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Risques thrombotiques et hémodynamiques chez les patients hospitalisés en réanimation présentant une fibrillation atriale de novo au cours d'un sepsis : caractérisation, stratification et stratégies thérapeutiques

Vincent Labbé

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Vincent Labbé

Risques thrombotiques et hémodynamiques chez les patients hospitalisés en réanimation présentant une fibrillation atriale de novo au cours d'un sepsis : caractérisation, stratification et stratégies thérapeutiques

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Liste des publications réalisées dans le cadre du projet de thèse (3)

- 1 **Labbé V**, Ederhy S, Lapidus N, Joffre J, Razazi K, Laine L, Sy O, Voicu S, Chemouni F, Aissaoui N, Smonig R, Doyen D, Carrat F, Voiriot G, Mekontso-Dessap A, Cohen A, Fartoukh M, FAST Study Group: Transesophageal echocardiography for cardiovascular risk estimation in patients with sepsis and new-onset atrial fibrillation: a multicenter prospective pilot study. *Ann Intensive Care* 11(1):146, 2021.
- 2 **Labbé V**, Ederhy S, Legouis D, Joffre J, Bagate F, Sy Oumar, Chemouni F, Mekontso-Dessap Armand, Fartoukh M, Cohen A, FAST Study group: Left atrial appendage dysfunction after cardioversion of new-onset atrial fibrillation in critically ill patients with sepsis. submitted (Nov 2023)
- 3 **Labbé V**, Desnos C, Preau S, Contou D, Bagate F, Doyen D, Muller G, Boissier F, Bertrand PM, Joffre J, Souweine B, Asfar P, Sy O, Dres M, Monnet X, Bonnet N, Carreira S, Pey V, Voicu S, Vivier E, Heming N, Lebreton C, Chevrel G, Annoni F, Taccone F, Fartoukh M, Durand D, Monthieux G, Berard L, Rousseau A, Mekontso-Dessap A. Effects of Risk, Rate and Rhythm Control in Patients with New Onset Atrial Fibrillation during Septic Shock: Protocol of CAFS Multicenter, Parallel-group, Open-label, Randomized Controlled Trial. Submitted (Nov 2023)

RESUME Risques thrombotiques et hémodynamiques chez les patients hospitalisés en réanimation présentant une fibrillation atriale de novo au cours d'un sepsis : caractérisation, stratification et stratégies thérapeutiques

Objectifs

La fibrillation atriale de novo (FAN) au cours d'un sepsis est associée à un surrisque thrombotique, une altération de l'état hémodynamique et un doublement de la mortalité. Sur le versant thrombotique, les objectifs étaient (i) d'évaluer la capacité des scores de risque cardiologiques et des anomalies échocardiographiques transoesophagienne (ETO) (dysfonction ventriculaire gauche systolique, dysfonction de l'auricule gauche (AG), athérome aortique) pour prédire le risque cardio-vasculaire (événements thrombotiques artériels, hémorragies, décès toute cause) et (ii) de caractériser le risque de formation d'un thrombus intra AG (incidence et délai de formation, prévalence de la sidération post cardioversion de l'AG) chez les patients ayant une FAN au cours d'un sepsis. Sur le versant hémodynamique notre objectif était d'établir un essai randomisé visant à comparer l'efficacité hémodynamique de trois stratégies de prise en charge usuelle du risque hémodynamique dans ce contexte.

Méthodes

Nous avons mené l'étude FAST (Fibrillation Atrial Sepsis Thrombus) observationnelle multicentrique prospective. Tous les adultes consécutifs sous ventilation mécanique présentant une FAN au cours d'un sepsis ont bénéficié d'une ETO dans les 48 heures suivant l'apparition de la FAN. Le critère d'évaluation principal était la survenue d'un événement cardiovasculaire à J28, incluant les événements thrombotiques artériels, les hémorragies majeures et le décès. La fonction de l'AG post cardioversion a été étudiée chez les patients en rythme sinusal au moment de l'ETO. L'essai CAFS (Control Atrial Fibrillation sepsis) est un essai de supériorité randomisé, multicentrique, en groupes parallèles, ouvert et contrôlé, visant à comparer l'efficacité et la sécurité de trois stratégies thérapeutiques chez les patients présentant une FAN au cours d'un choc septique. 240 patients seront randomisés pour recevoir soit un contrôle du risque (magnésium et contrôle des « triggers » de la FAN), soit un contrôle du rythme (contrôle du risque et faible dose d'amiodarone), soit un contrôle du rythme (contrôle du risque et forte dose d'amiodarone avec choc électrique externe si la FAN persiste). Le critère d'évaluation principal est un critère hiérarchique à J28 incluant la mortalité toute cause et la durée du choc septique.

Résultats et discussion

Les approches cardiologiques de stratification des risques thrombotiques (anomalies ETO, score CHA₂DS₂-VASc) et hémorragiques (score HAS-BLED) semblent limitées pour prédire le risque cardio-vasculaire. Une approche individualisée basée sur l'ETO et le score CHA₂DS₂-VASc pourrait néanmoins être intéressante. Ce travail a également mieux caractérisé le risque de formation d'un thrombus intra cardiaque : absence de thrombus dans les 48 h suivant le début de la FAN, prévalence rare de la sidération post cardioversion de l'AG. Enfin, nous avons confirmé l'équipose clinique au sujet des modalités du traitement anticoagulant (délai d'initiation, durée) à l'origine d'une grande hétérogénéité des pratiques usuelles justifiant la réalisation d'essais thérapeutiques. L'essai CAFS est en cours d'inclusion (92 patients/ 240 inclus) au sein de 28 unités de soins intensifs en France et en Belgique. L'essai cible une population bien sélectionnée, avec un objectif principal et un modèle expérimental appropriés, afin de fournir une réponse robuste quant à la meilleure stratégie de prise en charge hémodynamique de la FAN au cours du choc septique afin d'améliorer la survie et la durée du choc septique.

Conclusions

La prise en charge spécifique d'une FAN au cours du sepsis doit s'attacher à prévenir le risque thrombotique et limiter le risque d'aggravation hémodynamique. Au sein de cette population à très haut risque cardiovasculaire et d'altération hémodynamique, ce travail a permis de (i) poser les bases d'un futur essai afin d'évaluer la meilleure stratégie de traitement anticoagulant et (ii) mettre en place un essai actuellement en cours afin d'évaluer la meilleur stratégie de prise en charge du risque hémodynamique.

Mots clés

Fibrillation atriale, risque thrombotique, risque hémodynamique, sepsis, réanimation, stratégie thérapeutique, anticoagulation

SUMMARY Thrombotic and hemodynamic risks in intensive care unit patients with new-onset atrial fibrillation during sepsis: characterization, stratification, and therapeutic strategies

Objectives

New-onset atrial fibrillation (NOAF) during sepsis is associated with increased thrombotic risk, deterioration of hemodynamic status, and a 2-fold increase in mortality. Regarding the thrombotic risk, the objectives were (i) to assess the ability of cardiological risk scores and transesophageal echocardiographic (TEE) abnormalities (left ventricular (LV) systolic dysfunction, left atrial (LA) dysfunction, aortic atheroma) to predict cardiovascular risk (arterial thrombotic events, hemorrhage, all-cause death) and (ii) to assess the risk of LA thrombus formation (incidence and time course of formation, prevalence of post-cardioversion LA dysfunction) in patients with NOAF during sepsis. Regarding the hemodynamic risks, our objectives were to design and conduct a randomized trial to compare the hemodynamic efficacy of three usual strategies for managing hemodynamic risk in this context.

Methods

For the thrombotic risk objectives, we conducted the Fibrillation Atrial Sepsis Thrombus (FAST) observational multicenter prospective study. All consecutive mechanically ventilated adults with NOAF during sepsis underwent TEE within 48 hours of NOAF onset. The study outcome was a composite of cardiovascular events at day 28, including arterial thromboembolic events, major bleeding, and all-cause death. Post-cardioversion LA function was studied in patients in sinus rhythm at the time of TEE. For the hemodynamic risk objective, we have designed the Control Atrial Fibrillation Sepsis (CAFS) study, a multicenter, parallel-group, open-label, randomized controlled superiority trial comparing the efficacy and safety of three strategies in patients with NOAF during septic shock. A total of 240 patients will be randomized to receive either risk control (magnesium and control of NOAF triggers), rate control (low dose amiodarone), or rhythm control (high dose amiodarone with external electrical shock if NOAF persists). The primary endpoint is a hierarchical criterion at day 28 including all-cause mortality and the duration of septic shock.

Results

Cardiological strategies for stratifying thrombotic (TEE abnormalities, CHA₂DS₂-VASc score) and hemorrhagic (HAS-BLED score) risks seem limited. An individualized approach

based on TEE and the CHA2DS2-VASc score could be of interest. This thesis also enabled us to better characterize the risk of intra-cardiac thrombus formation: absence of thrombus within 48 hours of NOAF onset, low prevalence of post-cardioversion LA dysfunction. Finally, we have confirmed the clinical equipoise regarding the modalities of anticoagulant treatment (time of initiation, duration), which explains the marked variation in current clinical practice and justifies the need for therapeutic trials. The CAFS study is currently being run (92 patients) in 28 intensive care units (ICUs) in 23 hospitals in France and 5 hospitals in Belgium. The trial targets a well-selected population, with an appropriate, patient-relevant primary objective and experimental design, to provide a robust response (best strategy with respect to adverse events of NOAF, such as thrombotic and bleeding events).

Conclusions

The management of NOAF during sepsis requires a focus on preventing thrombotic events and limiting adverse hemodynamic effects. In this population at very high risk of cardiovascular and hemodynamic deterioration, this thesis has (i) provided the basis for a future trial to evaluate the best anticoagulant treatment strategy, and (ii) initiated an ongoing trial to evaluate the best hemodynamic risk management strategy.

Keywords

Atrial fibrillation, Thrombotic risk, Hemodynamic risk, sepsis, intensive care unit, Therapeutic strategies, Anticoagulation

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ABBREVIATIONS

AVC : accident vasculaire cérébral

CAFS: Control Atrial Fibrillation Sepsis

CHA₂DS₂-VASc: Congestive heart failure, Hypertension, Age \geq 65 years (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74 years, Sex category

ESC : European Society of Cardiology

ETO : échocardiographie trans-oesophagienne

FA : fibrillation atriale

FAN : fibrillation atriel de novo

FAST : Fibrillation Atrial Sepsis Thrombus

HAS-BLED : Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio (INR), Elderly, Drugs/alcohol concomitantly

IC : intervalle de confiance

OR : odds ratio (rapport de cotes)

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1. ETAT DES CONNAISSANCES

Le sepsis est une réponse inflammatoire systémique inapproprié de l'organisme à un agent infectieux [1] conduisant à une dysfonction vitale d'organe(s) (cardio-vasculaire, rénale, respiratoire, hématologique, ou hépatique) définie par un score « Sepsis Organ Failure Assessment » ≥ 2 [2]. Le sepsis constitue un véritable enjeu de santé publique avec approximativement 50 millions de personnes affectés et 11 millions de décès par an à travers le monde [3]. Environ 225 patients développent un sepsis pour 100 000 habitants en France, avec une mortalité hospitalière de 34% [4]. Le choc septique constitue la forme la plus grave de sepsis nécessitant l'administration de vasopresseurs pour maintenir une pression artérielle moyenne à une valeur d'au moins 65 mmHg, et par une concentration artérielle de lactate supérieure à 2 mmol/L [1]. L'incidence du choc septique est en constante augmentation, concernant 50000 patients hospitalisés en réanimation chaque année en France (10% des patients hospitalisés en réanimation), et dont la mortalité hospitalière peut dépasser 40% [1].

La fibrillation atriale de novo (absence d'antécédent de fibrillation atriale, FAN) demeure le trouble du rythme acquis le plus fréquent chez les patients en sepsis, survenant chez 3% à 48% des patients (**Table 1**). L'incidence varie en fonction de la gravité du sepsis, du type de recrutement (médical ou chirurgical) et du type d'étude (rétrospective ou prospective). Klein et al ont ainsi reporté que les patient en sepsis, sepsis sévère et choc septique (selon l'ancienne définition du sepsis), présentaient une incidence cumulée de FAN de 10%, 22% et 40%, respectivement [5]. La FA correspond à une activation électrique rapide et désynchronisée des myocytes atriaux. Ce rythme se traduit par une incompetence hémodynamique atriale. Sur l'électrocardiogramme, les ondes d'activation de l'oreillette correspondent à des oscillations rapides dont l'amplitude, la forme et la durée varient. Dans le contexte du sepsis, la FAN est associée à une augmentation du risque d'évènements thrombotiques artériels notamment

cérébraux [6], une altération de l'état hémodynamique [5,7] déjà précaire et un doublement du risque de décès intra-hospitalier [5] (**Table 1**).

La prise en charge spécifique de la survenue d'une FAN dans ce contexte doit ainsi poursuivre conjointement deux objectifs : prévenir le risque thrombotique et limiter le risque d'aggravation hémodynamique. La thèse s'organisera donc autour de ces deux thématiques

1.1 Fibrillation atriale de novo au cours du sepsis : physiopathologie

La physiopathologie de la survenue d'une FAN chez les patients septiques est complexe, résultante de l'interaction entre des facteurs directement liés à la réanimation (« triggers »), des facteurs liés à la pathologie aiguë, et des facteurs prédisposants liés au terrain du patient [8].

1.1.1 Les triggers

Le déclencheur de la FA est une décharge atriale ectopique, le plus souvent située au niveau des veines pulmonaires. Les décharges ectopiques atriales sont secondaires à une libération diatomique calcique du reticulum sarcoplasmique conduisant à des post-dépolarisations précoces et retardées. Ces post-dépolarisations peuvent être favorisées par des désordres électrolytiques tels que l'hypokaliémie ou l'hyponatrémie par action sur les pompes $\text{Na}^+/\text{Ca}^{2+}$ [9] [10]. L'hypomagnésémie est également un trigger identifié [11]. Le magnésium présente en effet des propriétés modulatrices des canaux potassiques et calciques myocardiques, et des propriétés stabilisatrices de membrane [12]. Une seule étude randomisée prospective sur un effectif de 199 patients ayant une FA rapide aux urgences, rapporte que l'administration systématique intraveineuse de magnésium permet d'obtenir plus fréquemment une baisse de la fréquence cardiaque (FC) et un retour en rythme sinusal, en comparaison à l'administration d'un placebo

[13]. L'activation sympathique pourrait également favoriser la survenue de décharges atriales ectopiques, que cette activation soit secondaire à la pathologie septique causale, ou à l'administration de catécholamines exogènes chronotropes positives [7,10,14–16]. L'hypovolémie pourrait contribuer à la survenue de FAN [17], possiblement en lien également avec une stimulation du système adrénergique. A l'inverse, un excès de remplissage est également à risque de survenue de FAN [10,14]. Dans une mise au point sur les interventions non anti-arythmiques chez les patients septiques présentant une FAN, Vieillard-Baron et al. expliquent cette constatation par une possible dilalation des oreillettes secondaire au remplissage excessif [12]. Enfin les mêmes auteurs alertent sur la nécessité d'éviter toute malposition des cathéters veineux centraux au niveau de l'oreillette droite qui pourrait favoriser la survenue de FAN [12].

1.1.2 Facteurs liés au sepsis

Au sein d'une large cohorte rétrospective incluant 8356 patients admis en réanimation médico-chirurgicale, une FAN survenait chez 8% des patients. Parmi les caractéristiques de bases des patients à l'admission, les facteurs les plus fortement associés à la survenue d'une FAN étaient l'âge avancé, l'insuffisance respiratoire aigüe et le sepsis [18]. Les mécanismes physiopathologiques qui sous tendent le développement d'une FAN dans le cadre du sepsis sont méconnus. Cependant la réponse inflammatoire systémique semble jouer un rôle prépondérant. Chez les patients cardiologiques non septiques, plusieurs études rapportent que l'élévation de la protéine C-réactive est associé à la survenue et la persistance de la FA [19,20]. Enfin, de nombreuses pathologies aigües non cardiaques potentiellement intriquées au sepsis peuvent également être associées à la survenue d'une FAN, telles que les pathologies pulmonaires aigües [6] ou l'insuffisance rénale aigue [6,7,14,15].

1.1.3 Facteurs liés au terrain

La FAN au cours d'un sepsis survient le plus souvent sur un terrain à risque comparable à celui décrit au sein de la population de cardiologie [21] associant l'âge, l'hypertension artérielle, l'obésité, ainsi que la présence de comorbidités cardio-vasculaires, pulmonaires ou endocriniennes [6,15,16,22–25]. Si le terme de FAN « secondaire » est utilisé en présence d'un facteur déclenchant potentiellement réversible, celui-ci est donc probablement réducteur, oubliant qu'il faut le plus souvent un substrat sous jacent pour développer une FA.

1.2 Risque thrombotique chez les patients en FA de novo au cours d'un sepsis

1.2.1 Incidence

Au sein d'une large cohorte rétrospective regroupant près de 50000 patients en sepsis [6], Walkey et al. ont montré que la FAN était associée à un doublement du risque d'AVC ischémique intra-hospitalier (2,6 % vs 0,6 % ; Odds ratio (OR): 2,70 [IC 95%, 2,05–3,57]) (Table 1).

Table 1 : Incidence, mortalité intra-hospitalière et risque d'évènement thrombotique artériel intra-hospitalier de la fibrillation atriale de novo (FAN) au cours d'un sepsis						
Auteurs (ref)	Dessin de l'étude	Nombre de patients	FAN: n (%)	Mortalité intra-hospitalière	Estimation du risque de décès	Evènement thrombotique artériel
				FAN versus Rythme sinusal		
Bosch [26]	Retrospective	9,528	233 (2.5)	39.1 vs. 20.1%; p < 0.001	OR, 2.54; 95% CI, 1.94–3.32	█
Steinberg [27]	Prospective	27	9 (33.3)	66.7 vs. 11.1%; p = 0.024	HR, 4.4; 95% CI, 1.07–18.20	█

Klein Klouwenberg [5]	Prospective	1,782	418 (23.4)	29 vs. 14%; p < 0.001	RR, 2.10; 95% CI, 1.61–2.73	
Lewis [28]	Retrospective	131	20 (15.3)	53 vs. 31%; p = 0.024	OR, 2.6; 95% CI, 0.83–8.05	
Liu [29]	Retrospective	503	240 (47.7)	61.3 vs. 17.5%; p < 0.001	OR, 3.3; 95% CI, 1.54–7.13	
Ferrera [30]	Prospective	507	52 (10.3)	48 vs. 25.6%; p < 0.05	OR, 1.9; 95% CI, 1.01–4.11	
Guenancia [24]	Prospective	66	29 (44)	24 vs. 19%; p = 0.61	-	Aucun AVC dans le suivi à J90
Seemann [7]	Prospective	71	23 (32.4)	42 vs. 48%; p = 0.63	-	
Walkey [6]	Retrospective	49,082	2896 (6)	56.3 vs. 37.7%; p < 0.001	RR, 1.07; 95% CI, 1.04–1.11	2.0 vs. 1.3%; p = 0.06; HR, 1.51; 95% CI, 0.98–2.33 (intra-hospitalier)
Meierhenrich [23]	Prospective	50	23 (46)	43.4 vs. 22.2%; p = 0.14	-	
Christian [31]	Retrospective	272	16 (5.9)	68.8 vs. 39.6%; p = 0.034	-	
Salman [25]	Retrospective	81	25 (30.9)	64 vs. 36%; p = 0.018	OR, 3.28; 95% CI, 1.12–9.57	Aucun AVC dans le suivi à J28

1.2.2 Physiopathologie des évènements thrombotiques artériels

1.2.2.1 Triade de Virchow et thrombose intra cardiaque

Les évènements thrombotiques artériels chez les patients de cardiologie en FA sont généralement attribués à l'embolie d'un thrombus formé dans l'appendice auriculaire gauche [32] et détectable en échocardiographie transoesophagienne (ETO) [33]. Les mécanismes physiopathologiques morphologiques et biologiques à l'origine de la formation d'un thrombus intra auricule gauche chez les patients de cardiologie ayant une FA sont présentés en **Figure 1** [34]. La formation d'un thrombus intra auricule gauche chez les patients en FA repose sur la

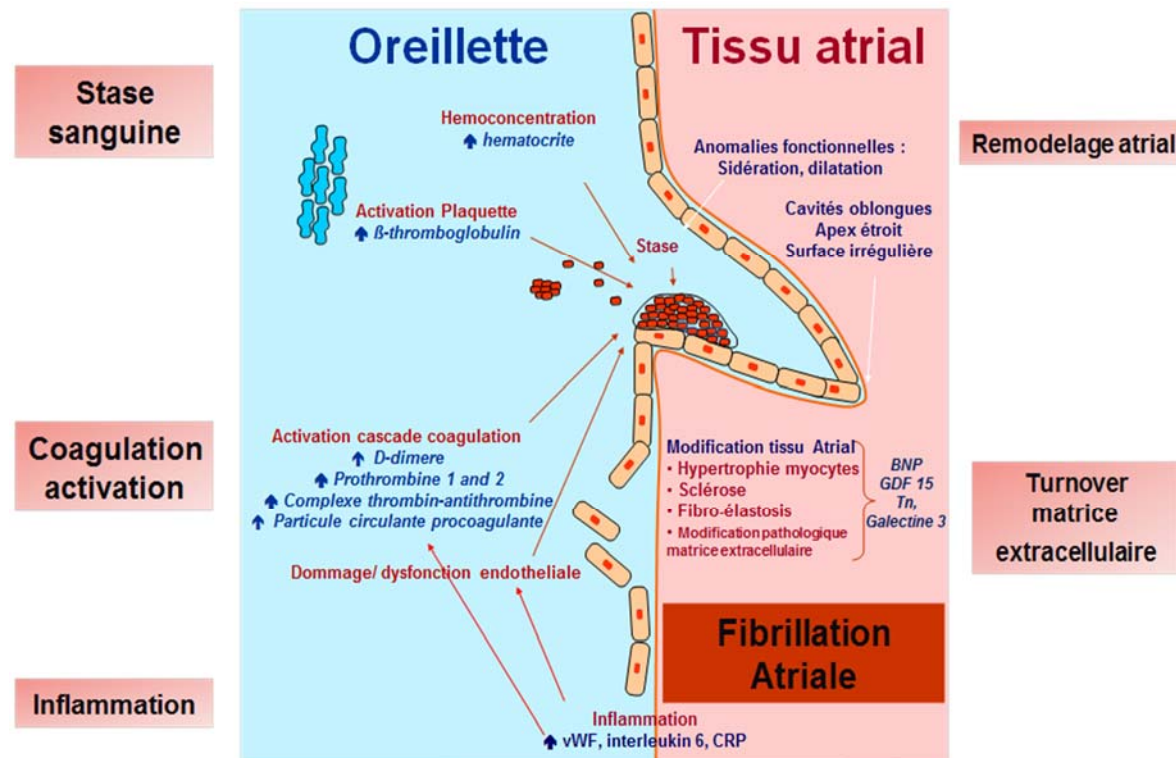
triade de Virchow comprenant stase, dysfonction endothéliale à l'origine d'une modification du tissu atrial et de sa matrice extracellulaire, et état d'hypercoagulabilité [32,34].

L'auricule gauche est une structure borgne, déclive, appendue à l'oreillette, s'abouchant en avant de la veine pulmonaire supérieure gauche. L'auricule gauche présente des caractéristiques morphologiques (cavité oblongue, apex étroit, surface irrégulière: muscles pectinés) et fonctionnelles (sidération avec baisse de la contractilité, dilatation) favorables au développement de la stase sanguine [34,35] (**Figure 1**).

Les conditions physiopathologiques pro-thrombotiques (dysfonction endothéliale et état d'hypercoagulabilité) exacerbées lors d'un état septique sévère pourraient ainsi favoriser la formation d'un thrombus intra cardiaque à l'origine d'évènements thrombotiques artériels [35]. La survenue d'une coagulopathie induite par le sepsis, à l'origine d'un état d'hypercoagulabilité, est fréquente et associée à un mauvais pronostic [36]. Les cytokines pro-inflammatoires induisent l'expression du Facteur Tissulaire endothélial et monocytaire qui active la coagulation à l'origine d'une production excessive de thrombine convertissant le fibrinogène en un réseau de fibrines insolubles [37]. L'augmentation de la production/activation d'inhibiteurs (thrombin-activable fibrinolysis inhibitor) conjointement à la diminution de l'activateur tissulaire du plasminogène (plasminogen activator inhibitor-1) participent à l'altération de la fibrinolyse [38]. Les neutrophiles activés libèrent des microvésicules [39] et des pièges extracellulaires neutrophiliques (neutrophil extracellular traps) [40,41] pro-coagulants. En outre, les anticoagulants naturels (protéine C, protéine S, thrombomoduline et antithrombine) et les «tissue factor pathway inhibitors», qui limitent l'activation de la coagulation, sont soit épuisés, soit moins actifs [42]. Cette coagulopathie pourrait contribuer à la formation d'un thrombus lors d'un épisode de FA, bien qu'aucune association n'ait été à ce jour démontrée.

Bien qu'il soit difficile de démontrer que la dysfonction endothéliale présente chez les patients septiques [43] puisse contribuer directement à la formation d'un thrombus dans le cadre d'une FA, celle-ci pourrait largement contribuer à un état d'hypercoagulabilité [44]. A l'état de repos, l'endothélium possède des propriétés antiagrégantes, anticoagulantes et anti-inflammatoires en produisant notamment de puissants antagonistes (oxyde nitrique/ monoxyde d'azote, prostacycline/ prostacycline) qui participent au maintien de l'homéostasie de l'endothélium. En cas de sepsis, l'endothélium vasculaire est activé directement par les « pathogen-associated molecular patterns » des bactéries, des virus et des champignons, ou indirectement par les pièges extracellulaires des neutrophiles (neutrophil extracellular traps, NETs) et les cytokines pro-inflammatoires [45–48]. L'un des premiers signes de dysfonctionnement endothélial dans le sepsis est la déconstruction du glycocalyx endothélial [49] qui recouvre la surface luminale des cellules endothéliales [50]. Les cellules endothéliales sont alors soumises à un processus de dégradation avec atteinte de l'intégrité de la barrière endothéliale [51]. Par ailleurs, les cellules endothéliales peuvent interagir avec les cellules immunitaires et notamment les neutrophiles activés, déclenchant la formation de thrombus, un processus impliqué dans la pathogenèse du sepsis [52].

Figure 1. Mécanismes physiopathologiques morphologiques et biologiques à l'origine de la triade de Virchow et la formation d'un thrombus intra auriculaire gauche chez les patients de cardiologie ayant une fibrillation atriale (d'après Watson et al.[34])



Abbreviations: BNP, B-type natriuretic peptide; GDF 15, Growth differentiation factor-15, Tn, troponine

1.2.2.2 Autres cause d'évènements thrombotiques artériels

Les évènements thrombotiques artériels chez les patients en FA pourraient être également dus à d'autres sources cardiaques d'embolie, ou à des pathologies athéromateuses localisées au niveau l'aorte ascendante et la crosse aortique proximale [53–55], également détectable en ETO [55,56].

1.2.3 Stratification du risque thrombotique chez les patients de cardiologie en FA

Il n'y a pas d'étude de stratification du risque thrombotique chez les patients ayant une FAN au cours d'un sepsis. Nous allons donc dans ce chapitre développer les modalités de stratification de ce risque au sein de la population de cardiologie afin d'y rechercher d'éventuels futurs outils extrapolables chez les patients septiques.

Si le bénéfice d'un traitement anticoagulant en prévention du risque d'évènements thrombotiques artériels au long cours dans la population de cardiologie ayant une FA est largement démontré, son usage est limité par le risque hémorragique. La stratégie d'anticoagulation repose donc sur l'analyse du rapport entre le bénéfice d'une prévention du risque d'évènements thrombotiques artériels et le risque d'évènements hémorragiques sévères.

1.2.3.1 Durée de la FA et formation de thrombus intra-cardiaque

Chez les patients de cardiologie, de nombreuses études en ETOs ont précisé l'incidence et le délai d'apparition d'un thrombus intra cardiaque, notamment au niveau de l'auricule gauche. La prévalence de thrombose de l'oreillette gauche et/ou de son auricule parmi les patients en FAN de plus de 48 h varie de 0% à 27% [57–62], dépendant de la « charge » en FA, la présence ou non d'un traitement anticoagulant ainsi que de la présence d'un AVC récent [63]. Sur ces données, les différentes sociétés savantes cardiologiques ont considéré que la formation d'un thrombus intra cardiaque nécessitait que la FA persiste au moins 48h [21,44]. Des thrombi ont cependant été visualisés en ETO dans des délais plus courts. Stoddard et al. ont ainsi rapporté une prévalence de thrombus intra cardiaque de 14% en cas de FA datant de moins de 48 heures [59]. Kleemann et al. retrouvaient une prévalence plus faible de 1,4 % chez les patients ayant une FA de moins de 48 heures sous anti vitamine K et de 4% chez les patients sans anti vitamine K [64].

1.2.3.2 La sidération de l'auricule gauche post cardioversion

De nombreuses études ETOs effectuées pendant la conversion de la FA en rythme sinusal ont rapporté la survenue d'une dysfonction auriculaire gauche (ou « sidération ») post cardioversion en rapport avec une perte de la contraction mécanique organisée [65]. La sidération de l'auricule gauche post cardioversion se manifeste par une réduction des vitesses de remplissage et de vidange de l'auricule gauche, malgré un retour en rythme sinusal [66–69]. Ce phénomène favorise la formation de thrombus intra auricule gauche post cardioversion, et ce quelle que soit la modalité de la cardioversion (électrique, médicamenteuse ou spontanée) [70]. La sidération atriale est maximale immédiatement après la cardioversion, avec une reprise progressive de sa fonction contractile en quelques jours à quelques semaines (jusqu'à 3 ou 4 semaines) [70,71]. Ces observations expliquent que 80% des évènements thrombotiques artériels surviennent dans les 3 premiers jours post cardioversion et que la quasi-totalité surviennent dans les 10 premiers jours [72]. Cela renforce la nécessité d'un traitement anticoagulant au cours de la période péri cardioversion, même en l'absence de thrombus préalablement visualisé [21]. Sur ces données, les différentes sociétés savantes cardiologiques considèrent que le risque de sidération atriale post cardioversion pendant 3 à 4 semaines justifie la poursuite du traitement anticoagulant au moins durant cette période, y compris chez les patients à faible score risque thrombo-embolique [66].

1.2.3.1 Scores de risque thrombotiques *CHA₂DS₂-VASc* et hémorragique HAS-BLED (Annexe 1)

De nombreuses études cardiologiques ont permis de distinguer des facteurs de risque cliniques d'évènements thrombotiques artériels «majeurs» et «non majeurs» liés aux patients ayant une FA non valvulaire chronique et non anticoagulés. Les facteurs de risque majeurs sont l'âge \geq 75 ans et la présence d'un antécédent d'AVC ischémique constitué, d'AVC ischémique

transitoire, ou d'accident artériel thrombo-embolique non cérébral [21,73]. Les facteurs de risque non majeurs sont une insuffisance cardiaque congestive, une dysfonction ventriculaire gauche systolique (fraction d'éjection ventriculaire gauche $\leq 40\%$), un diabète sucré, le sexe féminin, et un âge entre 65 et 74 ans [21,73]. Afin de mieux appréhender le risque d'ATE propre à chaque patient, le CHA₂DS₂-VASc score [*Congestive heart failure, Hypertension, Age ≥ 65 years (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74 years, Sex category (female)*] a été développés à partir de ces facteurs de risques [21,73]. Un score CHA₂DS₂-VASc ≥ 2 indique un haut risque d'évènements thrombotiques artériels.

1.2.3.2 Paramètres échocardiographiques

Echocardiographie transthoracique

L'existence d'une sténose mitrale identifie une population à haut risque d'évènements thrombotiques artériels [74]. La présence d'une dilatation de l'oreillette gauche et d'une dysfonction systolique ventriculaire gauche sont les seuls autres paramètres en échocardiographie transthoracique indépendamment associés à une augmentation du risque d'évènements thrombotiques artériels [75]. Chez les patients considérés à faible risque d'évènements thrombotiques artériels selon la stratification clinique, le taux d'AVC passe de 0,4% à 9,3% par an en présence d'une dysfonction systolique ventriculaire et de 4,4% à 15% par an dans la population à haut risque [76].

Echocardiographie transoesophagienne

L'ETO constitue un outil performant semi-invasif permettant l'étude des structures postérieures inaccessible (ou difficilement accessible) en échocardiographie transthoracique, notamment l'oreillette gauche, l'auricule gauche, et l'aorte thoracique. L'objectif de l'examen est d'évaluer au sein de ces structures les paramètres associés à un risque accru d'évènements thrombotiques artériels chez les patients de cardiologie présentant une FA [56,77].

La présence d'un contraste spontané intense dans le massif atrial, oreillette et auricule gauche, est le témoin échocardiographique de la stase sanguine dans la cavité atriale gauche. Le contraste spontané est défini par la présence d'un nuage dynamique d'échos de faible amplitude, animés d'un mouvement lent, répétitif, et circulaire ; la réflexion des ultrasons est plus élevée pour des faibles contraintes de cisaillement et dépend de l'hématocrite, de la concentration en fibrinogène et en macromolécules plasmatiques (**Figure 2, A₂**) [78–80]. La description du contraste spontané dans le massif atrial gauche est basée sur la classification de Fatkin qui distingue 4 niveaux de contraste (de 0 à 3) en fonction de l'intensité (modulé ou non par l'augmentation des gains) et la répartition du contraste spontané dans l'oreillette et l'auricule. Certains auteurs décrivent un stade supplémentaire, le « sludge » (ou état immédiatement pré thrombotique). Les patients présentant un contraste spontané atrial gauche de grade 3 (dit « intense ») ont un taux d'AVC important (22%) au long cours, et ce, malgré un traitement anticoagulant curatif [81].

La présence d'un thrombus intra auriculaire gauche est systématiquement recherché (**Figure 2, A₃**). L'ETO reste actuellement la technique de référence dans cette indication, permettant de détecter un thrombus avec une sensibilité et une spécificité élevées, qui varie entre 93 et 100 % [82].

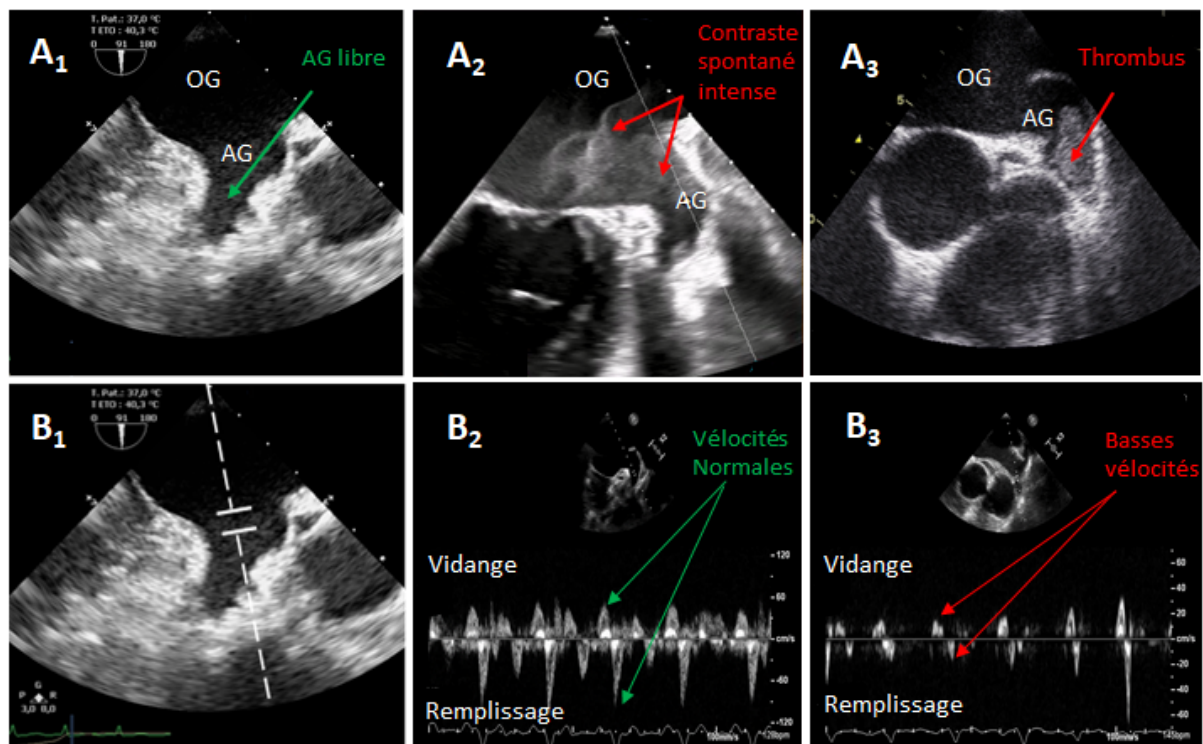
La fonction atriale est étudiée en ETO en mode Doppler pulsé. L'examen permettra de mesurer les vitesses de vidange (liées à la contraction de l'auricule gauche) et de remplissage de l'auricule gauche. La baisse des vitesses de vidange et de remplissage de l'auricule gauche est ainsi le témoin de sa « sidération » (**Figure 2, B₃**) [83]. Ces mesures participent à la stratification du risque thrombotique chez les patients de cardiologie en FA. Mügge et al ont montré que la prévalence du contraste spontané dans l'oreillette gauche était plus élevée lorsque les vitesses intra auriculaires gauches étaient inférieures à 25 cm/s [83]. Dans l'étude SPAF III, la présence d'un thrombus dans l'auricule gauche était plus fréquente dans le groupe de patient

ayant des vitesses intra auriculaires gauches basses (< 20 cm/s) [84]. Enfin les vitesses auriculaires gauches basses sont associées à un taux d'événements thrombotiques artériels majoré d'un facteur 2,6 [56].

L'athérome aortique complexe (plaque athéromateuse protrusive ≥ 4 mm, athérome mobile ou plaque atheromateuse ulcérée [85,86]) est associé à un risque accru d'évènements thrombotiques artériels chez les patients de cardiologie en FA (15,8% par an, multiplié par 4 par rapport au risque des patients sans athérome aortique complexe) [87]. L'association d'anomalies atriales gauches et d'un athérome aortique protrusif sélectionne un sous groupe de patients en FA à risque particulièrement élevé d'évènements thrombotiques artériels. Le risque d'AVC est de 7.5 % par an en présence d'un contraste spontané ou d'un thrombus atrial gauche, de 12 % par an en présence d'un athérome aortique ≥ 4 mm et de 20,5% par an si ces 2 facteurs sont associés. En leur absence, le risque d'AVC est de 1,2% par an [55].

L'ETO, réalisable au lit du patient, pourrait donc être particulièrement utile afin d'estimer le risque thrombotique chez les patients instables hospitalisés en réanimation et présentant une FA au cours d'un sepsis.

Figure 2. Anomalies de l'auricule gauche (AG) (en échocardiographie trans-oesophagienne coupe oesophagienne moyenne) associées à un risque accru d'évènements thrombotiques artériels chez les patients de cardiologie présentant une fibrillation atriale. **A₁** Incidence à 90°, AG libre, **A₂** Incidence à 90°, Contraste spontané intense dans l'auricule gauche défini par la présence d'un nuage dynamique d'échos de faible amplitude, animés d'un mouvement lent, répétitif, et circulaire ; la réflexion des ultrasons est plus élevée pour des faibles contraintes de cisaillement et dépend de l'hématocrite, de la concentration en fibrinogène et en macromolécules plasmatiques, **A₃** : Incidence à 0°, thrombus intra-AG. **B₁** : Incidence à 90°, mesure au doppler pulsé des vitesses de remplissage et de vidange intra-AG, **B₂** : normalité des vitesses (≥ 25 cm/s), **B₃** : baisse des vitesses (<25 cm/s)



Abbreviations : AG, auricule gauche ; ETO, échocardiographie trans-oesophagienne ; OG, oreillette gauche

1.2.4 Risque hémorragique

Au même titre que le risque thrombotique, le risque hémorragique est fortement majoré lors du sepsis. En effet, la dérégulation de la réponse inflammatoire secondaire à l'infection peut engendrer un état anti-thrombotique associant thrombopénie, consommation des facteurs de la coagulation, et augmentation de la fibrinolyse à l'origine de complications hémorragiques sévères [88–91].

