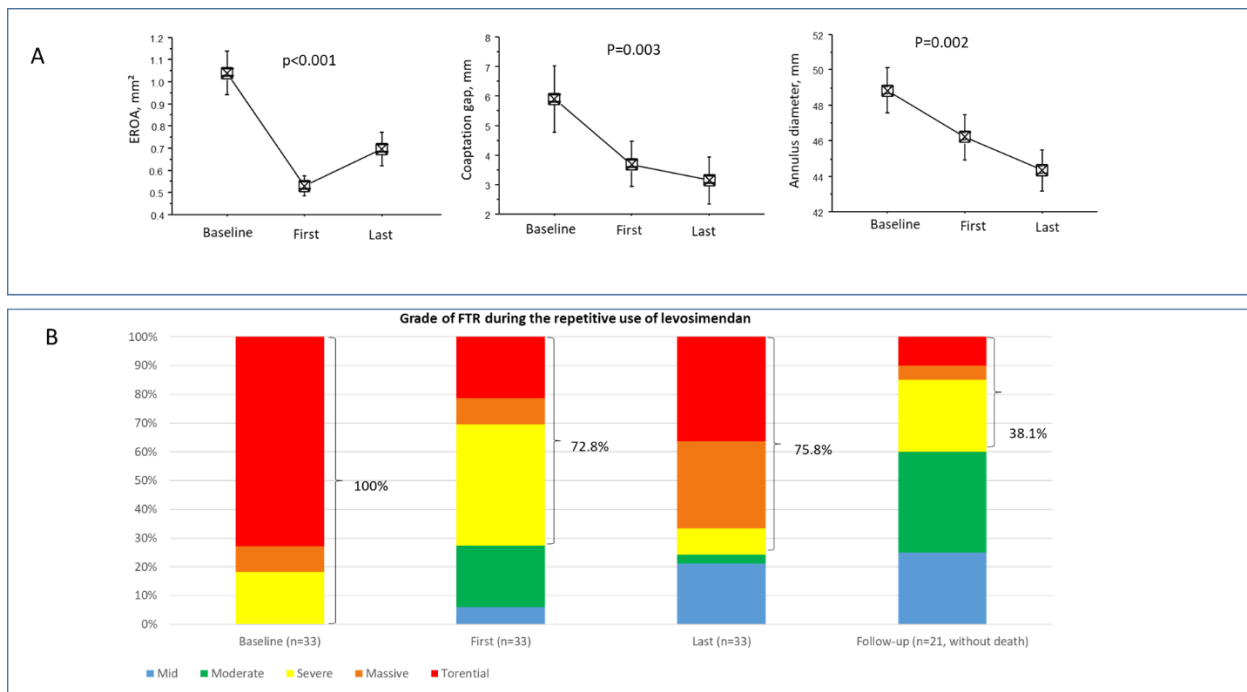
This is the first study reporting the impact of repeated use of levosimendan in severe FTR. Main results showed that levosimendan temporally improves patient's symptoms, decreases FTR severity and may improve the feasibility of percutaneous edge to edge repair. The main advantage of the levosimendan is its long-acting half-life allowing a prolonged inotrope and vasodilator effects over 2 weeks. The efficacy and safety of the repetitive use in chronic heart failure patients were assessed in 3 randomized study that showed a reduction in heart failure hospitalizations and a decrease of the natriuretic peptide concentrations (4). These results are in agreement with the clinical and biological improvement observed in the present study. However, the mortality remained high (41.7%, n=10/24). Functional and anatomical changes induced by levosimendan may not be sustained and should be viewed as a bridge to device therapy. In the present study, edge to edge repair became feasible for 6 patients due to a reduction of the coaptation gap and FTR severity.

This is the first pivotal study reporting the effect of levosimendan in the feasibility of edge-to-edge percutaneous tricuspid repair. The benefit of this strategy needs to be confirmed in a larger sample size study.

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Conflict of Interest statement covering: all authors have no conflict of interest to declare

Figure 1: Panel A: Changes in EROA (effective regurgitation orifice area), in coaptation gap and in annulus diameter during the first and the last levosimendan infusion. Panel B showed the distribution of Functional Tricuspid Regurgitation (FTR) severity at baseline, during and after levosimendan infusion.



References:

1- TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. Dreyfus J, Audureau E, Bohbot Y, Coisne A, Lavie-Badie Y, Bouchery M, Flagiello M, Bazire B, Eggenpieler F, Viau F, Riant E, Mbaki Y, Eyharts D, Senage T, Modine T, Nicol M, Doguet F, Nguyen V, Le Tourneau T, Tribouilloy C, Donal E, Tomasi J, Habib G, Selton-Suty C, Raffoul R, Lung B, Obadia JF, Messika-Zeitoun D. Eur Heart J. 2022 Feb.

2- Transcatheter edge-to-edge repair for reduction of tricuspid regurgitation: 6-month outcomes of the TRILUMINATE single-arm study. Nickenig G, Weber M, Lurz P, von Bardeleben RS, Sitges M, Sorajja P, Hausleiter J, Denti P, Trochu JN, Näbauer M, Dahou A, Hahn RT. Lancet. 2019.

3- 2021 ESC/EACTS Guidelines for the management of valvular heart disease.

Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Gilard M, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, Wojakowski W; ESC/EACTS Scientific Document Group. Eur Heart J. 2022

3- Repeated or intermittent levosimendan treatment in advanced heart failure: An updated meta-analysis. Silvetti S, Nieminen MS. Int J Cardiol. 2016.

Editorial 2

Tricuspid regurgitation: Light at the end of the tunnel?

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SCIENTIFIC EDITORIAL

Tricuspid regurgitation: Light at the end of the tunnel?

Insuffisance tricuspide : la lumière au bout du tunnel ?

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Transcatheter;
Outcome

MOTS CLÉS

Insuffisance tricuspide ;
TRI-SCORE ;
Chirurgie ;
Percutané ;
Pronostic

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; EACTS, European Association of Cardio-Thoracic Surgery; ESC, European Society of Cardiology; ITVS, Isolated Tricuspid Valve Surgery; LV, Left Ventricular; RV, Right Ventricle/Ventricular; TR, Tricuspid Regurgitation; TTVI, Transcatheter Tricuspid Valve Intervention; TV, Tricuspid Valve.

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Overlooked for decades, tricuspid regurgitation (TR) has attracted much attention recently. TR is a public health problem; moderate/severe TR is common, especially in ageing populations, and affects 4% of the population aged > 75 years [1], totalling approximately 1.6 million in the USA and 3 million in Europe. The literature is consistent, showing that TR is a serious condition, associated with morbidity (reduction in exercise capacity, heart failure) and mortality that increase with TR severity [2,3].

Current American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC)/European Association of Cardio-Thoracic Surgery

| A | | | B | | |
|--|--------------------|--------------------|---|-----|------|
| Recommendations | Class ^a | Level ^b | Recommendations | COR | LOE |
| Surgery is recommended in symptomatic patients with isolated severe primary tricuspid regurgitation without severe RV dysfunction. | I | C | In patients with signs and symptoms of right-sided HF and severe primary TR (stage D), isolated tricuspid valve surgery can be beneficial to reduce symptoms and recurrent hospitalizations. ¹¹⁻¹⁴ | 2a | B-NR |
| Surgery should be considered in asymptomatic or mildly symptomatic patients with isolated severe primary tricuspid regurgitation and RV dilation who are appropriate for surgery. | IIa | C | In patients with signs and symptoms of right-sided HF and severe isolated secondary TR attributable to annular dilation (in the absence of pulmonary hypertension or left-sided disease) who are poorly responsive to medical therapy (stage D), isolated tricuspid valve surgery can be beneficial to reduce symptoms and recurrent hospitalizations. ^{11, 12, 15-19} | 2a | B-NR |
| Recommendations on secondary tricuspid regurgitation | | | In asymptomatic patients with severe primary TR (stage C) and progressive RV dilation or systolic dysfunction, isolated tricuspid valve surgery may be considered. ^{11, 20} | 2b | C-LD |
| Surgery should be considered in patients with severe secondary tricuspid regurgitation (with or without previous left-sided surgery) who are symptomatic or have RV dilation, in the absence of severe RV or LV dysfunction and severe pulmonary vascular disease/hypertension. ^{418, 433e} | IIa | B | In patients with signs and symptoms of right-sided HF and severe TR (stage D) who have undergone previous left-sided valve surgery, reoperation with isolated tricuspid valve surgery may be considered in the absence of severe pulmonary hypertension or severe RV systolic dysfunction. ^{1, 2, 11, 18} | 2b | B-NR |
| Transcatheter treatment of symptomatic secondary severe tricuspid regurgitation may be considered in inoperable patients at a Heart Valve Center with expertise in the treatment of tricuspid valve disease. ^f | IIb | C | | | |

Figure 1. A. Management of tricuspid regurgitation according to 2021 European Society of Cardiology/European Association of Cardio-Thoracic Surgery guidelines. B. Management of tricuspid regurgitation according to 2020 American College of Cardiology/American Heart Association guidelines. Reproduced from Vahanian et al. [5] and Otto et al. [4]. COR: class of recommendation; HF: heart failure; LD: limited data; LOE: level of evidence; LV: left ventricular; NR: non-randomized; RV: right ventricular.

(EACTS) guidelines recommend performing isolated tricuspid valve surgery (ITVS) in patients with severe secondary (and primary) TR (with or without previous left-sided surgery), who are symptomatic or have right ventricle (RV) dilatation, in the absence of severe right ventricular (RV) or left ventricular (LV) dysfunction and severe pulmonary vascular hypertension (Fig. 1) [4,5].

Contrasting with TR prevalence and the magnitude of the problem, the majority of patients are treated medically with diuretics to relieve their symptoms, and a curative surgical treatment for isolated severe TR is seldom performed (approximately 120 patients/year in France) [6,7]. ITVS represents only 8% of all tricuspid valve (TV) surgeries, and a TV intervention is mostly performed at the same time as left-sided heart valve surgery. Thus, only 10% of patients admitted in France with a diagnosis of significant TR are referred for an intervention [8].