Dès les années 1990, Brown et al ont rapporté la survenue d'une hémorragie clinique lors du séjour en réanimation médico-chirurgicale chez 10% (138/1328) des patients [92]. Les facteurs de risque d'hémorragie étaient la mise sous traitement anticoagulant curatif (RR = 4.19), la dénutrition (RR=3.45), l'insuffisance rénale aiguë (RR= 3.36), une médication antiulcéreuse gastro-duodénale à l'admission (RR=3.36), ainsi que la ventilation mécanique (RR=1.82). La survenue d'une hémorragie en réanimation était un facteur de risque indépendant de mortalité hospitalière [92]. Plus récemment, Strauss et al ont confirmé ces résultats en rapportant une incidence d'évènements hémorragiques majeurs de 20% chez les patients hospitalisés en réanimation pour une cause médicale, souvent septique [93]. La présence d'une CIVD était significativement associée à un sur-risque hémorragique. Plus particulièrement chez les patients présentant une FA au cours d'un sepsis, Walkey et al. ont montré une incidence de 12.6% d'évènements hémorragiques majeurs [94].

Si le risque d'évènements thrombotique artériels peut légitimement poser la question de l'intérêt préventif du traitement anticoagulant, l'évaluation du risque hémorragique devra donc être systématique afin d'évaluer la balance bénéfique/risque d'un tel traitement. Le score HAS-BLED [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, labile International Normalized Ratio (INR), Elderly (âge > 65 years), Drugs/alcohol concomitantly] a été développé en cardiologie chez les patients ayant une FA

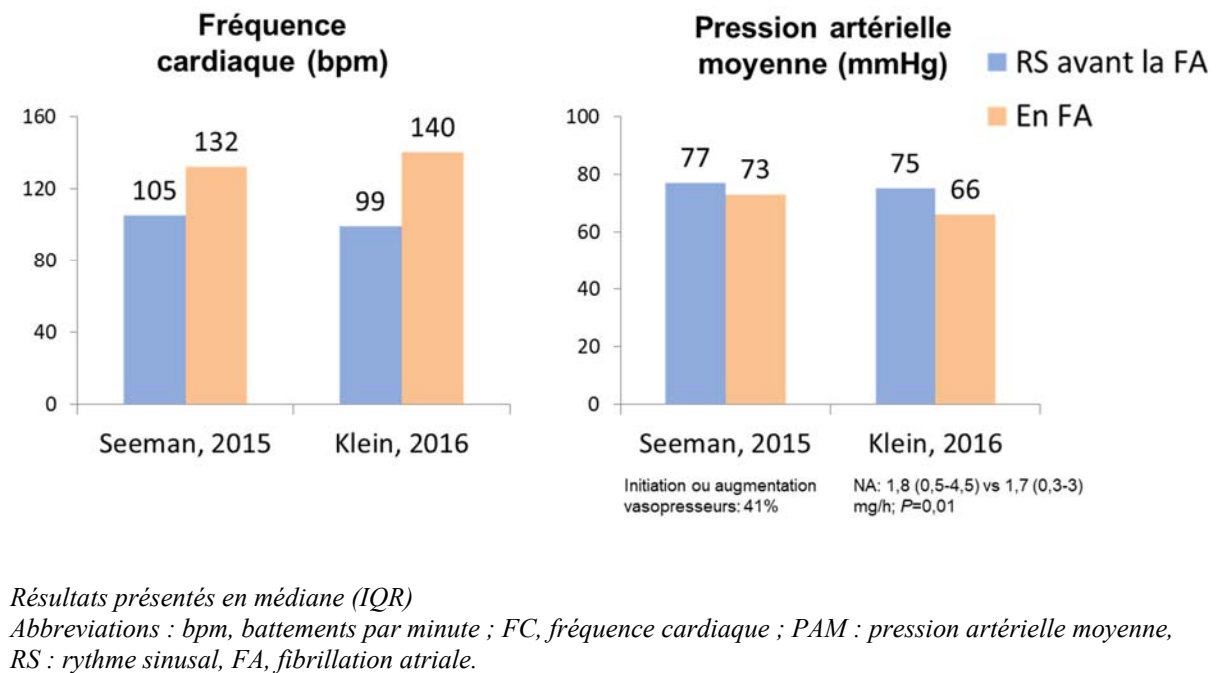
traitée par anticoagulation efficace pour prédire le risque d'hémorragie grave à 1 an [44]. Un score HAS-BLED ≥ 3 indique un haut risque de complication hémorragique en cas d'anticoagulation efficace.

1.3 Risques hémodynamiques chez les patients en FA de novo au cours d'un sepsis

1.3.1 Altération hémodynamique

La survenue d'une FAN au cours d'un sepsis est associée à une altération de l'état hémodynamique (**Figure 3**) [5,7]. Seemann et al. rapportent une augmentation significative des doses (médianes [IQR]) de noradrénaline de 1,7 mg/h [0,3-3] à 1,8 mg/h [0,5-4,5] dans l'heure suivant la survenue de la FAN chez 30 patients en choc septique [7]. Klein et al. décrivent une chute de la pression artérielle moyenne de 75 mm Hg (IQR 66-85) à 66 mm Hg (IQR 60-76) lors d'un premier épisode de FAN chez 418 patients en sepsis, malgré l'initiation ou la majoration des doses de vasopresseurs chez 41% d'entre eux [5].

Figure 3 : conséquences hémodynamiques chez les patients du passage en fibrillation atriale de novo au cours d'un sepsis [5,7]



1.3.2 Physiopathologie de l'altération hémodynamique

1.3.2.1 En milieu cardiologique

La FA peuvent engendrer une dysfonction diastolique et/ou systolique du ventricule gauche à l'origine d'une baisse du débit cardiaque. La dysfonction diastolique ventriculaire gauche est secondaire à : (i) la perte de la systole auriculaire et donc du remplissage ventriculaire télé-diastolique [95] ; (ii) l'irrégularité du temps diastolique qui engendre une diminution du remplissage ventriculaire d'autant plus importante que la durée de la diastole précédant la contraction est courte [96]. La dysfonction systolique ventriculaire gauche (tachycardiomyopathie ventriculaire) [97] est secondaire à : (i) une ischémie sous endocardique [98,99] avec altération de la contractilité intrinsèque du ventricule gauche due à une diminution des apports en oxygène par réduction du temps diastolique de perfusion coronaire et une augmentation des besoins en oxygène par augmentation de la FC ; (ii) une possible variation

battement par battement de l'inotropisme cardiaque due à l'irrégularité des contractions ventriculaires [100].

1.3.2.2 Particularités chez les patients septiques

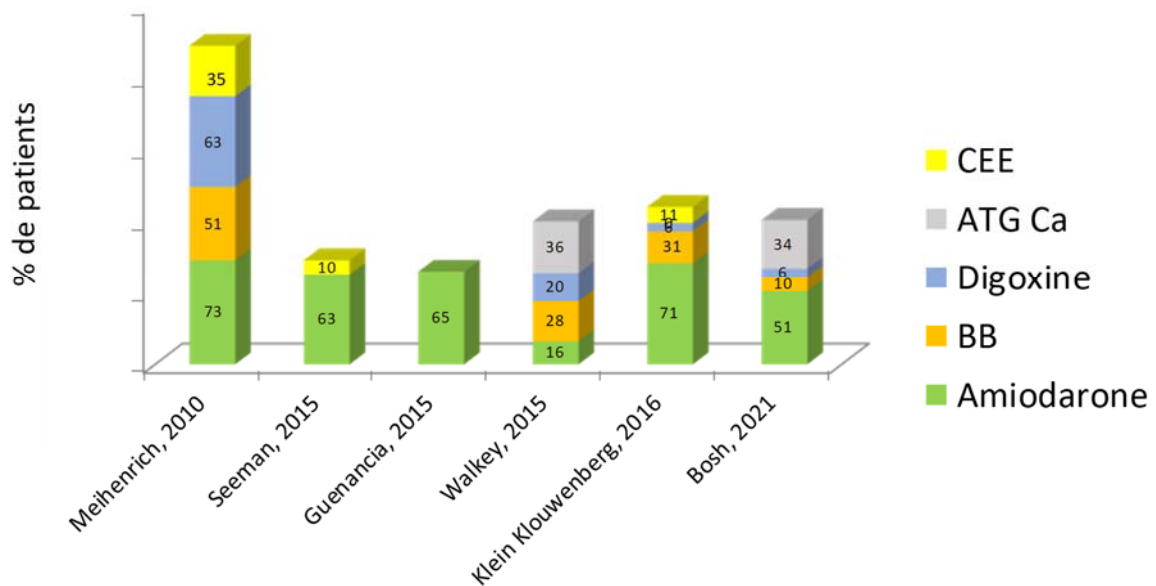
Les altérations hémodynamiques pourraient être exacerbées chez les patients en choc septique étant donné : (i) l'élévation de la FC préalablement à la survenue de la FAN ; (ii) la conduction ventriculaire rapide lors de la FAN; (iii) l'incidence élevée de dysfonction ventricule gauche diastolique et systolique chez les patients septiques. Klein et al. rapportent une fréquence ventriculaire médiane de 105 (IQR 89-119) battements par minute juste avant la survenue de la FAN chez 418 patients septiques [101] (**Figure 3**). Dans cette situation, le raccourcissement du temps diastolique explique que le remplissage ventriculaire soit fortement dépendant de la contraction auriculaire, et que sa disparition soit susceptible d'engendrer une chute du débit cardiaque [102]. Le remplissage ventriculaire est également en grande partie dépendant de la contraction auriculaire en cas de dysfonction diastolique ventricule gauche sous-jacente [103], présente chez 60% des patients en choc septique [104]. Lors de la survenue d'une FAN, Klein et al. décrivent une hausse de la fréquence ventriculaire à une médiane de 132 (IQR 116-152) bpm (**Figure 3**) pouvant accroître l'ischémie sous-endocardique par augmentation des besoins en oxygène du myocarde [101]. Enfin, les conséquences de la baisse de l'inotropisme ventriculaire gauche pourraient être d'autant plus marquées qu'il existe une baisse de la contractilité intrinsèque du ventricule gauche sous-jacente présente chez plus de deux-tiers des patients en choc septique [105].

1.3.3 Prise en charge hémodynamique actuelle de la FAN chez les patients en choc septique : 3 stratégies en pratique courante

Aucun essai randomisé n'a comparé les différentes stratégies de prise en charge hémodynamique des FANs chez les patients en choc septique, si bien qu'aucune

recommandation spécifique n'est disponible dans ce contexte. Par ailleurs, les recommandations 2020 de l'European Society of Cardiology (ESC) sont difficilement applicables chez les patients en choc septique, car ces derniers sont par définition défaillants sur le plan hémodynamique [66]. Les études observationnelles européennes rapportent ainsi une grande hétérogénéité des pratiques dans ce contexte (**Figure 4**) [5,7,23,24].

Figure 4 : Thérapeutiques spécifiques utilisées en pratique courante lors de la prise en charge des patients présentant une fibrillation atriale de novo au cours d'un sepsis



Abbreviations : CEE, choc électrique externe, ATG Ca, antagoniste calcique, BB, beta-bloquants

De cette hétérogénéité des pratiques, nous pouvons néanmoins identifier **3 stratégies usuelles de prise en charge du risque hémodynamique** :

- une stratégie de contrôle des « triggers » (Cf paragraphe 1.1.1) de la FAN, sans utilisation de traitement spécifique anti-arythmique [106] (contrôle du risque);

- une stratégie de contrôle de la FC, en association au contrôle des triggers, par l'utilisation d'anti-arythmiques, tels que l'amiodarone à faible doses ou les beta-bloquants de très courte durée d'action [5,7,106,107] ;
- une stratégie de contrôle du rythme cardiaque (RC), en association au contrôle des triggers, par l'utilisation d'anti-arythmiques, exclusivement l'amiodarone à fortes doses, et/ou la réalisation d'un choc électrique externe [5,7,106,107].

1.3.3.1 Stratégie usuelle de contrôle du risque

Un certain nombre d'épisodes de FAN pourrait être résolutif par le seul contrôle des triggers (cf paragraphe 1.1.1) [12]. En particulier, l'hypo-magnésémie est un trigger clairement identifié [11], et sa correction doit être envisagée selon de récentes recommandations d'experts [12]. De plus, le magnésium présente des propriétés stabilisatrices de membrane [12] et pourrait permettre un meilleur contrôle du RC et de la FC en association avec d'autres anti-arythmiques. Les effets secondaires notables (bradycardie) sont rares et surviennent essentiellement lors de l'administration de doses importantes [13,108]. La prévalence attendue d'un événement indésirable grave après la réalisation d'un bolus unique intra-veineux de 2g sur 20 minutes est donc très faible [109,110]. L'utilisation du magnésium, seul ou en association avec un traitement spécifique anti-arythmique, demeure ainsi une pratique courante chez les patients ayant une FAN en choc septique [106], et cela même en l'absence d'hypomagnésémie documentée (absence de corrélation démontrée entre magnésémie et efficacité clinique du magnésium dans ce contexte, [109]).

1.3.3.2 Stratégie usuelle de contrôle de la FC

Amiodarone faible dose

L'utilisation d'amiodarone intra-veineuse à faibles doses est usuelle lors d'une stratégie visant à limiter la tachycardie (contrôle de la FC). En effet, le choix thérapeutique demeure limité chez les patients en état de choc septique qui présentent constamment une diminution des résistances vasculaires, ainsi qu'une altération fréquente de la contractilité intrinsèque du ventricule gauche [105]. De plus, l'insuffisance rénale est fréquente dans cette population [7]. Dans ces circonstances, les bêtabloquants et les antagonistes calciques bradycardisants (vasodilatateurs périphériques et inotropes négatifs), ainsi que les digitaliques (risque de surdosage en cas d'insuffisance rénale), sont d'utilisation complexe et souvent contre-indiqués. L'ESC indique que l'amiodarone intra-veineuse peut être utilisée afin de contrôler la FC en cas d'instabilité hémodynamique, ou de dysfonction systolique ventriculaire gauche sévère [111].

En raison de l'absorption retardée et de la biodisponibilité incomplète de la voie entérale à l'origine d'une concentration plasmatique maximale tardive entre 3 et 7 heures [112], la voie intra-veineuse est initialement recommandée afin d'obtenir un effet thérapeutique rapide [111]. Du fait de la toxicité potentielle de l'amiodarone, la posologie idéale doit être la plus faible possible qui ait la capacité de diminuer significativement et rapidement la FC. La FC optimale d'un point de vue hémodynamique chez les patients ayant une FAN au cours du choc septique n'est cependant pas précisément connue. Chez les patients de cardiologie, l'ESC préconise l'obtention d'une FC inférieure à 110 bpm [15]. En réanimation, une «faible dose» d'attaque d'amiodarone permet de diminuer la FC de 37 ± 8 bpm [113]. Salem et al rapportent des résultats similaires à l'aide d'une modélisation de la relation effet-dose de l'amiodarone sur la réduction de la FC chez les patients ayant une FAN au cours d'un état de choc cardiogénique

ou d'un sepsis: une «faible dose» d'attaque d'amiodarone permet une diminution de la FC de 154 bpm à moins de 115 bpm [107].

Beta-bloquants de courte durée d'action

Les β bloquants β_1 hautement selectif de très courte durée d'action pourraient avoir un intérêt afin de contrôler la FC chez les patients en FA au cours du sepsis/ choc septique. En particulier, le landiolol présente une très courte demie-vie de 4 minutes et un moindre effet inotrope négatif en comparaison avec d'autre β -bloquant intra-veineux [114]. Okajima et al ont ainsi montré que le landiolol permettait une réduction significative de la FC (de 145 ± 14 bpm à 90 ± 20 bpm) sans détérioration de l'état hémodynamique chez 39 patients ayant une FA au cours d'un sepsis [115]. D'autres auteurs ont rapporté des résultats similaires chez les patients présentant une FA au cours d'une COVID-19 sévère [116].

1.3.3.3 Stratégie usuelle de contrôle du rythme cardiaque

Cardioversion médicamenteuse

L'amiodarone, la flécainide et le propafenone sont les trois molécules disponibles en France et recommandées par l'ESC pour la réalisation d'une cardioversion médicamenteuse chez les patients de cardiologie [111]. La flécainide et le propafenone sont cependant contre indiqués chez les patients ayant une cardiopathie sous-jacente [111]. Dans la mesure où plus de deux-tiers des patients présentent une baisse de la contractilité intrinsèque du ventricule gauche au cours du choc septique [105], l'amiodarone demeure la molécule anti-arythmique usuellement utilisée dans ce contexte pour une cardioversion médicamenteuse [106]. Afin d'optimiser le taux de cardioversion, l'ESC 2016 [111] et l'ANSM (Agence Nationale de Sécurité du Médicament) recommandent la réalisation d'un bolus intra-veineux initial de 5-7 mg/kg suivi d'une perfusion continue intra-veineuse de 1200 mg sur 24h. En effet, la concentration plasmatique d'amiodarone chute très rapidement par absorption tissulaire [112], et l'effet

thérapeutique s'épuise après 4 heures, justifiant la poursuite d'une perfusion continue IVSE [111] dans le cas où une forte dose est nécessaire. Plusieurs études menées chez les patients de cardiologie ayant une FA récente de moins de 15 jours rapportent que le taux de cardioversion obtenu avec l'amiodarone en bolus IV unique varie de 34 à 69%, contre 55 à 95% lorsque le bolus initial est suivi d'une perfusion continue [117]. A notre connaissance, il n'y a cependant pas de données chez les patients en choc septique concernant d'une part le taux de succès de la cardioversion médicamenteuse avec l'amiodarone, et d'autre part la dose d'attaque optimale d'amiodarone qui permettrait d'optimiser le taux de cardioversion.

En l'absence de dysfonction ventriculaire gauche systolique sous jacente, le propafenone pourrait constituer une alternative intéressante à l'amiodarone. Récemment, Balik et al. ont publié un essai randomisé, bi-centrique, contrôlé, en double aveugle, visant à comparer l'efficacité de l'amiodarone et du propafenone à forte dose intra-veineuse chez 209 patients ayant une FAN au cours d'un choc septique sans dysfonction ventriculaire gauche systolique sévère. Si il n'y avait pas de différence significative au regard du critère de jugement principal (pourcentage de patients en rythme sinusal à H24 du début de l'infusion) entre les deux molécules, le propafenone permettait cependant une cardioversion plus rapide (3,7 h [95% CI 2,3-6.,8] vs. 7,3 h [95% CI 5-11], $p = 0,02$) avec un taux de récurrence plus faible (52% vs 76%, $p < 0,001$) que l'amiodarone.

Cardioversion électrique : choc électrique externe

La réalisation d'un choc électrique externe est la seconde alternative usuellement choisie par le clinicien afin d'obtenir un retour en rythme sinusal chez les patients en choc septique [106]. Chez les patients hospitalisés en réanimation, l'efficacité de la cardioversion électrique demeure cependant limitée : près de deux patients sur trois récidivent la FAN dès la 1^{ère} heure [118] et trois patients sur quatre récidivent à 24 heures de la réalisation du choc électrique

externe [10,119,120]. Cette inefficacité explique en partie que les cliniciens privilégient usuellement la cardioversion médicamenteuse chez les patients septiques : selon les cohortes européennes, deux patients sur trois reçoivent de l'amiodarone alors que seulement un patient sur 10 bénéficie d'une cardioversion électrique (**Table 3**) [5,7].

2. PRINCIPAUX OBJECTIFS DE LA THESE

Les objectifs de ce travail de thèse sont d'étudier les risques thrombotiques et hémodynamiques chez les patients présentant une FAN au cours d'un sepsis/ choc septique:

2.1 Risque thrombotique (Article 1 et 2)

2.1.1 Questions non résolues chez les patients ayant une FAN au cours d'un sepsis

Les données prospectives sur les risques thrombotiques et hémorragiques sont peu nombreuses.

L'absence d'étude ETO ne permet pas d'appréhender à ce jour :

- l'incidence et le délai d'apparition de la thrombose intra-cardiaque dans ce contexte ;
- l'incidence des anomalies échocardiographiques associées au risque d'évènements thrombotiques artériels chez les patients de cardiologie en FA (Cf. paragraphe 1.2.3) ;
- L'incidence de survenue de la sidération de l'auricule gauche post cardioversion.

Les scores de risque thrombotique CHA₂DS₂-VASc et hémorragique HAS-BLED n'ont pas été étudiés dans ce contexte.

L'absence d'essai thérapeutique randomisé ne permet pas d'appréhender la balance bénéfice risque du traitement anticoagulant en prévention du risque thrombotique dans ce contexte.

2.1.2 Objectifs de la thèse

Concernant l'étude du risque thrombotique, nos objectifs sont de :

- Caractériser le risque d'évènements cardio-vasculaires associant les évènements thrombotiques artériels, les évènements hémorragiques sévères et le décès toute cause ;
- Etudier l'incidence des anomalies échocardiographiques connues pour être associées au risque d'évènements thrombotiques artériels chez les patients de cardiologie en FA (Cf. paragraphe 1.2.3) : contraste spontané intense au sein du massif atrial gauche (oreillette et auricule gauche), thrombus dans l'oreillette/auricule gauche, baisses des vitesses de vidange et de remplissage intra-auriculaire gauche, athérome aortique complexe, dysfonction ventriculaire gauche systolique ;
- Étudier d'éventuelles associations entre ces anomalies structurelles et fonctionnelles échocardiographiques et le risque cardio-vasculaire, notamment thrombotique ;
- Etudier l'incidence de survenue de la sidération de l'auricule gauche post cardioversion ;
- Etablir les bases d'un futur essai dont l'objectif sera d'évaluer la meilleure stratégie de traitement anticoagulant en terme de prévention des évènements thrombotiques artériels sans sur-risque hémorragique ou de décès.

Nous avons réalisé une étude prospective multicentrique échocardiographique au sein de 10 Services de Réanimation Française chez les patients ayant une FAN au cours d'un sepsis (Article 1, Article 2 : sous analyse de l'article 1).

2.2 Risque hémodynamique (Article 3)

2.2.1 Question non résolue chez les patients ayant une FAN au cours d'un sepsis

Quelle est la meilleur des stratégies de prise en charge hémodynamique des patients ayant une FAN au cours d'un état de choc septique ?

2.2.2 Objectifs de la thèse

Nos objectifs étaient de comparer l'efficacité hémodynamique des trois stratégies de prise en charge usuelle (Cf paragraphe 1.3.3 ; contrôle du risque, contrôle de la FC, contrôle du RC) chez les patients présentant une FA au cours d'un choc septique. Notre hypothèse est que les stratégies de contrôle du rythme et de la fréquence améliorent chacune l'hémodynamique comparativement à une stratégie de contrôle du risque, et que le contrôle du rythme cardiaque améliore l'hémodynamique comparativement au contrôle de la fréquence (Article 2).

3. RISQUE THROMBOTIQUE

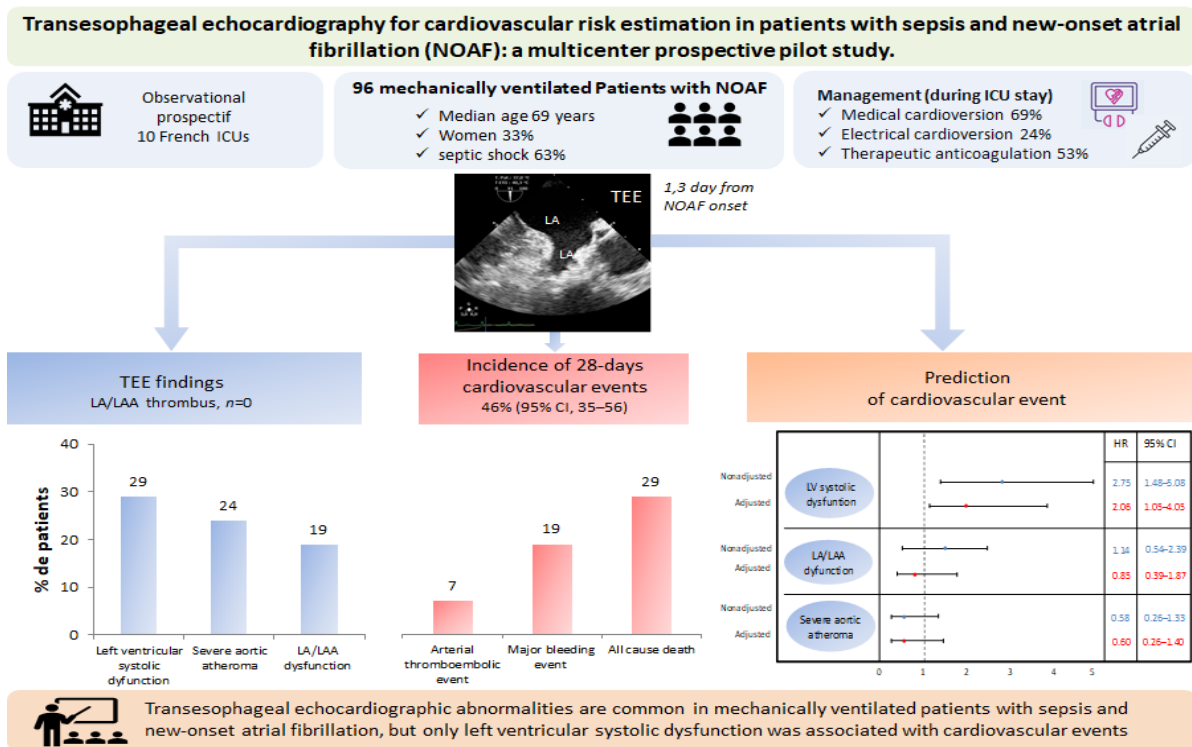
Article 1

Transesophageal echocardiography for cardiovascular risk estimation in patients with sepsis and new-onset atrial fibrillation: a multicenter prospective pilot study.

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Visual abstract



RESEARCH

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Transesophageal echocardiography for cardiovascular risk estimation in patients with sepsis and new-onset atrial fibrillation: a multicenter prospective pilot study

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Abstract

Background: Echocardiographic parameters have been poorly investigated for estimating cardiovascular risk in patients with sepsis and new-onset atrial fibrillation. We aim to assess the prevalence of transesophageal echocardiographic abnormalities and their relationship with cardiovascular events in mechanically ventilated patients with sepsis and new-onset atrial fibrillation.

Methods: In this prospective multicenter pilot study, left atrial/left atrial appendage (LA/LAA) dysfunction, severe aortic atheroma, and left ventricular systolic dysfunction were assessed using an initial transesophageal echocardiographic study, which was repeated after 48–72 h to detect LA/LAA thrombus formation. The study outcome was a composite of cardiovascular events at day 28, including arterial thromboembolic events (ischemic stroke, non-cerebrovascular arterial thromboembolism, LA/LAA thrombus), major bleeding, and all-cause death.

Results: The study population comprised 94 patients (septic shock 63%; 35% women; median age 69 years). LA/LAA dysfunction, severe aortic atheroma, and left ventricular systolic dysfunction were detected in 17 (19%), 22 (24%), and 27 (29%) patients, respectively. At day 28, the incidence of cardiovascular events was 46% (95% confidence interval [CI]: 35 to 56). Arterial thromboembolic events and major bleeding occurred in 7 (7%) patients (5 ischemic strokes, 1 non-cerebrovascular arterial thromboembolism, 2 left atrial appendage thrombi) and 18 (19%) patients, respectively. At day 28, 27 patients (29%) died. Septic shock (hazard ratio [HR]: 2.36; 95% CI 1.06 to 5.29) and left ventricular systolic dysfunction (HR: 2.06; 95% CI 1.05 to 4.05) were independently associated with cardiovascular events.

Conclusions: Transesophageal echocardiographic abnormalities are common in mechanically ventilated patients with sepsis and new-onset atrial fibrillation, but only left ventricular systolic dysfunction was associated with cardiovascular events at day 28.

Keywords: Atrial fibrillation, Transesophageal echocardiography, Stroke, Bleeding, Sepsis

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Background

New-onset atrial fibrillation (NOAF) is the commonest arrhythmia in the intensive care unit (ICU) occurring in one-third of critically ill patients with sepsis [1, 2]. In this setting, patients with NOAF are at greater risk

of arterial thromboembolic events [2] and death than patients without NOAF [1, 2]. Decision-making with regard to thrombo-prophylaxis should be based upon the absolute risks of cardiovascular events, including arterial thromboembolism event, bleeding, and death, and the net clinical benefit for a given patient. However, conventional score to assess thromboembolic and bleeding risk in patient with atrial fibrillation have not been validated in the specific setting of sepsis [3, 4].

Transesophageal echocardiography (TEE) abnormalities, such as left ventricular (LV) systolic dysfunction, left atrial/left atrial appendage (LA/LAA) dysfunction, and severe aortic atheroma, are associated with an increased risk of arterial thromboembolic event in patients with atrial fibrillation [5]. In particular, LA/LAA dysfunction, revealed by LAA low velocities and dense spontaneous echo contrast (SEC) resulting from blood stasis [6–8], remains strongly associated with thrombus formation [9]. So, bedside echocardiography could be useful in critically ill patients with sepsis and NOAF for estimating their cardiovascular risk.

We therefore conducted a prospective, multicenter, observational, echocardiographic pilot study (the Fibrillation Atrial Sepsis Thrombus [FAST] study) in 10 French ICUs in patients with sepsis and NOAF. Our objectives were to assess early LV systolic dysfunction, LA/LAA dysfunction, and severe aortic atheroma, and to investigate the relationship of these structural and functional parameters with the occurrence of cardiovascular events at day 28.

Methods

Patient selection

During a 24-month period (November 2014 to November 2016), all mechanically ventilated adult patients with sepsis/septic shock who experienced significant NOAF (including atrial fibrillation and atrial flutter) on ICU admission or during their ICU stay were eligible. Significant NOAF was defined by an AF in patients with no prior history of AF [10], lasting at least 6 h or recurred more than twice (>30 s) per day despite correction of modifiable risk factors such as hypokalemia or hypovolemia [11]. Sepsis/septic shock was defined according to the Sepsis-3 definition [12]. All episodes of NOAF were systematically recorded on an electrocardiogram assessed by two cardiologists (any discrepancy being solved by consensus), and classified as atrial fibrillation, or atrial flutter using standard definitions [13]. Patients with a history of atrial fibrillation for which the cardiovascular risk depends in part to their established previous medication regimen for atrial fibrillation [10], with valvular heart disease classifying AF as “valvular AF” (significant mitral stenosis, mechanical aortic or mitral

valve; [14]), with TEE contraindication [15], those who were moribund (expected survival <48 h), or with a decision to limit full care, and those refusing to participate, were not included.

The study was approved by the Comité de Protection des Personnes Ile-de-France 5 (ref. 14941), as a component of standard care, and patient consent was waived, as per French Law. Written and oral information about the study was given to the patients or their next of kin.

Data collection

Demographics, medical history, antithrombotic medications, admission category, Simplified Acute Physiology Score II [16], and CHA₂DS₂-VASc [14] and HAS-BLED [14] scores were recorded on ICU admission (detailed definitions in Additional file 1: Table S1). The type of infection and the Sepsis-Related Organ Failure assessment score [17] were recorded at NOAF onset (day 0). NOAF management during ICU stay was left at the discretion of the physicians in charge.

Echocardiography

Echocardiography were performed at the bedside by skilled intensivists, all of whom had ≥ 2 years of TEE experience, with competence in advanced critical care echocardiography [18]. Examinations were conducted with recent commercially available equipment (CX50, AFFINITY 70, and IE33; Philips Ultrasound system, Bothell, WA; VIVID 7, VIVID 9, and VIVID I, General Electric Healthcare system, Horten, Norway). All echocardiographic studies involved transthoracic echocardiography according to the recommendations of the European Association of Cardiovascular Imaging [19] with 2.5- and 3-MHz transducers, followed by TEE with 5-MHz multiplane transducers. Each patient underwent echocardiography within 48 h of NOAF onset (initial TEE). Based on the initial TEE findings, changes in treatment regarding therapeutic anticoagulation were left at the discretion of the physicians in charge. To investigate LA/LAA thrombus formation, a second echocardiography was performed 48 to 72 h after the initial TEE in patients who were still mechanically ventilated (second TEE). Supplementary echocardiography studies performed at the discretion of the physicians in charge were recorded.

LA or LAA thrombi, LA/LAA dysfunction (including LA/LAA dense SEC and LAA low velocities), LAA large area, and severe aortic atheroma were investigated as previously described [6, 7, 20–24]. A LA/LAA thrombus was considered present when there was a well-circumscribed, echodense, intra-cavitary mass that is acoustically distinct from the underlying endocardium and the pectinate muscles [21]. LA/LAA dense SEC was defined

as finely reticular pattern of dynamic, swirling intra-cavitary echoes localized within the LA or LAA persistent throughout the LA–LAA at normal gain [6, 21]. Velocity of the LAA was recorded with pulse-wave Doppler interrogation 1 cm within the orifice. Flow velocity was evaluated in anterograde (emptying) and retrograde (filling) directions, and was averaged over a minimum of 3 to 5 consecutive cardiac cycles as specified by protocol. LAA low velocity was defined as a LAA filling or emptying velocity < 25 cm/s [7, 23]. The area of the LAA was measured by planimetry at 90° view as specified by protocol. LAA large area was defined as a LAA area > 5 cm² [21]. The thoracic aorta was analyzed at each level, including the ascending aorta, the proximal and distal arch, and the descending aorta, as specified by protocol and according to previously described methods [20]. Severe aortic atheroma was defined as: protruding atherosclerotic plaques (highly echogenic areas that protruded ≥ 4 mm above the surface of the intima into the aortic lumen); or mobile atheroma; or ulcerated atheroma [20, 22, 24]. LV systolic dysfunction was defined as LV ejection fraction $\leq 45\%$ (mild, 31–45%; severe, $\leq 30\%$) using the biplane Simpson method [19].

All echocardiographic studies were analyzed off-line by two experienced observers (VL and SE) in a blinded manner. Differences between observers were resolved by consensus; if the observers could not agree, a third observer (AC) reviewed the studies, and that observer's judgment was binding.

Follow-up and outcomes

All patients were followed from day 0 (inclusion) to day 28. The primary outcome was the occurrence of a cardiovascular event, comprising arterial thromboembolic events (ischemic stroke, non-cerebrovascular thromboembolism, or thrombus of the LA/LAA on echocardiography studies [3]), major bleeding event (according to the International Society on Thrombosis and Hemostasis definition: symptomatic bleeding in a critical area or organ such as intracranial, bleeding associated with a reduction in hemoglobin of ≥ 1.24 mmol/L or leading to transfusion of ≥ 2 units blood or packed cells, or fatal bleeding; [25, 26]), and death from any cause. Secondary outcomes were individual components of the primary outcome (detailed definitions in Additional file 1: Table S1).

With the exception of the second TEE, no systematic screening of arterial thromboembolic events was performed. The diagnostic work-up of arterial thromboembolic events and major bleeding events included the usual investigations performed in the participating ICUs, and was collected by the attending intensivists. An independent committee adjudicated arterial thromboembolic

events and major bleeding events, and assessed the relationship of ischemic stroke and non-cerebrovascular thromboembolism with NOAF, using the Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment classification (detailed definitions in Additional file 1: Table S2, Fig. S1, [27]).

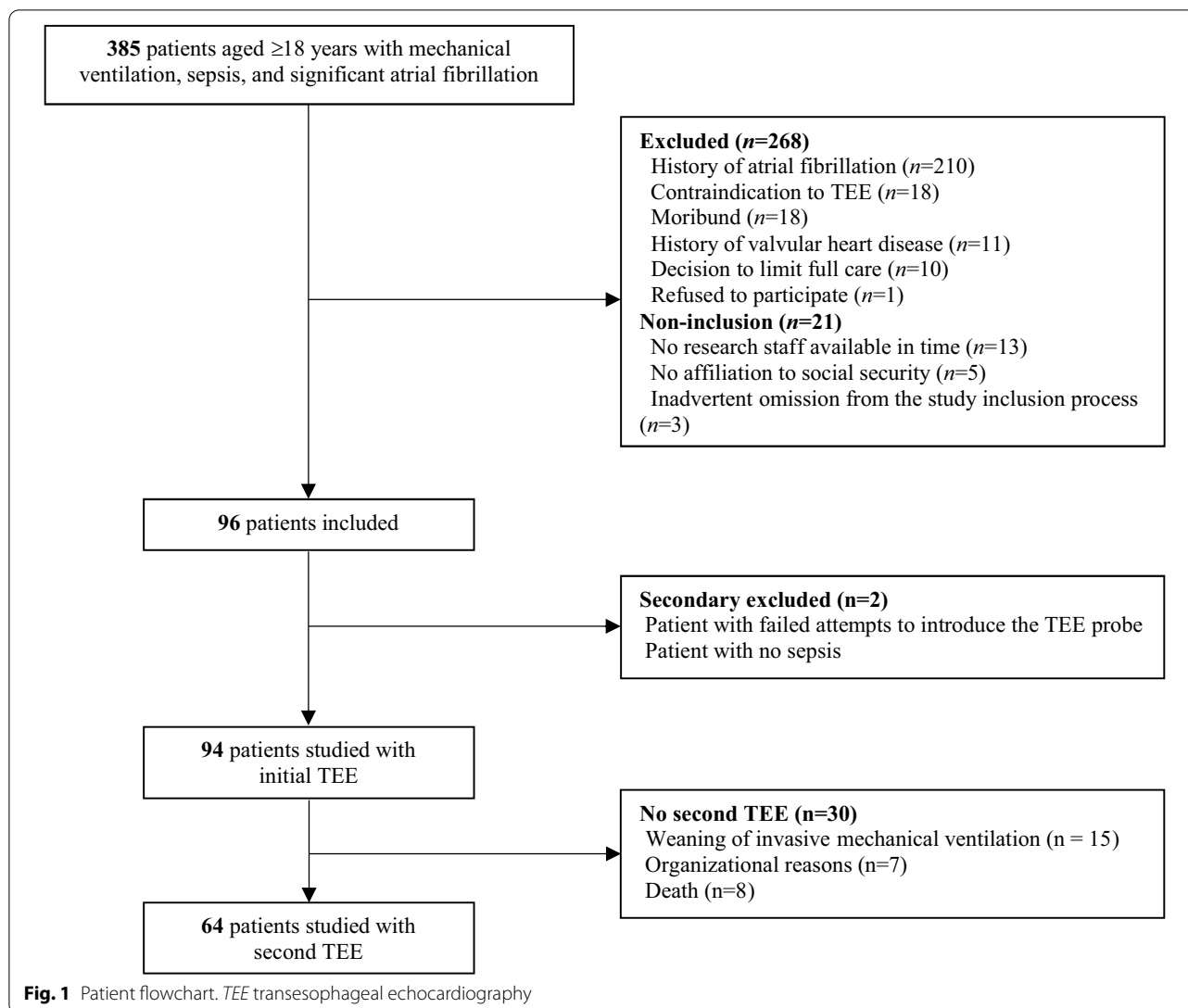
Statistical analysis

Data are reported as medians (interquartile range [IQR]) for quantitative variables, and as frequencies (percentages) for categorical variables. Associations with composite primary outcome (cardiovascular events) were tested by standard Cox models. A multivariable model for the primary outcome was built from studied TEE parameters (LV systolic dysfunction, LA/LAA dysfunction, severe aortic atheroma), with additional adjustment on variables associated with this outcome in the univariate analysis. Associations with secondary outcomes (individual component of the composite primary outcome) were tested by univariate cause-specific Cox models for the first occurrence of arterial thromboembolic event or major bleeding event (accounting for the competing risk of death), and by standard Cox models for the all-cause mortality. A multivariable model was built for the primary outcome only, as the number of events was judged too low to avoid overfitting for the other outcomes. All survival models were censored at day 28. Hazard ratios (HRs) were estimated and reported with their 95% confidence intervals (CIs). All tests were 2-tailed and p values < 0.05 were considered significant. Statistical analysis was conducted with R version 3.6.3 (R Core Team 2019; R foundation for statistical Computing, Vienna, Austria).