Reluctance to perform an ITVS can be explained on the one hand, by the limited evidence that TR correction improves outcomes and the falsely benign reputation of TR, and on the other hand, by the high (in-hospital) mortality of ITVS observed in most series ($\approx 10\%$, remarkably consistent across the literature) [6,7,9]. There was therefore a critical need to better assess the determinants of outcome after TV interventions. For this purpose, we built a large French multicentre registry, gathering all consecutive patients who

underwent a non-congenital ITVS on the native valve for severe TR in 12 tertiary centres during a 11-year period (2007–2017), representing $>40\%$ of all ITVS procedures at the national level. Among these 466 patients, in-hospital mortality was 10%, as in other series, but this average rate hid important disparities. Mortality rate was indeed markedly variable, and was predicted by the severity of the preoperative clinical, biological and echocardiographic presentation, whereas the TR mechanism/aetiology had limited impact [9]. However, our findings were of limited use to predict immediate and mid-term results of ITVS at the individual level, and a risk score model that could support clinical decisions for cardiologists and cardiac surgeons was cruelly lacking. It is worth noting that in contrast to aortic or mitral valve surgeries, there is no dedicated Society of Thoracic Surgeons (STS) risk score model for ITVS, and the logistic EuroSCORE [10] and EuroSCORE II [11] were not designed for ITVS.

TRI-SCORE [12] is a dedicated, simple and accurate risk score model for ITVS that could guide the clinical decision-making process. TRI-SCORE is based on eight clinical (age ≥ 70 years, New York Heart Association functional class III–IV, right-sided heart failure signs, daily dose of furosemide ≥ 125 mg), laboratory (glomerular filtration rate < 30 mL/min, elevated total bilirubin) and echocardiographic (LV ejection fraction $< 60\%$, moderate/severe RV

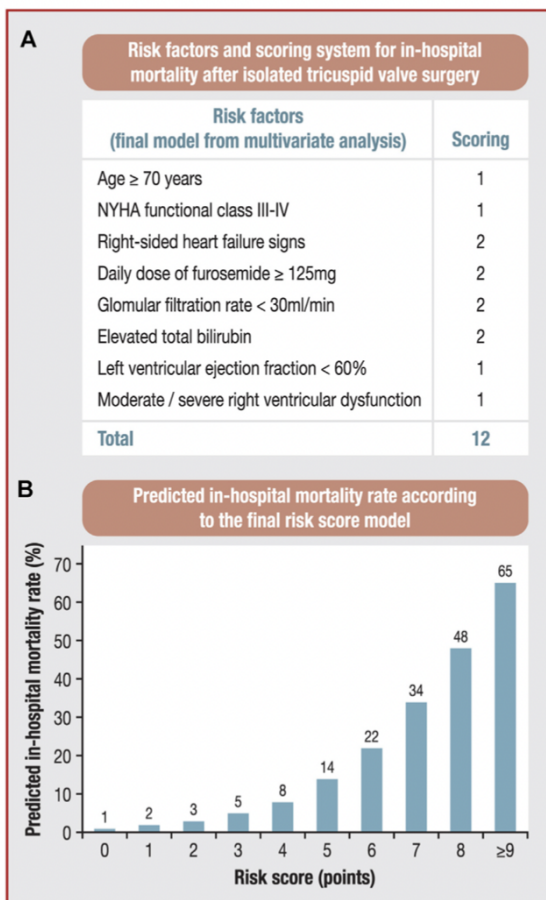


Figure 2. Risk score model to predict in-hospital mortality after isolated tricuspid valve surgery. A. Risk factors and scoring system. B. Predicted in-hospital mortality rate according to the final risk score model. Reproduced from Dreyfus et al. [12]. NYHA: New York Heart Association.

dysfunction) variables, which are easy to ascertain, and capture the impact of TR on the RV, liver and kidneys (Fig. 2). This risk score model, on a 0–12-point scale, provided both excellent discrimination (C-index $>$ 0.75) and calibration, with a predicted mortality rate ranging from 1% for 0 points to 65% for \geq 9 points, irrespective of TR mechanism/aetiology. Patients with functional/secondary TR presented with a higher in-hospital mortality rate than those with organic/primary TR, but the difference was the result of a worse clinical presentation (higher score), whereas aetiology/mechanism was not an independent determinant of outcome after adjustment for clinical presentation. Half of patients were referred for an intervention late in the course of the disease, with moderately elevated (4–6) or severely elevated ($>$ 6) scores, and therefore high mortality rates. In contrast, low in-hospital and 1-year mortality rates (0–4%) were achieved in patients with a low score (\leq 3).

Our results suggest adopting a more proactive approach to TV interventions, and to intervene earlier in the course of the disease in patients with severe isolated TR, irrespective of TR mechanism/aetiology, before the occurrence of advanced/irreversible consequences, such as severe RV dilatation/dysfunction, renal and liver failure and intractable heart failure. In this regard, the ACC/AHA recommendation to wait for signs and symptoms of right heart failure and poor response to medical therapy – i.e. diuretics – may lead to a TV intervention being performed in patients at end-disease stage, with possibly limited benefit for outcome. Patients with severe TR should be monitored closely, and intervention considered when the diuretic dose needs to be increased or in case of progressive RV enlargement. It is also critical to mention that the approach should be individualized, and availability of transcatheter tricuspid valve interventions (TTVIs), as a less-invasive alternative to surgery, may push for an extension to the number of patients treated. TTVIs are still at an early stage, with a large number of percutaneous TV devices currently under development. TTVIs are mostly a repair (especially edge-to-edge repair), with promising initial results in the first real-world registries with patients at high surgical risk [13]. Nevertheless, unlike mitral valves, many patients are not eligible for a TV repair strategy, and transcatheter TV replacement could be a better alternative for these patients. There are several important differences between the right side and the left side of the heart favouring TV replacement. First, the TV anatomy is highly variable. Second, there is no risk of out-flow tract obstruction on the right side. Third, paravalvular risk is less of a concern (i.e. no haemolysis). Fourth, durability of biological valves is expected to be longer on the right side.

Ongoing randomized controlled trials (TRILUMINATE Pivotal Trial, TRI-FR [14], CLASP II TR, TRISCEND II Pivotal Trial) aim to evaluate the benefits of transcatheter treatments over medical therapy, and will provide more evidence regarding the most appropriate timing and type of intervention to improve the outcome of patients with severe TR (Table 1). The latest ESC/EACTS guidelines – but not the ACC/AHA guidelines – suggest performance of a transcatheter intervention for symptomatic secondary severe TR in inoperable patients at a Heart Valve Centre with expertise in the treatment of TV disease (class IIbC) (Fig. 1) [5]. Importantly, TRI-SCORE will also provide a unique tool to characterize and compare populations enrolled in these trials, evaluating the benefit of TR correction. It is worth noting that even patients at low risk, as assessed using the TRI-SCORE, experienced a significant postoperative rate of major complications (15% for patients with TRI-SCORE = 0), although TRI-SCORE was not designed to predict complication rates. Whether transcatheter therapies could achieve lower complication rates (and at least similar procedural success) should also be carefully assessed.

TRI-SCORE will guide clinical decisions at the bedside level, and we do hope lead to earlier and wider surgical or transcatheter interventions in patients with severe TR before the occurrence of severe/irreversible consequences that markedly affect prognosis. A TRI-SCORE calculator is accessible online (<http://www.tri-score.com/>).

Table 1 All prospective multicentre randomized controlled trials for transcatheter treatment of tricuspid regurgitation.

| Trials | Inclusion criteria | Intervention arm (versus best medical treatment) | Primary outcome | Follow-up duration (months) | Countries | Estimated participants | Study start date |
|---------------------|---|---|--|-----------------------------|---------------------|------------------------|------------------|
| TRILUMINATE Pivotal | Severe symptomatic TR; high risk of TV surgery (heart team) | Percutaneous repair with Abbott TriClip device | Composite endpoint: all-cause mortality, TV surgery, HF hospitalizations and QOL (KCCQ) | 12 | USA; Canada; Europe | 700 | August 2019 |
| TRI-FR | Severe symptomatic secondary TR; high risk of TV surgery (heart team) | Percutaneous repair with Abbott TriClip device | Milton Packer clinical composite score | 12 | France; Belgium | 300 | February 2021 |
| CLASP II TR | Severe symptomatic TR; high risk of TV surgery (heart team) | Percutaneous repair with Edwards PASCAL device | Composite endpoint: all-cause mortality, RVAD implantation or heart transplant, TV surgery, HF hospitalizations and QOL (KCCQ) | 60 | USA; Canada | 825 | December 2019 |
| TRISCEND II Pivotal | Severe symptomatic TR; high risk of TV surgery (heart team) | Percutaneous replacement with Edwards EVOQUE device | TR grade reduction; major adverse events; composite endpoint (all-cause mortality, RVAD implantation or heart transplant, TV surgery, HF hospitalizations, KCCQ, NYHA functional class and 6-minute walk distance) | 12 | USA; Germany | 775 | April 2021 |

HF: heart failure; KCCQ: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; QOL: quality of life; RVAD: right ventricular assist device; TR: tricuspid regurgitation; TV: tricuspid valve.

Sources of funding

None.

Disclosure of interest

J. D. declares that he has no competing interest.

J.-F. O. Consultant fees from the companies Abbott, Carmat, Delacroix-Chevalier, Landanger, Medtronic and Sorin, outside the submitted work.

D. M.-Z. Unrestricted research grant from the company Edwards, outside the submitted work.

References

- [1] Topilsky Y, Maltais S, Medina Inojosa J, Oguz D, Michelena H, Maalouf J, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging* 2019;12:433–42.
- [2] Messika-Zeitoun D, Verta P, Gregson J, Pocock SJ, Boero I, Feldman TE, et al. Impact of tricuspid regurgitation on survival in patients with heart failure: a large electronic health record patient-level database analysis. *Eur J Heart Fail* 2020;22:1803–13.
- [3] Wang N, Fulcher J, Abey Suriya N, McGrady M, Wilcox I, Celermajer D, et al. Tricuspid regurgitation is associated with increased mortality independent of pulmonary pressures and right heart failure: a systematic review and meta-analysis. *Eur Heart J* 2018;40:476–84.
- [4] Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin 3rd JP, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;143:e72–227.
- [5] Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management

- of valvular heart disease. *Eur Heart J* 2022;43:561–632, <http://dx.doi.org/10.1093/eurheartj/ehab395>.
- [6] Dreyfus J, Ghalem N, Garbarz E, Cimadevilla C, Nataf P, Vahanian A, et al. Timing of referral of patients with severe isolated tricuspid valve regurgitation to surgeons (from a French Nationwide Database). *Am J Cardiol* 2018;122:323–6.
- [7] Zack CJ, Fender EA, Chandrashekar P, Reddy YNV, Bennett CE, Stulak JM, et al. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol* 2017;70:2953–60.
- [8] Messika-Zeitoun D, Candolfi P, Dreyfus J, Burwash IG, lung B, Philippon JF, et al. Management and outcome of patients admitted with tricuspid regurgitation in France. *Can J Cardiol* 2020;37:1078–85, <http://dx.doi.org/10.1016/j.cjca.2020.12.012> [Epub 2020 Dec 25].
- [9] Dreyfus J, Flagiello M, Bazire B, Eggensteiner F, Viau F, Riant E, et al. Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes. *Eur Heart J* 2020;41:4304–17.
- [10] Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;16:9–13.
- [11] Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. *Eur J Cardiothorac Surg* 2012;41:734–44 [discussion 44–5].
- [12] Dreyfus J, Audureau E, Bohbot Y, Coisne A, Lavie-Badie Y, Bouchery M, et al. TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. *Eur Heart J* 2022;43:654–62, <http://dx.doi.org/10.1093/eurheartj/ehab679>.
- [13] Taramasso M, Benfari G, van der Bijl P, Alessandrini H, Attinger-Toller A, Biasco L, et al. Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation. *J Am Coll Cardiol* 2019;74:2998–3008.
- [14] Donal E, Leurent G, Ganivet A, Lurz P, Coisne A, De Groot P, et al. Multicentric randomized evaluation of a tricuspid valve percutaneous repair system (clip for the tricuspid valve) in the treatment of severe secondary tricuspid regurgitation Tri.Fr Design paper. *Eur Heart J Cardiovasc Imaging* 2021;Dec 6:jeab255, <http://dx.doi.org/10.1093/ehjci/jeab255>.

Article 14

Multicentric randomized evaluation of a tricuspid valve percutaneous repair system (clip for the tricuspid valve) in the treatment of severe secondary tricuspid regurgitation.

Tri.Fr Design paper

Donal E, Leurent G, Ganivet A, Lurz P, Coisne A, De Groote P, Lafitte S, Leroux L, Karam N, Biere L, Rouleau F, Sportouch C, **Dreyfus J**, Nejjari M, Josselin JM, Anselmi A, Galli E, Bajoux E, Guerin P, Obadia JF, Trochu JN, Oger E

Eur Heart J Cardiovasc Imaging. 2022 Nov 17;23(12):1617-1627

Multicentric randomized evaluation of a tricuspid valve percutaneous repair system (clip for the tricuspid valve) in the treatment of severe secondary tricuspid regurgitation

Tri.Fr Design paper

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Aims

Tricuspid regurgitation (TR) is associated with significant morbidity and mortality. Its independent prognostic role has been repeatedly demonstrated. However, this valvular heart condition is largely undertreated because of the increased risk of surgical repair. Recently, transcatheter techniques for the treatment of TR have emerged, but their implications for the clinical endpoints are still unknown.

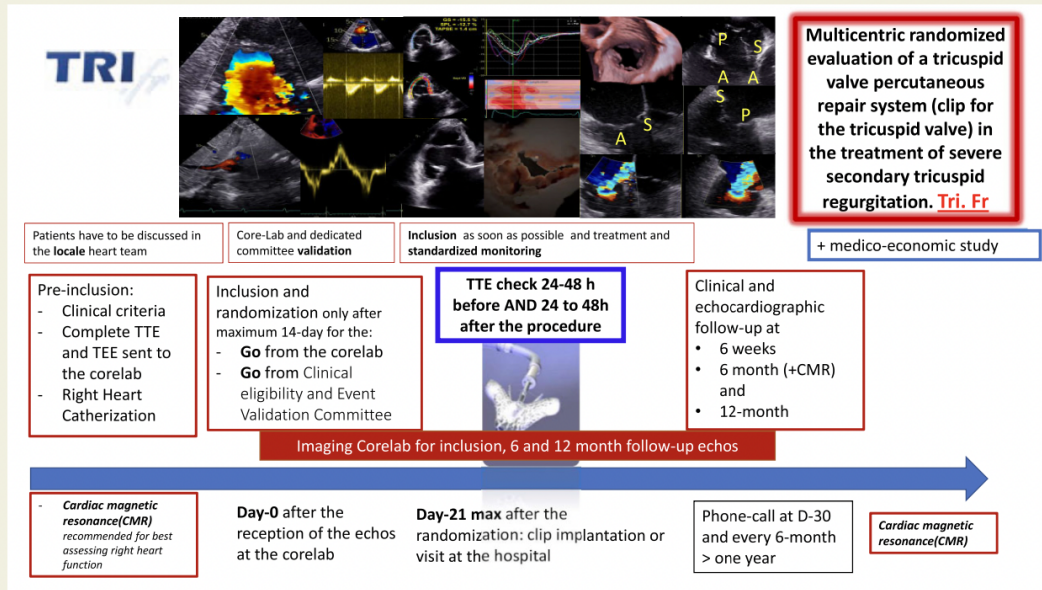
Methods and results

The Tri.fr trial will be a multicentre, controlled, randomized (1:1 ratio), superior, open-label, and parallel-group study conducted in 300 patients with severe secondary TR that is considered non-surgical by heart teams. Inclusion will be possible only after core laboratory review of transthoracic and transoesophageal echocardiography and after validation by the clinical eligibility committee. A description of the mechanisms of the TR will be conducted by the core laboratory. Atrial or ventricular impacts on the severity of the secondary TR will be taken into account for the randomization. The patients will be followed for 12-month, and the primary outcome will be the Packer composite clinical endpoint [combining New York Heart Association class, patient global assessment (PGA), and major cardiovascular events]. It will test the hypothesis that a tricuspid valve percutaneous repair strategy using a clip dedicated to the tricuspid valve is superior to best guideline-directed medical therapy in symptomatic patients with severe secondary TR.

Conclusion

Tri.fr will be the first randomized, academic, multicentre study testing the value of percutaneous correction in patients with severe secondary TR.

Graphical Abstract



Keywords

tricuspid regurgitation • heart failure • transoesophageal echocardiography • prognosis

Introduction

Tricuspid regurgitation (TR) is a long-neglected valvular pathology. Its prevalence is significant and is increasing with the ageing of the population.^{1,2} It is often a consequence of chronic left cardiac pathologies or atrial fibrillation.³ Secondary TR is load-dependent, and recent research has shed light on its pathophysiology and the quantification of regurgitation as well as on its right heart consequences. TR is mainly secondary (complicating left heart disease, pulmonary hypertension, atrial fibrillation, and atrial dilatation) and has a poor prognosis.⁴ The risk of death or hospitalization has been reported to be high.^{5,6} In-hospital mortality of patients undergoing TV repair or replacement is substantial with reported rates between 8% and 24%.^{7,8} Older age (≥ 60 years) and TV replacement instead of repair can further double the risk for in-hospital death.⁸

Medical management is suboptimal. Benfari *et al.*⁷ recently reported a 5-year survival of 34% and a 10-year survival of only 14% for patients with severe FTR and HF with reduced ejection fraction (HFrEF). Surgical correction is recommended in severe symptomatic TR or when the tricuspid annulus is dilated and the TR is identified prior to the scheduled left heart valve surgery,^{9,10} but patients are rarely referred to any surgical technique.¹¹ The literature on the outcomes of secondary TR treated by surgery (repair or replacement) is discouraging.¹² There is excessive morbidity and mortality related to

many factors, including comorbidities and the too delayed indication for repair.^{11,13} Patients with severe TR often represent a high-risk surgical population, which relies at least partly on late referral and advanced heart failure (HF) after left-sided heart surgery. Importantly, the excess mortality in TR seems to be independent of pulmonary hypertension and other concomitant clinical parameters, as recent studies suggest.^{7,14}

This justifies dedicated studies and the evaluation of alternative therapies for correcting TR with low interventional risk.¹⁵ A clip specifically designed for the tricuspid valve (Triclip, Abbott Structural, Santa Clara, CA, USA) has been evaluated in observational studies. The TRILUMINATE trial included 85 patients with moderate-to-severe symptomatic TR. The pre-implantation, implantation, and 6-month follow-up data were collected and justified further evaluation.¹⁶ The Triclip (Abbott Structural, Santa Clara, CA, USA) system appears to be safe and effective at reducing TR by at least one grade and has recently received the European Conformity (CE) mark.

Patients with secondary TR are heart failure (HF) patients. They are often hospitalized and complain of HF symptoms. In several trials, clinical composite scores have been more sensitive than conventional approaches in discerning the presence or absence of a true treatment effect.^{17,18} Therefore, a clinical composite score, which combines changes in the New York Heart Association (NYHA) class and the global assessment together with the information provided from the

occurrence of major clinical events, appears clinically meaningful. The use of these scores could correctly distinguish active therapy from placebo, and Packer^{17,18} provided convincing demonstrations that could avoid some misleading conclusions.

In the Tri.fr trial, we seek to demonstrate, over a period of 12 months after randomization, that, on the Packer composite clinical endpoint (CCS) [combining NYHA class, patient global assessment (PGA), and major cardiovascular events], the tricuspid valve percutaneous repair strategy is superior to best (optimized) medical treatment (BMT) in symptomatic patients with severe secondary TR.

Methods

Tri.fr will be a multicentre, controlled, randomized (1:1 ratio), superior, open-label, and parallel-group study. It is an academic study, sponsored by the French Ministry for solidarity and Health (PHRC). It tests, in 300 patients considered nonsurgical by the local heart team, the beneficial effect of an intervention (a clip on the tricuspid valve) in addition to optimized medical management. This is an academic sponsored study (French Ministry for Health) with the support of Abbott Structural (Santa Clara, CA, USA), which is supplying the devices.

The flow chart of the trial is displayed in *Figure 1*.