Results

Baseline clinical characteristics and TEE findings

During the study period, 94 patients were studied (63 men and 31 women) with a median age of 69 years (IQR: 61 to 77 years) (study flowchart in Fig. 1). Median time from ICU admission to NOAF onset was 2 days (IQR: 1 to 4 days) (atrial fibrillation, $n = 93$; atrial flutter, $n = 1$). Baseline clinical characteristics are displayed in Table 1. Median CHA₂DS₂-VASc score was 3 (IQR: 2 to 4), and HAS-BLED score was 2 (IQR: 1 to 3). Initial TEE studies were performed after a median time of 1.3 days (IQR: 0.7 to 2.1 days) from NOAF onset. NOAF was present during initial TEE in 47% of patients (details regarding other hemodynamic parameters during TEE are available in Additional file 1: Table S3). LA/LAA dysfunction was detected in 19% of patients, including LA/LAA SEC (7%) and LAA low velocities (12%). Severe aortic atheroma was diagnosed in 24% of patients. LV systolic dysfunction occurred in 29% of patients. None of the patients had thrombus in the LA



or LAA (Table 2). Regarding the therapeutic impact of TEE studies, therapeutic anticoagulation was initiated following TEE in 3% of patients due to LA/LAA dense SEC ($n = 2$) and severe aortic atheroma ($n = 1$).

NOAF management during ICU stay

Cardioversion was attempted in 67 patients (71%), using amiodarone in 65 patients (69%) and electric shock in 23 patients (24%). Management prior to electric shock included therapeutic anticoagulation in 8 of 23 patients and TEE to exclude LA/LAA thrombus in 13 of 23 patients. During ICU stay, therapeutic anticoagulation was administered in 50 patients (53%), after 1 day (IQR: 0 to 2 days) from NOAF onset. At day 28, NOAF was persistent in 15 patients (16%) (Additional file 1: Table S4).

Outcomes

The incidence of cardiovascular events at day 28 was 46% (95% CI: 35 to 56), and 27 patients (29%) died. 7 patients (7%) presented at least one arterial thromboembolic event occurring after a median of 6 days (IQR: 4 to 7 days) from NOAF onset. Arterial thromboembolic events included 5 ischemic strokes (three definitely, one probably, and one definitely not related to NOAF), 1 non-cerebral thromboembolism (probably related to NOAF), and 2 LAA thrombi. A second TEE was performed in 64 patients (Fig. 1) after 4.2 days (IQR: 3.3 to 5.1 days) from NOAF onset, and revealed 1 LAA thrombus. The second LAA thrombus was diagnosed in a further TEE, performed 17 days after NOAF onset because of the clinical occurrence of ischemic stroke. Details about the mechanisms of each arterial thromboembolic event are shown

Table 1 Baseline clinical characteristics, initial severity, and initial new-onset atrial fibrillation management according to 28-day arterial thromboembolic events, major bleeding events and death

Variable	Total (n = 94)	Arterial thromboembolic event		Major bleeding event		Death	
		No (n = 87)	Yes (n = 7)	No (n = 76)	Yes (n = 18)	No (n = 67)	Yes (n = 27)
Baseline clinical characteristics on ICU admission							
Age, median (IQR), years	69 (61–77)	69 (61–77)	69 (63–80)	69 (61–78)	67 (61–74)	69 (61–77)	68 (64–78)
Female sex, no. (%)	33 (35)	31 (36)	2 (29)	26 (34)	7 (39)	25 (37)	8 (30)
Cardiac disease, no. (%)	17 (18)	14 (16)	3 (43)	14 (18)	3 (17)	13 (19)	4 (15)
Left ventricular systolic dysfunction, no. (%)	3 (3)	3 (3)	0	3 (4)	0	3 (4)	0
Vascular disease, no. (%)	19 (20)	16 (18)	3 (43)	14 (18)	5 (28)	11 (16)	8 (30)
Stroke, no. (%)	8 (8)	8 (9)	0	7 (9)	1 (6)	5 (7)	3 (11)
Diabetes mellitus, no. (%)	24 (25)	23 (26)	1 (14)	21 (28)	3 (17)	14 (21)	10 (37)
Smoker, no. (%)	51 (54)	48 (55)	3 (43)	42 (55)	9 (50)	37 (55)	14 (52)
Hypertension, no. (%)	57 (61)	51 (59)	6 (86)	46 (60)	11 (61)	38 (57)	19 (70)
Clinical risk scores, median (IQR)							
CHA ₂ DS ₂ -VASc	3 (2–4)	3 (2–4)	3 (1–4)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)
HAS-BLED	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
Previous therapeutic anticoagulation, no. (%)	4 (4)	4 (5)	0	2 (3)	2 (11)	4 (6)	0
Admission category, no. (%)							
Medical	74 (79)	70 (80)	4 (57)	61 (80)	13 (72)	52 (78)	22 (81)
Scheduled surgery	5 (5)	5 (6)	0	4 (5)	1 (6)	4 (6)	1 (4)
Emergency surgery	15 (16)	12 (14)	3 (43) ^a	11 (14)	4 (22)	11 (16)	4 (15)
SAPS II score on ICU admission, median (IQR)	58 (47–74)	58 (44–74)	63 (51–68)	60 (44–74)	54 (50–73)	54 (43–73)	65 (55–74)
Severity and management on the day of NOAF onset							
SOFA score, median (IQR)	9 (7–11)	9 (7–11)	9 (6–9)	9 (7–11)	9 (6–11)	9 (7–11)	10 (6–13)
Septic shock, no. (%)	59 (63)	55 (63)	4 (57)	45 (59)	14 (78)	38 (57)	21 (78)
Catecholamine, no. (%)	75 (80)	70 (80)	5 (71)	60 (79)	15 (83)	52 (78)	23 (85)
Norepinephrine	71 (75)	66 (76)	5 (71)	57 (75)	14 (78)	50 (75)	21 (78)
Epinephrine	6 (6)	5 (6)	1 (14)	3 (4)	3 (17) ^b	4 (6)	2 (7)
Dobutamine	7 (7)	5 (6)	2 (29)	7 (9)	0	5 (7)	2 (7)
Cardioversion attempt, no. (%)	60 (64)	58 (67)	2 (29)	49 (64)	11 (61)	42 (63)	18 (67)
Medical (amiodarone)	59 (63)	57 (65)	2 (29)	48 (63)	11 (61)	41 (61)	18 (67)
Electrical	16 (17)	16 (18)	0	9 (12)	7 (39) ^b	10 (15)	6 (22)
Antiplatelet therapy, no. (%)	24 (25)	21 (24)	3 (43)	17 (22)	7 (39)	15 (22)	9 (33)
Therapeutic anticoagulation, no. (%)	28 (30)	25 (29)	3 (43)	23 (30)	5 (28)	23 (34)	5 (18)

CHA₂DS₂-VASc congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, sex category (female), HAS-BLED hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly, ICU intensive care unit, IQR interquartile, NOAF new-onset atrial fibrillation, SAPS Simplified Acute Physiology Score, SOFA Sepsis-Related Organ Failure Assessment

^a $p < 0.05$, when compared with the value for no arterial thromboembolic event

^b $p < 0.05$, when compared with the value for no major bleeding event

in Table 3. 18 patients (19%) had at least one major bleeding event occurring after a median of 8.5 days (IQR: 3.5 to 12 days) from NOAF onset. Major bleeding events included 21 extra-cranial and 2 intracranial bleedings (Additional file 1: Table S5). 10 patients (11%) presented a major bleeding event categorized as life-threatening, including fatal gastrointestinal bleeding in 2 of them. At the time of the first arterial thromboembolic and major bleeding events, therapeutic anticoagulation was used in 5 patients (71%) and 12 patients (67%), respectively.

Factors associated with cardiovascular events

Baseline clinical characteristics were similar between patients with or without cardiovascular event (Additional file 1: Table S6). Among initial severity and NOAF management, septic shock and electrical cardioversion attempt on the day of NOAF onset were associated with cardiovascular events (respectively, HR: 2.72; 95% CI 1.30 to 5.69 and HR: 2.33; 95% CI 1.17 to 4.65; Additional file 1: Table S6). Regarding TEE parameters,

Table 2 Initial transthoracic and transesophageal echocardiographic variables according to 28-day arterial thromboembolic events, major bleeding events, and death

Variable	Total (n = 94)	Arterial thromboembolic event		Major bleeding event		Death	
		No (n = 87)	Yes (n = 7)	No (n = 76)	Yes (n = 18)	No (n = 67)	Yes (n = 27)
LVEF, median (IQR), % (n = 94)	55 (45–61)	56 (45–62)	51 (33–57)	57 (49–62)	47 (43–57)	57 (49–61)	51 (30–61) ^c
LV systolic dysfunction (LVEF ≤ 45%), no. (%) (n = 94)	27 (29)	24 (28)	3 (43)	18 (23)	9 (50) ^b	16 (24)	11 (41)
LV systolic severe dysfunction (LVEF ≤ 30%), no. (%) (n = 94)	9 (10)	7 (8)	2 (29)	9 (12)	0	2 (3)	7 (26) ^c
RV dilatation, no. (%) (n = 90) ^d	27 (28)	25 (30)	2 (29)	22 (30)	5 (29)	21 (33)	6 (23)
Paradoxical septum, no. (%) (n = 94)	5 (5)	4 (5)	1 (14)	5 (5)	0	3 (4)	2 (7)
Significant left-sided valve disease, no. (%) (n = 94) ^e	4 (4)	2 (2)	2 (29) ^a	1 (1)	3 (17) ^b	2 (3)	2 (7)
LA area, median (IQR), cm ² (n = 70)	20 (16–24)	20 (16–23)	25 (18–28)	20 (16–23)	21 (18–24)	21 (16–25)	18 (15–22)
LA/LAA thrombus, no. (%) (n = 94)	0	0	0	0	0	0	0
LAA dysfunction, no. (%) (n = 88) ^f	17 (19)	16 (20)	1 (14)	12 (17)	5 (28)	12 (19)	5 (19)
LA/LAA dense SEC (n = 94)	7 (7)	6 (7)	1 (14)	6 (8)	1 (6)	5 (7)	2 (7)
LAA low velocity (n = 88) ^g	11 (12)	11 (14)	0	7 (10)	4 (22)	7 (11)	4 (15)
LAA emptying velocity, median (IQR), cm/s (n = 89)	66 (41–85)	67 (41–83)	63 (41–90)	66 (43–81)	65 (33–91)	61 (44–85)	70 (39–81)
LAA filling velocity, median (IQR), cm/s (n = 88)	60 (46–71)	59 (45–71)	65 (50–68)	62 (46–72)	56 (45–61)	58 (47–72)	62 (44–68)
LAA large area (> 5 cm ²), no. (%) (n = 87)	13 (15)	10 (12)	3 (43)	10 (14)	3 (18)	7 (11)	6 (24)
LAA area, median (IQR), cm ² (n = 87)	3.2 (2.4–4.3)	3.2 (2.4–4.1)	4.9 (3.0–5.3)	3.2 (2.4–4.3)	3.4 (2.3–4.5)	3.4 (2.3–4.2)	3.1 (2.4–4.5)
Severe aortic atheroma, no. (%) (n = 91)	22 (24)	21 (25)	1 (14)	18 (24)	4 (23)	18 (27)	4 (16)

IQR interquartile, LA left atrial, LAA left atrial appendage, LV left ventricular, LVEF left ventricular ejection fraction, RV right ventricular, SEC spontaneous echo contrast

^a $p < 0.05$, when compared with the value for no arterial thromboembolic event

^b $p < 0.05$, when compared with the value for no major bleeding event

^c $p < 0.05$, when compared with no death

^d RV dilatation was defined as RV and LV end-diastolic areas ratio in long-axis cardiac view

^e Aortic stenosis, $n = 2$; mitral regurgitation, $n = 1$; aortic regurgitation, $n = 1$

^f LA/LAA dense SEC or LAA low velocity

^g LAA emptying velocity < 25 cm/s or LAA filling velocity < 25 cm/s

only LV systolic dysfunction was associated with cardiovascular events (HR: 2.75; 95% CI 1.48 to 5.08; Additional file 1: Table S3). As compared with patients showing no LV systolic dysfunction, patients with mild LV systolic dysfunction had a higher cardiovascular risk (HR: 2.39; 95% CI 1.14 to 4.63) and those with severe LV systolic dysfunction had an even higher risk (HR: 4.2; 95% CI 1.79 to 10.05). A multivariable model built from TEE parameters with additional adjustment on septic shock and electrical cardioversion attempt on the day of NOAF onset identified LV systolic dysfunction (HR: 2.06; 95% CI 1.05 to 4.05) as the only independent predictor of cardiovascular events (Table 4). Additional adjustments on baseline clinical characteristics (SAPSII score, CHADS₂Vasc₂ and HAS-BLED) and antithrombotic management (antiplatelet therapy and therapeutic anticoagulation on the day of NOAF onset) did not substantially change the magnitude of reported hazard ratios (Additional file 1: Table S7).

Factors associated with each of the components of cardiovascular events

Arterial thromboembolic event

There was no significant difference in baseline clinical characteristics, severity, and management on the day of NOAF onset between patients with and without arterial thromboembolic event, with the exception of a context of emergency surgery (Table 1). In particular, the CHA₂DS₂-VAsc score was similar between the two groups. Regarding TEE parameters, only significant left-sided valve disease was associated with an increased risk of arterial thromboembolic event (Table 2).

Major bleeding event

Patients with major bleeding event more often received initial electrical cardioversion attempt, whereas the HAS-BLED score and initial therapeutic anticoagulation (Table 1) were similar between the two groups. LV systolic dysfunction and left-sided valve disease were

Table 3 Description of 28-day arterial thromboembolic events

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
CHA ₂ DS ₂ -VASC score	3	6	0	1	2	5	4
NOAF characteristics	Persistent	Sustained	Sustained	Sustained	Persistent	Sustained	Persistent
Time from NOAF onset, days	11	2	6	5	5	0	3
Initial TEE study							
LV systolic function, LVEF (%)	45	50	5	56	70	60	22
LA/LAA dysfunction ^a	No	No	No	No	No	No	Yes
Severe aortic atheroma	Yes	No	No	No	No	No	No
Management before arterial thromboembolic event							
Therapeutic anticoagulation	Yes	No	Yes	Yes	Yes	No	Yes
Cardioversion attempt	Yes	Yes	Yes	Yes	No	No	No
Type	Ischemic stroke	Ischemic stroke	Ischemic stroke	Ischemic stroke	Ischemic stroke; LAA thrombus ^b	Non-CVTE	LAA thrombus ^c
Mechanism ^d							
Causative subtypes of ischemic stroke ^e	Probable large artery atherosclerosis	Evident cardio-aortic embolism	Evident cardio-aortic embolism	Evident cardio-aortic embolism	Evident cardio-aortic embolism	–	–
Sources of embolism other than intracardiac thrombus ^f	–	No	VA ECMO	No	No	Suspicion of endocarditis	–
Relation to NOAF	Definitely not	Definitely	Probably	Definitely	Definitely	Probably	–
Fatal ischemic stroke or non-CVTE	No	No	No	No	No	No	–

CHA₂DS₂-VASC congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, sex category (female), CVTE cerebrovascular thromboembolism, LA left atrial, LAA left atrial appendage, LV left ventricular, LVEF left ventricular ejection fraction, NOAF new-onset supraventricular arrhythmia, TEE transesophageal echocardiography, VA ECMO veno-arterial extracorporeal membrane oxygenation

^a Including LA/LAA SEC and low LAA flow velocity

^b Revealed at a supplementary TEE performed 17 days after NOAF onset because of ischemic stroke

^c Revealed at the second TEE study performed in all patients with arterial thromboembolic event except patient 4

^d Arterial thromboembolic mechanism was assessed by an independent committee

^e Causative subtype of ischemic stroke (large artery atherosclerosis, cardio-aortic embolism, small-artery occlusion, other cause, or unknown cause) was determined using the Stop Stroke Study Trial of ORG 10172 in Acute Stroke Treatment classification criteria [27]

^f Among patients with non-cerebrovascular thromboembolism and those with evident cardio-aortic embolism as a causative subtype of ischemic stroke

Table 4 Univariate and multivariable analyses of factors associated with cardiovascular events^a

Variable	Univariate analysis		Multivariable analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Septic shock ^b	2.72 (1.30–5.69)	0.01	2.36 (1.06–5.29)	0.04
Electrical cardioversion attempt ^b	2.33 (1.17–4.65)	0.02	1.51 (0.72–3.17)	0.27
LV systolic dysfunction ^{c,d}	2.75 (1.48–5.08)	0.001	2.06 (1.05–4.05)	0.03
LA/LAA dysfunction ^{d,e}	1.14 (0.54–2.39)	0.73	0.85 (0.39–1.87)	0.69
Severe aortic atheroma ^d	0.58 (0.26–1.33)	0.20	0.60 (0.26–1.40)	0.24

CI confidence interval, HR hazard ratio, LA left atrial, LAA left atrial appendage, LV left ventricular

^a Composite of arterial thromboembolic events, major bleeding events, and death from any cause

^b On the first day of new-onset atrial fibrillation onset

^c LV ejection fraction $\leq 45\%$

^d At the first echocardiography

^e LA/LAA dense spontaneous echo contrast or LAA low velocity

the only TEE parameters associated with major bleeding events (Table 2).

28-day mortality

Baseline clinical characteristics, initial severity and NOAF management were similar between survivors and non-survivors, with the exception of the Simplified Acute Physiology Score II score on ICU admission, which was associated with mortality (Table 1). LV ejection fraction was the only TEE parameter associated with mortality (Table 2).

Discussion

Our study aimed at describing the early TEE abnormalities in critically ill mechanically ventilated patients with sepsis and NOAF, and at estimating the cardiovascular risk by performing a systematic comprehensive morphological work-up with TEE. We found that LV systolic dysfunction, severe aortic atheroma, and LA/LAA dysfunction were common, and that the incidence of cardiovascular events was very high, including arterial thromboembolic event (7%), major bleeding event (19%), and all-cause death (29%). Among the initial TEE abnormalities, only LV systolic dysfunction was independently associated with a poor prognosis.

Thrombotic and bleeding risks

In line with our results, Yoshida et al. reported a 4.6% incidence of stroke in ICU patients with NOAF [28]. Walkey et al. showed that septic patients with NOAF had a greater risk of in-hospital stroke, as compared with their counterparts [2]. We also report that major bleeding events, most of which were life-threatening, were almost three times more frequent than thromboembolic events (19% versus 7%). Similarly, Walkey et al. showed a 12.6% incidence of bleeding in a large retrospective cohort of patients with sepsis and NOAF [29]. Gastrointestinal bleedings in our cohort of patients were more common and severe than in previous cohort in critically ill patients [30]. Krag et al. reported a 2.4% incidence of clinically important gastrointestinal bleeding in 1034 critically ill patients, which none of them was fatal [30]. Upper gastrointestinal lesions commonly seen in ICU patients requiring mechanical ventilation [31] may also increase bleeding risk among patients with sepsis who are receiving therapeutic anticoagulation. Therefore, thrombotic and bleeding risks in patients with sepsis and NOAF seem to be higher than those reported in cardiology wards. In a recent clinical trial studying early versus delayed cardioversion in patients with NOAF in the Emergency Department, Pluymaerckers et al. reported a 0.5% incidence of arterial thromboembolic events and no major bleeding events within 4 weeks of follow-up [32].

The underlying mechanisms of the cardiovascular events are complex in this context. NOAF may be a marker of greater sepsis severity, associated with an increased risk of thrombotic and bleeding events through hemodynamic collapse, increased systemic inflammation, and coagulopathy [33, 34]. Sepsis could predispose to LA/LAA thrombus formation in patients with NOAF. Virchow's triad—including abnormal blood stasis, hypercoagulable state, and endothelial dysfunction—could be exacerbated in this context [35, 36]. In this setting, significant left-sided valve disease, associated with the occurrence of thrombotic events in our cohort, could be a potential etiologic factor in the development of them. In addition, due to inclusion criteria some of patients may have unrecognized pre-existing paroxysmal AF. At last, patients hospitalized in the ICU for sepsis and requiring mechanical ventilation seem to have a high baseline thrombotic and bleeding risks, irrespective of NOAF, as shown in our cohort of elderly patients with frequent comorbidities such as cardiovascular disease and arterial hypertension.

Therapeutic anticoagulation

Observational data suggested that therapeutic anticoagulation was not associated with a reduced risk of ischemic stroke, but was associated with a higher bleeding risk among propensity score-matched patients with sepsis and atrial fibrillation [29]. However, there are no robust data on the net clinical benefit of therapeutic anticoagulation in patients with sepsis and NOAF. In line with our results, Yoshida et al. reported that 40% of critically ill patients with NOAF received therapeutic anticoagulation [28]. In patients with septic shock eligible for early NOAF cardioversion (<24 h), a recent French survey has shown that 22% of intensivists initiated immediate therapeutic anticoagulation, whereas 27% initiated therapeutic anticoagulation after 24 h, and 44% after 48 h of sustained NOAF [37]. Similarly, we reported that only one-third of patients received therapeutic anticoagulation prior to electric shock. These deviations from recent European guidelines that recommend therapeutic anticoagulation before any emergent cardioversion [4, 10] confirm that the cardiologic approach does not seem appropriate in septic patient at high risk of bleeding. In the light of our results, specific therapeutic for NOAF in patients with sepsis such as electric shock and therapeutic anticoagulation should be used with caution. Hence, identifying patients with sepsis and NOAF most likely to benefit from therapeutic anticoagulation is a major clinical challenge. We found that the CHA₂DS₂-VASc and HAS-BLED scores, used for clinical decision-making on anticoagulation in the cardiology ward, were not associated with any of the cardiovascular events.

Similarly, Walkey et al. reported a poor performance of CHA₂DS₂-VASc scores to stratify risk of stroke during sepsis in a large retrospective cohort of patients with sepsis and atrial fibrillation [29]. Finally, our results confirm the need for bedside cardiovascular risk estimation tools, to help decisions to be made about therapeutic anticoagulation and its timing.

TEE for cardiovascular risk estimation

A TEE-guided strategy for estimating cardiovascular risk may be questionable. Although initial TEE revealed frequent LAA dysfunction (including dense SEC or low velocity), severe aortic atheroma, and LV systolic dysfunction, only the last of these was associated with a poor prognosis. Moreover, a systematic early TEE followed by a second TEE in two-thirds of patients revealed only one LAA thrombus. In line with our results, Seemann et al. reported myocardial dysfunction in 40% of patients with septic shock and NOAF [38]. LV systolic dysfunction and NOAF may be two components of myocardial septic dysfunction. The clinical and prognosis significances of LV systolic dysfunction during sepsis are a matter of debate [39]; however, our findings suggest that its association with NOAF is associated with a poor prognosis. Two previous studies reported the prevalence of thrombus, dense SEC and severe aortic atheroma in ambulatory cardiological patients undergoing TEE for NOAF cardioversion [40, 41]. In comparison with our results, Kleemann et al. reported a similar prevalence of thrombus (1%), dense SEC (9.5%), and aortic atheroma (21%), whereas Stoddart et al. reported a higher prevalence of thrombus (14%) and dense SEC (39%) [40, 41]. Those differences may be explained by the higher number of patients with structural heart disease in the study by Stoddart et al. (94%), as compared with the study by Kleemann et al. (49%) and our study (18%).

Study strengths and limitations

This multicenter study was conducted in 10 tertiary university ICUs, where TEE is routinely used in mechanically ventilated critically ill patients. The major strengths of our study are: (i) the comprehensive search for risk factors for cardiovascular events, including systematic morphological work-up with two sequential TEE studies (initial TEE to identify patients at high risk of cardiovascular events, and the second TEE to investigate LA/LAA thrombus formation); (ii) its prospective design with adjudication of arterial thromboembolic events and major bleeding events; and (iii) the mean level of inclusion of 0.5 patient per month per center seems to be an appropriate number with regard to the eligibility criteria and is consistent with consecutive and exhaustive recruitment. Our study has

several limitations. First, the relatively small number of patients limited power in all analyses. This may explain the absence of association between TEE abnormalities and outcomes. One could also object that arterial thromboembolic event might have been more relevant as a primary outcome, yet we did not consider this option, because of its low incidence. Instead, we used a composite outcome that reflects the net clinical benefit of therapeutic anticoagulation. Second, the incidence of arterial thromboembolic events may have been underestimated due to the fact that (i) the second TEE was not performed in all patients; (ii) TEEs performed in the first few days after NOAF onset may not capture LA/LAA thrombus formation within this time frame and (iii) cerebral magnetic resonance imaging was not systematic. Third, the present study was an observational study with potential indication bias. Rhythm/rate control and therapeutic anticoagulation could have influenced the occurrence of thrombotic and bleeding events. Fourth, we excluded patients who had a history of atrial fibrillation, in whom long-term cardiovascular risk stratification has been well studied [10]. Fifth, although an independent committee assessed arterial thromboembolic mechanism using a previous published classification, make a clear distinction between the “cardio-aortic embolism” and sepsis-related hypotension as a cause of stroke remains difficult. Finally, as this study was conducted in France, our findings may not be applicable elsewhere; however, the incidences of cardiovascular events reported in other nations [2, 3, 28, 29] were similar to our findings.

Conclusions

TEE abnormalities (including LA/LAA dysfunction, severe aortic atheroma, and LV dysfunction), and cardiovascular events were common in critically ill patients with sepsis and NOAF. However, only LV systolic dysfunction was independently associated with cardiovascular events. Consequently, transesophageal echocardiography appears to be limited in this context for estimating cardiovascular risk, albeit the sample size was relatively small.

Abbreviations

CHA₂DS₂-VASc: Congestive heart failure hypertension, hypertension, age \geq 75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, sex category (female); HAS-BLED: Hypertension abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; ICU: Intensive care unit; IQR: Interquartile range; LA: Left atrial; LAA: Left atrial appendage; LV: Left ventricular; NOAF: New-onset atrial fibrillation; SEC: Spontaneous echo contrast; TEE: Transesophageal echocardiography.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13613-021-00934-1>.

Additional file 1: Table S1. Definition of CHA₂DS₂-VASc and HAS-BLED risk scores, arterial thromboembolic events, and bleeding events. **Table S2.** Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment (SSS-TOAST) Classification Criteria to Determine Causative Subtypes of Acute Ischemic Stroke. **Figure S1.** The decision algorithm to assign a mechanism using the Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment (SSS-TOAST) Classification Criteria. **Table S3.** Initial transthoracic and transesophageal echocardiographic variables according to 28-day cardiovascular events. **Table S4.** New onset atrial fibrillation and sepsis management during 28-day follow-up in intensive care unit. **Table S5.** Description of 28-day ISTH major bleeding events. **Table S6.** Baseline clinical characteristics at intensive care unit admission, initial severity and new-onset atrial fibrillation management according to 28-day cardiovascular events. **Table S7.** Multivariate analyses of factors associated with cardiovascular events including baseline clinical characteristics (SAP-SII score, CHADS₂Vasc2 and HAS-BLED) and antithrombotic management (antiplatelet therapy and therapeutic anticoagulation on the day of NOAF onset).

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Authors' contributions

VL, SE, AC, and MF contributed to study conception and design. VL, SE, JJ, KR, LL, OS, SV, FC, NA, RS, and DD participated in acquiring the data. VL, SE, AC analyzed off-line echocardiographic studies. VL, SE, NL, FC, GV, AMD, AC and MF analyzed and interpreted the study data. VL and MF drafted the original manuscript. All authors revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

All data and materials are fully complying with field standards and might be available after request.

Declarations

Ethics approval and consent to participate

The study has been approved by the Comité de Protection des Personnes Ile-de-France 5 (ref. 14941) as a component of standard care and patient consent was waived, as per French Law. Written and oral information about the study was given to the patient or next of kin.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests related to the present study.

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References

- Klein Klouwenberg PMC, Frencken JF, Kuipers S, Ong DSY, Peelen LM, van Vught LA, et al. Incidence, predictors, and outcomes of new-onset atrial fibrillation in critically ill patients with sepsis. A cohort study. *Am J Respir Crit Care Med*. 2017;195:205–11.
- Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA*. 2011;306:2248–54.
- Champion S, Lefort Y, Gaüzère B-A, Drouet D, Bouchet BJ, Bossard G, et al. CHADS₂ and CHA₂DS₂-VASc scores can predict thromboembolic events after supraventricular arrhythmia in the critically ill patients. *J Crit Care*. 2014;29:854–8.
- January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the heart rhythm society in collaboration with the society of thoracic surgeons. *Circulation*. 2019;140:e125–51.
- Zabalgaitia M, Halperin JL, Pearce LA, Blackshear JL, Asinger RW, Hart RG. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke prevention in atrial fibrillation III investigators. *J Am Coll Cardiol*. 1998;31:1622–6.
- Asinger RW, Koehler J, Pearce LA, Zabalgaitia M, Blackshear JL, Fenster PE, et al. Pathophysiologic correlates of thromboembolism in nonvalvular atrial fibrillation: II. Dense spontaneous echocardiographic contrast (the stroke prevention in atrial fibrillation [SPAF-III] study). *J Am Soc Echocardiogr*. 1999;12:1088–96.
- Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. *J Am Coll Cardiol*. 1994;23:961–9.
- Pollick C, Taylor D. Assessment of left atrial appendage function by transesophageal echocardiography. Implications for the development of thrombus. *Circulation*. 1991;84:223–31.

9. Di Biase L, Natale A, Romero J. Thrombogenic and arrhythmogenic roles of the left atrial appendage in atrial fibrillation. *Circulation*. 2018;138:2036–50.
10. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42:373–498.
11. Vieillard-Baron A, Boyd J. Non-antiarrhythmic interventions in new onset and paroxysmal sepsis-related atrial fibrillation. *Intensive Care Med*. 2018;44:94–7.
12. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*. 2016;315:801–10.
13. Zipes D. Specific arrhythmias: diagnosis and treatment. In: Braunwald E, editor. *Heart disease: a textbook of cardiovascular medicine*. Philadelphia: Elsevier; 1992. p. 667–725.
14. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33:2719–47.
15. Slama M. Echocardiographie Doppler chez les patients en état critique: un outil de monitoring aux multiples modalités. In: Chabert M, editor. *Echocardiogr Doppler Chez Patients En État Critique*. Issy les moulineaux: Elsevier Masson; 2008. p. 9–24.
16. Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *JAMA*. 1993;270:2957–63.
17. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22:707–10.
18. Expert Round Table on Echocardiography in ICU. International consensus statement on training standards for advanced critical care echocardiography. *Intensive Care Med*. 2014;40:654–66.
19. 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;16:233–71.
20. Amarencu P, Cohen A, Tzourio C, Bertrand B, Hommel M, Besson G, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med*. 1994;331:1474–9.
21. Di Angelantonio E, Ederhy S, Benyounes N, Janower S, Boccaro F, Cohen A. Comparison of transesophageal echocardiographic identification of embolic risk markers in patients with lone versus non-lone atrial fibrillation. *Am J Cardiol*. 2005;95:592–6.
22. Montgomery DH, Ververis JJ, McGorisk G, Frohwein S, Martin RP, Taylor WR. Natural history of severe atheromatous disease of the thoracic aorta: a transesophageal echocardiographic study. *J Am Coll Cardiol*. 1996;27:95–101.
23. Mügge A, Kühn H, Nikutta P, Grote J, Lopez JA, Daniel WG. Assessment of left atrial appendage function by biplane transesophageal echocardiography in patients with nonrheumatic atrial fibrillation: identification of a subgroup of patients at increased embolic risk. *J Am Coll Cardiol*. 1994;23:599–607.
24. Tunick PA, Kronzon I. Atheromas of the thoracic aorta: clinical and therapeutic update. *J Am Coll Cardiol*. 2000;35:545–54.
25. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–51.
26. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692–4.
27. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol*. 2005;58:688–97.
28. Yoshida T, Uchino S, Sasabuchi Y, Hagiwara Y, AFTER-ICU study group. Prognostic impact of sustained new-onset atrial fibrillation in critically ill patients. *Intensive Care Med*. 2020;46:27–35.
29. Walkey AJ, Evans SR, Winter MR, Benjamin EJ. Practice patterns and outcomes of treatments for atrial fibrillation during sepsis: a propensity-matched cohort study. *Chest*. 2016;149:74–83.
30. Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, et al. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Med*. 2015;41:833–45.
31. van der Voort PH, van der Hulst RW, Zandstra DF, Geraedts AA, van der Ende A, Tytgat GN. Prevalence of *Helicobacter pylori* infection in stress-induced gastric mucosal injury. *Intensive Care Med*. 2001;27:68–73.
32. Pluymaekers NAHA, Dudink EAMP, Luermans JGLM, Meeder JG, Lenderink T, Widdershoven J, et al. Early or delayed cardioversion in recent-onset atrial fibrillation. *N Engl J Med*. 2019;380:1499–508.
33. Kreutz RP, Bliden KP, Tantry US, Gurbel PA. Viral respiratory tract infections increase platelet reactivity and activation: an explanation for the higher rates of myocardial infarction and stroke during viral illness. *J Thromb Haemost*. 2005;3:2108–9.
34. Zeerleder S, Hack CE, Wuillemin WA. Disseminated intravascular coagulation in sepsis. *Chest*. 2005;128:2864–75.
35. Semeraro N, Ammollo CT, Semeraro F, Colucci M. Coagulopathy of acute sepsis. *Semin Thromb Hemost*. 2015;41:650–8.
36. Watson T, Shantsila E, Lip GYH. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet*. 2009;373:155–66.
37. Labbé V, Bagate F, Cohen A, Voiriot G, Fartoukh M, Mekontso-Dessap A. A survey on the management of new onset atrial fibrillation in critically ill patients with septic shock. *J Crit Care*. 2020;61:18–20.
38. Seemann A, Boissier F, Razazi K, Carreaux G, de Prost N, Brun-Buisson C, et al. New-onset supraventricular arrhythmia during septic shock: prevalence, risk factors and prognosis. *Ann Intensive Care*. 2015;5:27.
39. Aneman A, Vieillard-Baron A. Cardiac dysfunction in sepsis. *Intensive Care Med*. 2016;42:2073–6.
40. Kleemann T, Becker T, Strauss M, Schneider S, Seidl K. Prevalence of left atrial thrombus and dense spontaneous echo contrast in patients with short-term atrial fibrillation < 48 hours undergoing cardioversion: value of transesophageal echocardiography to guide cardioversion. *J Am Soc Echocardiogr*. 2009;22:1403–8.
41. Stoddard MF, Dawkins PR, Prince CR, Ammass NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. *J Am Coll Cardiol*. 1995;25:452–9.

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ADDITIONAL FILES

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Additional file 1 Definition of CHA₂DS₂-VASc and HAS-BLED risk scores, arterial thromboembolic events, and bleeding events

Variable	Definition
Risk score	
CHA ₂ DS ₂ -VASc [1]	Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism (doubled) – Vascular disease, Age 65 to 74 years, Sex category (female).
HAS-BLED [1]	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly.
Stroke and non-CVTE	
Stroke	An acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.
Ischemic stroke	An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.
Hemorrhagic stroke	An acute episode of focal, global cerebral, or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.
Undetermined stroke	An acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, but with insufficient information to allow categorization as ischemic or hemorrhagic stroke.
Non-CVTE	An abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms.
Fatal stroke or non-CVTE	Death from any cause within 28 days of stroke or non-CVTE.
Causatives subtypes of ischemic stroke e	
Bleeding	
Major bleeding events (ISTH definition) [2]	Meets ≥1 of the following criteria: symptomatic bleeding in a critical area or organ, e.g., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome; bleeding associated with a reduction in hemoglobin of ≥ 1.24 mmol/L or leading to transfusion of ≥ 2 units blood or packed cells; fatal bleeding.
Life-threatening bleeding (RE-LY definition) [3]	Meets ≥1 of the following criteria (subcategory of major bleeding event): fatal bleeding; symptomatic intracranial bleeding; bleeding with a decrease in hemoglobin of ≥50 g/L, or bleeding requiring transfusion of ≥4 units of blood; necessitating surgical, endoscopic, or endovascular action.

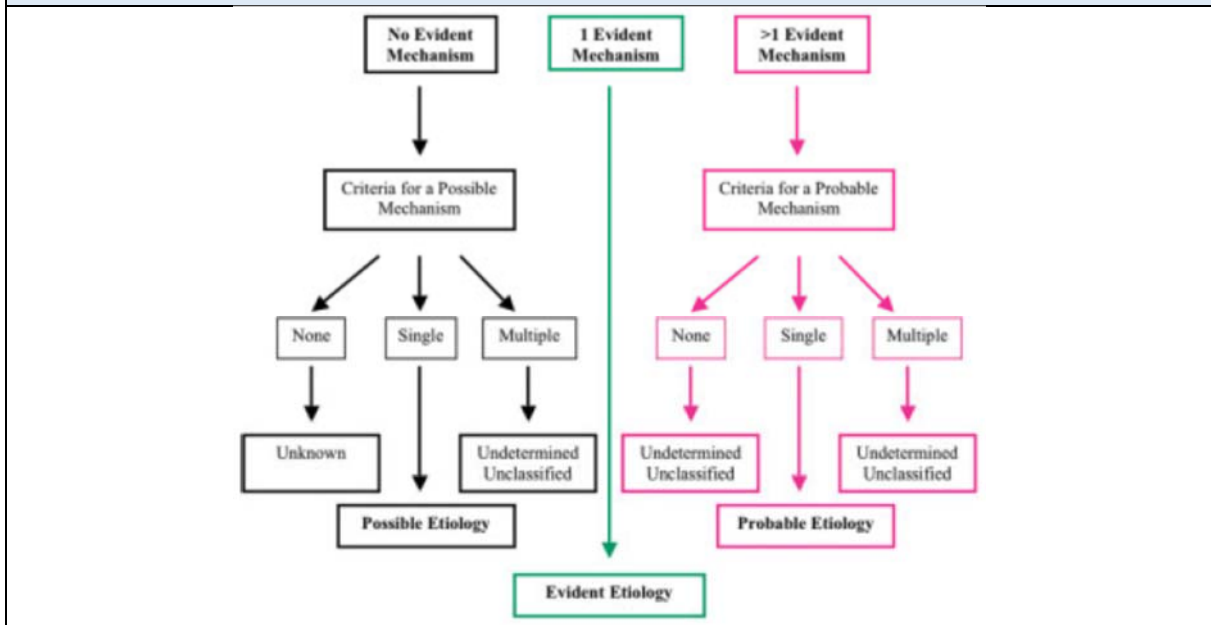
Intracranial bleeding (ISTH definition) [2]	Intracerebral, subdural, epidural, or subarachnoid bleeds
Fatal bleeding (ISTH definition) [2]	Bleeding event that is the primary cause of death or contributes directly to death.
Abbreviations: CVTE, cerebrovascular thromboembolism; ISTH, International Society on Thrombosis and Haemostasis; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy.	

Additional file 2 Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment (SSS-TOAST)

Classification Criteria to Determine Causative Subtypes of Acute Ischemic Stroke [4]

Stroke Mechanism	Level of Confidence	Criteria
Large artery atherosclerosis	Evident	1. Either occlusive or stenotic ($\geq 50\%$ diameter reduction) vascular disease judged to be due to atherosclerosis in the clinically relevant extracranial or intracranial arteries, <i>and</i> 2. The absence of acute infarction in vascular territories other than the stenotic or occluded artery
	Probable	1. Prior history of one or more transient monocular blindness (TMB), transient ischemic attacks (TIAs), or stroke from the territory of index artery affected by atherosclerosis within the last month, <i>or</i> 2. Evidence of near-occlusive stenosis or nonchronic complete occlusion judged to be due to atherosclerosis in the clinically relevant extracranial or intracranial arteries (except for the vertebral arteries), <i>or</i> 3. The presence of ipsilateral and unilateral internal watershed infarctions or multiple, temporally separate, infarctions exclusively within the territory of the affected artery
	Possible	1. The presence of an atherosclerotic plaque protruding into the lumen and causing mild stenosis ($< 50\%$) in a clinically relevant extracranial or intracranial artery and prior history of two or more TMBs, TIAs, or strokes from the territory of index artery affected by atherosclerosis, at least one event within the last month, <i>or</i> 2. Evidence for evident large artery atherosclerosis in the absence of complete diagnostic investigation for other mechanisms
Cardioaortic embolism	Evident	The presence of a high-risk cardiac source of cerebral embolism (including atrial fibrillation)
	Probable	1. Evidence of systemic embolism, <i>or</i> 2. Presence of multiple acute infarctions that have occurred closely related in time within both right and left anterior or both anterior and posterior circulations in the absence of occlusion or near-occlusive stenosis of all relevant vessels; other diseases that can cause multifocal ischemic brain injury such as vasculitides, vasculopathies, and hemostatic or hemodynamic disturbances must not be present
	Possible	1. The presence of a cardiac condition with low or uncertain primary risk of cerebral embolism, <i>or</i> 2. Evidence for evident cardioaortic embolism in the absence of complete diagnostic investigation for other mechanisms
Small-artery occlusion	Evident	Imaging evidence of a single clinically relevant acute infarction less than 20mm in greatest diameter within the territory of basal or brainstem penetrating arteries in the absence of any other pathology in the parent artery at the site of the origin of the penetrating artery (focal atheroma, parent vessel dissection, vasculitis, vasospasm, and so on)
	Probable	The presence of stereotypic lacunar TIAs within the past week
	Possible	1. Presenting with a classical lacunar syndrome in the absence of imaging that is sensitive enough to detect small infarctions, <i>or</i> 2. Evidence for evident small artery occlusion in the absence of complete diagnostic investigation for other mechanisms
	Evident Probable	Presence of a specific disease process that involves clinically appropriate brain arteries A specific disease process that has occurred in clear and close temporal relation to the onset of brain infarction such as arterial dissection, cardiac or arterial surgery, and cardiovascular interventions
Possible	Evidence for an evident other cause in the absence of complete diagnostic investigation for mechanisms listed above	

Additional file 3 The decision algorithm to assign a mechanism using the Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment (SSS-TOAST) Classification Criteria [4].



Additional file 4 Initial transthoracic and transesophageal echocardiographic variables according to 28-Day cardiovascular events

Variable	Available Data	No Cardiovascular Events (n = 51)	Cardiovascular Events (n = 43)	p Value
Hemodynamic parameters ^b				
Time from NOAF, median (IQR), days	93	1.3 (0.7–2.1)	1.3 (0.8–2.1)	0.48
NOAF during study, No. (%)	94	19 (37)	25 (58)	0.06
Mean arterial pressure, median (IQR), mmHg	87	83 (73–94)	78 (69–86)	0.20
Heart rate, median (IQR), beats/min	92	99 (82–123)	110 (89–137)	0.02
Catecholamines, No. (%)	93	29 (58)	36 (84)	0.03
Norepinephrine	93	27 (54)	33 (78)	0.07
Epinephrine	93	2 (4)	3 (7)	0.45
Dobutamine	93	1 (2)	3 (7)	0.29
Echocardiographic parameters				
LVEF, median (IQR), %	94	58 (50–63)	50 (36–61)	0.002
LV systolic dysfunction (LVEF ≤45%), No. (%)	94	7 (14)	20 (46)	0.001
LV systolic severe dysfunction (LVEF ≤30%), No. (%)	94	1 (2)	8 (19)	0.004
RV dilatation, No. (%) ^c	90	18 (37)	11 (27)	0.50
Paradoxical septum, No. (%)	94	2 (4)	3 (7)	0.40
Significant left-sided valve disease, No. (%)	93	0 (0)	4 (9)	0.06
LA area, median (IQR), cm ²	70	20 (16–24)	19 (16–24)	0.88
LA/LAA thrombus, No. (%)	94	0	0	-
LAA dysfunction ^d , No. (%)	88	7 (15)	10 (24)	0.73
LA/LAA dense SEC	94	4 (8)	3 (7)	0.49
LAA low velocity ^e	88	3 (6)	8 (19)	0.18
LAA emptying velocity median (IQR), cm/s	89	61 (46–82)	69 (38–87)	0.95
LAA filling velocity, median (IQR), cm/s	88	60 (48–73)	58 (44–67)	0.09
LAA large area >5 cm ² , No. (%)	87	5 (11)	8 (20)	0.33

LAA area, median (IQR), cm ²	87	3.2 (2.4–4)	3.3 (2.4–4.6)	0.45
Severe aortic atheroma, No. (%)	91	15 (30)	7 (17)	0.20
Abbreviations: IQR, interquartile; LA, left atrial; LAA, left atrial appendage; LV, left ventricular; LVEF, left ventricular ejection fraction; NOAF, new-onset atrial fibrillation; RV, right ventricular; SEC, spontaneous echo contrast; TEE, transesophageal echocardiography.				
^a Composite of arterial thromboembolic event, major bleeding event, or death.				
^b At the time of initial TEE study.				
^c Defined as RV and LV end-diastolic areas ratio in long-axis cardiac view >0.6.				
^d LA/LAA dense SEC or LAA low velocity.				
^e LAA emptying velocity <25 cm/s or LAA filling velocity <25 cm/s.				

Additional file 5 New onset atrial fibrillation and sepsis management during 28-Day follow-up in intensive care unit

Variable	All Patients (n = 94)
NOAF management during 28 days from NOAF onset	
Cardioversion attempt, No. (%)	67 (71)
Time from NOAF onset, median (IQR), days	0 (0–1)
Medical cardioversion attempt (amiodarone), No. (%)	65 (69)
Time from NOAF onset, median (IQR), days	0 (0–1)
Electrical cardioversion attempt, No. (%)	23 (24)
Time from NOAF onset, median (IQR), days	1 (0–2)
Antiarrhythmic drug, No. (%)	
Amiodarone	77 (82)
Beta-blockers	17 (18)
Calcium blockers	4 (4)
Antiplatelet, No. (%)	33 (35)
Time from NOAF onset, median (IQR), days	0 (0–2)
Therapeutic anticoagulation, No. (%) ^a	50 (53)
Time from NOAF onset, median (IQR), days	1 (0–2)
Organ failure management during 28 days from NOAF onset	
Catecholamines, No. (%)	79 (84)
Norepinephrine	74 (79)
Maximum dose, median (IQR), µg/kg/min ^b	0.62 (0.40–1.65)
Dobutamine	9 (10)
Maximum dose, median (IQR), µg/kg/min ^b	8 (5–10)
Epinephrine	8 (8)
Maximum dose, median (IQR), µg/kg/min ^b	0.76 (0.34–1.20)
Hemodialysis, No. (%)	8 (8)
Mechanical ventilation, No. (%)	94 (100)
Length of ICU stay, median (IQR), days	18 (10–30)
Abbreviations: ICU, intensive care unit; IQR, interquartile; NOAF, new-onset atrial fibrillation.	
^a Indication (n = 50): NOAF (n = 42; 84%), extracorporeal membrane oxygenation (n = 2; 4%), pulmonary embolism (n = 4; 8%), dialysis (n = 1; 2%).	
^b Only patients who received the drug during septic shock were considered.	

Additional file 6 Description of 28-Day ISTH major bleeding events

Patient Number ^b	Age, yrs	HAS-BLED Score	Septic Shock	Therapeutic Anticoagulation Before Bleeding	Time From NOAF Onset, days ^c	Source	Severity Variables ^d	Hemostasis Action Reported	Life-threatening Bleeding ^e	Fatal
Patient 1	50	3	Yes	No	3	Soft tissue	1	No	No	No
Patient 2	85	1	Yes	Yes	6	Upper gastrointestinal	1	No	No	No
					12	Upper gastrointestinal	1	No	No	No
Patient 3	69	4	Yes	Yes	19	Soft tissue	2	No	Yes	No
Patient 4	40	2	Yes	No	1	Hemoptysis	1	No	No	No
					6	Upper gastrointestinal	1	No	No	No
					19	Intra-articular (knee)	0	No	No	No
Patient 5	63	1	Yes	No	24	Upper gastrointestinal	1	No	No	No
Patient 6	77	1	Yes	Yes	15	Upper gastrointestinal	1	No	No	No
					17	Hemoptysis	0	BAE	Yes	No
Patient 7	71	1	Yes	No	11	Upper gastrointestinal	1	No	No	No
Patient 8	75	3	Yes	Yes	12	Lower gastrointestinal	2	No	Yes	No
					28	Lower gastrointestinal	2	Surgery	Yes	No
Patient 9	65	2	No	Yes	3	Upper gastrointestinal	2	Surgery	Yes	Fatal
Patient 10	54	2	Yes	No	2	Upper gastrointestinal	2	No	Yes	Fatal
Patient 11	69	2	Yes	Yes	5	Upper gastrointestinal	1	Endoscopic hemostasis	Yes	No
Patient 12	62	1	No	No	7	Intracranial	0	No	Yes	No
Patient 13	66	4	Yes	Yes	14	Upper gastrointestinal	2	Endoscopic hemostasis	Yes	No
Patient 14	77	2	No	Yes	3	Upper and lower gastrointestinal	2	No	Yes	No
Patient 15	61	1	No	Yes	12	Intracranial	0	No	Yes	No
Patient 16	76	2	No	Yes	12	Uterine	1	No	No	No
Patient 17	56	3	Yes	Yes	9	Lower gastrointestinal	1	No	No	No
Patient 18	70	4	Yes	Yes	8	Soft tissue	1	No	No	No

Abbreviations: BAE, bronchial artery embolization; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; ISTH, International Society on Thrombosis and Hemostasis; NOAF, new-onset atrial fibrillation.

^a Investigator assessed.

^b Three patients had two adjudicated ISTH major bleeding events and one patient had three adjudicated ISTH major bleeding events.

^c 1 = day of NOAF.

^d Severity variables: 1 = Bleeding associated with a reduction in haemoglobin of at least 2g/dL or leading to transfusion of two or more units of blood or packed cells; 2 = Bleeding associated with a reduction in haemoglobin of at least 5g/dL or leading to transfusion of at least four units of blood or packed cells.

^e According to the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) definition [3].

Additional file 7 Baseline clinical characteristics at intensive care unit admission, initial severity and new onset atrial fibrillation management according to 28-Day cardiovascular events ^a

Variable	No Cardiovascular Event (n = 51)	Cardiovascular Event (n = 43)	p Value
Baseline clinical characteristics on ICU admission			
Age, IQR, interquartile, median (IQR), yrs	69 (61–77)	69 (62–76)	0.83
Female sex, No. (%)	18 (35)	15 (35)	0.82
Cardiac disease, No. (%)	10 (20)	7 (16)	0.34
Vascular disease, No. (%)	7 (14)	12 (28)	0.20
Left ventricular systolic dysfunction, No. (%)	3 (6)	0	>0.99
Stroke, No. (%)	4 (8)	4 (9)	0.83
Diabetes mellitus, No. (%)	11 (22)	13 (30)	0.42
Smoker, No. (%)	29 (57)	22 (51)	0.64
Hypertension, No. (%)	29 (57)	28 (65)	0.46
Clinical risk scores, median (IQR)			
CHA ₂ DS ₂ -VASc	3 (2–4)	3 (2–4)	0.61
HAS-BLED	2 (1–3)	2 (1–3)	0.73
Previous therapeutic anticoagulation, No. (%)	2 (4)	2 (5)	>0.95
Admission category, No. (%)			
Medical	42 (82)	32 (75)	0.42
Scheduled surgery	3 (6)	2 (5)	0.82
Emergency surgery	6 (12)	9 (21)	0.30
Site of infection, No. (%)			
Lung	37 (72)	31 (72)	0.96
Abdomen	12 (23)	10 (23)	0.79
Other	9 (18)	7 (16)	0.69
SAPS II score on ICU admission, median (IQR)	54 (42–73)	63 (52–74)	0.18
Severity and management on the day of NOAF onset			
SOFA score, median (IQR)	9 (7–11)	9 (6–12)	0.79
Septic shock, No. (%)	25 (49)	34 (79)	0.01
Catecholamines, No. (%)	38 (74)	37 (86)	0.24
Norepinephrine	37 (72)	34 (79)	0.58
Epinephrine	1 (2)	5 (12)	0.03

Dobutamine	4 (8)	3 (7)	0.64
Cardioversion attempt, No. (%)	32 (63)	28 (65)	0.81
Medical (amiodarone)	31 (61)	28 (65)	0.67
Electrical	5 (10)	11 (26)	0.02
Antiplatelet therapy, No. (%)	9 (18)	15 (35)	0.08
Therapeutic anticoagulation, No. (%)	18 (35)	10 (23)	0.18
Abbreviations: CHA ₂ DS ₂ -VASc, Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category (female); HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; ICU, intensive care unit; IQR, interquartile; NOAF, new-onset atrial fibrillation; SAPS, Simplified Acute Physiology Score; SOFA, sepsis-related organ failure assessment.			
^a Composite of arterial thromboembolic event, major bleeding event, or death.			

Additional file 8 Multivariate analyses of factors associated with cardiovascular events ^a including baseline clinical characteristics (SAPSII score, CHADS2Vasc2 and HAS-BLED) and antithrombotic management (antiplatelet therapy and therapeutic anticoagulation on the day of NOAF onset)

Variable	HR (95% CI)	p Value
CHA ₂ DS ₂ -VASc	1.11 (0.91–1.35)	0.29
Septic shock ^b	2.30 (1.03–5.14)	0.04
Electrical cardioversion attempt ^b	1.52 (0.73–3.18)	0.27
LV systolic dysfunction ^{c, d}	2.22 (1.12–4.40)	0.02
LA/LAA dysfunction ^{d, e}	0.73 (0.31–1.68)	0.46
Severe aortic atheroma ^d	0.61 (0.27–1.40)	0.24
HASBLED	1.13 (0.88–1.45)	0.33
Septic shock ^b	2.38 (1.06–5.32)	0.03
Electrical cardioversion attempt ^b	1.45 (0.69–3.07)	0.33
LV systolic dysfunction ^{c, d}	2.13 (1.09–4.18)	0.03
LA/LAA dysfunction ^{d, e}	0.78 (0.35–1.75)	0.55
Severe aortic atheroma ^d	0.56 (0.24–1.30)	0.17
SAPS II score	1.00 (0.99–1.02)	> 0.99
Septic shock ^b	2.36 (1.04–5.34)	0.04
Electrical cardioversion attempt ^b	1.51 (0.70–3.27)	0.29
LV systolic dysfunction ^{c, d}	2.06 (1.04–4.08)	0.04
LA/LAA dysfunction ^{d, e}	0.85 (0.39–1.88)	0.70
Severe aortic atheroma ^d	0.61 (0.26–1.41)	0.25
Antiplatelet therapy ^b	1.40 (0.68–2.89)	0.37
Septic shock ^b	2.18 (0.95–5.00)	0.06
Electrical cardioversion attempt ^b	1.62 (0.76–3.48)	0.21
LV systolic dysfunction ^{c, d}	1.99 (1.01–3.94)	0.05
LA/LAA dysfunction ^{d, e}	0.76 (0.33–1.74)	0.51
Severe aortic atheroma ^d	0.62 (0.27–1.43)	0.26
Therapeutic anticoagulation ^b	0.76 (0.36–1.62)	0.48
Septic shock ^b	2.36 (1.06–5.29)	0.04
Electrical cardioversion attempt ^b	1.56 (0.75–3.28)	0.24
LV systolic dysfunction ^{c, d}	2.10 (1.07–4.11)	0.03
LA/LAA dysfunction ^{d, e}	0.85 (0.39–1.86)	0.68
Severe aortic atheroma ^d	0.63 (0.27–1.45)	0.28

Abbreviations: CI, confidence interval; HR, hazard ratio; LA, left atrial; LAA, left atrial appendage; LV, left ventricular.

^a Composite of arterial thromboembolic events, major bleeding events, and death from any cause.

^b On the first day of new-onset atrial fibrillation onset.

^c LV ejection fraction $\leq 45\%$.

^d At the first echocardiography.

^e LA/LAA dense spontaneous echo contrast or LAA low velocity.

REFERENCES

1. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J.* 2012;33:2719–47.
2. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost JTH.* 2005;3:692–4.
3. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139–51.
4. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol.* 2005;58:688–97.

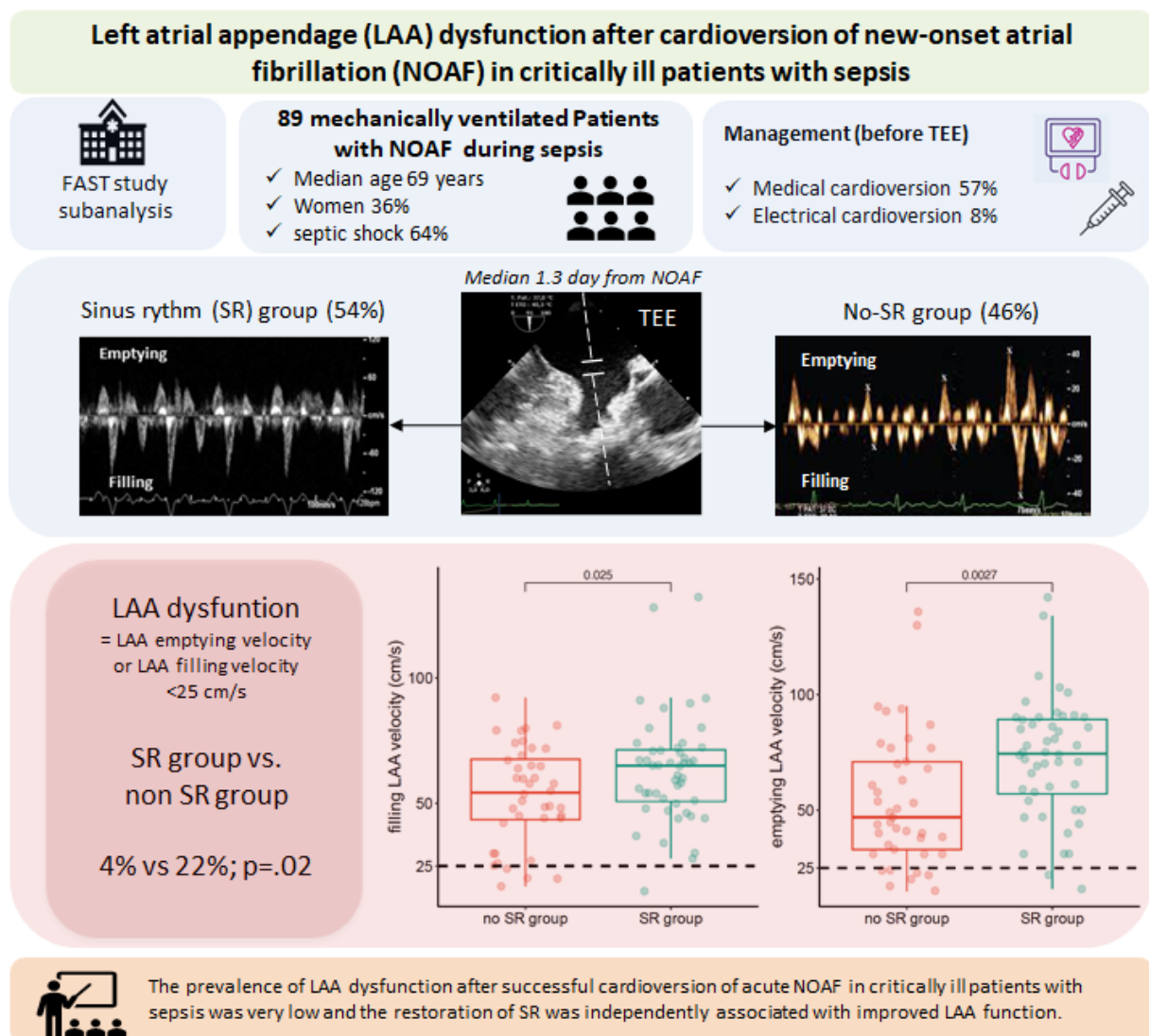
Article 2 (sous analyse de l'article 1)

Left atrial appendage dysfunction after cardioversion of new-onset atrial fibrillation in critically ill patients with sepsis. submitted

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Visual abstract



Left atrial appendage dysfunction after cardioversion of new-onset atrial fibrillation in critically ill patients with sepsis. An exploratory investigation

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Recent guidelines recommend therapeutic anticoagulation for four weeks after cardioversion in critically ill patients with acute (<48 hours) new-onset atrial fibrillation (NOAF) (1). These recommendations are based on observational studies in cardiological outpatients reporting an increased post-cardioversion thrombotic risk, even in the absence of pre-existing thrombus (2). One of the main mechanisms is a post-cardioversion (whatever the type of cardioversion) transient left atrial appendage (LAA) dysfunction (named stunning) predisposing to LAA thrombus formation, and manifested by a reduction in transesophageal echocardiography (TEE) LAA flow velocities despite return to a sinus rhythm (SR) (3–6). However, post cardioversion LAA function has not been investigated in critically ill patients with NOAF during sepsis. We therefore, conducted an exploratory sub-analysis of results from the prospective observational Fibrillation Atrial Sepsis Thrombus (FAST) study (7), which included 94 patients with sepsis and NOAF hospitalized in 10 French intensive care units, to investigate the prevalence of post-cardioversion LAA dysfunction and explore the impact of return to a SR on LAA function.

Methods

From November 2014 to November 2016, consecutive mechanically ventilated adult patients with NOAF during sepsis/septic shock were enrolled in the FAST study (7). Exclusion criteria included patients with valvular heart disease, contraindications to TEE, patients with a decision to withdraw life-sustaining treatment, moribund patients, and refusal to participate (7). NOAF was defined as AF occurring in a patient with no prior history of AF and lasting at least six hours or recurring more than twice (>30 s) per day despite correction of modifiable risk factors such as hypokalemia or hypovolemia (7). As previously described (7), within 48 hours of diagnosis of NOAF, each patient underwent a TEE with 5-MHz multiplane transducers to investigate the LAA function. At the time of TEE, patients were categorized

according to the return to a SR (SR group) or not (no SR group). LAA dysfunction was defined as a low (<25 cm/s) emptying or filling LAA velocity (8) evaluated with pulse-wave Doppler interrogation 1 cm within the orifice in anterograde (emptying) and retrograde (filling) directions, averaged over a minimum of 3-5 consecutive cardiac cycles (8). The presence of a thrombus in the LA or LAA were also investigated. All echocardiographic studies were analyzed of-line by two experienced observers (VL and SE) in a blinded manner. Patients whose LAA function could not be recorded (n=5) were secondarily excluded. The local ethical committee approved the FAST study (Comité de Protection des Personnes Ile-de-France 5, ref. 14941); patient consent was waived due to the observational nature of the study.

Categorical and continuous variables were compared for the study outcome using the Fisher exact test or χ^2 test and the t test or the Mann-Whitney U test, respectively. To mitigate unbalance between SR and non SR patients, we fitted a propensity score for the return to a SR through a nonparametric gradient boosting machine learning algorithm included in the Twang package (9). Confounding factors included in the propensity score were clinical characteristics (age, sex, congestive heart failure, SAPS II score on admission, SOFA score on the day of TEE, type of cardioversion attempted, time from NOAF onset to cardioversion, catecholamines), biological findings (pH, PaO₂/FiO₂ ratio, arterial lactate, hemoglobin), and TEE parameters (left ventricular ejection fraction). Their balance among the two groups was assessed by the absolute standardized mean difference before and after weighting, with a value lower than 25% being considered as sufficient to support the assumption of balance between groups (10). The propensity score was further used in a weighted linear model to estimate the effect of a return to a SR. In the weighted population, it was possible to assess the association with LAA velocities in a pseudo-population in which the characteristics of subjects who returned or not

to a SR were balanced. P-values were two-tailed and a value lower than 0.05 was considered significant. All analyses were performed using R software.

Results

Eighty-nine patients were included (32[36%] women; age 69[61–77] years; septic shock 64%; SAPS II score 58[47–74], table 1). At the time of the TEE studies, 48 (54%) patients had returned to SR, either spontaneously (n=19) or after receiving medical (n=28) and/or electrical (n=3) cardioversion. The median time from NOAF onset to TEE studies was longer in the SR group as compared with the non-SR group (36[19–53] days vs. 21[13–46] hours, $p=0.02$). Baseline clinical characteristics, NOAF management before TEE, and SOFA score on the day of TEE did not differ between the two groups, as well as the left ventricular ejection fraction and hemodynamic parameters during TEE, except for a lower median heart rate in the SR group (90[82–109] vs. 127[99–147] beats/min, $p<0.001$). The SR group had less LAA dysfunction (2(4%) vs 9 (22%), $p=0.002$) and higher LAA emptying (74[57–89] vs. 47[33–71], $p=0.003$) and filling (65[51–71] vs. 54[43–67], $p=0.02$) velocities compared with the non-SR group (Figure 1). No patient had LA/ LAA thrombus. In comparison with no return to SR, the return to SR was significantly associated with higher LAA emptying and filling velocities both in the crude linear model (+20.2 [7.7–32.7] cm/s and +9.7[0.1–19.2] cm/s, respectively) and the propensity-weighted linear model (+18.8 [6.0–31.6] cm/s and +9.5[0.0–19.0] cm/s, respectively, respectively).

Discussion

To our knowledge, this is the first study assessing the LAA function after cardioversion for acute (< 48h) NOAF in critically ill patient with sepsis. The main findings are as follows: (i)

the prevalence of LAA dysfunction is very low (<5%) in patients with return to a SR and (ii) the return to a SR is independently associated with an improvement in LAA function.

In cardiologic outpatients with chronic AF, Harjai et al have demonstrated that restoration of sinus rhythm was associated with a significant decrease in the LAA filling velocities (0.42 ± 0.20 m/s pre-cardioversion vs 0.29 ± 0.14 m/s post-cardioversion) and LAA emptying velocities (0.40 ± 0.22 m/s pre-cardioversion vs 0.29 ± 0.18 m/s post-cardioversion) (6), consistent with the results of others authors (4, 5). Our results suggest a different behavior of LAA function in sepsis-triggered AF as compared with that in chronic AF with significant atrial remodeling and endothelial dysfunction (11).

European guidelines for prevention of NOAF cardioversion-related arterial thromboses in critically ill patients are debated, leading to major variations in practice patterns. In a recent French survey, we found that, in critically ill patients with sepsis, almost one in two intensivists initiate anticoagulation later than recommended (only when NOAF is sustained more than 48h), and almost two-thirds of them use it for a shorter than recommended duration (for a maximum of 7 days after successful cardioversion) (12). Our results may suggest that the “cardiologic approach” does not seem appropriate in septic patients at high risk of anticoagulation-related bleeding (13).

Our study has several limitations. First, we did not assess LAA velocities prior to SR restoration in order to investigate the potential worsening of LAA function after cardioversion, termed stunning. However, restoration to SR was independently associated with an LAA function improvement. Second, we cannot exclude a very transient LAA dysfunction that could have recovered before TEE exploration. However, the delay between TEE studies and the onset of NOAF (and therefore the return to SR) was short (<48h). In conclusion, in this preliminary investigation, the prevalence of LAA dysfunction after successful cardioversion of acute NOAF in critically ill patients with sepsis was very low and

the restoration of a SR was independently associated with an improvement of the LAA function. Specific guidelines for prevention of NOAF cardioversion-related arterial thromboses in patients with sepsis would require randomized clinical trials to evaluate the best anticoagulation strategies in this setting.

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We would like the names of the individual members of the FAST study group to be searchable through their individual PubMed records.

Reference

1. Boriani G, Fauchier L, Aguinaga L, Beattie JM, Blomstrom Lundqvist C, Cohen A, *et al.* European Heart Rhythm Association (EHRA) consensus document on management of arrhythmias and cardiac electronic devices in the critically ill and post-surgery patient, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), Cardiac Arrhythmia Society of Southern Africa (CASSA), and Latin American Heart Rhythm Society (LAHRS). *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol* 2019;21:7–8.
2. Airaksinen KEJ, Grönberg T, Nuotio I, Nikkinen M, Ylitalo A, Biancari F, *et al.* Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. *J Am Coll Cardiol* 2013;62:1187–1192.
3. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, *et al.* 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;42:373–498.
4. Fatkin D, Kuchar DL, Thorburn CW, Feneley MP. Transesophageal echocardiography before and during direct current cardioversion of atrial fibrillation: evidence for “atrial stunning” as a mechanism of thromboembolic complications. *J Am Coll Cardiol* 1994;23:307–316.
5. Falcone RA, Morady F, Armstrong WF. Transesophageal echocardiographic evaluation of left atrial appendage function and spontaneous contrast formation after chemical or electrical cardioversion of atrial fibrillation. *Am J Cardiol* 1996;78:435–439.

6. Harjai K, Mobarek S, Abi-Samra F, Gilliland Y, Davison N, Drake K, *et al.* Mechanical dysfunction of the left atrium and the left atrial appendage following cardioversion of atrial fibrillation and its relation to total electrical energy used for cardioversion. *Am J Cardiol* 1998;81:1125–1129.
7. Labbé V, Ederhy S, Lapidus N, Joffre J, Razazi K, Laine L, *et al.* Transesophageal echocardiography for cardiovascular risk estimation in patients with sepsis and new-onset atrial fibrillation: a multicenter prospective pilot study. *Ann Intensive Care* 2021;11:146.
8. Mügge A, Kühn H, Nikutta P, Grote J, Lopez JA, Daniel WG. Assessment of left atrial appendage function by biplane transesophageal echocardiography in patients with nonrheumatic atrial fibrillation: identification of a subgroup of patients at increased embolic risk. *J Am Coll Cardiol* 1994;23:599–607.
9. Griffin B, Ridgeway G, Mccafrey D, Morral A, Burgette L. Toolkit for weighting and analysis of nonequivalent groups : a tutorial for the twang package [Internet]. 2013;1–30.
10. Stuart EA. Matching methods for causal inference: A review and a look forward. *Stat Sci Rev J Inst Math Stat* 2010;25:1–21.
11. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, *et al.* EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol* 2016;18:1455–1490.
12. Labbé V, Bagate F, Cohen A, Voiriot G, Fartoukh M, Mekontso-Dessap A. A survey on the management of new onset atrial fibrillation in critically ill patients with septic shock. *J Crit Care* 2021;61:18–20.
13. Wetterslev M, Hylander Møller M, Granholm A, Hassager C, Haase N, Lange T, *et al.* Atrial Fibrillation (AFIB) in the ICU: Incidence, Risk Factors, and Outcomes: The

International AFIB-ICU Cohort Study. *Crit Care Med*

2023;doi:10.1097/CCM.0000000000005883.

Table 1. Baseline clinical characteristics, biological data, SOFA score and NOAF management according to the cardiac rhythm *					
Variable	Available Data	Total (n=89)	SR group (n=48)	Non-SR group (n=41)	p Value
Baseline clinical characteristics					
Age, median (IQR), yrs	89	69 (61–77)	65 (59–76)	70 (63–78)	0.13
Female sex, No. (%)	89	32 (36)	19 (40)	13 (32)	0.51
Congestive heart failure, No. (%)	89	15 (17)	6 (12)	9 (22)	0.27
Vascular disease, No. (%)	89	17 (19)	9 (19)	8 (19)	>0.99
Stroke, No. (%)	89	6 (7)	2 (4)	4 (10)	0.41
CHA ₂ DS ₂ -VASc scores (0-9), median (IQR)	89	3 (2–4)	3 (2–3)	4 (2–4)	0.19
SAPS II score on ICU admission, median (IQR)	89	58 (47–74)	58 (44–72)	63 (50–74)	0.27
Septic shock, No. (%)	89	57 (64)	30 (62)	27 (66)	0.83
Biological data †					
Cardiac troponin (x the URL)	76	4 (1–12)	4 (1–9)	4 (2–15)	0.32
PaO ₂ /FiO ₂ ratio, median (IQR), mmHg	88	196 (152–284)	242 (170–291)	188 (132–279)	0.10
Arterial PH	88	7.3 (7.3–7.4)	7.4 (7.3–7.4)	7.3 (7.2–7.4)	0.01
Arterial Lactate (mmol/L)	87	1.8 (1.2–2.7)	1.8 (1.3–2.2)	1.9 (1.2–2.8)	0.69
Leukocytes (10 ³ /L)	89	15 (9–24)	16 (9–24)	14 (9–23)	0.81
Haemoglobin (g/dL)	87	10 (9–11)	10 (9–11)	10 (9–11)	0.41
SOFA score, median (IQR) †	89	9 (7–12)	9 (6–11)	9 (7–13)	0.25
Management of the NOAF, No. (%)					
Medical cardioversion attempted ‡	87	50 (57)	28 (58)	22 (55)	0.83
Electrical cardioversion attempted ‡	84	7 (8)	3 (6)	4 (10)	0.70
Therapeutic anticoagulation †	89	25 (28)	11 (23)	14 (34)	0.34
TEE parameters *					
Time from NOAF, median (IQR), hours	88	29 (17-49)	36 (19-53)	21 (13-46)	0.02
Mean arterial pressure, median (IQR), mmHg	82	80 (71-88)	81 (73-90)	80 (69-87)	0.37
Heart rate, median (IQR), beats/min	87	101 (85-129)	90 (82-109)	127 (99-147)	<0.001
Catecholamines, No. (%)	88	64 (73)	32 (68)	32 (78)	0.34
Norepinephrine	88	57 (65)	29 (62)	28 (68)	0.65
Norepinephrine dose, median (IQR), µg/kg/min §	88	0.8 (0.0, 2.5)	0.3 (0.0, 2.0)	1.3 (0.0, 3.0)	0.13
Epinephrine	88	5 (6)	2 (4)	3 (7)	0.66
Dobutamine	88	4 (4)	1 (2)	3 (7)	0.33

LVEF, median (IQR), %	89	55 (45–61)	55 (45–61)	55 (44–61)	0.87
LV systolic dysfunction (LVEF ≤45%), No. (%)	89	27 (30)	14 (29)	13 (32)	0.82
LA area, median (IQR), cm ²	69	20 (16–24)	20 (16–23)	20 (16–25)	0.44
LA/LAA thrombus	89	0	0	0	-
LA/LAA dense SEC	89	7 (8)	4 (8)	3 (7)	>0.99
LAA emptying velocity median (IQR), cm/s	89	66 (41–85)	74 (57–89)	47 (33–71)	0.001
LAA filling velocity, median (IQR), cm/s	88	59 (46–71)	65 (51–71)	54 (43–67)	0.05
LAA low velocity	88	11 (12)	2 (4)	9 (22)	0.02

Definitions of abbreviations: CHA₂DS₂-VASc, Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category (female); FiO₂, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile; LA, left atrial; LAA, left atrial appendage; LV, left ventricular; LVEF, left ventricular ejection fraction; MD, miss data; NOAF, new-onset atrial fibrillation; PaO₂, partial pressure of arterial oxygen; SAPS, Simplified Acute Physiology Score; SEC, spontaneous echocardiographic contrast; SOFA, sepsis-related organ failure assessment; SR: sinus rhythm; TEE, transesophageal echocardiography.

* At the time of transesophageal echocardiography study.

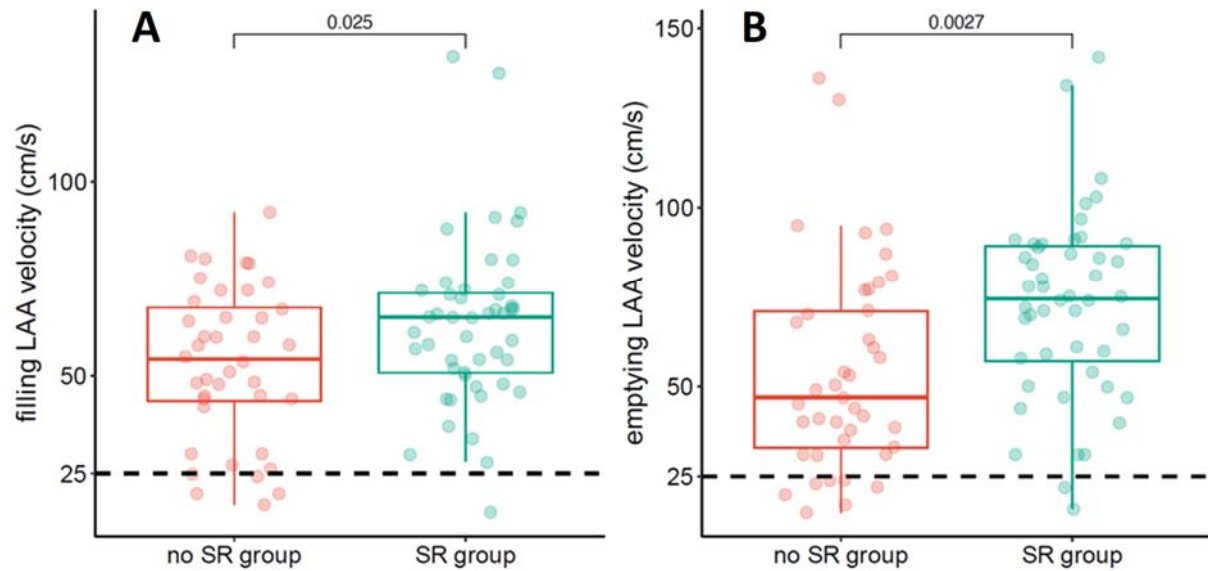
† On the day of transesophageal echocardiography study

‡ Before transesophageal echocardiography study

§ Only patients who received norepinephrine during transesophageal echocardiography study were considered.

|| LAA emptying velocity <25 cm/s or LAA filling velocity <25 cm/s.

Figure 1. Filling LAA velocity (A) and emptying LAA velocity (B) according to the restoration of sinus rhythm (SR group) or not (non-SR group) after cardioversion for acute new-onset atrial fibrillation in critically ill patients with sepsis. The middle line indicates the median; box base, 25th percentile; box top, 75th percentile; whiskers, range.