Patients will be recruited for the study if symptomatic with a diagnosis of secondary severe TR [Carpentier Type IIIB (restrictive) and/or I (tricuspid annulus dilation)] under medical management and stable for at least 30 days.

Inclusion and exclusion criteria are provided in detail in *Tables 1 and 2*. Patients with left ventricular (LV) dysfunction (LVEF \leq 35%) will be excluded. End-stage renal failure (except if long-standing dialysis is already being performed), severe hepatic insufficiency [disruption of liver metabolism associated with coagulation disorders (factor V $<$ 50%)], stroke or acute coronary syndrome in the previous 3-months, uncontrolled

precapillary pulmonary hypertension (right catheterization required) (systolic pulmonary pressure $>$ 60 mmHg), any other treatment like pace-maker, Mitraclip should have been implanted at least 3-month before any inclusion in Tri.fr. Patients have to be clinically stable. Inclusion in TRI.fr cannot be applied in an emergency setting.

Factors that affect the capacity for guiding the clips implantation are part of the exclusion criteria. For instance, it is the case for mechanical prosthesis in the left heart.

The goal is to test on TR management; the *clinical eligibility committee* (independent committee with every week meetings) has to be extremely consistent in ensuring that patients' prognosis is driven by the TR and no other cardiac or extra-cardiac condition. The TR severity, the quality of the echocardiographic assessment, and the feasibility of the clipping have to be validated before any randomization (*independent echocardiographic core lab*, CIC-IT 1414, Iso9001, Rennes, France).

Patients will be completely informed and will be required to sign the informed consent form. This study will be conducted following the 'Good Clinical Practice' guidelines of the Declaration of Helsinki and was approved by the National Ethical Committees of every participating centre (35RC18_8851_TRI.FR). This study is registered at clinicaltrials.gov (identifier NCT 04646811).

An electronic case report form (e-CRF) will be made available, and the data entry will be completed at the centres through a WEB interface (Clinsight software, Ennov, Paris 75, France).

- Before any inclusion, standardized transthoracic (TTE) and transoesophageal (TEE) will have to be performed and validated by the core laboratory (CIC-IT, CHU Rennes) to confirm the grade of the TR and the suitability of the anatomy for clip implantation (*Figures 2 and 3*).
- Afterwards, the eligibility committee will validate the clinical relevance of the inclusion based on the clinical, pharmacological, and biological predefined parameters. This will be based on the data collected in the e-CRF and on an interview of the local investigator by the committee members (web-conference organized every Wednesday evening).

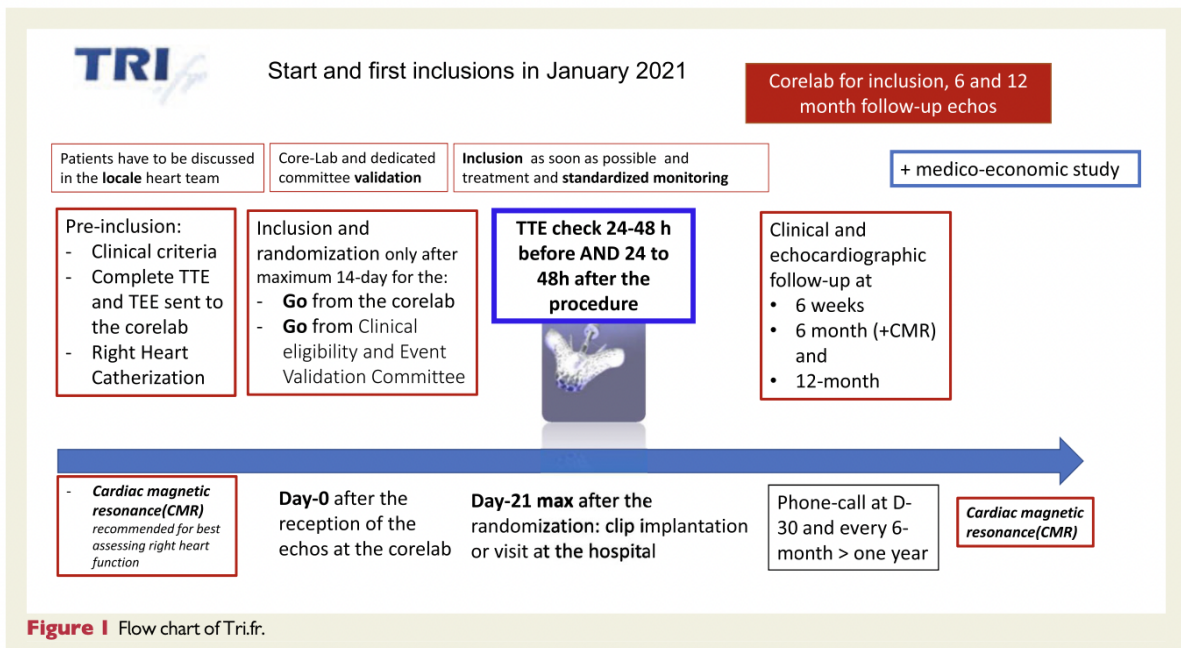


Table 1 The inclusion criteria

- Symptomatic secondary (at least) severe TR [Carpentier Type IIIB (restrictive) and/or I (tricuspid annulus dilation)] stable for at least 30 days
- TR characterized before implantation by at least one of the following criteria (Figure 2):
 - Regurgitation volume greater than 45 mL/beat
 - Surface of the regurgitant orifice greater than 40 mm²
 - Vena contracta > 7 mm
 - Gap between leaflets ≤ 7 mm
- NYHA functional Class II–IV without cirrhosis and/or ascites
- Signs of heart failure in the previous 12 months with or without hospitalization
- Stable optimized medical and/or interventional treatment for at least 30 days (validated by the eligibility committee meeting every week).
- Ineligible for corrective action on the valve by a surgical approach after a specialized multidisciplinary consultation ('heart team') including at least a cardio-thoracic surgeon, an interventional cardiologist, an imaging-cardiologist and an anaesthesiologist.
- Signature on the informed consent form.

Table 2 Exclusion criteria

- Patients treated with Mitraclip or other percutaneous approaches to the mitral valve in the past 3 months
- Any prior tricuspid valve procedure that would interfere with placement of the Triclip (Abbott Structural, Santa Clara, CA, USA) device
- Tricuspid valve leaflet anatomy may preclude clip implantation, proper clip positioning on the leaflets or sufficient reduction in TR. These may include:
 - Tricuspid valve anatomy not evaluable by TTE and TEE
 - Active endocarditis
 - Evidence of calcification in the grasping area
 - Evidence of stenosis (mean pressure gradient > 5 mmHg or surface area ≤1 cm²)
 - Presence of a severe coaptation defect (>10 mm) of the tricuspid leaflets
 - Severe leaflet defect(s) preventing proper device placement
 - Epstein anomaly—identified by having a normal annulus position while the valve leaflets are attached to the walls and septum of the right ventricle
- Myocardial infarction or coronary bypass surgery in the past 3 months
- Left ventricular ejection fraction ≤35%
- Cardiac resynchronization therapy for less than 3 months and patients having a TR that is clearly related to the right ventricular lead positioning
- Cardioversion for less than 6 weeks
- Life expectancy irrespective of valvular heart disease <1 year (due to comorbidities)
- Other scheduled cardiac surgery (including registration with a cardiac transplant list)
- Coronary angioplasty in the preceding month
- Current infection requiring a prescription of antibiotics
- End-stage renal failure (except if long-standing dialysis is already being performed)
- Severe hepatic insufficiency [disruption of liver metabolism associated with coagulation disorders (factor V < 50%)]
- Stroke in the previous 3-month
- Uncontrolled pre-capillary pulmonary hypertension (right catheterization required) (systolic pulmonary pressure > 60 mmHg)
- Mechanical prosthetic valve in the left heart
- Pacemaker lead or ICD lead that would prevent appropriate placement of the Triclip (Abbott Structural, Santa Clara, CA, USA)
- Nitinol allergy
- Contraindication, allergy or hypersensitivity to dual antiplatelet and anticoagulant therapy
- Ongoing infection requiring antibiotic therapy
- Evidence of intra-vascular or intra-cardiac thrombus
- Patients who are included in another research protocol
- Protected person [adults legally protected (under judicial protection, guardianship or supervision), person deprived of their liberty, pregnant woman, lactating woman, minors]
- Absence of coverage by a social security system

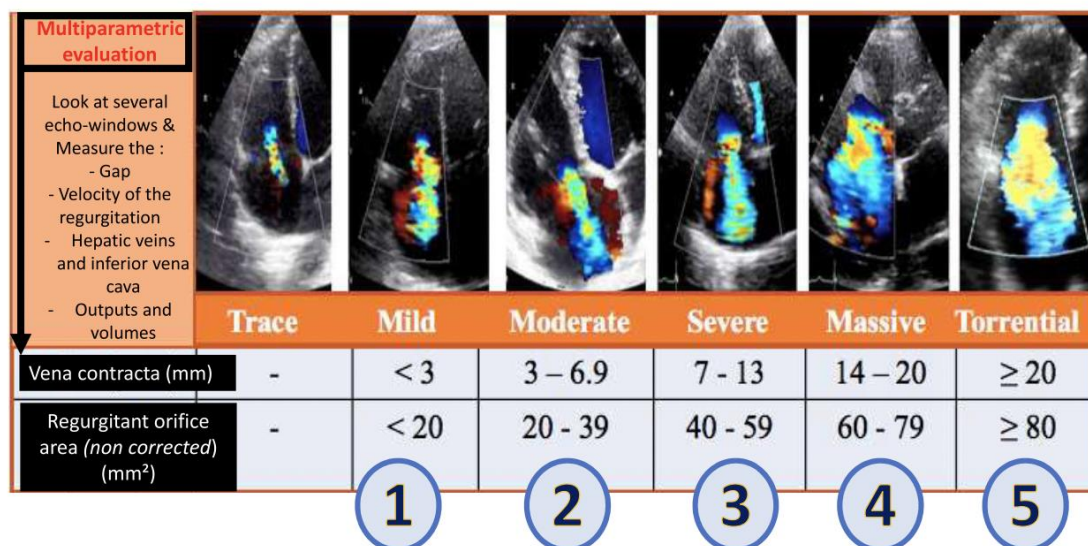


Figure 2 Quantification of tricuspid regurgitation in five grades.