Abbreviation: LAA, left atrial appendage; SR, sinus rhythm

4. RISQUE HEMODYNAMIQUE

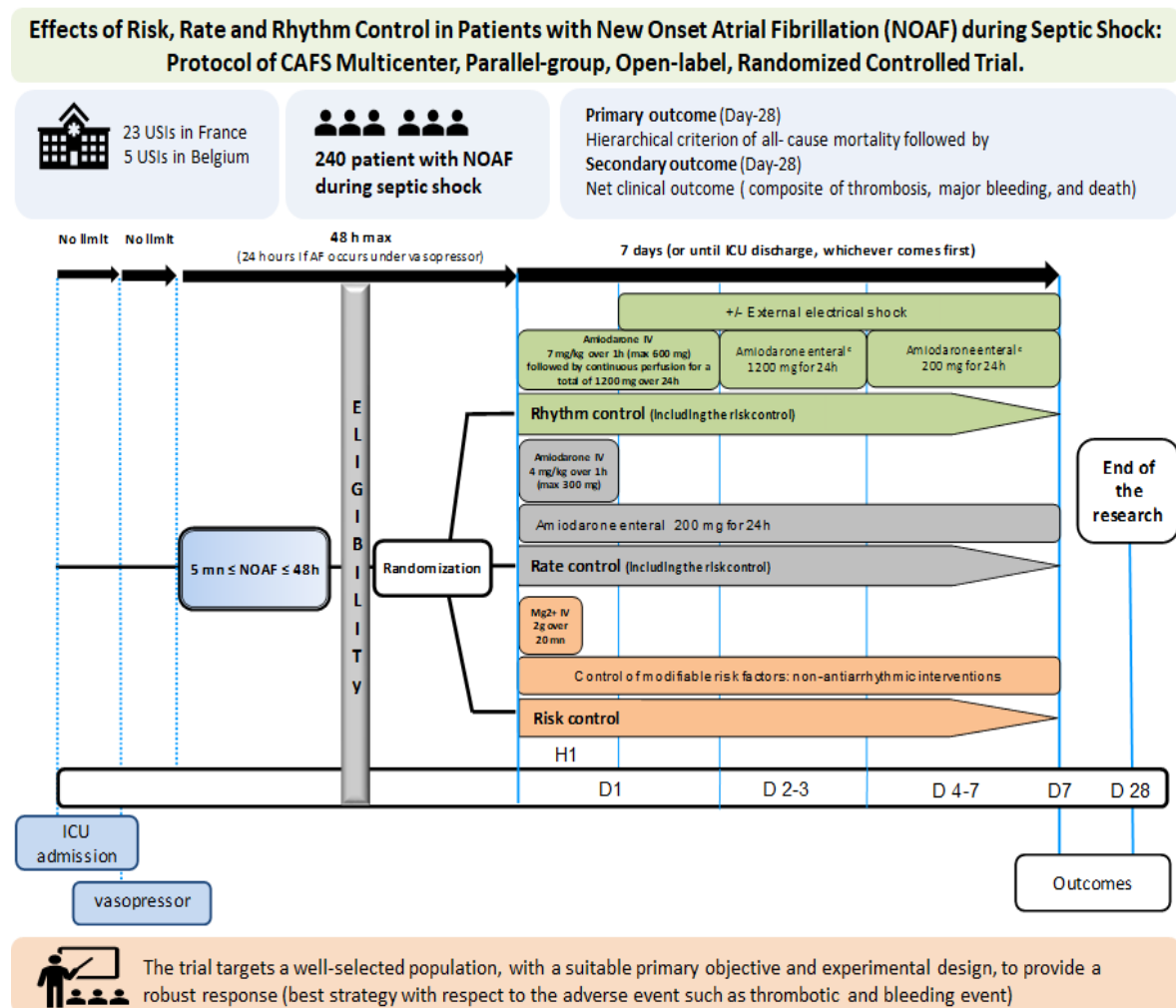
Article 3

Effects of Risk, Rate and Rhythm Control in Patients with New Onset Atrial Fibrillation during Septic Shock: Protocol of CAFS Multicenter, Parallel-group, Open-label, Randomized Controlled Trial.

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Visual abstract



Effects of Risk, Rate, and Rhythm Control in Patients with New Onset Atrial Fibrillation during Septic Shock: Protocol for the CAFS Multicentre, Parallel-group, Open- label, Randomised Controlled Trial

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ABSTRACT

Introduction: New-onset atrial fibrillation (NOAF) is the most common arrhythmia in intensive care unit (ICU) patients with septic shock, and is associated with haemodynamic alterations and increased mortality rates. Therefore, efforts to determine the most effective management strategies are important. In the absence of data from randomised trials, clinical practice varies widely. In this setting, heart rate or heart rhythm control could be beneficial in limiting the duration of shock and preventing evolution to multi-organ dysfunction.

Methods and analysis: The Control Atrial Fibrillation Sepsis (CAFS) study is a binational (French and Belgium), multicentre, parallel-group, open-label, randomised controlled superiority trial to compare the efficacy and safety of three strategies in patients admitted to the ICU who have NOAF (heart rate ≥ 110 bpm lasting 5 minutes) during septic shock. Patients will be randomised to receive either risk control (magnesium and control of NOAF risk factors), rate control (risk control and low dose of amiodarone), or rhythm control (risk control and high dose of amiodarone with external electrical shock if NOAF persists) for 7 days. Patients with a history of AF, NOAF lasting more than 48 h, recent cardiac surgery, or a contraindication to amiodarone will not be included. We will recruit 240 patients. Patients will be randomised on a 1:1:1 basis, and stratified by centre. The primary endpoint is a hierarchical criterion at day 28 including all-cause mortality and the duration of septic shock defined as the period from randomisation to successful weaning of vasopressors. Secondary outcomes include individual components of the primary endpoint; effectiveness at controlling cardiac rhythm at day 7; arterial lactate clearance at day 3; proportion of patients free from organ dysfunction at day 7; ventricular arrhythmia, conduction disorders, thrombotic events and major bleeding events, and acute hepatitis related to amiodarone at day 28; ICU and hospital lengths of stay at day 28.

Ethics and dissemination: The study has been approved by an ethics committee. Patients will be included after obtaining signed informed consent. The results will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT04844801

Strengths and limitations of the study

- ▶ This randomised controlled trial may contribute to the establishment of recommendations with a high level of evidence on the best strategy to limit the duration of shock in patients with sepsis and new onset atrial fibrillation and to prevent evolution to multi-organ dysfunction in these patients.
- ▶ Pragmatic design comparing three common strategies in an intention-to-treat approach.
- ▶ Limitation: not blinded.

INTRODUCTION

Background and rationale

New-onset atrial fibrillation (NOAF) is reported in 40 % of patients with septic shock and is associated with haemodynamic alterations and increased mortality [1,2]. Efforts to determine the most effective management strategies are therefore important. In a recent preliminary study from our research team, successful cardioversion for NOAF in patients with sepsis seemed to be associated with a better prognosis [3]. However, because no randomised clinical trial data are available, there is no consensus regarding best management for NOAF during septic shock, which has led to major variations in practice [1,2,4–7]. Three treatment strategies are commonly used: (i) heart rate control (hereafter rate control) with the use of antiarrhythmic drugs, essentially based on administration of low dose amiodarone [8–10]; (ii) rhythm control using antiarrhythmic drugs, essentially based on administration of high doses of amiodarone and electrical cardioversion [9,10]; and (iii) control of modifiable NOAF risk factors (hereafter risk control) without using antiarrhythmic drugs [11].

Advocates of a rhythm control strategy contend that conversion to sinus rhythm may improve haemodynamics by restoring diastolic function and decreasing cardiac metabolic demand, reduce thromboembolic risk, and minimise exposure to anticoagulants. Proponents of rate control counter that this approach limits the potential adverse effects of high dose amiodarone and/or of electrical cardioversion, while still improving haemodynamics. Finally, the risk control strategy minimises the adverse effects of amiodarone while still resulting in conversion of AF in some patients.

Determining the effectiveness and safety of these three strategies for NOAF during septic shock may provide information to improve clinical decision making and resource utilisation for this highly prevalent condition. Therefore, we will conduct a multicentre, parallel group, open-label, randomised controlled superiority trial to compare head-to-head risk control, rate control and rhythm control in this setting.

Hypothesis

Our hypotheses are formulated in patients who have NOAF during septic shock to assess: i) first, that rate control and rhythm control each improve haemodynamic status, thus decreasing mortality and shock duration, compared to risk control; ii) second, that rhythm control outperforms rate control in this setting.

Objectives

Primary objective

The main objective is to compare the efficacy of three strategies (risk control, rate control, rhythm control) in reducing mortality and the duration of shock.

Secondary objectives

Secondary objectives are to compare the benefit and risks of the three strategies (risk control, rate control, and rhythm control) in terms of: i) rhythm control efficacy, ii) mortality, morbidity, and organ dysfunction; iii) safety, including thrombotic events, bleeding events, net clinical benefit, and serious adverse events related to amiodarone and electrical cardioversion.

METHODS AND ANALYSIS

Trial design

This is a binational, multicentre, parallel-group, open-label, randomised controlled superiority trial to compare the efficacy and safety of three strategies (risk control, rate control and rhythm control) in patients with NOAF during septic shock. The trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trial (SPIRIT) reporting guidelines.

Study setting

The study will be conducted in 28 intensive care units (ICUs) in 23 hospitals in France and 5 hospitals in Belgium (list of the study sites in Appendix A).

Eligibility criteria

Inclusion criteria

Adult patients (age ≥ 18 years) admitted to the ICU will be eligible as soon as they meet all the following criteria:

- 1- Septic shock, defined by the association of the following criteria:
 - Documented or suspected infection, with initiation of antibiotic therapy
 - Initiation of vasopressors (noradrenaline, adrenaline) for at least 1 hour to maintain the mean arterial pressure (MAP) > 65 mmHg
- 2- NOAF (including atrial fibrillation, atrial flutter, and atrial tachycardia) with heart rate ≥ 110 bpm lasting 5 minutes or more
- 3- Written informed consent (patient, next of kin or emergency situation)

- 4- Affiliation to a social security system

Exclusion criteria

Patients presenting any of the following criteria will not be included:

1. Refractory shock defined by a dose of noradrenaline base or adrenaline base $> 1.2 \mu\text{g/kg/min}$
2. Cardiac surgery or cardiac transplant in the previous month
3. Aortic or mitral valve mechanical prosthesis, significant mitral stenosis (mitral surface $< 1.5 \text{ cm}^2$)
4. Congenital heart disease other than bicuspid aortic valve, atrial defect, or patent foramen ovale
5. History of NOAF before septic shock, defined as paroxysmal AF with long-term antiarrhythmic and/or therapeutic anticoagulation, or permanent AF
6. NOAF lasting at most 48 hours * (or 24 hours if AF occurs under vasopressor). *: In case of NOAF of more than 48 hours, the patient can be included after transoesophageal echocardiography (only in mechanically ventilated patients) to eliminate an intracardiac thrombus coupled with initiation of therapeutic anticoagulation (in the absence of contraindication)
7. Electrical cardioversion or use of amiodarone, other antiarrhythmic, or drug inducing bradycardia (beta-blockers, bradycardic calcium channel blocker, digitalis, flecainide) in the 6 hours prior to inclusion
8. Contraindication to amiodarone: history of a serious adverse event related to amiodarone, history of lung disease related to amiodarone, history of hyperthyroidism related to amiodarone, PR interval $> 240 \text{ ms}$, severe sinus node dysfunction with no pacemaker, 2°/ 3° atrioventricular block with no pacemaker, QTc $>480 \text{ ms}$, known or treated hyperthyroidism, hypersensitivity to iodine, amiodarone or to any of the excipients, severe hepatocellular insufficiency (prothrombin rate $<20\%$), diffuse interstitial lung disease
9. Kalaemia $< 3 \text{ mmol/L}$
10. Pregnant or breast-feeding
11. Moribund or death expected from underlying disease during the current admission; patients deprived of liberty and persons subject to institutional psychiatric care
12. Participation in another interventional trial on septic shock and/or arrhythmic disease

Intervention

All consecutive adult patients admitted to the ICU in one of the participating centres who have NOAF during septic shock will be systematically screened for inclusion and non-inclusion criteria. The number of patients who do not meet the inclusion criteria will be reported prospectively in a paper register by each of the participating centres. A patient identification number and the reason for non-inclusion will be noted (local register of non-inclusion in each of the concerned centres).

The experimental plan is shown in **Figure 1**. After verification of the inclusion and non-inclusion criteria, the patient will be enrolled and randomised (Day 1) as soon as possible, and within 48 hours from the onset of AF (or 24 hours if AF occurs under vasopressor). They should then immediately receive the appropriate strategy according to their randomised group –risk control, rate control, or rhythm control– for 7 days (or until ICU discharge, whichever comes first). The risk control strategy will consist of (i) 2 g intravenous bolus of magnesium sulphate over 20 min (if creatinine clearance >30 mL/min), and (ii) control of NOAF risk factors, such as hypovolaemia and metabolic disorders (details in **Table 1**). The rate control strategy will consist of (i) control of NOAF risk factors as described above, and (ii) ‘low dose’ amiodarone (details in Figure 1). The rhythm control strategy will consist of (i) control of NOAF risk factors as described above, (ii) ‘high dose’ amiodarone (details in Figure 1), and (iii) if NOAF persists, electrical cardioversion in sedated patients receiving invasive mechanical ventilation (modalities according to the European Society of Cardiology (ESC) guidelines [12]; details in Figure 1). The course of the three strategies depending on the rhythm and haemodynamic evolution of the patients is shown in **Figure 2**. Therapeutic anticoagulation is recommended in the absence of contraindications if NOAF persists more than 48 hours (modalities of therapeutic anticoagulation will be left to the discretion of the attending physicians). After Day 7 (or after discharge from the ICU if prior to Day 7), NOAF management will be at the discretion of the attending physicians. All patients will be followed until Day 28.

In all groups, current recommendations for the management of septic shock will be followed [13].

Criteria and procedures for premature withdrawal of a participant from the study

In compliance with the conventional management of patients with NOAF during septic shock, the randomised rate control strategy and rhythm control strategy will be discontinued if one of the following occurs:

- ventricular arrhythmia: torsade de pointe, sustained ventricular tachycardia, ventricular fibrillation;
- Conduction disorders: severe bradycardia (< 50 beats per minute), 2nd or 3rd degree atrioventricular block, sinus dysfunction (significant sinus pause of at least 3 seconds), need for a pacemaker, QTc prolongation > 480 ms;
- Acute hepatitis related to amiodarone defined by a significant (x10) increase in transaminases (hepatic cytolysis) compared to values before the first dose administered without any other identified cause of hepatitis;
- Hyperthyroidism, as defined by a TSH < 0.1 mIU/L detected on the blood sample performed before amiodarone initiation [14].

Follow-up visits

The trial clinical examination will be part of routine practice. Parameters collected in the study are those usually collected for management of patients with NOAF during septic shock. The trial follow-up visits will be on day 2, day 3, day 7, and day 28. If the patient is still hospitalised on day 28, data will be collected from the patient's medical records with the possible assistance of a clinical research technician (CRT). If the patient is discharged:

- the CRT will collect the medical records from the clinical departments where the patient stayed; these will be analysed by the investigator who included the patient.
- the CRT will collect data on the patient's vital status and occurrence of serious adverse events during the follow up period:
 - ✓ (if necessary) telephone the patient (three different attempts, days, and times over 15 days);
 - ✓ (if necessary) telephone the physician in charge of the patient during the follow-up period;
 - ✓ (if necessary) telephone the patient's treating or referring physician(s);
 - ✓ (if necessary) contact the town hall of the patient's birthplace

Endpoints

Primary endpoint

The primary endpoint is a hierarchical criterion assessed at day 28 and includes all-cause mortality and the duration of shock. It is calculated in such a manner that death constitutes a worse outcome than duration of shock.

The duration (days) of septic shock is defined as the time from randomisation to successful weaning of vasopressors (no reintroduction or death during the first 48 hours after discontinuation).

Secondary endpoints

Secondary endpoints will include the following:

(1) Effectiveness of treatment on converting cardiac rhythm at day 7 (or at discharge or death if before day 7)

- Number of patients with sinus rhythm
- Number of days alive with sinus rhythm
- Number of days alive with NOAF and heart rate < 110 bpm
- Proportion of patients receiving therapeutic anticoagulation after randomisation

(2) Efficacy on morbidity and mortality and organ function at day 28

- Duration of septic shock at day 28
- Proportion of patients alive free of vasopressors at day 7 (or at discharge or death if before day 7)
- Arterial lactate clearance at day 3 defined as the percentage decrease in arterial lactate concentration between randomisation (day 1) and day 3 [15].
- Proportion of patients alive free from organ dysfunction at day 7 (or at discharge or death if before day 7). Organ dysfunction will be defined as a sequential organ failure assessment (SOFA) score ≥ 3 for the following organs: cardiovascular, renal, neurological, hepatic, respiratory, or coagulation [16].
- Length of ICU stay at day 28
- Length of hospital stay at day 28
- All-cause deaths at day 28.

(3) Safety at day 7 and day 28

- Proportion of patients with at least one arterial thrombotic event including ischaemic stroke and non-cerebrovascular arterial thrombotic event [17]
- Proportion of patients with at least one major bleeding event defined as a bleed that meets at least one of the following criteria: bleeding in a critical area or organ (e.g., intracranial, intraspinal, intraocular, retroperitoneal); bleeding requiring surgical,

endoscopic or endovascular haemostasis action; a life-threatening bleed; and a fatal bleed [18];

- Proportion of patients with at least one serious adverse event related to amiodarone or to magnesium including ventricular arrhythmia, conduction disorders, and acute hepatitis related to amiodarone as described above;
- Proportion of patients with at least one serious adverse event associated with electrical cardioversion (for patients receiving electrical cardioversion) including ventricular arrhythmia, conduction disorders, and arterial thrombotic event.

Diagnostic investigations were left to the discretion of the treating clinicians.

(4) Combined efficacy and safety outcome at day 28

- Proportion of patients with a net clinical outcome as assessed by the presence of all-cause death, arterial thrombotic event, major bleeding event, or at least one serious adverse event related to amiodarone or to magnesium or to electrical cardioversion at day 28

Sample size and its statistical justification

The required number of participants to be randomised is 240 patients. Estimates, derived from previous studies in similar populations [19], show that a sample of at least 240 patients (80 per group) suffices to achieve $\geq 80\%$ power to detect a statistically significant difference in the ranked composite primary endpoint.

Sample size calculation also considered the pairwise comparisons between the groups. For each performed comparison, 1000 samples were simulated using R software. Based on data from our two previous studies in patients with NOAF during sepsis [3,6], sample size calculation assumed 28-day mortality rates of 35%, 30%, and 25% for the risk control, rate control, and rhythm control groups, respectively, and durations of septic shock of 4.9 ± 2.4 days (standard deviation), 3.9 ± 2.4 days, and 2.9 ± 2.4 days, respectively.

Within each sample/pairwise comparison, an individual score was calculated by comparing each patient in one group with all patients in the second group (23). These scores were then compared between groups using a Mann-Whitney/Wilcoxon test in each of the 1000 samples, and the p-value of each test was recorded. For each pairwise comparison, the percentage of tests with a p-value < 0.05 was at least 81% with 80 subjects in each group. Therefore, we expect 80

subjects per group for a minimum power of 81% to detect a difference in the primary endpoint with an alpha=5%.

Recruitment

The expected duration of patient enrolment is 42 months starting from November 2021. The chronogram of the study is as follows: i) 2018: public grant award received from the French Ministry of Health (Programme Hospitalier de Recherche Clinique); ii) May 2019: promotion by Assistance Publique-Hôpitaux de Paris (AP-HP); iii) July 2020: approval by an independent ethics committee; iv) November 2021-May 2025: inclusion of patients; iv) 2025: end of inclusion, monitoring by the participating centres and research work by the investigators; cleaning and closure of the database; blind review to screen for protocol violation, to define intention-to-treat and per-protocol analysis populations; v) 2025-2026: data analysis, writing of the manuscript, and submission for publication.

Allocation of intervention and data management

After the patient or their relative has signed the study consent form, all inclusion/exclusion criteria will be checked by the investigator before randomisation. Centralised block randomisation using a 1:1:1 ratio will be prepared by the Clinical Research Unit before the start of the trial. Randomisation will be carried out in balanced blocks and stratified by hospital centre. Patients will be randomised electronically when the investigator logs in to the centralised electronic case report form (e-CRF) website “Cleanweb” provided by Telemedicine technologies.

Non-identifying data will be entered into the e-CRF via a web browser by a trained investigator or research assistant at each centre. The participating centres have access to e-CRFs via a web-based data collection system (unique identification and password by user). Patient follow-up and task schedules are detailed in the study Gantt chart (**Table 2**). The e-CRF was devised by the principal investigator and the scientific supervisor of the study in collaboration with the data manager of the clinical research unit, Saint-Antoine Hospital AP-HP. e-CRFs and a data dictionary (containing coding variables and definitions) will be saved and archived in the clinical research unit – Saint Antoine Hospital, AP-HP secured servers. Paper CRFs are available in the documentation provided at each site. The e-CRFs (CleanWeb Telemedecine) use the secured computer servers of AP-HP. The computer files used for this research are implemented in compliance with the French (amended “*Informatique et Libertés*” law

governing data protection) and European (General Data Protection Regulation – GDPR) regulations. The sponsor has already obtained authorisation from CNIL (French Data Protection Agency) before implementing any data processing of data from this research (Ref.: MLD/MFI/AR2012389). Database quality control is undertaken by the Data manager of the clinical research unit – Saint Antoine Hospital, AP-HP (missing data, range checks on quantitative values, date chronology check; R-Project computer programming) and put at the disposal of the investigation team. Data management procedures are validated by the clinical research quality specialist and recorded in their secured servers and on paper.

Statistical methods

All analyses will be performed by the study statistician according to a predefined statistical analysis plan, using Stata v9.4 (or next version, StataCorp, College Station, TX, USA). A two-tailed p-value of less than 0.05 will indicate statistical significance.

In compliance with the SPIRIT statement, a flow diagram will describe the progress of the three groups of patients throughout the different phases of the trial (enrolment, allocation, received interventional agents, follow-up, and data analysis). The analysis will be performed on an intention-to-treat (ITT) basis. In case of premature interruption or withdrawal from the study, patients will not be substituted. Missing values will be described and, according to their nature and frequency, multiple imputation methods will be applied. A per-protocol analysis will be conducted as the trial sensitivity analysis since it excludes patients incorrectly randomised or who did not receive the allocated intervention.

Comparative analyses will be done systematically with (main analysis) and without adjustment for randomisation stratification factors. There is no intention to perform interim analyses. The primary endpoint analysis will be done on the ITT population with supportive analyses on the per protocol (PP) population. The latter aim is to investigate PP-excluded patients and their impact on the ITT analysis, and eventually to check whether similar results can be obtained for a robust interpretation. All secondary endpoints analyses will be conducted on ITT and PP populations to assess the robustness of the results.

Descriptive analysis

Descriptive statistical analyses will be conducted on the whole study population to describe general and baseline characteristics, demographics, past history, as well as numbers of premature study withdrawals. Quantitative variables will be presented as mean (\pm standard deviation) or median (25th-75th percentiles) according to the normality of their distribution as

assessed by Shapiro-Wilk tests and graphical methods. Qualitative variables will be presented as numbers (%).

Analysis of the primary endpoint

The pre-specified primary endpoint will be a ranked composite score that incorporates death and duration of shock, calculated in such a manner that death constitutes a worse outcome than longer duration shock. Each patient will be compared with every other patient in the study and assigned a score (equality: 0, win: +1, loss: -1) for each pairwise comparison based on who fared better. For example, if one patient survives and the other does not, the first will be attributed +1 and the latter -1 for that pairwise comparison. If both patients in the pairwise comparison survive, the scoring will depend on duration (days) of septic shock: fewer days earns a score of +1, and more days earns a score of -1. If both patients survive and had the same duration of septic shock, or if both patients die, both will score 0 for that pairwise comparison. For each patient, scores of all pairwise comparisons will be summed to obtain a cumulative score. These cumulative scores will be ranked and compared across the three groups via non-parametric Mann-Whitney test.

Analysis of secondary endpoints

Comparisons between randomised groups at given timepoints will be conducted using Chi square or Fisher exact tests for categorical variables, and using a t-test or non-parametric Mann-Whitney test (pairwise comparisons), and ANOVA or Kruskal Wallis tests (comparisons of >2 groups) for quantitative variables, as appropriate. Pairwise comparisons within groups (across timepoints) will be conducted using tests for paired data, i.e., McNemar test for qualitative data, and t-tests for paired data or Wilcoxon signed ranks for continuous data, as appropriate.

For all-cause mortality at day 28, the number of patients with sinus rhythm at day 7, the number of patients free of vasopressors at day 7, and survival without serious adverse event, calculation of time-to-event endpoints based on follow-up censored data will be employed, taking into account the competing risks of hospital discharge (for mortality evaluation) and death (for number of patients with sinus rhythm at day 7 and the number of patients free of vasopressor at day 7). Kaplan-Meier survival curves and cumulative incidence curves will be plotted for each treatment group, and Cox models will be used to calculate sub-hazard ratios along with their 95% confidence intervals and corresponding p-values.

Analyses of independent determinants of quantitative secondary endpoints will be performed using multivariable linear regression models adjusting for baseline characteristics. As for global longitudinal analysis, we will use generalised linear regression mixed models to test interactions

between timepoints, groups, and pre-specified predictors while entering patient level as a random effect to take into consideration the hierarchical structure of repeated data.

Data monitoring

The trial steering committee (principal investigator, senior investigator, and methodologist) will supervise the progression and monitoring of the study. Research assistants will regularly perform on site monitoring at all centres to check protocol adherence and accuracy of the recorded data. An investigator at each centre will be responsible for daily patient screening, patient enrolment, adherence to protocol, and completion of the e-CRF. Since the three treatment strategies are currently used in routine practice, no data safety monitoring board was required by the ethics committee.

Patient and public involvement

Patients and/or the public were not involved in the development of this study.

ETHICS AND DISSEMINATION

Ethical approval

The study has been approved by independent ethics committee (Comité Sud-Ouest and Outre-Mer II, France, registration number 2019-A02624-53; and Comité éthique de l'hôpital Erasme, Belgium, registration number CCB B4062023000179).

Consent to participate

Patients will be included after signing a written informed consent (Appendix B). If the patient is not able to understand the information given in the consent form, they can be included if a next of kin consents or helps obtain the consent. Eligible patients unable to receive information and for whom a substitute decision maker is not present, can still be included through a process of deferred consent; after recovery, the patient's agreement to stay in the trial will be sought.

Confidentiality

Data will be handled according to the French law on data protection and the European General Data Protection Regulation (GDPR). All original records will be archived at the trial sites for 15 years.

Declaration of interest

This study was funded by a grant from the French Ministry of Health obtained in 2018 (Programme Hospitalier de Recherche Clinique). The sponsor is Assistance Publique-Hôpitaux de Paris, AP-HP (Délégation à la Recherche Clinique et à l'Innovation, DRCI).

Access to data

Investigators will make the documents and individual data required for monitoring, quality control, and audit of the study available to dedicated persons, in fulfilment with the law.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at national and international meetings. Communications, reports, and publication of the results of the study will be placed under the responsibility of the principal investigator-coordinator of the study and the steering committee. Reporting will adhere to the SPIRIT statement, and rules of publication will follow the international recommendations as for *The Uniform Requirements for Manuscripts* (ICMJE, April 2010) (SPIRIT checklist, appendix C).

DISCUSSION

This pragmatic, multicentre, randomised controlled trial will compare the effectiveness and safety of risk control, rate control, and rhythm control for NOAF in patients with septic shock. Despite many observational studies showing that tachycardia and atrial fibrillation are key prognostic factors for septic shock [1,2,20], no randomised controlled trials have been conducted to investigate the best strategy to manage NOAF in this setting.

Strengths of our pragmatic trial come from its design comparing three distinct commonly used strategies in this setting in an ITT approach, the generalisability embedded in the multicentre design, in which both university and non-university hospitals from two countries (France and Belgium) will recruit patients, and the carefully selected population. Indeed, in regards to this last point, we will exclude patients with a significant history of AF (for which the cardiovascular risk depends in part on their established previous medication regimen for AF), and patients with a high thrombotic risk (AF more than 48 hours, recent cardiac surgery, and valvular heart disease classifying AF as ‘valvular AF’ [21]). Importantly, this is an investigator-initiated trial, funded by a grant from the French Ministry of Health with no competing commercial or financial interests involved.

Our study however has several limitations. Since it is an open-label trial, some bias, such as clinical decision-making preferences, is inevitable. Duration of septic shock, the second component of the hierarchical primary endpoint, may be subjective, thus liable to performance bias. Reporting bias is unlikely for the primary outcome given that (i) all cause death is objective, and (ii) ICU hospitalisation and haemodynamic support to determine the duration of septic shock are unambiguously supported by medical records. Nonetheless, an independent clinical events committee will blindly adjudicate all relevant safety outcomes.

In summary, the CAFS trial is an open label, randomised controlled trial testing the efficacy of three routinely used strategies (risk control, rate control, and rhythm control) for NOAF during septic shock to improve survival and reduce duration of shock. The trial targets a well-selected population, with an appropriate, patient relevant primary objective and experimental design, to provide a robust response (best strategy with respect to the adverse event such as thrombotic and bleeding event). This trial’s results may therefore provide high quality evidence for the development of international recommendations for the optimal strategy to improve outcomes in patients with NOAF during septic shock.

APPENDICES

Appendix A: List of study sites

Appendix B: Model of the consent form

Appendix C: SPIRIT Checklist

REFERENCES

1. Seemann A, Boissier F, Razazi K, Carteaux G, de Prost N, Brun-Buisson C, et al. New-onset supraventricular arrhythmia during septic shock: prevalence, risk factors and prognosis. *Ann Intensive Care*. 2015;5:27.
2. Klein Klouwenberg PMC, Frencken JF, Kuipers S, Ong DSY, Peelen LM, van Vught LA, et al. Incidence, Predictors, and Outcomes of New-Onset Atrial Fibrillation in Critically Ill Patients with Sepsis. A Cohort Study. *Am J Respir Crit Care Med*. 2017;195:205–11.
3. Labbé V, Ederhy S, Legouis D, Joffre J, Razazi K, Sy O, et al. Clinical impact of successful cardioversion for new-onset atrial fibrillation in critically ill septic patients: A preliminary study. *Arch Cardiovasc Dis*. 2023;116:230–3.
4. Meierhenrich R, Steinhilber E, Eggermann C, Weiss M, Voglic S, Bogelein D, et al. Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study. *Crit Care*. 14:R108.
5. Guenancia C, Binquet C, Laurent G, Vinault S, Bruyère R, Prin S, et al. Incidence and Predictors of New-Onset Atrial Fibrillation in Septic Shock Patients in a Medical ICU: Data from 7-Day Holter ECG Monitoring. *PloS One*. 2015;10:e0127168.
6. Labbé V, Ederhy S, Lapidus N, Joffre J, Razazi K, Laine L, et al. Transesophageal echocardiography for cardiovascular risk estimation in patients with sepsis and new-onset atrial fibrillation: a multicenter prospective pilot study. *Ann Intensive Care*. 2021;11:146.
7. Labbé V, Bagate F, Cohen A, Voiriot G, Fartoukh M, Mekontso-Dessap A. A survey on the management of new onset atrial fibrillation in critically ill patients with septic shock. *J Crit Care*. 2021;61:18–20.
8. Salem J-E, El-Aissaoui M, Alazard M, Hulot J-S, Aissaoui N, Le-Heuzey J-Y, et al. Modeling of Amiodarone Effect on Heart Rate Control in Critically Ill Patients with Atrial Tachyarrhythmias. *Clin Pharmacokinet*. 2016;55:991–1002.
9. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42:373–498.

10. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140:e125–51.
11. Vieillard-Baron A, Boyd J. Non-antiarrhythmic interventions in new onset and paroxysmal sepsis-related atrial fibrillation. *Intensive Care Med*. 2018;44:94–7.
12. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol*. 2016;18:1609–78.
13. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med*. 2021;47:1181–247.
14. Basaria S, Cooper DS. Amiodarone and the thyroid. *Am J Med*. 2005;118:706–14.
15. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303:739–46.
16. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22:707–10.
17. Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME, et al. Rate Control versus Rhythm Control for Atrial Fibrillation after Cardiac Surgery. *N Engl J Med*. 2016;374:1911–21.
18. Decousus H, Prandoni P, Mismetti P, Bauersachs RM, Boda Z, Brenner B, et al. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *N Engl J Med*. 2010;363:1222–32.
19. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. 2020;382:1787–99.
20. Parker MM, Shelhamer JH, Natanson C, Alling DW, Parrillo JE. Serial cardiovascular variables in survivors and nonsurvivors of human septic shock: heart rate as an early predictor of prognosis. *Crit Care Med*. 1987;15:923–9.
21. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33:2719–47.
22. Vieillard-Baron A, Boyd J. Non-antiarrhythmic interventions in new onset and paroxysmal sepsis-related atrial fibrillation. *Intensive Care Med*. 2018;44:94–7.

23. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med.* 2017;

Table 1: Non-antiarrhythmic interventions for the risk control strategy [22]

Modifiable risk factor	Objective	Modalities
Hypovolaemia	MAP \geq 65 mmHg with at least one negative fluid-responsiveness test if the patient is still hypotensive	Fluid resuscitation with crystalloid or colloids according to sepsis guidelines [23]
Hypokalaemia	Potassium \geq 3.5 mmol/L	Concurrent replacement of potassium ^a
Hyponatraemia	Natraemia \geq 135 mmol/L	Avoid hypotonic solutions in initial resuscitation and consider correcting hyponatraemia, if any ^a
Hypoxaemia	Arterial oxygen saturation $>$ 90%	Adjustment of the inspiratory oxygen fraction and/or the positive expiratory pressure in patients with ventilatory support
Acidosis	pH $>$ 7.35	Adjustment of tidal volume, circuit dead space and/or adapted filling fluids, depending on the mechanism of acidosis
Excess chronotropy due to catecholamines	To limit the arrhythmic effects of catecholamines	According to the sepsis guidelines [23] ^a : <ul style="list-style-type: none"> ○ Lowest vasopressor dose to achieve MAP=65 mmHg ○ Noradrenaline as first line; ○ Dobutamine as a second-line drug, in cases of myocardial dysfunction requiring a positive inotrope to improve tissue perfusion; ○ Adrenaline as a second-line replacement for noradrenaline in refractory shock.
Persistent fever	Body temperature \leq 38.1°C	External cooling and anti-pyretics could be discussed ^a
Mal-positioned central venous catheter	Correctly positioned catheter	Withdraw catheter to caval-atrial junction

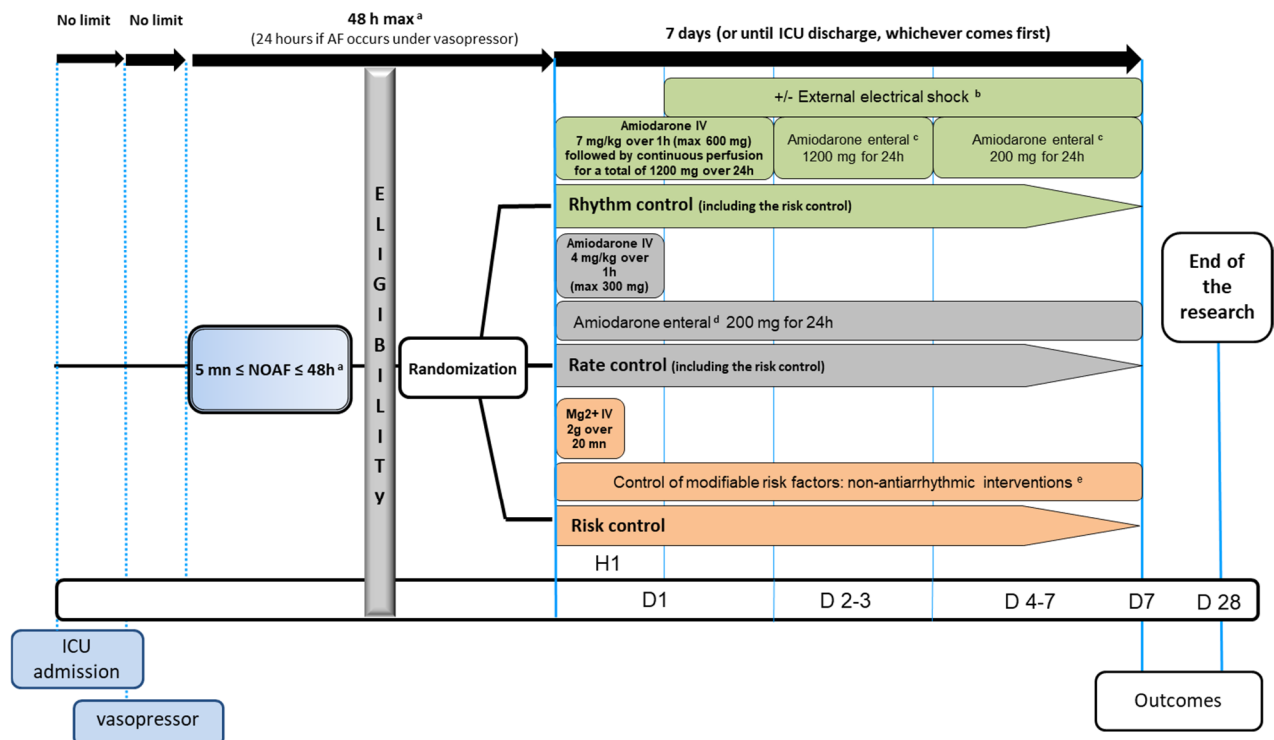
Abbreviations: MAP, mean arterial pressure

^a Left to the discretion of the attending physicians

Table 2 Study Gantt chart (task schedule)

Procedures and assessments	D1	D2-D7^a	D28 +/- 2 d
Inclusion and non-inclusion criteria	R		
Enrolment			
Informed consent	R		
Intervention			
Risk control strategy	C	C	
Rate control strategy	C	C	
Rhythm control strategy	C	C	
Assessments			
Characteristics of the patient ^b	C		
Characteristics of the septic shock ^c	C	C	C
Organ dysfunction and management ^d	C	C	
Thyroid blood sample	C		
Other biological data ^e	C		
Cardiac rhythm	C	C	
Time of septic shock ^f			C
Adverse event			C
ICU length of stay and hospital length of stay			C
Vital status			C
Abbreviations: C, Care; ICU, intensive care unit; R, research			
^a or until ICU discharge, whichever comes first			
^b Characteristics of patients include age, sex, height, weight, severity score indicated by the Simplified Acute Physiological Score II score, CHA ₂ DS ₂ VASc thrombotic risk score, HASBLED bleeding risk score, pre-existing conditions (arterial hypertension, diabetes mellitus, alcohol, chronic cardiovascular, respiratory, renal, liver, thrombotic or bleeding event, stroke, neoplasia, positive serology for human immunodeficiency virus), previous medication (antithrombotic, corticosteroids, gastric anti-ulcer, non steroidal anti-inflammatory)			
^c Site of infection, pathogen (type, sensitivity to initial anti-infective therapies), source control modalities, hospital- or community-acquired infection, duration of septic shock			
^d Severity score indicated by the Sequential Organ Failure Assessment score, haemodynamic data (if available: left ventricular ejection fraction, stroke volume; arterial lactate), organ support (fluid resuscitation, catecholamine, invasive mechanical ventilation, renal replacement therapy), corticosteroids			
^e potassium, sodium, magnesium, arterial PH, bicarbonates, white blood cell count, transaminase			
^f time from randomisation to successful weaning of vasopressors (no reintroduction or death during the first 48 hours after discontinuation).			