The eligibility committee will be particularly attentive about accepting patients where the TR is supposed to be the main driver of symptoms and prognosis. Additionally, people with a life expectancy ≤ 12 months were excluded.

The *primary objective* is to determine, over a period of 12 months after randomization, that, on the Packer composite clinical endpoint (CCS) [combining NYHA class, patient global assessment (PGA), and major cardiovascular events (all-cause mortality, cardiovascular mortality, tricuspid valve surgery, heart failure hospitalizations, cardiovascular and non-cardiovascular hospitalizations)], whether a tricuspid valve percutaneous repair strategy with a clip for the tricuspid valve is superior to best (optimized) medical treatment (BMT) in symptomatic patients with severe secondary TR. The Packer clinical composite score is a three-level ordered categorical endpoint, with each randomized patient being classified as improved, unchanged, or worse, depending on the clinical response over the follow-up period and at the endpoint of 12 months.¹⁸

This endpoint has been used previously. Basically, the primary endpoint of the study is a HF clinical composite response. Using this endpoint, we classify patients into one of three response groups at 12 months after randomization: worsened, unchanged, or improved. Patients are judged to be worsened if they die, are hospitalized (at any time during the 12 months) because of or associated with worsening HF, demonstrate worsening in NYHA functional class at their 12-month visit, or reported moderately or markedly worse heart failure symptoms compared to before randomization (Patient Global Assessment) when asked at the 12-month follow-up. Patients are judged to be improved if they have not worsened and have demonstrated improvement in NYHA functional class at 12 months and/or report moderately or markedly improved heart failure symptoms at the 12-month follow-up. Patients who are not worsened or improved are classified as unchanged. Hospitalizations contributed to the endpoint if the independent Adverse Event Advisory/Endpoint Committee verify their relatedness to HF. Because asymptomatic patients (NYHA functional Class I) were included in the study and

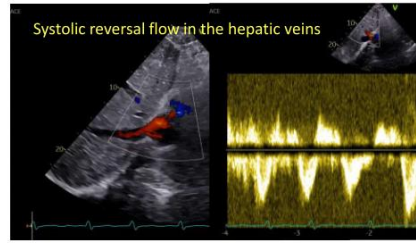
their NYHA status cannot improve, the percent of patients worsened is used to compare the efficacy of the clip between study groups.

The *secondary objectives* are:

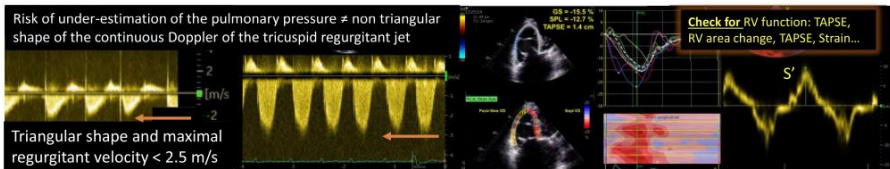
- (1) To determine, over a period of 12 months after randomization, whether individual parameters included in the composite endpoint [all-cause mortality, cardiovascular mortality, tricuspid valve surgery, heart failure hospitalizations, cardiovascular and non-cardiovascular hospitalizations, NYHA and quality of life (QoL), walking distance] were improved by a tricuspid valve percutaneous repair strategy vs. best (optimized) medical treatment (BMT) in symptomatic patients with at least severe secondary TR.
- (2) To determine, at 6 and 12 months, whether a significant improvement in the 'interventional group' occurred for
 - The severity of the TR (the quantification of TR will be made in a centralized core laboratory according to five grades); (Figure 2, Table 3)^{19,20}
 - The echocardiographic parameters (right ventricular function, right heart size, haemodynamic parameters such as cardiac output);
 - The cardiac magnetic resonance imaging parameters (right ventricular function, volumes); a dedicated sub-analysis of the cardiac magnetic resonance images on the right heart are planned for chamber quantification, chamber functions, and quantification of the regurgitation.
 - The biological parameters (liver and renal functions, natriuretic peptides).
- (3) To test the safety profile of the clip for the tricuspid valve repair procedure (including occurrence of tricuspid stenosis, clip 'detachment, vascular complications...')
- (4) To test the impact of the mechanism of TR (atrial dilatation versus tethering) on the response to treatment.

A

- TTE:
 ⇒ check the collapsibility of the vena cava and the hepatic vein flow (reversal)
 ⇒ Check for parasternal and apical views for anatomy, size of the gap between leaflets
 ⇒ Quantification is requiring bi-plan acquisition of 2 orthogonal views with an aliasing velocity around 30cm/s



B



C

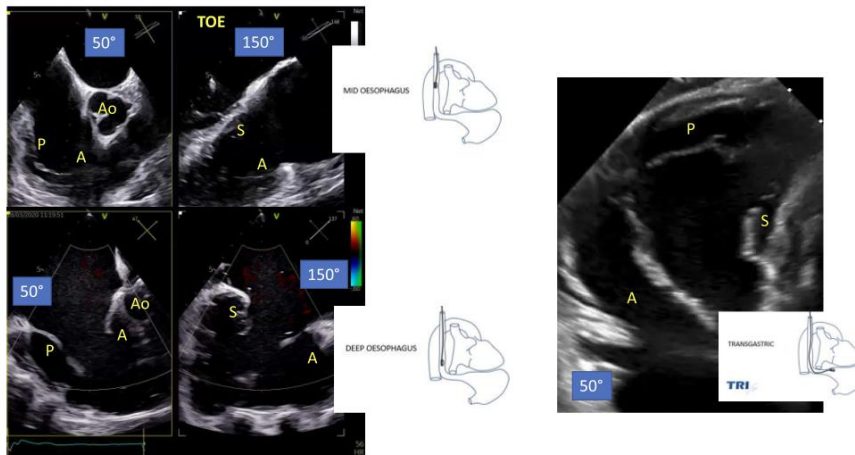


Figure 3 Key images (mandatory) that imagers will have to record when screening and following patients for Tri.fr. A, anterior; P, posterior; S, septal; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Table 3 Summary of the main outcome measures in Triluminate pivotal trial and in Tri.fr

| |
|--|
| <p>Primary outcome measurements:</p> <ol style="list-style-type: none"> 1. <i>Triluminate pivotal trial</i> (ClinicalTrials.gov Identifier: NCT03904147) Hierarchical composite of number of participants with all-cause mortality or number of participants with tricuspid valve surgery, rate of heart failure hospitalizations, and assessment of quality-of-life improvement using the KCCQ (Time Frame: 12 months) 2. <i>Tri.fr</i> (ClinicalTrials.gov Identifier: NCT04646811) Milton Packer clinical composite score (Time Frame: 12 months) Milton Packer clinical composite score classifies each patient into 1 of 3 categories (improved, worsened, unchanged), and is determined aggregating evaluation functional using NYHA class, quality of life score using patient global assessment and number of major cardiovascular events <p>Four main secondary outcome measurements for <i>Triluminate Pivotal Trial</i>:</p> <ol style="list-style-type: none"> 1. Change in TR from severe to moderate or less (Time Frame: 30 days) 2. Freedom from major adverse events (MAE) occurring after procedure attempt (Time Frame: 30 days) 3. Change in quality of life as assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) Score (Time Frame: 12 months) KCCQ score ranges from 0 to 100, with 100 representing the least burden of symptoms 4. Change in 6 minute walk test (6MWT) (Time Frame: 12 months) <p>For <i>Tri.fr</i></p> <ol style="list-style-type: none"> 1. Number of participants with all-cause mortality (Time Frame: 12 months) 2. Number of participants with tricuspid valve surgery (Time Frame: 12 months) 3. Rate of heart failure hospitalizations (Time Frame: 12 months) 4. Assessment of quality of life improvement (Time Frame: 0 and 12 months) <p>Nb: Kansas City Cardiomyopathy Questionnaire score (KCCQ) The responses are categorized under 3 subscales (symptom burden, physical limitation and quality of life) with a range of possible subscale scores from 0 to 100, with 100 representing the least burden of symptoms. The total KCCQ score represents the mean of the three subscale scores</p> |
|--|

- (5) To conduct a medico-economic evaluation (cost-utility study) comparing the two strategies ('Clip for the tricuspid valve' group vs. 'BMT') on the dual dimension of efficiency and costs at 12 months for the last 150 patients included up to 24 months and the first 150 ones included, with data collected from the French National Healthcare Insurance.

Participants will be randomly assigned through an automated web-based system in a 1:1 ratio:

- to undergo either implantation of a clip for the tricuspid valve in addition to best medical therapy,
- or best medical therapy (BMT) alone.

A permuted block randomization scheme will be used with stratification according to the clinical site and TR aetiology (three classes: torrential regurgitation, severe regurgitation with a predominantly dilated right atria, or severe regurgitation with a predominantly dilated right ventricle).

Crossover from the assigned treatment is prohibited before the 12-month assessment. Table 3 is providing a comparison of the main objectives of triFr and of an ongoing American study on the same subject (Triluminate pivotal trial sponsored by Abbott).

This methodology thus takes into account the different phenotypes of TR and potentially their distinct response to treatments (medical or medical + interventional).

The logistics of this study are described in Table 4 and Figure 1:

- A screening visit: Visit 1: inclusion/exclusion criteria; written informed consent; echocardiography measurements and a recording for the core laboratory (Corelab).

The patient is then discussed by the local heart team. If there is consensus, the images are sent to Corelab, the e-CRF is fulfilled, and the patient is discussed with the eligibility committee.

- An inclusion visit: Visit 2: randomization; medical history and a complete physical examination,
- An intervention visit: Visit 3: Triclip™ implantation; optimization of medical therapy,
- And follow-up visits (Visits 4–6 at 3, 6, and 12 months: complete physical examination).

To conduct the medico-economic study, after the first 12 months of follow-up, the EQ5D-5 L questionnaire will be administered at 18 months and 24 months by phone call to assess the health-related quality of life of the first 150 patients included.

Procedures

Triclip™ (Abbott Structural, Santa Clara, CA, USA) implantation

The percutaneous installation procedure of the tricuspid valve™ clip is carried out in a catheterization room that has a level of asepsis equivalent to an operating room with a nearby recovery hall (also called interventional cardiology rooms or so-called hybrid rooms). The procedure is carried out by a multidisciplinary team involving practitioners who have benefitted from the specific training and is typically comprised of two operators, including at least one interventional cardiologist and a cardiologist specializing in echocardiography. The typical operating protocol is as follows:

- The patient is under general anaesthesia;
- A femoral venous catheter is placed, and then the clip and its release system are positioned in the atrium and right ventricle;
- The clip is set up with the heartbeat under radioscopic control and echocardiographic (TOE) monitoring;²¹ (biplane mid and deep

Table 4 Summary of the different steps of the Tri.fr protocol

| | Pre-inclusion | Definite inclusion | Hospitalization, intervention | Phone call à 30 days | Follow-up visit at 3 months | Follow-up visit at 6 months | Follow-up visit at 12 months |
|--|---------------|--------------------|---|--|-----------------------------------|-----------------------------------|------------------------------------|
| | V1 | V2 | V3 'CLIP FOR THE TRICUSPID VALVE' T0 + 21 days maximum | V3 'CONTROLS' T0 + 30 days [±5 days] | V4 T0 + 3 months [±14 days] | V5 T0 + 6 months [±14 days] | V6 T0 + 12 months [±21 days] |
| Visit | | | | | | | |
| Timing | | T0 = randomization | | | | | |
| Information and informed consent signature | X | | | | | | |
| Clinic exam | X | X | X (pre-intervention and post-intervention) | | X | X | X |
| Walking test 6 min | X | | | | X | X | X |
| ECG | X | | X (pre-intervention and post-intervention) | | X | X | X |
| Transthoracic echocardiography | X | | X (post-intervention) | | X | | X |
| Transoesophageal echocardiography | X | | X (per-intervention) | | | | |
| Echocardiographic criteria validation | | X | | | | | |
| Experimental procedure | | | X | | | | |
| Collection of intervention characteristics | | | X | | | | |
| Efficacy collection | | | X | X | X | X | X |
| Collection of tolerance | | | X | X | X | X | X |
| Biological parameters ^a | X | | X (Pre-intervention and post-intervention) | | X | X | X |
| Quality of life questionnaires | X | | | | X | X | X |
| Patient global assessment | | | | | X | X | X |
| Medico-economical data ^b | X | | X | X | X | X | X |
| Adverse events | | | X | X | X | X | X |
| MRI | X | | | | | | (X) |

X: Act Added by the Research

X: Act of Routine Care

X: Centralized lecture

^aBiological parameters: Haemoglobin, Haematocrit, Platelets, Leucocytes, INR (International Normalized Ratio), Sodium, Creatinine, Bilirubin, ASAT (aspartate aminotransferases), ALAT (alanine aminotransferases), Gamma-GT, BNP (brain natriuretic peptide), NTpro BNP, BUN (blood urea nitrogen), Troponin.

^bMedico-economic data: Follow-up visit at 18 months and 24 months; EQ5D-5 L questionnaire by phone contact for the first 150 patients included.

transoesophageal images at 45°/135°, transgastric en face view of the tricuspid valve (50°) (Figures 3)

- Depending on the degree of residual tricuspid leakage after the first clip is installed, a second or third clip may be positioned. Clipping should treat the main regurgitation, usually starting by grasping the septal-anterior leaflets and, if required, the residual gap between the posterior and septal leaflets should be treated.

Given the implantation of prosthetic material, patients will benefit from thromboprophylaxis treatment, such as that currently prescribed and usual in this framework in common practice.

After the procedure for the implantation of the clip for the tricuspid valve™ system (trclip™), patients benefitted from medical management optimized according to the state of the art for the treatment of symptomatic secondary TR. This is presented below as part of the description of the treatment for the conventional strategy.

Optimized medical treatment or guideline-directed medical therapy

In accordance with the recommendations of the European Society of Cardiology,^{20,22} guideline-directed medical therapy (GDMT) consists mainly of drug management, taking into account contraindications or particular intolerances, diuretics, and an aldosterone antagonist. Mandatory in patients with left ventricular ejection fraction $\leq 40\%$, but not for others, a stable and maximal dosage of beta-blockers and conversion enzyme inhibitor (ACE-inhibitors) (or an angiotensin 2 receptor antagonist in the case of ACE-inhibitor intolerance), or of sacubitril-valsartan. Stability is defined as the absence of an increase of more than 100% or a decrease of less than 50% of the dose in the previous month.

Acute cardiac decompensations are symptomatically treated according to the recommendations (mainly oral or parenteral diuretic agents according to their severity).

Statistics

This trial is designed to determine whether a device (TRI-CLIP implantation) is better than optimized medical treatment of patients with at least severe TR who are not suitable for surgery. This study is a prospective, multicentre, controlled, randomized (1:1 ratio), superior, open-label, and parallel-group study.

Statistical software used for the analysis will be SAS version 9.4 (SAS Institute, Cary, NC, USA).

Description of planned statistical methods

Planned number of persons to be enrolled in the study and planned number of persons in each centre with statistical justification

Considering that our primary endpoint is ordinal with three levels, 300 patients would provide 90% power to show that the device is superior to the standard-of-care, with a one-sided 0.025 alpha level and the following assumptions: proportions of improved, unchanged, or worse (0.05, 0.45, 0.5) in the 'standard-of-care' group and (0.15, 0.5, 0.35) in the 'device' group. This hypothesis is based on a French registry, the existing literature and Triluminate.^{23,24}

Planned degree of statistical significance

Statistical tests for the primary outcome will be carried out with a one-sided 0.025% level of significance ($P < 0.025$).

Discussion

Secondary TR has a high prevalence and is associated with marked clinical limitations.^{5,25,26} Its management remains a major clinical challenge and justifies the proposal of a randomized study evaluating new approaches to transcatheter valve repair. In fact, evidence for correcting secondary TR is lacking. The Triluminate study brought enthusiasm but was not designed to demonstrate the clinical benefit of a strategy based on GDMT plus correction of the regurgitation using a percutaneous approach.¹⁶ The 1-year results are encouraging compared to surgical surveys reporting an overall hospital mortality of $\sim 8.8\%$.^{11,27,28} Most patients are unsuitable for surgery, and some patients remain highly symptomatic and have a poor prognosis despite optimized medical management.²⁹

Therefore, it seems necessary to conduct a study to evaluate the contribution of a clip manufactured specifically for the tricuspid valve (Triclip™, Abbott Structural, Santa Clara, CA, USA) compared to GDMT in patients who are unsuitable for surgically isolated correction of the TR. It will be necessary to demonstrate its impact on major cardiac events and on the patient's clinical status and quality of life. Specific analyses of the echocardiographic and subclinical benefits of percutaneous treatment vs. GDMT will be performed. Best understanding of right heart adaptability and remodelling after clipping the TR will be looked at. The consequences of the clipping will be studied thanks to echocardiographic and cardiac magnetic resonance sub-studies. A lot remains to be known.

Imaging of the secondary TR

TR is often clinically unsuspected, and cardiac auscultation is rarely typical.³⁰ Thus, in routine practice, its diagnosis mostly depends on echocardiography.³¹ Judging anatomy and severity of TR by echocardiography has often proven difficult. The anatomy is complex and in addition to surgical classifications,³² a recent echocardiographic classification has been proposed.³³ This is requiring a standardized and optimized TEE recording in mid-, deep-oesophagus but also using the 'en-face' transgastric view of the tricuspid valve. The biplane trans-oesophageal and the transgastric view are mandatory and should provide an optimal visualization of the leaflets (all the leaflets) and the gap(s). Echocardiographic methods of quantifying TR are based primarily on the vena contracta (2D and better 3D) and the regurgitant orifice area calculation.^{34,35} Considering transthoracic echocardiography, based on the complex anatomy of the tricuspid valve and the presence of at least 3 leaflets, 3D modality (or at least bi-plan) for evaluating valve morphology and function might have a significant impact on the accuracy of TR characterization. The effective regurgitant orifice area (EROA) is a fundamental but complex measurement performed mainly without any angle-correction. The ability to average the measurement made in two orthogonal views is a must for Tri.fr (Figure 2). As a matter of fact, the functional nature of the TR is requiring to take into account the non-hemispheric nature of the PISA, like the vena contracta is not a circle. Vena contracta, in an attempt to quantitate the severity of TR, has been advocated using 2D.³⁶ The vena contracta is the smallest high-velocity region of the flow jet on the atrial side of the tricuspid orifice [a vena contracta width > 7.0 mm is considered to indicate severe TR (Figure 2)].^{19,20} The volumetric approach for quantifying the regurgitant volume and regurgitant fraction (RF) provides also key complementary

information. Hepatic vein flow reversal, triangular dense regurgitant jet and the gap between leaflets (assessed on several windows to get the largest one) have to be reported.³⁷ This multi-parametric method has significant limitations, but it helps to apply a pragmatic approach based on five grades of TR that can be measured pre- and post-clip implantation (even if it is much harder after the clip positioning if several regurgitant jet remain).³

Therefore, imagers have to be concerned and well-trained for getting the views and images that make possible the understanding, the planification of the treatment and the quantification of the regurgitation.³³ Imagers should have sufficient skills to obtain the best images with standardized settings (particularly colour Doppler). These settings are important for longitudinal studies and comparisons of the regurgitation from one evaluation to the next. Imagers should try their best to obtain 2D and 3D images of the right heart (Figure 2).³¹ Considering all of the limits (including respiratory changes) related to the precise quantification of TR in different patients and in different clinical conditions, we have to combine all of the parameters and centralize the analysis of the TR grading (Corelab).³⁷⁻⁴¹ Also, imagers should have a clinical impact and should evaluate only patients who have been treated for being as much as possible evolemic. Over the individual follow-up, TR quantification may vary due to RV plasticity and changes in size and shape. Changing the anatomy will affect the TR characterization. Additionally, the impact of treatment on remodelling of the right atrium and ventricle will have to be considered. Tri.fr was thus designed to record a large set of echocardiographic but also cardiac magnetic resonance images.