Figure 1: Experimental scheme



Abbreviations: IV, intravenous; IP, infusion pump

^a In case of NOAF > 48 hours, the patient can be included after a transesophageal echocardiography (only in mechanically ventilated intubated patients) to eliminate an intracardiac thrombus coupled with initiation of therapeutic anticoagulation (in the absence of contraindication)

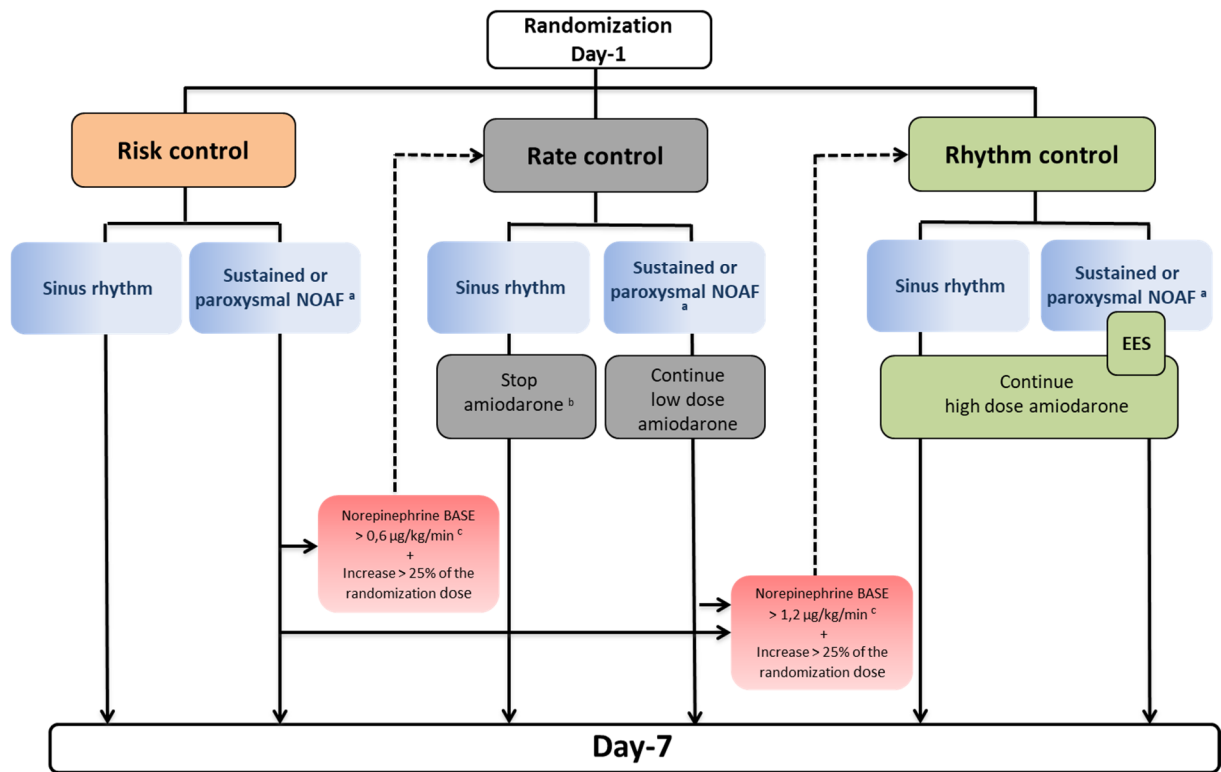
^b Only in sedated patients receiving invasive mechanical ventilation in the two following cases: (i) NOAF persists after initial IV bolus of amiodarone and norepinephrine base (or epinephrine base) doses > 0.3 µg/kg/mn or (ii) NOAF persists > 6 h after initial IV amiodarone bolus. A maximum of three consecutive cardioversions with energy delivery of 150, 200, and 300 will be done using a synchronised biphasic defibrillator with anterior–posterior electrode positions. In case of recurrence of NOAF after a first electrical cardioversion, indication for a new external electrical shock is left to the discretion of the treating physicians.

^c Enteral route unavailable: 720 mg continuous IV over 24 h (0.5 mg/mn IV over 24h)

^d Enteral route unavailable: 150 mg IV over 1 h

^e Hypovolaemia, hypokalaemia, hyponatraemia, hypoxaemia, acidosis, excess chronotropy due to catecholamines, persistent fever, mal-positioned central venous catheter

Figure 2: Course for the three strategies according to the rhythm and haemodynamic evolution of the randomised patients



Abbreviations: EES, external electrical shock; NOAF, New Onset Atrial Fibrillation

^a Therapeutic anticoagulation is recommended in the absence of contraindications if sustained or paroxysmal NOAF > 48 hours. If therapeutic anticoagulation is contraindicated, patients in the rhythm control group will be switched to the rate control group.

^b In the case of sinus rhythm of more than 24h

^c Dose thresholds reduced by half in cases of severe cellular hypoxia defined by an arterial lactate level >3 mmol/L

--- : Possibility of switching to a rate or rhythm control strategy in case of persistent NOAF and significant haemodynamic alteration

Administrative information

Primary Registry and Trial Identification Number

ClinicalTrials.gov Identifier, NCT04844801

Date of Registration in Primary Registry

April 14, 2021

Secondary Identifying Numbers

APHP190070

Registry Identifier: IDRCB; 2019-A02624-53

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Public Title

Comparison of three strategies in patients with atrial fibrillation during septic shock

Scientific Title

Effects of Risk, Rate and Rhythm Control in Patients with New Onset Atrial Fibrillation during Septic Shock: the Protocol of the CAFS Multicentre, Parallel-group, Open-label, Randomised Controlled Trial

Protocol version

Version 5.0 dated 20/01/2023

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Primary sponsor

The sponsor is *Assistance Publique – Hôpitaux de Paris, AP-HP (Délégation à la Recherche Clinique et à l'Innovation, DRCI)*.

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Secondary sponsor

None

Disclaimer

None

Contributors

VL, AMD in collaboration with all authors designed the study and wrote the manuscript together. AR provided substantial contributions to the conception and design of the study, and wrote the statistical analysis plan and estimated the sample size. VL, CD, SP, DC, FB, FB, DD, JJ, MD, OS, SC, XM, GM, BS, PA, NB, P-MB, SV, BM, NH, EV, CL, GC, FA, FT, MF, DD, GM, LB, AR, and AMD contributed to drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. VL, CD, SP, DC, FB, FB, DD, JJ, MD, OS, SC, XM, GM, BS, PA, NB, P-MB, SV, BM, NH, EV, CL, GC, FA, FT, MF, DD, GM, LB, AR, and AMD gave their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of it.

Steering committee

Composition: principal investigator (VL), scientific supervisor (AM-D), biostatistician (AR), and the sponsor's appointed representatives of the trial: Clinical Research Associate in charge of the project (GM) and project manager URC DRCI (clinical research unit, Saint-Antoine Hospital AP-HP), and project manager of the DRCI promotion unit.

Role: Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the trial.

Competing interests

AM-D reports lectures for Leo Pharma.

VL receives advisory board fees from AOP, and grants from Leo Pharma unrelated to the present study

Provenance and peer review

Not commissioned; externally peer reviewed.

5. Discussion

5.1 Risque thrombotique et hémorragique

5.1.1 Incidence

Nous rapportons une incidence d'évènements thrombotiques artériels élevée (7%) relativement similaire à celle rapportée par Yoshida et al. (4,6%) au sein d'une cohorte prospective de patients présentant une FAN en réanimation [121]. L'incidence des évènements hémorragiques majeurs est également importante (19%), en cohérence avec les résultats de Walkey et al. qui rapportent une incidence de 12,6% chez les patients ayant une FAN au cours d'un sepsis [94].

Les risques thrombotiques et hémorragiques chez les patient en FAN au cours d'un sepsis sont ainsi bien supérieurs à ceux rapportés chez les patients de cardiologie en situation d'urgence. Au sein d'un récent essai clinique comparant la cardioversion précoce versus retardée chez les patients prises en charge pour une FAN au sein de services des urgences, Pluymaerkers et al. ont rapporté une incidence de 0,5% d'évènements thrombotiques artériels et aucun évènement hémorragique majeur au cours des 4 semaines de suivi [122].

Ces résultats confirment la nécessité de disposer d'outils de stratification du risque cardiovasculaire utilisable au lit des patients, afin d'identifier les patients les plus susceptibles de bénéficier d'un traitement anticoagulant pour prévenir le risque thrombotique sans sur-risque hémorragique.

5.1.2 Stratification du risque

5.1.2.1 Les scores cardiologiques

Les scores « cardiologiques » de stratification des risques thrombotiques CHA₂DS₂-VASc et

hémorragiques HAS-BLED, semblent être limitées pour prédire les événements cardio-vasculaires chez les patients ayant une FAN au cours d'un sepsis [123]. De même, Walkey et al. ont rapporté dans ce contexte une faible performance du score CHA₂DS₂-VASc pour stratifier le risque d'AVC au sein d'une large cohorte rétrospective [94].

5.1.2.2 Paramètres échocardiographiques

Les anomalies cardiaques structurelles et fonctionnelles en échocardiographie (dysfonction de l'auricule gauche, athérome aortique sévère, dysfonction systolique du ventricule gauche) sont fréquents chez les patients présentant une FAN au cours d'un sepsis. Cependant, seule la dysfonction systolique du ventricule gauche, visible en échocardiographie transthoracique, était associée de manière indépendante aux événements cardio-vasculaires.

La réalisation d'une étude échocardiographique morphologique complète et systématique, comprenant une première ETO dans les 48 heures suivant l'apparition de la FAN, suivie d'une seconde ETO chez les deux tiers d'entre eux, n'a révélé qu'un seul thrombus intra-auriculaire gauche. De plus, aucun thrombus n'a été rapporté chez six patients ayant développé un événement thrombotique artériel. Plusieurs hypothèses peuvent être envisagées :

- Un thrombus peut s'être développé secondairement en raison de la persistance de la FAN ;
- La survenue d'une sidération post-cardioversion de l'auricule gauche malgré le retour en rythme sinusal peut favoriser la formation de thrombus [124];
- Un thrombus peut passer inaperçu lorsqu'une ETO est réalisée après l'événement embolique ;
- Enfin, nous rapportons un AVC ischémique probablement dû à une plaque d'athérosclérose instable, et deux accidents thrombotiques artériels possiblement dus à d'autres sources cardiaques d'embolie. De même, des séries cardiologiques antérieures ont rapporté que 25%

des AVC ischémiques chez les patients atteints de FA pouvaient être dus à d'autres sources cardiaques d'embolie ou à une pathologie athéromateuse de l'aorte proximale [125,126].

Par conséquent, une stratégie basée sur la réalisation systématique d'une ETO afin d'estimer le risque cardio-vasculaire, notamment thrombotique, semble limitée.

Etant donné la fréquence observée des anomalies de l'auricule gauche dans cette première étude, nous avons effectué une sous-analyse de l'étude FAST (**Annexe 2**) afin de caractériser une approche individualisée de l'ETO basée sur le score CHA₂DS₂-VASc. Les anomalies de l'oreillette/auricule gauche comprenant la baisse des vitesses de vidange et de remplissage intra-auriculaire gauche, la dilatation de l'auricule gauche, ainsi que la présence d'un thrombus ou un contraste spontané intense, sont associées au score de risque thrombotique CHA₂DS₂-VASc [127] et aux événements thrombotiques artériels chez les patients cardiologiques présentant une FA [128], nous avons ainsi évalué la capacité du score CHA₂DS₂-VASc à prédire les anomalies de l'oreillette/auricule gauche à l'ETO chez les patients présentant une FAN au cours d'un sepsis. La prévalence des anomalies de l'oreillette/auricule gauche augmentait significativement avec le score CHA₂DS₂-VASc. L'aire sous la courbe ROC (95%CI) du score CHA₂DS₂-VASc pour prédire les anomalies de l'oreillette/auricule gauche était de 0,66 (0,53-0,76). Un seuil de 5 pour le CHA₂DS₂-VASc a donné une précision diagnostique (c'est-à-dire la proportion de tous les tests avec un résultat correct) de 0,71(0,61-0,80), avec une valeur prédictive négative de 28% (13-47), une valeur prédictive positive de 91% (81-97), une sensibilité de 57% (29-82), et une spécificité de 74% (63-83). Les résultats de cette étude ancillaire pourraient suggérer une approche individualisée de l'ETO réalisée chez les patients à haut risque d'anomalies de l'oreillette/ auricule gauche (CHA₂DS₂-VASc \geq 5) et pour lesquels la balance bénéfique/risque de l'anticoagulation est particulièrement difficile.

5.1.2.3 Vers des biomarqueurs sanguins ?

De nombreuses données convergentes ont montré l'intérêt des biomarqueurs en complément de la stratification clinique pour prédire les risques thrombotiques, hémorragiques et de décès chez les patients de cardiologie en FA chronique [129]. Les biomarqueurs cardiaques (troponine, B-type natriuretic peptide), d'activation plaquettaire et de la coagulation (D-dimères, Fibrinogène, Fragments pro-thrombinique 1 et 2, Complexe thrombine-antithrombine, Fibrinopeptide A, microparticules procoagulantes circulantes), de stress oxydatif et fibrose myocardique (GDF 15, galectine-3), de dysfonction rénale (créatinine, cystatine C), d'inflammation (C-réactive protein, Interleukines 6), de dysfonction endothéliale (von Willebrand factor) et de renouvellement de la matrice extra-cellulaire (Métalloprotéinases matricielles) ont ainsi été associés à un risque accru d'évènements cardio-vasculaires sévères [130–132] (**Annexe 3**). Plus particulièrement réalisées au sein de notre service, des études ont montré une association entre le taux de C-reactive protéine à l'admission et l'augmentation de la mortalité chez le patient en FA [19], une relation entre le taux plasmatique de facteur Willebrand à l'admission et le risque d'insuffisance cardiaque et de mortalité toute cause [134], et une augmentation du taux de microparticules procoagulantes circulantes chez le patient en FA [135].

A notre connaissance, ces biomarqueurs n'ont pas été étudiés chez les patients présentant une FA au cours du choc septique. Au-delà de mieux caractériser les mécanismes physiopathologiques à l'origine des risques pro-thrombotiques et hémorragiques accrus dans ce contexte, l'utilisation de ces biomarqueurs pourrait permettre une meilleure stratification des risques cardio-vasculaires. Nous souhaitons mener l'étude BAFS (Biomarkers Atrial Fibrillation Sepsis) qui permettra d'étudier les concentrations sériques des biomarqueurs circulants chez les patients présentant une FAN au cours du choc septique et d'évaluer la capacité de ces biomarqueurs circulants à prédire le risque cardiovasculaire dans ce contexte.

5.1.3 Le traitement anticoagulant curatif : l'équipoise clinique

L'évaluation de la balance bénéfique/risque de l'anticoagulation curative demeure un vrai challenge quotidien pour les intensivistes en l'absence (i) d'outil performant de stratification des risques cardio-vasculaires à court terme et (ii) l'absence de données robustes (essais cliniques randomisés) sur le bénéfice net (absence d'évènement cardiovasculaire associant évènement thrombotique artériel, évènement hémorragique, et décès de cause cardio-vasculaire) du traitement anticoagulant dans ce contexte. En cohérence avec nos résultats, plusieurs études rapportent ainsi l'administration d'un traitement anticoagulant chez un patient sur deux présentant une FAN en réanimation [10,121,136–138].

5.1.3.1 Stratégie libérale "cardiologique"

Les recommandations européennes actuelles pour la prévention des évènements thrombotiques artériels peri-cardioversion de la FAN préconisent l'initiation précoce d'une anticoagulation thérapeutique (dès que possible avant la cardioversion, quelle que soit la durée de la FAN), pour une durée prolongée (au moins 4 semaines post-cardioversion) [139]. Comme développé dans le paragraphe 1.2.3, ces recommandations sont basées sur des études observationnelles menées chez des patients cardiologiques rapportant (i) un risque de formation de thrombus atrial gauche même en cas de FAN aiguë (<48 heures) [140] et (ii) un risque thrombotique post-cardioversion accru [141,142].

5.1.3.2 Vers une stratégie conservatrice ?

La stratégie libérale "cardiologique" pourrait être remise en question chez les patients présentant une FAN au cours d'un sepsis.

Tout d'abord, au sein de notre cohorte prospective de 96 patients présentant une FAN au cours d'un sepsis, aucun patient n'a présenté de thrombus intra-oreillette/ auricule gauche au cours des 48 premières heures suivant la survenue de la FAN [143].

Ensuite, nous montrons que la prévalence d'une dysfonction de l'auricule gauche post-cardioversion est très rare (4%) chez les patients présentant une FAN au cours d'un sepsis (Article 2). Ces résultats pourraient suggérer un comportement différent de l'auricule gauche lors de la FA dans le contexte d'un sepsis par rapport à celui de la FA chronique incluant remodelage auriculaire et dysfonctionnement endothélial [144].

De plus, l'étude FAST a rapporté que les événements hémorragiques majeurs, dont la plupart menaçaient le pronostic vital, étaient presque trois fois plus fréquents que les événements thrombotiques artériels (19% contre 7%) [143]. Enfin, au sein d'une large cohorte de patients appariés par score de propension et présentant une FA au cours d'un sepsis, le traitement anticoagulant était associé à une augmentation du risque hémorragique sans diminution significative du risque thrombotique [94].

Ces arguments suggèrent que la stratégie libérale cardiologique pourrait ne pas être appropriée chez les patients septiques présentant un risque hémorragique élevé [123]. Il en découle une importante hétérogénéité des pratiques usuelles. Dans une enquête de pratique que nous avons menée auprès de 356 intensivistes (**Annexe 4**) [106], nous avons ainsi constaté que, chez les patients présentant une FAN au cours d'un choc septique, 44% des intensivistes initient le traitement anticoagulant curatif plus tardivement (uniquement lorsque la FAN est persistante plus de 48 heures), et 59% d'entre eux l'utilisent pour une durée plus courte (pendant un maximum de 7 jours après une cardioversion réussie).

En résumé, la stratégie libérale cardiologique (traitement anticoagulant à début précoce et durée prolongée) peut minimiser le risque hémorragique, mais également augmenter le risque

hémorragique. À l'inverse, une stratégie conservatrice (c'est-à-dire une initiation plus tardive et une durée plus courte du traitement anticoagulant) pourrait également prévenir le risque thrombotique, tout en réduisant l'exposition au traitement anticoagulant à risque hémorragique.

Nous souhaitons donc dans un avenir proche effectuer un essai clinique randomisé dont l'objectif sera de déterminer la meilleure stratégie de traitement anticoagulant.

5.1.4 Incidence et facteurs prédictifs d'évènements cardio-vasculaires à long terme

Les travaux de cette thèse se sont particulièrement intéressés à la caractérisation et la stratification des risques cardio-vasculaires à court terme de la FAN au cours d'un sepsis. Cependant plusieurs travaux indiquent que la survenue d'un tel évènement constitue un marqueur de risque à moyen et long terme de complications cardio-vasculaires [145] impliquant d'identifier précocement les patients à risque afin de mettre en place un suivi et des traitements spécifiques adaptés. Au sein d'une cohorte rétrospective de patients survivant d'un sepsis, Walkey et al ont rapporté que les patients ayant une FAN au cours du sepsis, en comparaison aux patients n'ayant pas de FAN au cours du sepsis, présentaient un risque à long terme plus élevé de récurrence de FA (54,9% vs. 15,5%), d'hospitalisation pour insuffisance cardiaque (11,2% vs 8,2% ; HR, 1,25 [IC 95% 1,16-1,34]), d'AVC (5,3% vs 4,7%; HR, 1,22 [IC 95% 1,10-1,36]), et de décès (74,8% vs 72,1%; HR 1,04 [IC 95% 1,01-1,07]) [145]. Par ailleurs, parmi les patients ayant une FAN et un AVC ischémique lors du suivi, près de la moitié n'avaient eu aucune récurrence de FA préalablement à l'AVC ischémique. La survenue d'une FA de novo lors d'un sepsis pourrait ainsi être la dernière « opportunité » d'envisager une thromboprophylaxie chez certains patients [145]. Ces données s'opposent ainsi à la pensée selon laquelle une FA de novo au cours d'un sepsis serait un évènement transitoire réversible et sans conséquence après la résolution du sepsis. Au contraire, la FAN pourrait être l'expression

clinique d'une pathologie plus profonde et plus chronique de l'oreillette gauche où le remodelage atrial (structurel, électrique, biochimique [146]), la dysfonction endothéliale et l'état pro-thrombotique y sont associés [147]. L'interaction complexe entre ces différents mécanismes pourrait créer un cercle vicieux de cardiomyopathie atriale qui ne cesse de s'aggraver entraînant un risque plus élevé de FA et d'évènements thrombotiques artériels [147–149]. Ainsi, identifier précocement la cardiomyopathie atriale et les facteurs impliqués dans son développement permettrait d'adapter les thérapeutiques et notamment la stratégie anticoagulante [147,150].

Au-delà des scores cliniques de risque et les anomalies morphologiques détectées en échocardiographie « conventionnelle », des données plus récentes ont montré que l'évaluation morphologique de l'oreillette gauche en échocardiographie tridimensionnelle [151,152], et fonctionnelle grâce à l'étude de la déformation myocardique (strain) sont désormais particulièrement utile pour stratifier le risque d'évènements thrombotiques artériels à long terme chez les patients de cardiologie [146,153–159]. Comme vu dans le paragraphe 5.1.2, de nombreuses données ont également montré l'intérêt des biomarqueurs en complément de la stratification clinique et échocardiographique pour prédire les risques d'évènements cardiovasculaires à long terme [130–132] chez les patients de cardiologie en FA permanente.

L'objectif d'un prochain travail sera donc de pouvoir affiner l'évaluation des patients survivants d'un sepsis compliqué de FAN par une approche combinée clinique (scores de risque conventionnels), biologique (nouveaux biomarqueurs), et échocardiographique (notamment utilisation de nouvelles techniques: strain, étude OG tridimensionnelle) afin d'identifier précocement les patients ayant un risque à long terme d'évènements cardiovasculaires associés à la FA.

5.2 Risque hémodynamique

Malgré de nombreuses études observationnelles rapportant que la FAN est indépendamment associée à une aggravation hémodynamique et un doublement de la mortalité hospitalière [5–7], aucun essai contrôlé randomisé n'a étudié la meilleure stratégie de prise en charge hémodynamique dans ce contexte. Ceci explique pourquoi les places respectives du contrôle du risque, du rythme cardiaque (RC) ou de la fréquence cardiaque (FC) ne sont pas établies et n'ont jamais fait l'objet de recommandation ni même de consensus professionnel. Il existe donc une forte équivoque clinique : i) le contrôle du risque minimiserait la iatrogénie tout en permettant la résolution d'un certain nombre de FAN ; ii) le contrôle de la FC (en sus du contrôle du risque) limiterait les effets indésirables potentiels des fortes doses d'amiodarone et de la cardioversion électrique, tout en stabilisant l'hémodynamique; iii) le contrôle du RC (en sus du contrôle du risque) optimiserait davantage l'hémodynamique, en améliorant rapidement la fonction diastolique et en réduisant la demande métabolique cardiaque et pourrait réduire le risque de formation d'un thrombus intra-cardiaque et le recours à un traitement anticoagulant. L'essai multicentrique randomisé et contrôlé CAFS compare l'efficacité et la sécurité de trois stratégies usuelles de prise en charge hémodynamique de la FAN au cours du choc septique : contrôle du risque, contrôle de la FC et contrôle du RC (Identifiant IDRCB; 2019-A02624-53 ; Trial registration number: NCT04844801).

A ce sujet, les essais menés précédemment ont concerné les patients stables sur le plan hémodynamique, qu'il s'agisse des patients de cardiologie ayant une FA chronique [160], ou les patients en post opératoire de chirurgie cardiaque [161]. Ces essais visaient à comparer les stratégies médicamenteuses de contrôle de la FC ou du RC, en incluant la possibilité d'une cardioversion électrique. L'essai AFFIRM a suggéré, chez les patients de cardiologie en FA non valvulaire chronique, l'absence de différence significative entre ces deux stratégies sur la

mortalité et la morbidité à 5 ans (accident thrombo-embolique et accident hémorragique à long terme) [39]. Le contrôle du RC était cependant associé à des ré-hospitalisations plus fréquentes en comparaison au contrôle de la FC. De la même façon, les effets secondaires médicamenteux, notamment la survenue de bradycardie et d'un allongement du QT étaient plus fréquents dans le groupe contrôle du RC par rapport au groupe contrôle de la FC. Ainsi, au cours de la FA non valvulaire, l'ESC préconise en première intention une stratégie de contrôle de la FC, réservant le contrôle du RC à la persistance des symptômes liés à la FA [66]. Dans le contexte post-opératoire de chirurgie cardiaque, Gillinov et al. ont également comparé les stratégies de contrôle de la FC et du RC chez des patients stables sur le plan hémodynamique [161]. Le groupe contrôle du RC bénéficiait de la mise sous amiodarone accompagnée de la réalisation d'une cardioversion électrique si la FA persistait plus de 24h. Dans le groupe contrôle de la FC, le clinicien pouvait choisir, seul ou en association, un beta-bloquant, un antagoniste calcique bradycardisant, ou un digitalique. Si la FA persistait plus de 48h, un traitement anticoagulant était recommandé. Les auteurs ne rapportent aucune différence entre ces deux stratégies en termes de nombre de jours d'hospitalisation à 3 mois, de survenue d'évènements thrombotiques artériels, de complications hémorragiques, ou de persistance de FA à 60 jours [161]. Ces résultats sont cependant difficilement extrapolables aux patients en sepsis/choc septique chez lesquels l'enjeu principal est l'altération d'un état hémodynamique déjà précaire. Les points forts de notre étude pragmatique sont (i) sa conception qui compare trois stratégies usuelles distinctes en intention de traiter et en restant aussi proche que possible du scénario clinique, (ii) la généralisation des résultats liée à la conception multicentrique de l'essai (hôpitaux universitaires et non universitaires, essai bi-national), et (iii) la population bien sélectionnée. En effet, en ce qui concerne ce dernier point, nous excluons les patients ayant des antécédents significatifs de FA (pour lesquels le risque cardio-vasculaire dépend en partie de leur traitement antérieur pour la FA), et les patients présentant un risque thrombotique élevé

(FA > 48 heures sans ETO préalable excluant la présence d'un thrombus intra-cardiaque, post opératoire de chirurgie cardiaque, et cardiopathie valvulaire). Il est important de noter qu'il s'agit d'un essai à l'initiative des investigateurs, financé par une subvention du ministère français de la santé, sans aucun intérêt commercial ou financier concurrent.

Notre étude présente plusieurs limites. De nombreux biais (biais de suivi, d'interprétation...) sont inévitables dans cet essai ouvert. Le délai de survenue du choc septique, deuxième composante du critère d'évaluation primaire hiérarchique, peut être trop subjectif et donc sujet à un biais. Le biais de déclaration est peu probable pour le critère primaire étant donné que (i) le décès toutes causes confondues est objectif, et (ii) l'hospitalisation en réanimation et le support hémodynamique déterminant la durée du choc septique sont sans équivoque documentés au sein du dossier médical.

Les résultats de cet essai, si nos hypothèses se confirment, contribueront à améliorer la prise en charge du choc septique par la démonstration «fondée sur des preuves» du bénéfice d'une stratégie pragmatique susceptible de réduire la durée de la défaillance hémodynamique et des autres défaillances d'organes, avec in fine, un effet potentiel sur la mortalité des patients en choc septique.

6. CONCLUSION DE LA THESE

La survenue d'une FAN au cours d'un sepsis est particulièrement fréquente et grave, associée à un sur-risque thrombotique, une altération de l'état hémodynamique déjà précaire et un doublement du risque de décès intra-hospitalière. La prise en charge spécifique d'une FAN dans ce contexte doit s'attacher à prévenir le risque thrombotique et limiter le risque d'aggravation hémodynamique. La thèse s'est articulée autour de ce double objectif.

Nous confirmons que le risque d'évènements cardio-vasculaires majeurs est élevé chez les patients ayant une FAN au cours d'un sepsis. Dans ce contexte, les approches cardiologiques de stratification des risques thrombotiques (anomalies ETO, score CHA₂DS₂-VASc) et hémorragiques (score HAS-BLED) afin de prédire ce risque semblent limitées. L'étude d'une approche individualisée basée sur l'ETO couplée avec le score CHA₂DS₂-VASc pourrait néanmoins être intéressante. Ce travail a également permis de caractériser le risque de formation d'un thrombus intra-cardiaque (absence de thrombus dans les 48 h suivant le début de la FA, prévalence rare de la sidération post cardioversion de l'auricule gauche). Enfin, nous avons confirmé l'équivalence clinique au sujet des modalités de traitement anticoagulant (délai d'initiation, durée) à l'origine d'une grande hétérogénéité des pratiques usuelles justifiant la réalisation d'essais thérapeutiques. Les résultats apportés par cette thèse posent les bases d'un futur essai dont l'objectif sera d'évaluer la meilleure stratégie de traitement anticoagulant dans la prévention des évènements thrombotiques artériels sans sur-risque hémorragique ou de décès.

Le second volet de la thèse s'est attaché à la prise en charge du risque hémodynamique de la FAN au cours d'un état de choc septique. La réalisation de l'essai CAFS (inclusion en cours) randomisé contrôlé ouvert teste l'efficacité de trois stratégies couramment utilisées (contrôle du risque, contrôle de la fréquence cardiaque et contrôle du rythme cardiaque) dans ce contexte. L'essai cible une population bien sélectionnée, avec un objectif principal et un modèle expérimental approprié, afin de fournir une réponse robuste quant à la meilleure stratégie de prise en charge hémodynamique de la FAN au cours du choc septique dans l'objectif d'améliorer la survie et la durée du choc septique. Nous pensons que les résultats de cet essai contribueront à la publication de recommandations consensuelles dans la prise en charge hémodynamique des patients ayant une FAN au cours d'un choc septique.

7. REFERENCES BIBLIOGRAPHIQUES

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315:801–10.
2. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22:707–10.
3. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet Lond Engl*. 2020;395:200–11.
4. Dupuis C, Bouadma L, Ruckly S, Perozziello A, Van-Gysel D, Mageau A, et al. Sepsis and septic shock in France: incidences, outcomes and costs of care. *Ann Intensive Care*. 2020;10:145.
5. Klein Klouwenberg PMC, Frencken JF, Kuipers S, Ong DSY, Peelen LM, van Vught LA, et al. Incidence, Predictors, and Outcomes of New-Onset Atrial Fibrillation in Critically Ill Patients with Sepsis. A Cohort Study. *Am J Respir Crit Care Med*. 2017;195:205–11.
6. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA J Am Med Assoc*. 2011;306:2248–54.
7. Seemann A, Boissier F, Razazi K, Carreaux G, de Prost N, Brun-Buisson C, et al. New-onset supraventricular arrhythmia during septic shock: prevalence, risk factors and prognosis. *Ann Intensive Care*. 2015;5:27.
8. Labbe V, Ederhy S. Faut-il anticoaguler les patients présentant une fibrillation atriale de novo en réanimation ? 2015;
9. Lu Y-Y, Cheng C-C, Chen Y-C, Lin Y-K, Chen S-A, Chen Y-J. Electrolyte disturbances differentially regulate sinoatrial node and pulmonary vein electrical activity: A contribution to hypokalemia- or hyponatremia-induced atrial fibrillation. *Heart Rhythm*. 2016;13:781–8.
10. Kanji S, Williamson DR, Yaghchi BM, Albert M, McIntyre L, Canadian Critical Care Trials Group. Epidemiology and management of atrial fibrillation in medical and noncardiac surgical adult intensive care unit patients. *J Crit Care*. 2012;27:326.e1-8.
11. Khan AM, Lubitz SA, Sullivan LM, Sun JX, Levy D, Vasan RS, et al. Low serum magnesium and the development of atrial fibrillation in the community: the Framingham Heart Study. *Circulation*. 2013;127:33–8.
12. Vieillard-Baron A, Boyd J. Non-antiarrhythmic interventions in new onset and paroxysmal sepsis-related atrial fibrillation. *Intensive Care Med*. 2018;44:94–7.
13. Davey MJ, Teubner D. A randomized controlled trial of magnesium sulfate, in addition to usual care, for rate control in atrial fibrillation. *Ann Emerg Med*. 2005;45:347–53.

14. Shaver CM, Chen W, Janz DR, May AK, Darbar D, Bernard GR, et al. Atrial Fibrillation Is an Independent Predictor of Mortality in Critically Ill Patients. *Crit Care Med*. 2015;43:2104–11.
15. Goodman S, Shirov T, Weissman C. Supraventricular arrhythmias in intensive care unit patients: short and long-term consequences. *Anesth Analg*. 2007;104:880–6.
16. Annane D, Sebillé V, Duboc D, Le Heuzey JY, Sadoul N, Bouvier E, et al. Incidence and prognosis of sustained arrhythmias in critically ill patients. *Am J Respir Crit Care Med*. 2008;178:20–5.
17. Edwards JD, Wilkins RG. Atrial fibrillation precipitated by acute hypovolaemia. *Br Med J Clin Res Ed*. 1987;294:283–4.
18. Moss TJ, Calland JF, Enfield KB, Gomez-Manjarres DC, Ruminski C, DiMarco JP, et al. New-Onset Atrial Fibrillation in the Critically Ill. *Crit Care Med*. 2017;45:790–7.
19. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation*. 2001;104:2886–91.
20. Issac TT, Dokainish H, Lakkis NM. Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data. *J Am Coll Cardiol*. 2007;50:2021–8.
21. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 31:2369–429.
22. Arora S, Lang I, Nayyar V, Stachowski E, Ross DL. Atrial fibrillation in a tertiary care multidisciplinary intensive care unit—incidence and risk factors. *Anaesth Intensive Care*. 2007;35:707–13.
23. Meierhenrich R, Steinhilber E, Eggermann C, Weiss M, Voglic S, Bogelein D, et al. Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study. *Crit Care*. 14:R108.
24. Guenancia C, Binquet C, Laurent G, Vinault S, Bruyère R, Prin S, et al. Incidence and Predictors of New-Onset Atrial Fibrillation in Septic Shock Patients in a Medical ICU: Data from 7-Day Holter ECG Monitoring. *PLoS One*. 2015;10:e0127168.
25. Salman S, Bajwa A, Gajic O, Afessa B. Paroxysmal atrial fibrillation in critically ill patients with sepsis. *J Intensive Care Med*. 2008;23:178–83.
26. Bosch NA, Massaro JM, Winter MR, Quinn EK, Chon KH, McManus DD, et al. New-Onset Atrial Fibrillation as a Sepsis-Defining Organ Failure. *Ann Am Thorac Soc*. 2019;16:1332–4.
27. Steinberg I, Brogi E, Pratali L, Trunfio D, Giuliano G, Bignami E, et al. Atrial Fibrillation in Patients with Septic Shock: A One-Year Observational Pilot Study. *Turk J Anaesthesiol Reanim*. 2019;47:213–9.
28. Lewis O, Ngwa J, Gillum RF, Thomas A, Davis W, Poddar V, et al. Incidence, Risk Factors and Outcomes of New Onset Supraventricular Arrhythmias in African American Patients with Severe Sepsis. *Ethn Dis*. 2016;26:205–12.
29. Liu WC, Lin WY, Lin CS, Huang HB, Lin TC, Cheng SM, et al. Prognostic impact of restored sinus rhythm in patients with sepsis and new-onset atrial fibrillation. *Crit Care Lond Engl*. 2016;20:373.

30. Ferrera C, Vilacosta I, Fernández C, López J, Sarriá C, Olmos C, et al. Usefulness of New-Onset Atrial Fibrillation, as a Strong Predictor of Heart Failure and Death in Patients With Native Left-Sided Infective Endocarditis. *Am J Cardiol.* 2016;117:427–33.
31. Christian SA, Schorr C, Ferchau L, Jarbrink ME, Parrillo JE, Gerber DR. Clinical characteristics and outcomes of septic patients with new-onset atrial fibrillation. *J Crit Care.* 2008;23:532–6.
32. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *J Am Coll Cardiol.* 57:e101-98.
33. Aschenberg W, Schlüter M, Kremer P, Schröder E, Siglow V, Bleifeld W. Transesophageal two-dimensional echocardiography for the detection of left atrial appendage thrombus. *J Am Coll Cardiol.* 1986;7:163–6.
34. Watson T, Shantsila E, Lip GYH. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet Lond Engl.* 2009;373:155–66.
35. Labbé V, Ederhy S, Fartoukh M, Cohen A. Should we administrate anticoagulants to critically ill patients with new onset supraventricular arrhythmias? *Arch Cardiovasc Dis.* 2016;109:656–8.
36. Hjorleifsson E, Sigurdsson MI, Gudmundsdottir BR, Sigurdsson GH, Onundarson PT. Prediction of survival in patients suspected of disseminated intravascular coagulation. *Acta Anaesthesiol Scand.* 2015;59:870–80.
37. Lane DA, Philippou H, Huntington JA. Directing thrombin. *Blood.* 2005;106:2605–12.
38. Delabranche X, Helms J, Meziani F. Immunohaemostasis: a new view on haemostasis during sepsis. *Ann Intensive Care.* 2017;7:117.
39. Meziani F, Delabranche X, Asfar P, Toti F. Bench-to-bedside review: circulating microparticles--a new player in sepsis? *Crit Care Lond Engl.* 2010;14:236.
40. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, et al. Neutrophil extracellular traps kill bacteria. *Science.* 2004;303:1532–5.
41. Yipp BG, Kubes P. NETosis: how vital is it? *Blood.* 2013;122:2784–94.
42. Delabranche X, Helms J, Meziani F. Immunohaemostasis: a new view on haemostasis during sepsis. *Ann Intensive Care.* 2017;7:117.
43. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med.* 369:840–51.
44. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *J Am Coll Cardiol.* 57:e101-98.

45. Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. *Blood*. 2019;133:906–18.
46. Kang S, Tanaka T, Inoue H, Ono C, Hashimoto S, Kioi Y, et al. IL-6 trans-signaling induces plasminogen activator inhibitor-1 from vascular endothelial cells in cytokine release syndrome. *Proc Natl Acad Sci U S A*. 2020;117:22351–6.
47. Szotowski B, Antoniak S, Poller W, Schultheiss H-P, Rauch U. Procoagulant soluble tissue factor is released from endothelial cells in response to inflammatory cytokines. *Circ Res*. 2005;96:1233–9.
48. Vlachogiannis NI, Sachse M, Georgiopoulos G, Zormpas E, Bampatsias D, Delialis D, et al. Adenosine-to-inosine Alu RNA editing controls the stability of the pro-inflammatory long noncoding RNA NEAT1 in atherosclerotic cardiovascular disease. *J Mol Cell Cardiol*. 2021;160:111–20.
49. Zullo JA, Fan J, Azar TT, Yen W, Zeng M, Chen J, et al. Exocytosis of Endothelial Lysosome-Related Organelles Hair-Triggers a Patchy Loss of Glycocalyx at the Onset of Sepsis. *Am J Pathol*. 2016;186:248–58.
50. Lukasz A, Hillgruber C, Oberleithner H, Kusche-Vihrog K, Pavenstädt H, Rovas A, et al. Endothelial glycocalyx breakdown is mediated by angiotensin-2. *Cardiovasc Res*. 2017;113:671–80.
51. Yang X, Meegan JE, Jannaway M, Coleman DC, Yuan SY. A disintegrin and metalloproteinase 15-mediated glycocalyx shedding contributes to vascular leakage during inflammation. *Cardiovasc Res*. 2018;114:1752–63.
52. Iba T, Levi M, Levy JH. Intracellular communication and immunothrombosis in sepsis. *J Thromb Haemost JTH*. 2022;20:2475–84.
53. Miller VT, Rothrock JF, Pearce LA, Feinberg WM, Hart RG, Anderson DC. Ischemic stroke in patients with atrial fibrillation: effect of aspirin according to stroke mechanism. *Stroke Prevention in Atrial Fibrillation Investigators*. *Neurology*. 1993;43:32–6.
54. Bogousslavsky J, Van Melle G, Regli F, Kappenberg L. Pathogenesis of anterior circulation stroke in patients with nonvalvular atrial fibrillation: the Lausanne Stroke Registry. *Neurology*. 1990;40:1046–50.
55. Predictors of thromboembolism in atrial fibrillation: II. Echocardiographic features of patients at risk. *The Stroke Prevention in Atrial Fibrillation Investigators*. *Ann Intern Med*. 1992;116:6–12.
56. Zabalgoitia M, Halperin JL, Pearce LA, Blackshear JL, Asinger RW, Hart RG. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. *Stroke Prevention in Atrial Fibrillation III Investigators*. *J Am Coll Cardiol*. 1998;31:1622–6.
57. Manning WJ, Silverman DI, Gordon SP, Krumholz HM, Douglas PS. Cardioversion from atrial fibrillation without prolonged anticoagulation with use of transesophageal echocardiography to exclude the presence of atrial thrombi. *N Engl J Med*. 1993;328:750–5.
58. Manning WJ, Silverman DI, Waksmonski CA, Oettgen P, Douglas PS. Prevalence of residual left atrial thrombi among patients with acute thromboembolism and newly recognized atrial fibrillation. *Arch Intern Med*. 1995;155:2193–8.