Conclusion

This TRI-FR study will be the first randomized, academic, trial testing the efficacy of a percutaneous correction of TR in symptomatic patients. These patients will have a precise centralized quantification of TR as well as heart function at inclusion and during the follow-up. Additionally, the Milton Packer composite endpoint will provide information regarding the functional benefit for the patient as well as information about the risk of death or hospitalization for any cardiovascular reason.

Conflict of interest: Abbott is providing the implanted device, but the study is academic, independent and financed by the French Minister for Health (PHRC-N).

References

- Messika-Zeitoun D, Verta P, Gregson J, Pocock SJ, Boero I, Feldman TE et al. Impact of tricuspid regurgitation on survival in patients with heart failure: a large electronic health record patient-level database analysis. *Eur J Heart Fail* 2020;**22**: 1803-13.
- Enriquez-Sarano M, Messika-Zeitoun D, Topilsky Y, Tribouilloy C, Benfari G, Michelena H. Tricuspid regurgitation is a public health crisis. *Prog Cardiovasc Dis* 2019;**62**:447-51.
- Guerin A, Dreyfus J, Le Tourneau T, Sportouch C, Lairez O, Eicher JC et al. Secondary tricuspid regurgitation: do we understand what we would like to treat? *Arch Cardiovasc Dis* 2019;**112**:642-51.
- Donal E, Galli E, Bidaut A. Advocacy for more consideration of the secondary tricuspid regurgitation. *Heart* 2019;**105**:1221-2.
- Chorin E, Rozenbaum Z, Topilsky Y, Konigstein M, Ziv-Baran T, Richert E et al. Tricuspid regurgitation and long-term clinical outcomes. *Eur Heart J Cardiovasc Imaging* 2020;**21**:157-65.
- Prihadi EA, Delgado V, Leon MB, Enriquez-Sarano M, Topilsky Y, Bax JJ. Morphologic types of tricuspid regurgitation: characteristics and prognostic implications. *JACC Cardiovasc Imaging* 2019;**12**:491-9.

- Benfari G, Antoine C, Miller WL, Thapa P, Topilsky Y, Rossi A et al. Excess mortality associated with functional tricuspid regurgitation complicating heart failure with reduced ejection fraction. *Circulation* 2019;**140**:196-206.
- Zack CJ, Fender EA, Chandrashekar P, Reddy YNV, Bennett CE, Stulak JM et al. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol* 2017;**70**:2953-60.
- Dumont C, Galli E, Oger E, Fournet M, Flecher E, Leclercq C et al. Pre- and postoperative tricuspid regurgitation in patients with severe symptomatic aortic stenosis: importance of pre-operative tricuspid annulus diameter. *Eur Heart J Cardiovasc Imaging* 2018;**19**:319-28.
- Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ et al.; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739-91.
- Dreyfus J, Flagiello M, Bazire B, Eggenspieler F, Viau F, Riant E et al. Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes. *Eur Heart J* 2020;**41**:4304-17.
- Chikwe J, Itagaki S, Anyanwu A, Adams DH. Impact of concomitant tricuspid annuloplasty on tricuspid regurgitation, right ventricular function, and pulmonary artery hypertension after repair of mitral valve prolapse. *J Am Coll Cardiol* 2015; **65**:1931-8.
- Alqahtani F, Berzingi CO, Aljohani S, Hijazi M, Al-Hallak A, Alkhouli M. contemporary trends in the use and outcomes of surgical treatment of tricuspid regurgitation. *J Am Heart Assoc* 2017;**6**:e007597.
- Topilsky Y, Maltais S, Medina Inojosa J, Oguz D, Michelena H, Maalouf J et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging* 2019;**12**:433-42.
- Hausleiter J, Braun D, Orban M, Latib A, Lurz P, Boekstegers P et al. Patient selection, echocardiographic screening and treatment strategies for interventional tricuspid repair using the edge-to-edge repair technique. *EuroIntervention* 2018; **14**:645-53.
- Nickenig G, Weber M, Lurz P, von Bardeleben RS, Sitges M, Sorajja P et al. Transcatheter edge-to-edge repair for reduction of tricuspid regurgitation: 6-month outcomes of the TRILUMINATE single-arm study. *Lancet* 2019;**394**:2002-11.
- Packer M. Unbelievable folly of clinical trials in heart failure: the inconvenient truth about how investigators and guidelines weigh evidence. *Circ Heart Fail* 2016;**9**:e002837.
- Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail* 2001;**7**:176-82.
- Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. *Eur Heart J Cardiovasc Imaging* 2017;**18**:1342-3.
- Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2021;ehab395. doi: 10.1093/eurheartj/ehab395.
- Hahn RT, Nabauer M, Zuber M, Nazif TM, Hausleiter J, Taramasso M et al. Intraprocedural imaging of transcatheter tricuspid valve interventions. *JACC Cardiovasc Imaging* 2019;**12**:532-53.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al.; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129-200.
- Chen E, L'Official G, Guerin A, Dreyfus J, Lavie-Badie Y, Sportouch C et al. Natural history of functional tricuspid regurgitation: impact of cardiac output. *Eur Heart J Cardiovasc Imaging* 2021.
- Lurz P, Stephan von Bardeleben R, Weber M, Sitges M, Sorajja P, Hausleiter J et al. Transcatheter edge-to-edge repair for treatment of tricuspid regurgitation. *J Am Coll Cardiol* 2021;**77**:229-39.
- Peri Y, Sadeh B, Sherez C, Hochstadt A, Biner S, Aviram G et al. Quantitative assessment of effective regurgitant orifice: impact on risk stratification, and cut-off for severe and torrential tricuspid regurgitation grade. *Eur Heart J Cardiovasc Imaging* 2020;**21**:768-76.
- Taramasso M, Benfari G, van der Bijl P, Alessandrini H, Attinger-Toller A, Biasco L et al. Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation. *J Am Coll Cardiol* 2019;**74**:2998-3008.
- Wong WK, Chen SW, Chou AH, Lee HA, Cheng YT, Tsai FC et al. Late outcomes of valve repair versus replacement in isolated and concomitant tricuspid valve surgery: a nationwide cohort study. *J Am Heart Assoc* 2020;**9**:e015637.
- Axtell AL, Bhambhani V, Moonsamy P, Healy EW, Picard MH, Sundt TM 3rd et al. Surgery does not improve survival in patients with isolated severe tricuspid regurgitation. *J Am Coll Cardiol* 2019;**74**:715-25.
- Muraru D, Previtero M, Ochoa-Jimenez RC, Guta AC, Figliozzi S, Gregori D et al. Prognostic validation of partition values for quantitative parameters to grade functional tricuspid regurgitation severity by conventional echocardiography. *Eur Heart J Cardiovasc Imaging* 2021;**22**:155-65.

30. Topolsky Y, Tribouilloy C, Michelena HI, Pislaru S, Mahoney DW, Enriquez-Sarano M. Pathophysiology of tricuspid regurgitation: quantitative Doppler echocardiographic assessment of respiratory dependence. *Circulation* 2010;**122**: 1505–13.
31. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, et al.; European Association of Echocardiography. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr* 2010;**11**:307–32.
32. Joudinaud TM, Flecher EM, Duran CM. Functional terminology for the tricuspid valve. *J Heart Valve Dis* 2006;**15**:382–8.
33. Hahn RT, Weckbach LT, Noack T, Hamid N, Kitamura M, Bae R et al. Proposal for a standard echocardiographic tricuspid valve nomenclature. *JACC Cardiovasc Imaging* 2021;**14**:1299–305.
34. Muraru D, Previtro M, Ochoa-Jimenez RC, Guta AC, Figliozzi S, Gregori D et al. Prognostic validation of partition values for quantitative parameters to grade functional tricuspid regurgitation severity by conventional echocardiography. *Eur Heart J Cardiovasc Imaging* 2020.
35. Badano LP, Caravita S, Rella V, Guida V, Parati G, Muraru D. The added value of 3-dimensional echocardiography to understand the pathophysiology of functional tricuspid regurgitation. *JACC Cardiovasc Imaging*. 2020.
36. Fortuni F, Dietz MF, Prihadi EA, van der Bijl P, De Ferrari GM, Bax JJ et al. Ratio between vena contracta width and tricuspid annular diameter: prognostic value in secondary tricuspid regurgitation. *J Am Soc Echocardiogr* 2021;**34**:944–54.
37. Peugnet F, Bohbot Y, Chadha G, Delpierre Q, Kubala M, Delabre J et al. Improvement of the prognosis assessment of severe tricuspid regurgitation by the use of a five-grade classification of severity. *Am J Cardiol* 2020;**132**:119–25.
38. Hahn RT, Ben-Yehuda O, Leon MB. Endpoints for tricuspid regurgitation transcatheter therapy trials. *Prog Cardiovasc Dis* 2019;**62**:479–81.
39. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al.; Scientific Document Committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;**14**:611–44.
40. Hahn RT, Thomas JD, Khalique OK, Cavalcante JL, Praz F, Zoghbi WA. Imaging assessment of tricuspid regurgitation severity. *JACC Cardiovasc Imaging* 2019;**12**:469–90.
41. Zoghbi WA, Asch FM, Bruce C, Gillam LD, Grayburn PA, Hahn RT et al. Guidelines for the evaluation of valvular regurgitation after percutaneous valve repair or replacement: a report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Angiography and Interventions, Japanese Society of Echocardiography, and Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2019;**32**:431–75.

Editorial 3

Tricuspid Transcatheter Edge-to-Edge Valve Repair: Sooner Rather Than Later

Dreyfus J, Burwash IG, Messika-Zeitoun D

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EDITORIAL COMMENT

Tricuspid Transcatheter Edge-to-Edge Valve Repair



Sooner Rather Than Later*

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Tricuspid regurgitation (TR) is a heterogeneous condition, mostly of functional etiology secondary to left-sided disease or pulmonary hypertension.¹ The literature is fairly consistent in showing that TR is associated with an increased risk of death or heart failure that increases with TR severity.^{2,3} The prevalence of moderate or severe TR in the population has been shown to be as high as 0.55%, similar to that of aortic stenosis.¹ Current guidelines recommend performing isolated tricuspid valve surgery in patients with severe TR who are symptomatic in the absence of severe right ventricular (RV) dysfunction or severe pulmonary vascular hypertension,^{4,5} but contrasting with the prevalence, TR is often left untreated, and most TR interventions are performed at the time of left-sided surgery.^{6,7} Transcatheter tricuspid valve interventions are emerging, and if proven to be safe and efficient, they may offer a less invasive alternative to surgery to cure a larger number of individuals with severe TR. One critical element will be the timing of the intervention and whether performing any intervention at an advanced disease stage should be considered as futile.

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In this issue of *JACC: Cardiovascular Interventions*, Stolz et al⁸ report the outcome of 305 patients (mean

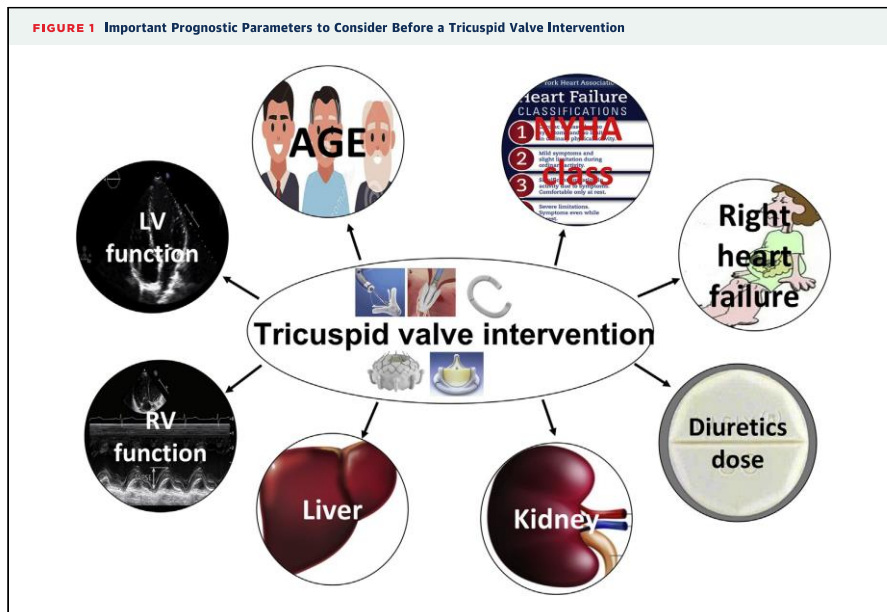
age 77 years, 49% women) who underwent a tricuspid transcatheter edge-to-edge repair (T-TEER) for severe TR at 2 high-volume German academic centers between 2016 and 2020 and more specifically evaluate the impact of the cardio-hepatic syndrome (CHS), defined as an elevation of at least 2 of 3 cholestasis laboratory parameters (bilirubin, alkaline phosphatase, gamma-glutamyltransferase). Most patients enrolled in this cohort were referred at an advanced disease stage; they were severely symptomatic (89% New York Heart Association [NYHA] functional class III/IV), were often in atrial fibrillation (87%), and received a high dose of furosemide (81 ± 96 mg). TR was massive or torrential in 30% and significant RV dysfunction was observed in 47%. The procedure was successful (moderate or less residual TR) in 86%, and 1-year mortality rate and 1-year readmission rate for heart failure were 24% and 17%, respectively. Importantly, procedural results were sustained over time, and a significant functional improvement was also observed. CHS was observed in 45% of the population and was associated with a higher degree of TR, impairment of right and left systolic function, lower 6-minute walk distance, higher doses of diuretics, and a trend toward a more severe NYHA functional class. They also presented more often with a permanent pacemaker. Patients with CHS experienced higher 1-year rates of mortality and of heart failure readmission compared with those with no CHS (mortality: 34% vs 16%; $P < 0.01$; and heart failure readmission: 23% vs 12%; $P < 0.01$), and their worse outcome persisted in multivariate analysis (in addition to NYHA functional class, creatinine, TR severity, and procedural results). Nevertheless, a functional improvement was observed irrespective of the presence of CHS, and laboratory parameters improved during follow-up.

Notwithstanding its important methodological limitations (retrospective observational study, limited

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).



and incomplete follow-up, absence of centralized evaluation of both clinical events and echocardiographic parameters), this study illustrates the impact of late presentation and of adverse cardiac and noncardiac consequences including liver impairment on the outcomes of patients with severe TR. These results are fully in line with prior studies including our own showing that the poor outcome observed after tricuspid valve surgery is mainly driven by the advanced disease stage at the time of the intervention.^{9,10} Therefore, in order to achieve the best outcome, a tricuspid valve intervention should be performed early in the course of the disease before the occurrence of severe symptoms, severe heart failure and requirement of high dose of furosemide, severe RV dilatation and dysfunction, and kidney insufficiency (Figure 1). The prognostic accuracy of integrating these parameters into the TRI-SCORE has been recently demonstrated.¹¹ It is critical to underline that neither The Society of Thoracic Surgeons score nor the EuroSCORE (European System for Cardiac Operative Risk Evaluation) I or II was designed to predict the mortality of tricuspid valve interventions. Two parameters deserve special comment. First, the prognostic impact of RV systolic pulmonary pressure (RVSP) as measured using Doppler echocardiography is inconsistent across the published reports. The most plausible explanation is its inaccurate value (RVSP

underestimation) when TR is laminar. In a recent study, patients with discordance between echocardiographic (normal) and invasive (elevated) measurements of RVSP experienced a worse outcome after T-TEER.¹² Second, the Model for End-Stage Liver Disease score, used to stratify patients awaiting liver transplantation, has also been shown to predict mortality related to isolated tricuspid valve surgery.¹³ The MELD score relies on 3 variables that reflect liver and renal function (international normalized ratio, total bilirubin, and creatinine). However, its validity may be altered, as most patients referred for T-TEER are in atrial fibrillation and receiving oral anticoagulation, which affects the international normalized ratio.

What are the next steps? First, it is critical to close the loop and to formally demonstrate that TR is not a bystander of the worse outcome observed in patients with TR, but rather that TR correction improves outcome. Ongoing randomized controlled trials (ie, TRILUMINATE Pivotal trial [Clinical Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System Pivotal], TRI-FR [Evaluation of Tricuspid Valve Percutaneous Repair System in the Treatment of Severe Secondary Tricuspid Disorders] trial, CLASP II TR [Edwards PASCAL Transcatheter Valve Repair System Pivotal Clinical Trial] TRISCEND II Pivotal trial [Edwards EVOQUE Transcatheter Tricuspid Valve Replacement:

Pivotal Clinical Investigation of Safety and Clinical Efficacy Using a Novel Device)) will provide more evidence in this regard. Second, 2 critical parameters should be considered into the equation: the timing of the intervention and the type of intervention performed. In order to achieve an optimal outcome and maximize its potential benefit, the tricuspid valve intervention should be performed early in the course of the disease. Discrepancies in trial findings may be the result of differences in the characteristics of the populations enrolled and of the disease stage. Such differences are possibly responsible of the divergent results of COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) and MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) trials.^{14,15} A precise characterization of the populations enrolled in trials and of disease stage as measured, for example, by the TRI-SCORE, will be of paramount importance. Type of intervention, repair, or replacement, either performed surgically or through a transcatheter approach, may also affect the outcome. Anatomic considerations may lead to enrollment of patients with the more advanced disease in replacement trials precluding demonstration of the benefit of the intervention. On the other hand,

enrollment of patients with severely dilated tricuspid annuli and large coaptation gaps in T-TEER trials may lead to suboptimal procedural results with significant residual TR, also precluding the demonstration of the benefit of intervention.

In summary and in the interim of the publication of ongoing randomized controlled trials comparing transcatheter intervention to medical management, the present study adds to the body of evidence showing that clinical presentation and cardiac and noncardiac consequences of TR are the main determinants of outcome of patients with severe TR referred for intervention. Therefore, if one aims to achieve the best outcomes, intervention should be performed sooner rather than later in the course of the disease.

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REFERENCES

1. Topitsky Y, Maltais S, Medina Inojosa J, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *J Am Coll Cardiol Img*. 2019;12:433-442.
2. Messika-Zeitoun D, Verta P, Gregson J, et al. Impact of tricuspid regurgitation on survival in patients with heart failure: a large electronic health record patient-level database analysis. *Eur J Heart Fail*. 2020;22:1803-1813.
3. Topitsky Y, Inojosa JM, Benfari G, et al. Clinical presentation and outcome of tricuspid regurgitation in patients with systolic dysfunction. *Eur Heart J*. 2018;39:3584-3592.
4. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77:e25-e197.
5. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. Published online August 28, 2021. <https://doi.org/10.1093/eurheartj/ehab395>
6. Messika-Zeitoun D, Candolfi P, Dreyfus J, et al. Management and outcome of patients admitted with tricuspid regurgitation in France. *Can J Cardiol*. 2021;37:1078-1085.
7. Zack CJ, Fender EA, Chandrashekar P, et al. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol*. 2017;70:2953-2960.
8. Stolz L, Orban M, Besler C, et al. Cardiohepatic syndrome is associated with poor prognosis in patients undergoing tricuspid transcatheter edge-to-edge valve repair. *J Am Coll Cardiol Intv*. 2022;15:179-189.
9. Dreyfus J, Flagiello M, Bazire B, et al. Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes. *Eur Heart J*. 2020;41:4304-4317.
10. Dreyfus J, Ghalem N, Garbarz E, et al. Timing of referral of patients with severe isolated tricuspid valve regurgitation to surgeons (from a French Nationwide Database). *Am J Cardiol*. 2018;122:323-326.
11. Dreyfus J, Audureau E, Bohbot Y, et al. TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. *Eur Heart J*. Published online September 29, 2021. <https://doi.org/10.1093/eurheartj/ehab679>
12. Lurz P, Orban M, Besler C, et al. Clinical characteristics, diagnosis, and risk stratification of pulmonary hypertension in severe tricuspid regurgitation and implications for transcatheter tricuspid valve repair. *Eur Heart J*. 2020;41:2785-2795.
13. Ailawadi G, Lapar DJ, Swenson BR, et al. Model for end-stage liver disease predicts mortality for tricuspid valve surgery. *Ann Thorac Surg*. 2009;87:1460-1467 [discussion: 1467-1468].
14. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379:2297-2306.
15. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307-2318.

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Notes