59. Stoddard MF, Dawkins PR, Prince CR, Ammash NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. *J Am Coll Cardiol.* 1995;25:452–9.
60. Klein AL, Grimm RA, Black IW, Leung DY, Chung MK, Vaughn SE, et al. Cardioversion guided by transesophageal echocardiography: the ACUTE Pilot Study. A randomized, controlled trial. *Assessment of Cardioversion Using Transesophageal Echocardiography. Ann Intern Med.* 1997;126:200–9.
61. Di Angelantonio E, Ederhy S, Benyounes N, Janower S, Boccara F, Cohen A. Comparison of transesophageal echocardiographic identification of embolic risk markers in patients with lone versus non-lone atrial fibrillation. *Am J Cardiol.* 2005;95:592–6.
62. Ederhy S, Di Angelantonio E, Dufaitre G, Meuleman C, Masliah J, Boyer-Chatenet L, et al. C-reactive protein and transesophageal echocardiographic markers of thromboembolism in patients with atrial fibrillation. *Int J Cardiol.* 2012;159:40–6.
63. Ariel Cohen, Pascal Guéret. *Manuel d'échocardiographie clinique. MÉDECINE SCIENCES PUBLICATIONS / LAVOISIER, editor.* 2012.
64. Kleemann T, Becker T, Strauss M, Schneider S, Seidl K. Prevalence of left atrial thrombus and dense spontaneous echo contrast in patients with short-term atrial fibrillation < 48 hours undergoing cardioversion: value of transesophageal echocardiography to guide cardioversion. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr.* 2009;22:1403–8.
65. Grimm RA, Stewart WJ, Maloney JD, Cohen GI, Pearce GL, Salcedo EE, et al. Impact of electrical cardioversion for atrial fibrillation on left atrial appendage function and spontaneous echo contrast: characterization by simultaneous transesophageal echocardiography. *J Am Coll Cardiol.* 1993;22:1359–66.
66. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J.* 2021;42:373–498.
67. Fatkin D, Kuchar DL, Thorburn CW, Feneley MP. Transesophageal echocardiography before and during direct current cardioversion of atrial fibrillation: evidence for “atrial stunning” as a mechanism of thromboembolic complications. *J Am Coll Cardiol.* 1994;23:307–16.
68. Falcone RA, Morady F, Armstrong WF. Transesophageal echocardiographic evaluation of left atrial appendage function and spontaneous contrast formation after chemical or electrical cardioversion of atrial fibrillation. *Am J Cardiol.* 1996;78:435–9.
69. Harjai K, Mobarek S, Abi-Samra F, Gilliland Y, Davison N, Drake K, et al. Mechanical dysfunction of the left atrium and the left atrial appendage following cardioversion of atrial fibrillation and its relation to total electrical energy used for cardioversion. *Am J Cardiol.* 1998;81:1125–9.
70. Khan IA. Atrial stunning: determinants and cellular mechanisms. *Am Heart J.* 2003;145:787–94.

71. Dunn MI, Marcum JL. Atrial mechanical performance following internal and external cardioversion of atrial fibrillation: its relationship to peripheral embolization and acute cerebrovascular accident. *Chest*. 2002;121:1–3.
72. Berger M, Schweitzer P. Timing of thromboembolic events after electrical cardioversion of atrial fibrillation or flutter: a retrospective analysis. *Am J Cardiol*. 1998;82:1545–7, A8.
73. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33:2719–47.
74. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 31:2369–429.
75. Predictors of Thromboembolism in Atrial Fibrillation: II. Echocardiographic Features of Patients at Risk. *Ann Intern Med*. 1992;116:6–12.
76. Echocardiographic predictors of stroke in patients with atrial fibrillation: a prospective study of 1066 patients from 3 clinical trials. *Arch Intern Med*. 1998;158:1316–20.
77. Di Biase L, Natale A, Romero J. Thrombogenic and Arrhythmogenic Roles of the Left Atrial Appendage in Atrial Fibrillation. *Circulation*. 2018;138:2036–50.
78. Asinger RW, Koehler J, Pearce LA, Zabalgoitia M, Blackshear JL, Fenster PE, et al. Pathophysiologic correlates of thromboembolism in nonvalvular atrial fibrillation: II. Dense spontaneous echocardiographic contrast (The Stroke Prevention in Atrial Fibrillation [SPAF-III] study). *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 1999;12:1088–96.
79. Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. *J Am Coll Cardiol*. 1994;23:961–9.
80. Pollick C, Taylor D. Assessment of left atrial appendage function by transesophageal echocardiography. Implications for the development of thrombus. *Circulation*. 1991;84:223–31.
81. Bernhardt P, Schmidt H, Hammerstingl C, Lüderitz B, Omran H. Patients at high risk with atrial fibrillation: a prospective and serial follow-up during 12 months with transesophageal echocardiography and cerebral magnetic resonance imaging. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 2005;18:919–24.
82. Santiago D, Warshofsky M, Li Mandri G, Di Tullio M, Coromilas J, Reiffel J, et al. Left atrial appendage function and thrombus formation in atrial fibrillation-flutter: a transesophageal echocardiographic study. *J Am Coll Cardiol*. 1994;24:159–64.
83. Mügge A, Kühn H, Nikutta P, Grote J, Lopez JA, Daniel WG. Assessment of left atrial appendage function by biplane transesophageal echocardiography in patients with nonrheumatic atrial fibrillation: identification of a subgroup of patients at increased embolic risk. *J Am Coll Cardiol*. 1994;23:599–607.

84. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. *Stroke J Cereb Circ.* 1999;30:1223–9.
85. Montgomery DH, Ververis JJ, McGorisk G, Frohwein S, Martin RP, Taylor WR. Natural history of severe atheromatous disease of the thoracic aorta: a transesophageal echocardiographic study. *J Am Coll Cardiol.* 1996;27:95–101.
86. Tunick PA, Kronzon I. Atheromas of the thoracic aorta: clinical and therapeutic update. *J Am Coll Cardiol.* 2000;35:545–54.
87. Blackshear JL, Pearce LA, Hart RG, Zabalgaitia M, Labovitz A, Asinger RW, et al. Aortic plaque in atrial fibrillation: prevalence, predictors, and thromboembolic implications. *Stroke.* 1999;30:834–40.
88. Semeraro N, Ammollo CT, Semeraro F, Colucci M. Coagulopathy of Acute Sepsis. *Semin Thromb Hemost.* 2015;41:650–8.
89. Baughman RP, Lower EE, Flessa HC, Tollerud DJ. Thrombocytopenia in the intensive care unit. *Chest.* 1993;104:1243–7.
90. Helling H, Stephan B, Pindur G. Coagulation and complement system in critically ill patients. *Clin Hemorheol Microcirc.* 2015;61:185–93.
91. Gulati D, Novak A, Stanworth SJ. Common haemostasis issues in major bleeding and critical illness. *Clin Med Lond Engl.* 2018;18:320–3.
92. Brown RB, Klar J, Teres D, Lemeshow S, Sands M. Prospective study of clinical bleeding in intensive care unit patients. *Crit Care Med.* 1988;16:1171–6.
93. Strauss R, Wehler M, Mehler K, Kreutzer D, Koebnick C, Hahn EG. Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. *Crit Care Med.* 2002;30:1765–71.
94. Walkey AJ, Evans SR, Winter MR, Benjamin EJ. Practice Patterns and Outcomes of Treatments for Atrial Fibrillation During Sepsis: A Propensity-Matched Cohort Study. *Chest.* 2016;149:74–83.
95. Muntinga HJ, Gosselink AT, Blanksma PK, De Kam PJ, Van Der Wall EE, Crijns HJ. Left ventricular beat to beat performance in atrial fibrillation: dependence on contractility, preload, and afterload. *Heart Br Card Soc.* 1999;82:575–80.
96. Greenfield JC, Harley A, Thompson HK, Wallace AG. Pressure-flow studies in man during atrial fibrillation. *J Clin Invest.* 1968;47:2411–21.
97. Nerheim P, Birger-Botkin S, Piracha L, Olshansky B. Heart failure and sudden death in patients with tachycardia-induced cardiomyopathy and recurrent tachycardia. *Circulation.* 2004;110:247–52.
98. Jeremias A, Gibson CM. Narrative review: alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. *Ann Intern Med.* 2005;142:786–91.
99. Bakshi TK, Choo MK, Edwards CC, Scott AG, Hart HH, Armstrong GP. Causes of elevated troponin I with a normal coronary angiogram. *Intern Med J.* 2002;32:520–5.

100. Brookes CI, White PA, Staples M, Oldershaw PJ, Redington AN, Collins PD, et al. Myocardial contractility is not constant during spontaneous atrial fibrillation in patients. *Circulation*. 1998;98:1762–8.
101. Klein Klouwenberg PMC, Frencken JF, Kuipers S, Ong DSY, Peelen LM, van Vught LA, et al. Incidence, Predictors and Outcomes of New-onset Atrial Fibrillation in Critically Ill Patients with Sepsis: a Cohort Study. *Am J Respir Crit Care Med*. 2016;
102. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358:2667–77.
103. Al-Omari MA, Finstuen J, Appleton CP, Barnes ME, Tsang TSM. Echocardiographic assessment of left ventricular diastolic function and filling pressure in atrial fibrillation. *Am J Cardiol*. 2008;101:1759–65.
104. Landesberg G, Gilon D, Meroz Y, Georgieva M, Levin PD, Goodman S, et al. Diastolic dysfunction and mortality in severe sepsis and septic shock. *Eur Heart J*. 2012;33:895–903.
105. Boissier F, Razazi K, Seemann A, Bedet A, Thille AW, de Prost N, et al. Left ventricular systolic dysfunction during septic shock: the role of loading conditions. *Intensive Care Med*. 2017;43:633–42.
106. Labbé V, Bagate F, Cohen A, Voiriot G, Fartoukh M, Mekontso-Dessap A. A survey on the management of new onset atrial fibrillation in critically ill patients with septic shock. *J Crit Care*. 2021;61:18–20.
107. Salem J-E, El-Aissaoui M, Alazard M, Hulot J-S, Aissaoui N, Le-Heuzey J-Y, et al. Modeling of Amiodarone Effect on Heart Rate Control in Critically Ill Patients with Atrial Tachyarrhythmias. *Clin Pharmacokinet*. 2016;55:991–1002.
108. Brodsky MA, Orlov MV, Capparelli EV, Allen BJ, Iseri LT, Ginkel M, et al. Magnesium therapy in new-onset atrial fibrillation. *Am J Cardiol*. 1994;73:1227–9.
109. Onalan O, Crystal E, Daoulah A, Lau C, Crystal A, Lashevsky I. Meta-analysis of magnesium therapy for the acute management of rapid atrial fibrillation. *Am J Cardiol*. 2007;99:1726–32.
110. Joshi PP, Deshmukh PK, Salkar RG. Efficacy of intravenous magnesium sulphate in supraventricular tachyarrhythmias. *J Assoc Physicians India*. 1995;43:529–31.
111. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol*. 2016;18:1609–78.
112. Pourbaix S, Berger Y, Desager JP, Pacco M, Harvengt C. Absolute bioavailability of amiodarone in normal subjects. *Clin Pharmacol Ther*. 1985;37:118–23.
113. Clemo HF, Wood MA, Gilligan DM, Ellenbogen KA. Intravenous amiodarone for acute heart rate control in the critically ill patient with atrial tachyarrhythmias. *Am J Cardiol*. 1998;81:594–8.
114. Sasao J, Tarver SD, Kindscher JD, Taneyama C, Benson KT, Goto H. In rabbits, landiolol, a new ultra-short-acting beta-blocker, exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol. *Can J Anaesth J Can Anesth*. 2001;48:985–9.

115. Okajima M, Takamura M, Taniguchi T. Landiolol, an ultra-short-acting β 1-blocker, is useful for managing supraventricular tachyarrhythmias in sepsis. *World J Crit Care Med.* 2015;4:251–7.
116. Hariri G, Urbina T, Mazerand S, Bige N, Baudel J-L, Ait-Oufella H. Rate control in atrial fibrillation using Landiolol is safe in critically ill Covid-19 patients. *Crit Care Lond Engl.* 2021;25:33.
117. Khan IA, Mehta NJ, Gowda RM. Amiodarone for pharmacological cardioversion of recent-onset atrial fibrillation. *Int J Cardiol.* 2003;89:239–48.
118. Arrigo M, Jaeger N, Seifert B, Spahn DR, Bettex D, Rudiger A. Disappointing Success of Electrical Cardioversion for New-Onset Atrial Fibrillation in Cardiosurgical ICU Patients. *Crit Care Med.* 2015;43:2354–9.
119. Arrigo M, Ishihara S, Feliot E, Rudiger A, Deye N, Cariou A, et al. New-onset atrial fibrillation in critically ill patients and its association with mortality: A report from the FROG-ICU study. *Int J Cardiol.* 2018;266:95–9.
120. Mayr AJ, Dünser M, Jochberger S, Fries D, Klingler A, Joannidis M, et al. Antifactor Xa activity in intensive care patients receiving thromboembolic prophylaxis with standard doses of enoxaparin. *Thromb Res.* 2002;105:201–4.
121. Yoshida T, Uchino S, Sasabuchi Y, Hagiwara Y, AFTER-ICU study group. Prognostic impact of sustained new-onset atrial fibrillation in critically ill patients. *Intensive Care Med.* 2020;46:27–35.
122. Pluymaekers NAHA, Dudink EAMP, Luermans JGLM, Meeder JG, Lenderink T, Widdershoven J, et al. Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation. *N Engl J Med.* 2019;380:1499–508.
123. Wetterslev M, Hylander Møller M, Granholm A, Hassager C, Haase N, Lange T, et al. Atrial Fibrillation (AFIB) in the ICU: Incidence, Risk Factors, and Outcomes: The International AFIB-ICU Cohort Study. *Crit Care Med.* 2023;
124. Black IW, Fatkin D, Sagar KB, Khandheria BK, Leung DY, Galloway JM, et al. Exclusion of atrial thrombus by transesophageal echocardiography does not preclude embolism after cardioversion of atrial fibrillation. A multicenter study. *Circulation.* 1994;89:2509–13.
125. Miller VT, Rothrock JF, Pearce LA, Feinberg WM, Hart RG, Anderson DC. Ischemic stroke in patients with atrial fibrillation: effect of aspirin according to stroke mechanism. *Stroke Prevention in Atrial Fibrillation Investigators. Neurology.* 1993;43:32–6.
126. Bogousslavsky J, Van Melle G, Regli F, Kappenberger L. Pathogenesis of anterior circulation stroke in patients with nonvalvular atrial fibrillation: the Lausanne Stroke Registry. *Neurology.* 1990;40:1046–50.
127. Willens HJ, Gómez-Marín O, Nelson K, DeNicco A, Moscucci M. Correlation of CHADS2 and CHA2DS2-VASc scores with transesophageal echocardiography risk factors for thromboembolism in a multiethnic United States population with nonvalvular atrial fibrillation. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr.* 2013;26:175–84.
128. Thambidorai SK, Murray RD, Parakh K, Shah TK, Black IW, Jasper SE, et al. Utility of transesophageal echocardiography in identification of thrombogenic milieu in patients with atrial fibrillation (an ACUTE ancillary study). *Am J Cardiol.* 2005;96:935–41.

129. Watson T, Shantsila E, Lip GYH. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet Lond Engl.* 2009;373:155–66.
130. Hijazi Z, Oldgren J, Siegbahn A, Wallentin L. Application of Biomarkers for Risk Stratification in Patients with Atrial Fibrillation. *Clin Chem.* 2017;63:152–64.
131. Kornej J, Apostolakis S, Bollmann A, Lip GYH. The emerging role of biomarkers in atrial fibrillation. *Can J Cardiol.* 2013;29:1181–93.
132. Thomas MR, Lip GYH. Novel Risk Markers and Risk Assessments for Cardiovascular Disease. *Circ Res.* 2017;120:133–49.
133. Ederhy S, Di Angelantonio E, Dufaitre G, Meuleman C, Masliah J, Boyer-Chatenet L, et al. C-reactive protein and transesophageal echocardiographic markers of thromboembolism in patients with atrial fibrillation. *Int J Cardiol.* 2012;159:40–6.
134. Ancedy Y, Berthelot E, Lang S, Ederhy S, Boyer-Chatenet L, Di Angelantonio E, et al. Is von Willebrand factor associated with stroke and death at mid-term in patients with non-valvular atrial fibrillation? *Arch Cardiovasc Dis.* 2018;111:357–69.
135. Ederhy S, Di Angelantonio E, Mallat Z, Hugel B, Janower S, Meuleman C, et al. Levels of circulating procoagulant microparticles in nonvalvular atrial fibrillation. *Am J Cardiol.* 2007;100:989–94.
136. Champion S, Lefort Y, Gaüzère B-A, Drouet D, Bouchet BJ, Bossard G, et al. CHADS2 and CHA2DS2-VASc scores can predict thromboembolic events after supraventricular arrhythmia in the critically ill patients. *J Crit Care.* 2014;29:854–8.
137. Walkey AJ, Quinn EK, Winter MR, McManus DD, Benjamin EJ. Practice Patterns and Outcomes Associated With Use of Anticoagulation Among Patients With Atrial Fibrillation During Sepsis. *JAMA Cardiol.* 2016;1:682–90.
138. Jacobs MS, Loef B, Reidinga AC, Postma MJ, Van Hulst M, Tieleman RG. Incidence, treatment and mortality of new-onset atrial fibrillation patients at the intensive care unit. *Open Heart.* 2020;7:e001226.
139. Boriani G, Fauchier L, Aguinaga L, Beattie JM, Blomstrom Lundqvist C, Cohen A, et al. European Heart Rhythm Association (EHRA) consensus document on management of arrhythmias and cardiac electronic devices in the critically ill and post-surgery patient, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), Cardiac Arrhythmia Society of Southern Africa (CASSA), and Latin American Heart Rhythm Society (LAHRS). *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol.* 2019;21:7–8.
140. Stoddard MF, Dawkins PR, Prince CR, Ammash NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. *J Am Coll Cardiol.* 1995;25:452–9.
141. Nuotio I, Hartikainen JEK, Grönberg T, Biancari F, Airaksinen KEJ. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. *JAMA.* 2014;312:647–9.

142. Airaksinen KEJ, Grönberg T, Nuotio I, Nikkinen M, Ylitalo A, Biancari F, et al. Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. *J Am Coll Cardiol*. 2013;62:1187–92.
143. Labbé V, Ederhy S, Lapidus N, Joffre J, Razazi K, Laine L, et al. Transesophageal echocardiography for cardiovascular risk estimation in patients with sepsis and new-onset atrial fibrillation: a multicenter prospective pilot study. *Ann Intensive Care*. 2021;11:146.
144. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol*. 2016;18:1455–90.
145. Walkey AJ, Hammill BG, Curtis LH, Benjamin EJ. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. *Chest*. 2014;146:1187–95.
146. Molnár AA, Sánta A, Pásztor DT, Merkely B. Atrial Cardiomyopathy in Valvular Heart Disease: From Molecular Biology to Clinical Perspectives. *Cells*. 2023;12:1796.
147. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol*. 2016;18:1455–90.
148. Goette A, Lendeckel U. Atrial Cardiomyopathy: Pathophysiology and Clinical Consequences. *Cells*. 2021;10:2605.
149. D’Alessandro E, Winters J, van Nieuwenhoven FA, Schotten U, Verheule S. The Complex Relation between Atrial Cardiomyopathy and Thrombogenesis. *Cells*. 2022;11:2963.
150. Li M, Ning Y, Tse G, Saguner AM, Wei M, Day JD, et al. Atrial cardiomyopathy: from cell to bedside. *ESC Heart Fail*. 2022;9:3768–84.
151. Buechel RR, Stephan FP, Sommer G, Bremerich J, Zellweger MJ, Kaufmann BA. Head-to-head comparison of two-dimensional and three-dimensional echocardiographic methods for left atrial chamber quantification with magnetic resonance imaging. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 2013;26:428–35.
152. Mor-Avi V, Yodwut C, Jenkins C, Kühl H, Nesser H-J, Marwick TH, et al. Real-time 3D echocardiographic quantification of left atrial volume: multicenter study for validation with CMR. *JACC Cardiovasc Imaging*. 2012;5:769–77.
153. Soulat-Dufour L, Lang S, Ederhy S, Ancedy Y, Beraud A-S, Adavane-Scheuble S, et al. Batrial remodelling in atrial fibrillation: A three-dimensional and strain echocardiography insight. *Arch Cardiovasc Dis*. 2019;112:585–93.
154. Soulat-Dufour L, Addetia K, Miyoshi T, Citro R, Daimon M, Fajardo PG, et al. Normal Values of Right Atrial Size and Function According to Age, Sex, and Ethnicity: Results of the World Alliance Societies of Echocardiography Study. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 2021;34:286–300.

155. Azemi T, Rabdiya VM, Ayirala SR, McCullough LD, Silverman DI. Left atrial strain is reduced in patients with atrial fibrillation, stroke or TIA, and low risk CHADS₂ scores. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 2012;25:1327–32.
156. Leung M, van Rosendaal PJ, Abou R, Ajmone Marsan N, Leung DY, Delgado V, et al. Left atrial function to identify patients with atrial fibrillation at high risk of stroke: new insights from a large registry. *Eur Heart J*. 2018;39:1416–25.
157. Obokata M, Negishi K, Kurosawa K, Tateno R, Tange S, Arai M, et al. Left atrial strain provides incremental value for embolism risk stratification over CHA₂DS₂-VASc score and indicates prognostic impact in patients with atrial fibrillation. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 2014;27:709-716.e4.
158. Shih J-Y, Tsai W-C, Huang Y-Y, Liu Y-W, Lin C-C, Huang Y-S, et al. Association of decreased left atrial strain and strain rate with stroke in chronic atrial fibrillation. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 2011;24:513–9.
159. Soulat-Dufour L, Lang S, Addetia K, Ederhy S, Adavane-Scheuble S, Chauvet-Droit M, et al. Restoring Sinus Rhythm Reverses Cardiac Remodeling and Reduces Valvular Regurgitation in Patients With Atrial Fibrillation. *J Am Coll Cardiol*. 2022;79:951–61.
160. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358:2667–77.
161. Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME, et al. Rate Control versus Rhythm Control for Atrial Fibrillation after Cardiac Surgery. *N Engl J Med*. 2016;374:1911–21.
162. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA J Am Med Assoc*. 2001;285:2864–70.
163. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–72.
164. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093–100.
165. Marín F, Roldán V, Climent VE, Ibáñez A, García A, Marco P, et al. Plasma von Willebrand factor, soluble thrombomodulin, and fibrin D-dimer concentrations in acute onset non-rheumatic atrial fibrillation. *Heart Br Card Soc*. 2004;90:1162–6.
166. Habara S, Dote K, Kato M, Sasaki S, Goto K, Takemoto H, et al. Prediction of left atrial appendage thrombi in non-valvular atrial fibrillation. *Eur Heart J*. 2007;28:2217–22.
167. Ohara K, Inoue H, Nozawa T, Hirai T, Iwasa A, Okumura K, et al. Accumulation of risk factors enhances the prothrombotic state in atrial fibrillation. *Int J Cardiol*. 2008;126:316–21.
168. Somló M, Tomcsányi J, Nagy E, Bodó I, Bezzegh A. D-dimer determination as a screening tool to exclude atrial thrombi in atrial fibrillation. *Am J Cardiol*. 2003;92:85–7.

169. Sadanaga T, Sadanaga M, Ogawa S. Evidence that D-dimer levels predict subsequent thromboembolic and cardiovascular events in patients with atrial fibrillation during oral anticoagulant therapy. *J Am Coll Cardiol*. 2010;55:2225–31.
170. Vene N, Mavri A, Kosmelj K, Stegnar M. High D-dimer levels predict cardiovascular events in patients with chronic atrial fibrillation during oral anticoagulant therapy. *Thromb Haemost*. 2003;90:1163–72.
171. Christersson C, Wallentin L, Andersson U, Alexander JH, Ansell J, De Caterina R, et al. D-dimer and risk of thromboembolic and bleeding events in patients with atrial fibrillation--observations from the ARISTOTLE trial. *J Thromb Haemost JTH*. 2014;12:1401–12.
172. Sakurai K, Hirai T, Nakagawa K, Kameyama T, Nozawa T, Asanoi H, et al. Left atrial appendage function and abnormal hypercoagulability in patients with atrial flutter. *Chest*. 2003;124:1670–4.
173. Turgut N, Akdemir O, Turgut B, Demir M, Ekuklu G, Vural O, et al. Hypercoagulopathy in stroke patients with nonvalvular atrial fibrillation: hematologic and cardiologic investigations. *Clin Appl Thromb Off J Int Acad Clin Appl Thromb*. 2006;12:15–20.
174. Tsai LM, Chen JH, Tsao CJ. Relation of left atrial spontaneous echo contrast with prethrombotic state in atrial fibrillation associated with systemic hypertension, idiopathic dilated cardiomyopathy, or no identifiable cause (lone). *Am J Cardiol*. 1998;81:1249–52.
175. Furui H, Taniguchi N, Yamauchi K, Sotobata I, Saito H, Inagaki H. Effects of treadmill exercise on platelet function, blood coagulability and fibrinolytic activity in patients with atrial fibrillation. *Jpn Heart J*. 1987;28:177–84.
176. Kamath S, Blann AD, Chin BSP, Lip GYH. Platelet activation, haemorheology and thrombogenesis in acute atrial fibrillation: a comparison with permanent atrial fibrillation. *Heart Br Card Soc*. 2003;89:1093–5.
177. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation*. 2001;104:2886–91.
178. Dernellis J, Panaretou M. C-reactive protein and paroxysmal atrial fibrillation: evidence of the implication of an inflammatory process in paroxysmal atrial fibrillation. *Acta Cardiol*. 2001;56:375–80.
179. Feinberg WM, Macy E, Cornell ES, Nightingale SD, Pearce LA, Tracy RP, et al. Plasmin-alpha2-antiplasmin complex in patients with atrial fibrillation. *Stroke Prevention in Atrial Fibrillation Investigators*. *Thromb Haemost*. 1999;82:100–3.
180. Shinohara H, Fukuda N, Soeki T, Takeichi N, Yui Y, Tamura Y, et al. Relationship between flow dynamics in the left atrium and hemostatic abnormalities in patients with nonvalvular atrial fibrillation. *Jpn Heart J*. 1998;39:721–30.
181. Lip GY, Lip PL, Zarifis J, Watson RD, Bareford D, Lowe GD, et al. Fibrin D-dimer and beta-thromboglobulin as markers of thrombogenesis and platelet activation in atrial fibrillation. Effects of introducing ultra-low-dose warfarin and aspirin. *Circulation*. 1996;94:425–31.

182. Kaplan KL, Nossel HL, Drillings M, Lesznik G. Radioimmunoassay of platelet factor 4 and beta-thromboglobulin: development and application to studies of platelet release in relation to fibrinopeptide A generation. *Br J Haematol.* 1978;39:129–46.
183. Kunishima S, Hattori M, Kobayashi S, Hattori H, Iwama Y, Imai Y, et al. Activation and destruction of platelets in patients with rheumatic heart disease. *Eur Heart J.* 1994;15:335–8.
184. Minamino T, Kitakaze M, Asanuma H, Ueda Y, Koretsune Y, Kuzuya T, et al. Plasma adenosine levels and platelet activation in patients with atrial fibrillation. *Am J Cardiol.* 1999;83:194–8.
185. Yamauchi K, Furui H, Taniguchi N, Sotobata I. Plasma beta-thromboglobulin and platelet factor 4 concentrations in patients with atrial fibrillation. *Jpn Heart J.* 1986;27:481–7.
186. Kamath S, Chin BSP, Blann AD, Lip GYH. A study of platelet activation in paroxysmal, persistent and permanent atrial fibrillation. *Blood Coagul Fibrinolysis Int J Haemost Thromb.* 2002;13:627–36.
187. Feinberg WM, Pearce LA, Hart RG, Cushman M, Cornell ES, Lip GY, et al. Markers of thrombin and platelet activity in patients with atrial fibrillation: correlation with stroke among 1531 participants in the stroke prevention in atrial fibrillation III study. *Stroke.* 1999;30:2547–53.
188. Vischer UM. von Willebrand factor, endothelial dysfunction, and cardiovascular disease. *J Thromb Haemost JTH.* 2006;4:1186–93.
189. Heppell RM, Berkin KE, McLenachan JM, Davies JA. Haemostatic and haemodynamic abnormalities associated with left atrial thrombosis in non-rheumatic atrial fibrillation. *Heart Br Card Soc.* 1997;77:407–11.
190. Conway DSG, Pearce LA, Chin BSP, Hart RG, Lip GYH. Prognostic value of plasma von Willebrand factor and soluble P-selectin as indices of endothelial damage and platelet activation in 994 patients with nonvalvular atrial fibrillation. *Circulation.* 2003;107:3141–5.
191. Lip GYH, Lane D, Van Walraven C, Hart RG. Additive role of plasma von Willebrand factor levels to clinical factors for risk stratification of patients with atrial fibrillation. *Stroke.* 2006;37:2294–300.
192. Alonso A, Tang W, Agarwal SK, Soliman EZ, Chamberlain AM, Folsom AR. Hemostatic markers are associated with the risk and prognosis of atrial fibrillation: the ARIC study. *Int J Cardiol.* 2012;155:217–22.
193. Roldán V, Marín F, Muiña B, Torregrosa JM, Hernández-Romero D, Valdés M, et al. Plasma von Willebrand factor levels are an independent risk factor for adverse events including mortality and major bleeding in anticoagulated atrial fibrillation patients. *J Am Coll Cardiol.* 2011;57:2496–504.
194. Nakamura Y, Nakamura K, Fukushima-Kusano K, Ohta K, Matsubara H, Hamuro T, et al. Tissue factor expression in atrial endothelia associated with nonvalvular atrial fibrillation: possible involvement in intracardiac thrombogenesis. *Thromb Res.* 2003;111:137–42.
195. Black IW, Chesterman CN, Hopkins AP, Lee LC, Chong BH, Walsh WF. Hematologic correlates of left atrial spontaneous echo contrast and thromboembolism in nonvalvular atrial fibrillation. *J Am Coll Cardiol.* 1993;21:451–7.
196. Rastegar R, Harnick DJ, Weidemann P, Fuster V, Collier B, Badimon JJ, et al. Spontaneous echo contrast videodensity is flow-related and is dependent on the relative concentrations of fibrinogen and red blood cells. *J Am Coll Cardiol.* 2003;41:603–10.

197. Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation*. 2007;116:1242–9.
198. Eggers KM, Lind L, Ahlström H, Bjerner T, Ebeling Barbier C, Larsson A, et al. Prevalence and pathophysiological mechanisms of elevated cardiac troponin I levels in a population-based sample of elderly subjects. *Eur Heart J*. 2008;29:2252–8.
199. Jeremias A, Gibson CM. Narrative review: alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. *Ann Intern Med*. 2005;142:786–91.
200. Providência R, Paiva L, Faustino A, Botelho A, Trigo J, Casalta-Lopes J, et al. Cardiac troponin I: prothrombotic risk marker in non-valvular atrial fibrillation. *Int J Cardiol*. 2013;167:877–82.
201. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–51.
202. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, et al. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. *Circulation*. 2012;125:1605–16.
203. Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J*. 2009;157:805–10, 810.e1-2.
204. Daniels LB, Maisel AS. Natriuretic peptides. *J Am Coll Cardiol*. 2007;50:2357–68.
205. Hijazi Z, Wallentin L, Siegbahn A, Andersson U, Christersson C, Ezekowitz J, et al. N-terminal pro-B-type natriuretic peptide for risk assessment in patients with atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation). *J Am Coll Cardiol*. 2013;61:2274–84.
206. Roldán V, Vílchez JA, Manzano-Fernández S, Jover E, Gálvez J, Puche CM, et al. Usefulness of N-terminal pro-B-type natriuretic Peptide levels for stroke risk prediction in anticoagulated patients with atrial fibrillation. *Stroke*. 2014;45:696–701.
207. Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. *Ann Intern Med*. 1998;128:639–47.
208. McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE, et al. Biochemical detection of left-ventricular systolic dysfunction. *Lancet Lond Engl*. 1998;351:9–13.
209. Goetze JP, Friis-Hansen L, Rehfeld JF, Nilsson B, Svendsen JH. Atrial secretion of B-type natriuretic peptide. *Eur Heart J*. 2006;27:1648–50.
210. Cermak J, Key NS, Bach RR, Balla J, Jacob HS, Vercellotti GM. C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. *Blood*. 1993;82:513–20.
211. Neumann FJ, Ott I, Marx N, Luther T, Kenngott S, Gawaz M, et al. Effect of human recombinant interleukin-6 and interleukin-8 on monocyte procoagulant activity. *Arterioscler Thromb Vasc Biol*. 1997;17:3399–405.

212. Burstein SA. Cytokines, platelet production and hemostasis. *Platelets*. 1997;8:93–104.
213. Amrani DL. Regulation of fibrinogen biosynthesis: glucocorticoid and interleukin-6 control. *Blood Coagul Fibrinolysis Int J Haemost Thromb*. 1990;1:443–6.
214. Burstein SA, Peng J, Friese P, Wolf RF, Harrison P, Downs T, et al. Cytokine-induced alteration of platelet and hemostatic function. *Stem Cells Dayt Ohio*. 1996;14 Suppl 1:154–62.
215. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol*. 1999;19:972–8.
216. Roldán V, Marín F, Díaz J, Gallego P, Jover E, Romera M, et al. High sensitivity cardiac troponin T and interleukin-6 predict adverse cardiovascular events and mortality in anticoagulated patients with atrial fibrillation. *J Thromb Haemost JTH*. 2012;10:1500–7.
217. Conway DS g, Buggins P, Hughes E, Lip GYH. Prognostic significance of raised plasma levels of interleukin-6 and C-reactive protein in atrial fibrillation. *Am Heart J*. 2004;148:462–6.
218. Hermida J, Lopez FL, Montes R, Matsushita K, Astor BC, Alonso A. Usefulness of high-sensitivity C-reactive protein to predict mortality in patients with atrial fibrillation (from the Atherosclerosis Risk In Communities [ARIC] Study). *Am J Cardiol*. 2012;109:95–9.
219. Lip GYH, Patel JV, Hughes E, Hart RG. High-sensitivity C-reactive protein and soluble CD40 ligand as indices of inflammation and platelet activation in 880 patients with nonvalvular atrial fibrillation: relationship to stroke risk factors, stroke risk stratification schema, and prognosis. *Stroke*. 2007;38:1229–37.
220. Aulin J, Siegbahn A, Hijazi Z, Ezekowitz MD, Andersson U, Connolly SJ, et al. Interleukin-6 and C-reactive protein and risk for death and cardiovascular events in patients with atrial fibrillation. *Am Heart J*. 2015;170:1151–60.
221. Hijazi Z, Aulin J, Andersson U, Alexander JH, Gersh B, Granger CB, et al. Biomarkers of inflammation and risk of cardiovascular events in anticoagulated patients with atrial fibrillation. *Heart Br Card Soc*. 2016;102:508–17.
222. Kempf T, Zarbock A, Widera C, Butz S, Stadtmann A, Rossaint J, et al. GDF-15 is an inhibitor of leukocyte integrin activation required for survival after myocardial infarction in mice. *Nat Med*. 2011;17:581–8.
223. Schlittenhardt D, Schober A, Strelau J, Bonaterra GA, Schmiedt W, Unsicker K, et al. Involvement of growth differentiation factor-15/macrophage inhibitory cytokine-1 (GDF-15/MIC-1) in oxLDL-induced apoptosis of human macrophages in vitro and in arteriosclerotic lesions. *Cell Tissue Res*. 2004;318:325–33.
224. Growth differentiation factor 15, a marker of oxidative stress and inflammation, for risk assessment in patients with atrial fibrillation: insights... - PubMed - NCBI [Internet]. [cited 2019 Sep 20]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/25294786>
225. Sharma UC, Pokharel S, van Brakel TJ, van Berlo JH, Cleutjens JPM, Schroen B, et al. Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. *Circulation*. 2004;110:3121–8.

226. Laterza OF, Price CP, Scott MG. Cystatin C: an improved estimator of glomerular filtration rate? *Clin Chem*. 2002;48:699–707.
227. Abrahamson M, Olafsson I, Palsdottir A, Ulvsbäck M, Lundwall A, Jensson O, et al. Structure and expression of the human cystatin C gene. *Biochem J*. 1990;268:287–94.
228. Fox KAA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J*. 2011;32:2387–94.
229. Hijazi Z, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. *Circulation*. 2014;129:961–70.
230. Tziakas DN, Chalikias GK, Papanas N, Stakos DA, Chatzikyriakou SV, Maltezos E. Circulating levels of collagen type I degradation marker depend on the type of atrial fibrillation. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol*. 2007;9:589–96.
231. Marín F, Roldán V, Climent V, Garcia A, Marco P, Lip GYH. Is thrombogenesis in atrial fibrillation related to matrix metalloproteinase-1 and its inhibitor, TIMP-1? *Stroke*. 2003;34:1181–6.

8. Annexes

8.2 Annexe 1

Scores de stratification des risques thrombotiques et hémorragiques au long cours validés chez les patients de cardiologie ayant une fibrillation atriale chronique non valvulaire [42–44].

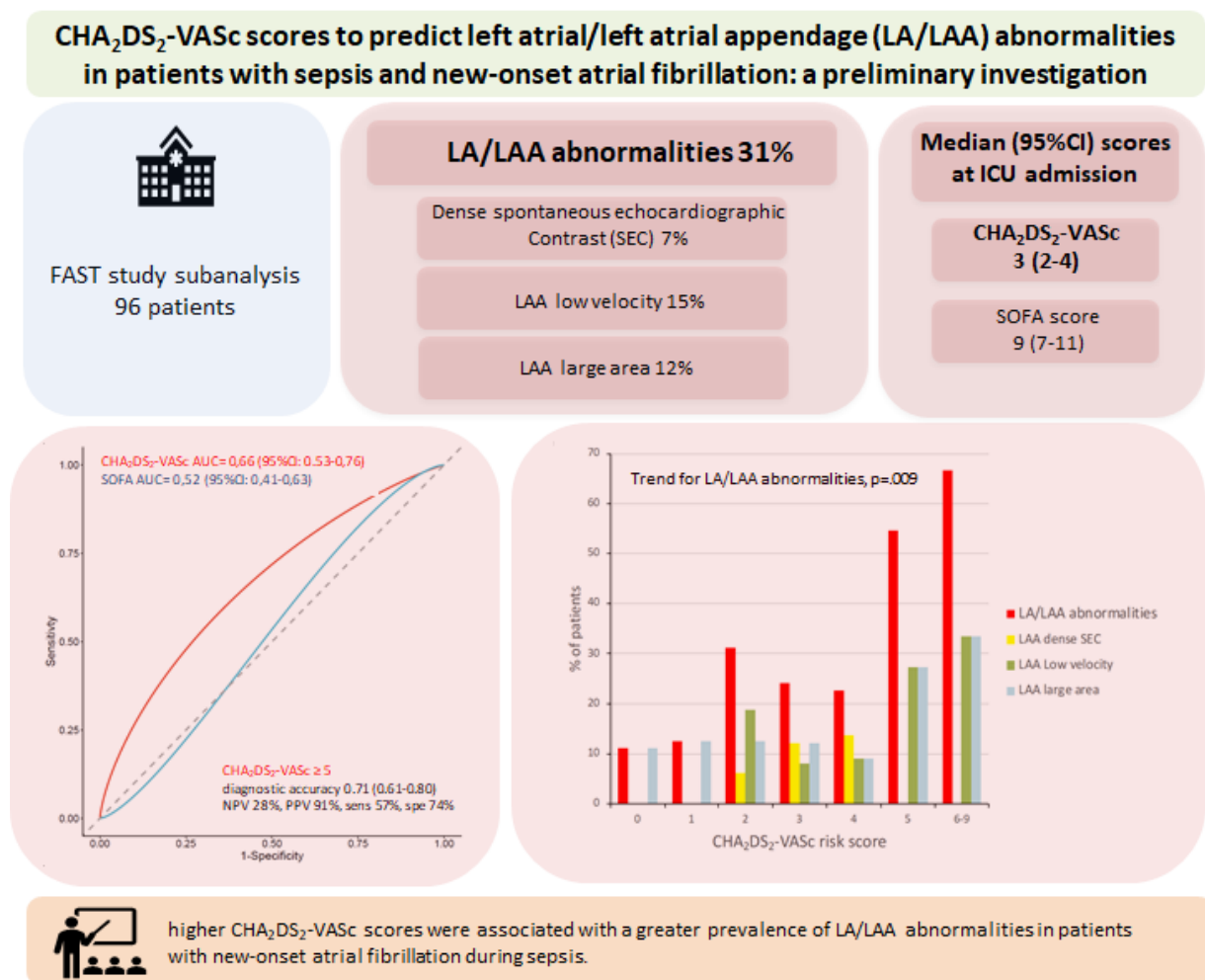
CHA ₂ DS ₂ -VASc critères	Point	HAS-BLED critères	Point
IC congestive / dysfonction VG	1	HTA	1
HTA	1	Anomalie de la fonction rénale ou hépatique	1 ou 2
Age ≥ 75 ans	2	AVC	1
Diabète	1	Hémorragie	1
AVC/AIT/ATE	2	INRs labiles	2
Maladie vasculaire	1	Age > 65 ans	1
Age 65-74 ans	1	Médicaments ou alcool	1 ou 2
Sexe féminin	1		
CHA ₂ DS ₂ -VASc score	Taux d'AVC (% / an)	HAS-BLED score	Hémorragie/ 100 patients années
0	0%	0	1,13
1	1,3%	1	1,02
2	2,2%	2	1,88
3	3,2%	3	3,74
4	4%	4	8,70
5	6,7%	5	12,50
6	9,8%	6	-
7	9,6%	7	-
8	6,7%	8	-
9	15,2%	9	-

Abréviations: AIT: accident ischémique transitoire ; AVC: accident vasculaire cérébral ; FE: fraction d'éjection ; CHA₂DS₂-VASc [Congestive heart failure, Hypertension, Age ≥ 65 years (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74 years, Sex category (female)] [43]; HAS-BLED [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio (INR), Elderly (age > 65 ans), Drugs/alcohol concomitantly] [44]; IC : insuffisance cardiaque ; INR: international normalized ratio ; VG: ventricule gauche

8.3 Annexe 2

CHA₂DS₂-VASc scores to predict left atrial/left atrial appendage abnormalities in patients with sepsis and new-onset atrial fibrillation: a preliminary investigation. Labbé V, Ederhy S, Legouis D, Joffre J, Razazi K, Sy Oumar, Chemouni F, Mekontso-Dessap Armand, Fartoukh M, Cohen A, FAST Study group: Submitted (Nov 2023)

Visual abstract



CHA₂DS₂-VASc scores to predict left atrial/left atrial appendage abnormalities in patients with sepsis and new-onset atrial fibrillation: a preliminary investigation

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Short tweet: Higher CHA₂DS₂-VASc scores are associated with a greater prevalence of LA/LAA abnormalities in patients with NOAF during sepsis

Keywords:

Atrial fibrillation, CHA₂DS₂-VASc scores, left atrial appendage, thrombus, sepsis, critically ill patients

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

AUC: area under the curve

CHA₂DS₂-VASc: Congestive heart failure, Hypertension, Age ≥ 75 years (doubled), Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category

ICU: intensive care unit

IQR: interquartile

LA/LAA: left atrial/left atrial appendage

NOAF: new-onset atrial fibrillation

TEE: transesophageal echocardiography

New-onset atrial fibrillation (NOAF) is associated with an increased risk of arterial thrombotic events and mortality in critically ill patients with sepsis ¹. Transesophageal echocardiography (TEE) left atrium/left atrial appendage (LA/LAA) abnormalities, including thrombus, dense spontaneous echo contrast (SEC) resulting from blood stasis ², low LAA velocities, and large LAAs, are associated with the CHA₂DS₂-VASc score of thrombotic risk ³ and arterial thrombotic events in cardiology outpatients with AF ⁴. In patients with NOAF during sepsis, these LA/LAA abnormalities are reported with a relatively high incidence ⁵, but a relationship with the CHA₂DS₂-VASc score has not been studied. We, therefore, conducted a sub-analysis of results from the prospective observational Fibrillation Atrial Sepsis Thrombus (FAST) study ⁵, which included 94 patients with sepsis and NOAF hospitalized in 10 French intensive care units (ICUs), to evaluate the relationship of the CHA₂DS₂-VASc score with LA/LAA abnormalities in this setting.

Methods

From November 2014 to November 2016, consecutive mechanically ventilated adult patients with NOAF during sepsis/septic shock were enrolled in the FAST study ⁵. NOAF was defined as AF with no prior history of AF and lasting at least six hours or recurring more than twice (>30 s) ⁵. Main exclusion criteria were valvular heart disease and TEE contraindications ⁵. The CHA₂DS₂-VASc score ³ were calculated on ICU admission. Each patient underwent transthoracic echocardiography followed by TEE with 5-MHz multiplane transducers within 48 hours of diagnosis of NOAF. The echocardiographic methodology have been described previously ⁵ (detailed in supplemental Method 1). The primary outcome was the presence of at least one LA/LAA abnormality, comprising large LAA area (> 5 cm² ⁶), low emptying or filling LAA velocities (<25 cm/s ⁷), or the presence of a thrombus or a dense

SEC in the LA or LAA. All echocardiographic studies were analyzed offline by two experienced observers in a blinded manner.

To evaluate the capacity of the CHA₂DS₂-VASc score to predict LA/LAA abnormalities, confidence intervals for the area under the receiver operating characteristic curve (AUC) and performance tests were calculated using bootstrap and exact binomial tests, respectively. The optimal cut-off point was chosen according to the Youden index.

Results

Ninety-four patients (61[65%] men; age 69[61-77] years) were included (Table 1). The median (IQR) CHA₂DS₂-VASc score was 3(2-4). TEE studies were performed a median of 1(1-2) day after NOAF onset. NOAF was present during TEE studies in 44(47%) patients (hemodynamic parameters during TEE detailed in supplemental Table1). LA/LAA abnormalities were detected in 29(31%) patients including dense SEC, low LAA velocity, and large LAA in 7(7%), 11(12%), and 13(15%) patients, respectively. No patient had a thrombus. Patients with LA/LAA abnormalities had a significantly higher median CHA₂DS₂-VASc score than patients without abnormalities (3.5[2.2-5.0] vs. 3.0[2.0-4.0], p=0.04; Table 1). There were no statistically significant differences between the groups in any other variables (Table 1). The prevalence of LA/LAA abnormalities increased significantly with increasing CHA₂DS₂-VASc scores (p=0.009, Figure 1). The AUC (95%CI) of the CHA₂DS₂-VASc score for predicting LA/LAA abnormalities was 0.66(0.53-0.76). A cut-off point for CHA₂DS₂-VASc of 5 gave a diagnostic accuracy (*i.e.*, the proportion of all tests with a correct result) of 0.71(0.61-0.80), with a negative predictive value of 28%(13-47), a positive predictive value of 91%(81-97), a sensitivity of 57%(29-82), and a specificity of 74%(63-83).

Discussion

Similar to results in cardiology patients³, CHA₂DS₂-VASc scores appear valuable for predicting LA/LAA abnormalities in septic patients with NOAF, even though the AUC indicated a moderate ability to predict LA/LAA abnormalities. Our primary analysis of the FAST study found no association between LA/LAA abnormalities and arterial thrombotic events⁵. This lack of association may be explained by (1) the small number of studied patients and (2) therapeutic anticoagulation was left to the clinician's discretion based, in part, on the echocardiographic findings. Despite these possible reasons, a systematic TEE-guided strategy therefore appears to have limited value in septic patients with NOAF. However, based on the assumption that LA/LAA abnormalities are reasonable surrogates for AF-related arterial thrombotic events, our current results could suggest an individualized TEE approach in cases where the benefit/risk balance of anticoagulation is particularly challenging: patients with low or moderate risk of LA/LAA abnormalities (CHA₂DS₂-VASc score < 5) may not require TEE, whereas those with high risk (CHA₂DS₂-VASc ≥ 5) should have TEE to detect any LA/LAA abnormalities.

Our study has several limitations. First, there may have been selection biases and uncontrolled confounding factors in this sub-analysis of a prospective cohort study. Second, we evaluated invasively ventilated patients; thus, results may not be generalizable to other critically ill patients. Third, the overall study group was small, resulting in wide 95% CIs for our AUC.

In conclusion, higher CHA₂DS₂-VASc scores were associated with a greater prevalence of LA/LAA abnormalities in patients with NOAF during sepsis. Further studies on the relationship of the CHA₂DS₂-VASc score with LA/LAA abnormalities and thrombotic events are warranted in larger populations.

Authors' contributions

VL, SE, DL, MF, and AC contributed to study conception and design. VL, SE, JJ, KR, OS, FC, and AMD participated in acquiring the data. VL, SE, AC analyzed off-line echocardiographic studies. VL, SE, DL, and AC analyzed and interpreted the study data. VL drafted the original manuscript. All authors revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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We would like the names of the individual members of the FAST study group to be searchable through their individual PubMed records.

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References

1. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA*. 2011 Nov 23;306(20):2248–54.
2. Asinger RW, Koehler J, Pearce LA, Zabalgoitia M, Blackshear JL, Fenster PE, et al. Pathophysiologic correlates of thromboembolism in nonvalvular atrial fibrillation: II. Dense spontaneous echocardiographic contrast (The Stroke Prevention in Atrial Fibrillation [SPAF-III] study). *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 1999 Dec;12(12):1088–96.
3. Willens HJ, Gómez-Marín O, Nelson K, DeNicco A, Moscucci M. Correlation of CHADS2 and CHA2DS2-VASc scores with transesophageal echocardiography risk factors for thromboembolism in a multiethnic United States population with nonvalvular atrial fibrillation. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 2013 Feb;26(2):175–84.
4. Thambidorai SK, Murray RD, Parakh K, Shah TK, Black IW, Jasper SE, et al. Utility of transesophageal echocardiography in identification of thrombogenic milieu in patients with atrial fibrillation (an ACUTE ancillary study). *Am J Cardiol*. 2005 Oct 1;96(7):935–41.
5. Labbé V, Ederhy S, Lapidus N, Joffre J, Razazi K, Laine L, et al. Transesophageal echocardiography for cardiovascular risk estimation in patients with sepsis and new-onset atrial fibrillation: a multicenter prospective pilot study. *Ann Intensive Care*. 2021 Oct 18;11(1):146.
6. Di Angelantonio E, Ederhy S, Benyounes N, Janower S, Boccara F, Cohen A. Comparison of transesophageal echocardiographic identification of embolic risk markers in patients with lone versus non-lone atrial fibrillation. *Am J Cardiol*. 2005 Mar 1;95(5):592–6.
7. Mügge A, Kühn H, Nikutta P, Grote J, Lopez JA, Daniel WG. Assessment of left atrial appendage function by biplane transesophageal echocardiography in patients with nonrheumatic atrial fibrillation: identification of a subgroup of patients at increased embolic risk. *J Am Coll Cardiol*. 1994 Mar 1;23(3):599–607.

Table 1. Baseline clinical characteristics, biological data, transthoracic echocardiographic parameters, sequential organ failure assessment (SOFA) score and management of new onset atrial fibrillation (NOAF) according to presence or absence of left atrial/left atrial appendage (LA/LAA) abnormalities ^a

Variable	Total (n=94)	LA/LAA abnormalities (n = 29)	No LA/LAA abnormalities (n=65)	<i>p</i> Value
Components of CHA ₂ DS ₂ -VASc score				
Congestive heart failure	17 (18)	5 (19)	12 (18)	>0.99
Hypertension	57 (61)	17 (65)	40 (59)	0.64
Age, yrs	69 (61-77)	72 (65-78)	68 (60-77)	0.15
Diabetes mellitus	24 (25)	8 (31)	16 (23)	0.60
Stroke	7 (7)	4 (15)	3 (4)	0.09
Vascular disease	19 (20)	8 (31)	11 (16)	0.15
Women	33 (35)	10 (38)	23 (34)	0.81
CHA ₂ DS ₂ -VASc scores (0-9)	3.0 (2.0-4.0)	3.5 (2.2-5.0)	3.0 (2.0-4.0)	0.04
SAPS II score on ICU admission	58 (47-74)	63 (45-74)	58 (48-73)	0.82
Biological data ^b				
Cardiac troponin (x the URL) (MD = 15)	6 (2-18)	10 (2- 26)	5 (2- 13)	0.16
Lactate (mmol/L) (MD = 1)	2.2 (1.7-3.5)	2.2 (1.5-3.1)	2.5 (1.7-3.7)	0.28
Leukocyte count (10 ³ /L)	16.1 (10.1-24.0)	15.4 (8.8-22.3)	16.3 (10.5-26.2)	0.27
Fibrinogen (mmol/L) (MD = 11)	7.0 (5.2-8.3)	7.3 (4.6-8.5)	7.0 (5.4-8.0)	0.96
Transthoracic echocardiography parameters				
LVEF, %	55 (45-62)	56 (40-60)	55 (48-63)	0.33
LV systolic dysfunction (LVEF ≤45%)	27 (29)	10 (38)	17 (25)	0.21
LV systolic severe dysfunction (LVEF ≤30%)	9 (10)	4 (15)	5 (7)	0.26
RV dilatation (MD=4) ^c	23 (26)	5 (19)	18 (28)	0.44
Significant left-sided valve disease	4 (4)	2 (8)	2 (3)	0.31
LA area, median (IQR), cm ² (MD=24)	33 (47)	23 (17-24)	20 (16-23)	0.20
SOFA score ^b	9.0 (7.0-11.0)	9.0 (6.2-10.0)	9.0 (7.0-12.0)	0.64
Septic shock	59 (63)	19 (73)	40 (59)	0.24
NOAF Management ^b				
Catecholamines	75 (79)	22 (85)	53 (78)	0.57
Cardioversion	60 (64)	17 (65)	43 (63)	>0.99
Therapeutic anticoagulation	28 (30)	9 (35)	19 (28)	0.62

Data are presented as median (25th–75th percentile) or n (%), unless otherwise specified. Comparisons were made using Mann-Whitney or Fisher’s exact tests, as appropriate.

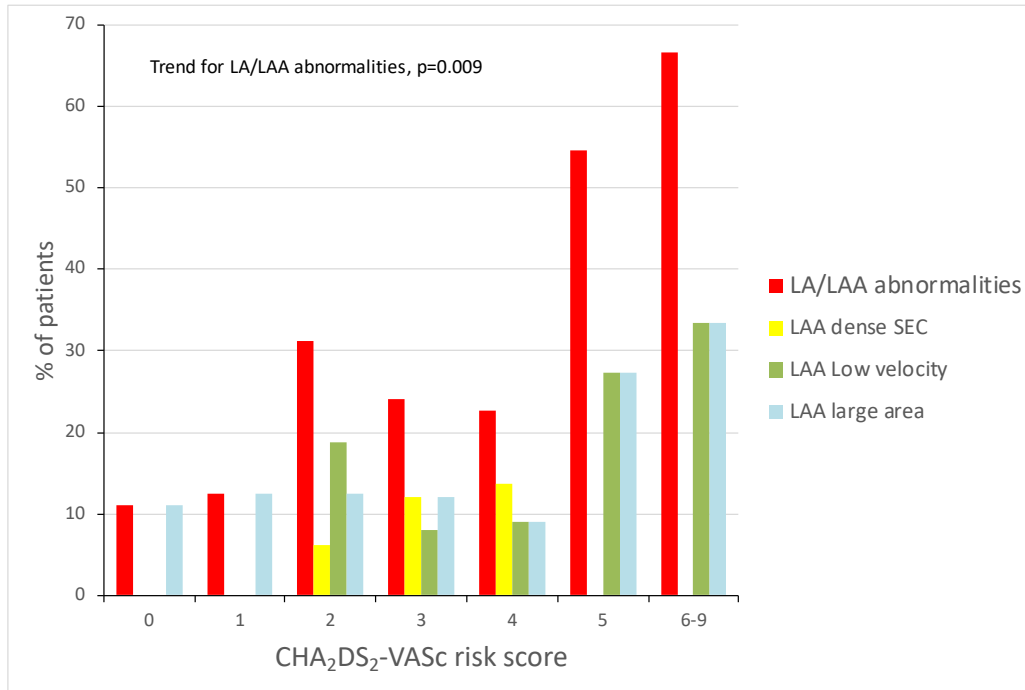
Abbreviations: CHA₂DS₂-VASc, Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category (female); ICU, intensive care unit; IQR, interquartile; LV, left ventricular; LVEF, left ventricular ejection fraction; MD, missing data; RV, right ventricular; SAPS, Simplified Acute Physiology Score.

^a Composite of LA/LAA thrombus, LA/LAA dense spontaneous echo contrast, LAA low velocity (MD=6), or large LAA area (MD=7) on transesophageal echocardiography.

^b On the day of NOAF onset

^c RV dilatation was defined as RV/LV end-diastolic area ratio ≥ 1 in long-axis cardiac view

Figure 1. Prevalence (percentage) of left atrial/left atrial appendage (LA/LAA) abnormalities^a and their individual components for different values of the CHA₂DS₂-VASc risk score



Footnote

Abbreviations: CHA₂DS₂-VASc, Congestive heart failure, Hypertension, Age ≥ 75 years (doubled), Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category (female); SEC, spontaneous echo contrast.

P values shown on the figure are the evolution of the prevalence of LAA abnormalities according to the CHA₂DS₂-VASc risk score (0, n=9; 1, n=8; 2, n=16, 3, n=25; 4, n=22; 5, n=11; 6-9, n=3) using the Mantel–Haenszel’s chi-square test for trend

^a Composite of LA/LAA thrombus, LA/LAA dense spontaneous echo contrast, low LAA velocity, or LAA large area (LA/LAA thrombus, n=0).

Supplemental material

Methods 1. Echocardiography

Table 1. Conditions at the time of the transesophageal echocardiography according to

presence or absence of left atrial/left atrial appendage (LA/LAA) abnormalities

Electronic supplementary material

Method S1. Echocardiography ¹.

Echocardiography were performed at the bedside by skilled intensivists, all of whom had ≥ 2 years of TEE experience, with competence in advanced critical care echocardiography ². Examinations were conducted with recent commercially available equipment (CX50, AFFINITY 70, and IE33; Philips Ultrasound system, Bothell, WA; VIVID 7, VIVID 9, and VIVID I, General Electric Healthcare system, Horten, Norway). All echocardiographic studies involved transthoracic echocardiography according to the recommendations of the European Association of Cardiovascular Imaging ³ with 2.5- and 3-MHz transducers, followed by TEE with 5-MHz multiplane transducers. Each patient underwent echocardiography within 48 hours of NOAF onset (initial TEE).

LA or LAA thrombi, LA/LAA dense SEC, LAA low velocities, and LAA large area, were investigated as previously described ⁴⁻¹⁰. A LA/LAA thrombus was considered present when there was a well-circumscribed, echodense, intra-cavitary mass that is acoustically distinct from the underlying endocardium and the pectinate muscles ⁷. LA/LAA dense SEC was defined as finely reticular pattern of dynamic, swirling intracavitary echoes localized within the LA or LAA persistent throughout the LA-LAA at normal gain ^{4,7}. Velocity of the LAA was recorded with pulse-wave Doppler interrogation 1 cm within the orifice. Flow velocity was evaluated in anterograde (emptying) and retrograde (filling) directions, and was averaged over a minimum of 3 to 5 consecutive cardiac cycles as specified by protocol. LAA low velocity was defined as a LAA filling or emptying velocity < 25 cm/s ^{5,9}. The area of the LAA was measured by planimetry at 90° view as specified by protocol. LV systolic dysfunction was defined as LV ejection fraction $\leq 45\%$ (mild, 31-45%; severe, $\leq 30\%$) using the biplane Simpson method³.

All echocardiographic studies were analyzed off-line in a blinded manner by two

cardiologist experts with board certification in echocardiography and level 3 competence according to the American Society of Echocardiography Standards ¹¹ (VL and SE).

Differences between observers were resolved by consensus; if the observers could not agree, a third cardiologist expert ¹¹ (AC) reviewed the studies, and that observer's judgment was binding.

Table S1. Conditions at the time of the transesophageal echocardiography according to presence or absence of LA/LAA abnormalities ^a

Variable	Total (n=94)	LA/LAA abnormalities (n = 29)	No LA/LAA abnormalities (n=65)	p Value
Time from NOAF, days	1 (1- 2)	1 (1- 1)	1 (1- 2)	0.07
NOAF during TEE	44 (47)	15 (58)	29 (43)	0.25
Mean arterial pressure, mmHg (MD=7)	81 (71- 88)	80 (75- 86)	82 (69- 91)	0.75
Heart rate, beats/min (MD=2)	102 (85- 129)	91 (81- 134)	107 (87- 129)	0.26
Catecholamines, (MD=1)	67 (72)	22 (85)	45 (67)	0.12
Norepinephrine	60 (64)	17 (65)	43 (64)	>0.99
Epinephrine	5 (5)	3 (11)	2 (3)	0.13
Dobutamine	4 (4)	1 (4)	3 (4)	>0.99
Data are presented as median (25th–75th percentile) or n (%)				
Abbreviations: IQR, interquartile; LA/LAA, left atrial/left atrial appendage; MD, miss data; TEE, transesophageal echocardiography; NOAF, new onset atrial fibrillation.				
^a Composite of LA/LAA thrombus, LA/LAA dense spontaneous echo contrast, low LAA velocity, or large LAA area.				

Bibliography

1. Labbé V, Ederhy S, Lapidus N, Joffre J, Razazi K, Laine L, et al. Transesophageal echocardiography for cardiovascular risk estimation in patients with sepsis and new-onset atrial fibrillation: a multicenter prospective pilot study. *Ann Intensive Care*. 2021 Oct 18;11(1):146.
2. Expert Round Table on Echocardiography in ICU. International consensus statement on training standards for advanced critical care echocardiography. *Intensive Care Med*. 2014 May;40(5):654–66.
3. 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 Mar 1;16(3):233–71.
4. Asinger RW, Koehler J, Pearce LA, Zabalgoitia M, Blackshear JL, Fenster PE, et al. Pathophysiologic correlates of thromboembolism in nonvalvular atrial fibrillation: II. Dense spontaneous echocardiographic contrast (The Stroke Prevention in Atrial Fibrillation [SPAF-III] study). *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 1999 Dec;12(12):1088–96.
5. Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. *J Am Coll Cardiol*. 1994 Mar 15;23(4):961–9.
6. Amarenco P, Cohen A, Tzourio C, Bertrand B, Hommel M, Besson G, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med*. 1994 Dec 1;331(22):1474–9.
7. Di Angelantonio E, Ederhy S, Benyounes N, Janower S, Boccara F, Cohen A. Comparison of transesophageal echocardiographic identification of embolic risk markers in patients with lone versus non-lone atrial fibrillation. *Am J Cardiol*. 2005 Mar 1;95(5):592–6.
8. Montgomery DH, Ververis JJ, McGorisk G, Frohwein S, Martin RP, Taylor WR. Natural history of severe atheromatous disease of the thoracic aorta: a transesophageal echocardiographic study. *J Am Coll Cardiol*. 1996 Jan;27(1):95–101.
9. Mügge A, Kühn H, Nikutta P, Grote J, Lopez JA, Daniel WG. Assessment of left atrial appendage function by biplane transesophageal echocardiography in patients with nonrheumatic atrial fibrillation: identification of a subgroup of patients at increased embolic risk. *J Am Coll Cardiol*. 1994 Mar 1;23(3):599–607.
10. Tunick PA, Kronzon I. Atheromas of the thoracic aorta: clinical and therapeutic update. *J Am Coll Cardiol*. 2000 Mar 1;35(3):545–54.
11. Writing Committee Members, Wiegers SE, Ryan T, Arrighi JA, Brown SM, Canaday B, et al. 2019 ACC/AHA/ASE Advanced Training Statement on Echocardiography (Revision of the 2003 ACC/AHA Clinical Competence Statement on

Echocardiography): A Report of the ACC Competency Management Committee. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr. 2019 Aug;32(8):919–43.

8.4 Annexe 3

Biomarqueurs étudiés dans l'objectif de stratifier les risques thrombotiques et hémorragiques chez les patients de cardiologie ayant une fibrillation atriale.

Biomarqueurs	Rôle du biomarqueur	Données de la littérature cardiologique chez les patients en fibrillation atriale
Activation plaquettaire et de la coagulation		
- D dimère	- Marqueur du turnover de la fibrine	- Associé à la présence d'un thrombus intra AG [165–168], la survenue d'ETA [169–171], d'évènements hémorragiques sévères et de décès. - Associé à la présence d'une dysfonction auriculaire gauche [172].
- Microparticules pro coagulantes circulantes	- Micro vésicules membranaires pro coagulante d'origine essentiellement plaquettaire et cellules endothéliales en réponse à une activation ou agression cellulaire [137]	- augmentée chez les patients en FA [137]
- Fragments pro-thrombinique 1 et 2 - Complexe thrombine-antithrombine - Fibrinopeptide A	- Marqueur d'une activation de la coagulation - Complexe prothrombotique	- Associé à la survenue d'un ETA [173]. - Corrélié à la présence d'un contraste spontanée intra AG [172,174].
- Tissu-plaminogen activator antigène - t-PA inhibiteur-1 - Complexe plasmine-antiplasmine	- Marqueur d'une augmentation de la fibrinolyse - Système fibrinolytique - en réponse à l'état pro-thrombotique [175,176], l'inflammation et les dommages endothéliaux [177,178] chez les patients en FA	- Associée à présence de facteur de risque d'ETA tel que l'âge, la présence d'une insuffisance cardiaque congestive, une dysfonction VG systolique, et la survenue d'une FA de novo récente (essai SPAF III (Stroke Prevention in Atrial Fibrillation) [179]
- β-thromboglobuline	- Marqueur d'une activation plaquettaire et du relargage d' α -granules durant l'agrégation plaquettaire et la formation du thrombus - Rôle potentiel des plaquettes dans l'état pro-thrombotique - Pourrait cependant être essentiellement en lien avec les conditions vasculaires athéromateuse sous-jacentes présente chez ces mêmes patients.	- Rapporté chez les patients en FA en comparaison aux patients en rythme sinusal [180–186]. - Absence d'association entre la concentration plasmatique de β -thromboglobuline et la survenue d'ETA (étude issue de l'essai SPAF-III [187].
- Von Willebrand factor	- Marqueur de dysfonction/ dommage endothéliale et activation plaquettaire - Glycoprotéine produite par les cellules endothéliales [188] jouant un rôle majeur dans les processus d'adhésion plaquettaire et de formation du thrombus.	- Lien avec la présence d'un thrombus intra AG [189], la survenue d'ATE [190,191], d'accident hémorragique sévère et de décès [188,190,192,193] chez les patients en FA. - Surexpression de vWF par l'endocarde atrial chez les patient en FA compliqué d'un ATE, spécifiquement au niveau de zones contenant des cellules inflammatoires et de l'endocarde dénudé [194].
- Fibrinogène		- Contraste spontané intra auriculaire gauche = traduction échocardiographique d'une interaction accru entre le fibrinogène et les érythrocytes dépendante des concentrations de chacun de ces deux éléments [195,196].

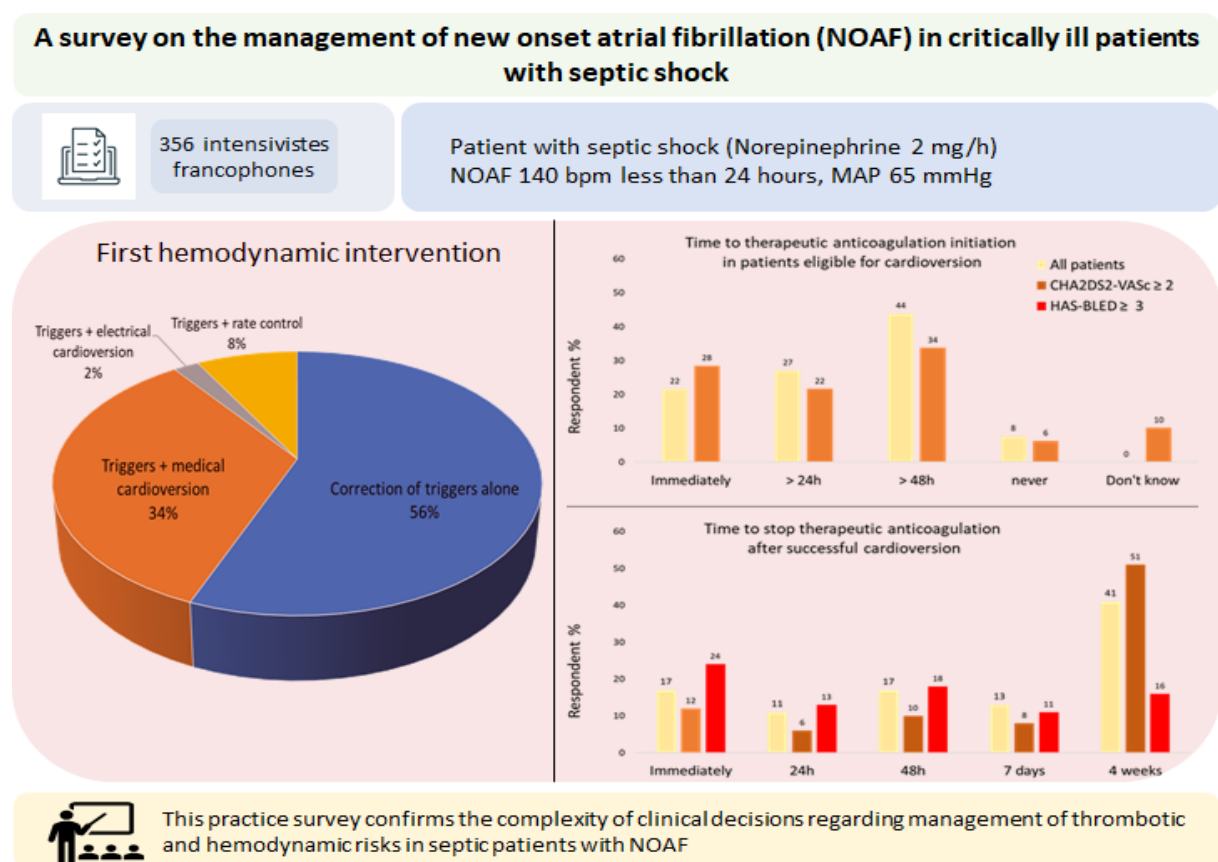
Biomarqueurs cardiaques		
- Troponine cardiaque	- Marqueurs de souffrance myocardique - Protéine secrétée par les myocytes en réponse à des mécanismes multiples [197–200] : vulnérabilité tissulaire, nécrose, ischémie et stress myocardique dû à l'augmentation et la variabilité de la fréquence cardiaque, dysfonction myocardique secondaire aux variations des volumes atriales et ventriculaires et des pressions de remplissage.	- Risque d'ATE, de décès et d'évènement hémorragique sévère, multiplié respectivement par 1.7, 3 et 1.9 fois (étude des biomarqueurs issue de l'étude RELY [201–203])
- B-type natriuretic peptide - N-terminal pro B-type natriuretic peptide	- Marqueur diagnostique très sensible d'une dysfonction VG systolique et diastolique - Neuro-hormone sécrétée par les myocytes principalement en réponse à une augmentation de la tension pariétale secondaire par exemple à une surcharge de volume ou de pression. - NTproBNP : fragment inactif du BNP de longue demi-vie d'élimination, augmente durant les états de stress hémodynamique comme l'insuffisance cardiaque, les syndrome coronarien aigue, et les arythmies tel que la FA [202,204].	- Associé à un risque élevé d'ETA et de mortalité cardio-vasculaire [202,205,206] - Association avec la présence d'une dysfonction atriale et d'un thrombus intra auriculaire gauche [207–209].
Inflammation, Stress oxydatif et Fibrose		
- CRP - Interleukine 6	- Marqueurs de l'inflammation - La CRP et l'interleukine 6 stimulent la production de facteur tissulaire à partir de monocytes in vitro [210,211] - L'interleukine 6 augmente la production de plaquettes et la sensibilité à la thrombine, [212] stimule la transcription du fibrinogène [213] et est liée à l'activation et aux dommages endothéliaux [214,215].	- Associé avec le risque de mortalité et d'évènements cardiovasculaire [216–219]. - Prédicatifs de mortalité toute cause confondue ajusté sur des modèles incluant d'autres biomarqueurs pronostic tel que la troponine et le NT pro BNP [220,221].
- Growth differentiation factor 15	- Marqueur de l'inflammation et du stress cellulaire (ischémie cellulaire, stress oxydatif et mécanique) [222,223]. - Exprimé par de nombreuses cellules telles que les adipocyte et les myocytes	- Association significative et indépendante (ajusté sur les autres facteurs de risque clinique et autres biomarqueurs) avec la survenue d'ETA, de décès, et d'évènements hémorragiques sévères [224].
- Galectine-3	- Impliquée dans plusieurs processus pathologiques tels que l'inflammation et la fibrose [225].	- Association avec la mortalité (étude de biomarqueurs ARISTOTLE) - Pas d'association indépendante avec le risque d'ETA ou d'évènement hémorragique sévère.
Biomarqueur de la fonction rénal		
- cystatine C	- marqueur plus fiable de la fonction rénale que la créatinine sérique [226], en particulier pour la détection de petites réductions du débit de filtration glomérulaire. - Inhibiteur de la cystéine protéase synthétisé à un taux constant dans toutes les cellules nucléées et éliminé par filtration glomérulaire [227]	- Association entre l'insuffisance rénale et le risque d'évènement cardiovasculaire incluant les ETA, les évènements hémorragiques sévères, et la mortalité [228] - Cystatine C associée à des taux plus élevés d'ATE, de mortalité et de saignements majeurs [229].
Renouvellement de la matrice extracellulaire		
- Métalloprotéinases matricielles	- Marqueur d'un renouvellement possiblement pathologique de la matrice extracellulaire [230,231] - L'atteinte de cette structure pourrait favoriser la thrombogénèse en induisant un remodelage auriculaire pathologique associant fibrose et infiltration de l'endocarde.	- Les patients en FA présentent une élévation de concentration de diverses métalloprotéinases matricielles (MMP, leurs inhibiteurs (inhibiteur tissulaire des MMP [TIMP]) et divers facteurs de croissance [230,231]

Abbreviations: BNP, B-type natriuretic peptide; FA, fibrillation atriale, ETA, évènement thrombotique artériel ; NT Pro-BNP, N-terminal B-type natriuretic peptide

8.5 Annexe 4

A survey on the management of new onset atrial fibrillation in critically ill patients with septic shock. Labbé V, Bagate F, Cohen A, Voiriot G, Fartoukh M, Mekontso-Dessap A: J Crit Care 61:18–20, 2021.

Visual abstract





A survey on the management of new onset atrial fibrillation in critically ill patients with septic shock



New onset atrial fibrillation (NOAF) is the most frequent rhythm disorder in critically ill patients with septic shock, and is associated with high rates of arterial thrombotic event (ATE), hemodynamic alteration and mortality [1–3]. However, international guidelines failed to establish clear treatment modalities of this entity [1,4]. We sought to assess practices in the management of hemodynamic and thrombotic risks of NOAF in this context.

An anonymous online survey was electronically sent by email to French-speaking intensivists. The 18-questions survey consisted of questions based on an illustrative case and related to various modalities of hemodynamic and thrombotic risk management, followed by questions related to the characteristics of respondents. Surveys were collected from January 10th to February 25th 2020.

Three hundred and fifty-six intensivists replied to the survey (response rate of 11.2%) including anaesthesiologists (40%), pulmonologists (13%), internal medicine specialists (12%), intensive care specialists (10%) and cardiologists (8%) from university (45%), public (43%) or private (11%) hospitals (Supplemental Digital Content 1. Supplement Table 1). NOAF management strategies are reported in Table 1. All intensivists aimed at controlling reversible “triggers” of NOAF, while 36% and 8% of them associated rhythm or rate control medications, respectively. In patients eligible for early (<24 h) cardioversion, 22% of intensivists initiated immediate therapeutic anticoagulation, whereas 27% initiated therapeutic anticoagulation after 24 h, and 44% after 48 h of sustained NOAF. Therapeutic anticoagulation was mainly achieved using intravenous unfractionated heparin, and discontinued by more than half of physicians within seven days of successful cardioversion. When CHA₂DS₂-VASc stroke risk score was ≥ 2 [4], 11% of intensivists initiated therapeutic anticoagulation earlier, while 18% stopped therapeutic anticoagulation later, as compared with their usual strategy. HAS-BLED bleeding risk score ≥ 3 [4] and bleeding risk factors in critically-ill patients [5] were considered as justifying an earlier discontinuation of therapeutic anticoagulation by 29% and 22% of physicians, respectively. Results did not differ according to the type of institution or primary specialty of the respondent, except for therapeutic anticoagulation initiation before any cardioversion regardless of the duration of NOAF, which was more

frequently proposed by cardiologists as compared to their counterparts [13/29 (45%) vs 64/327 (20%), $p < 0.01$].

In line with previous observational studies, we report non-consensual management of NOAF during septic shock [2,3,6,7]. Whereas control of reversible “triggers” [8] was systematic, less than half of the respondents associated specific anti-arrhythmic interventions for cardioversion or ventricular rate control. The benefit of both strategies, as recommended by European guidelines in patients with hemodynamic instability [1,4], are uncertain in septic patients. Although high ventricular rates and loss of atrial systole may lead to haemodynamic deterioration, rapid ventricular response may be a compensatory response to underlying condition [1]. When the ventricular rate control was considered, physicians used mainly intravenous amiodarone, as proposed by the European guidelines in critically ill patients [4]. Recent European guidelines in critically ill patients recommend therapeutic anticoagulation initiation before any emergent cardioversion regardless of the duration of NOAF, and for at least 4 weeks after successful cardioversion [1]. In contrast, more than half of the respondents initiated therapeutic anticoagulation later, and for a shorter duration. These deviations from the guidelines (which apply to cardiology wards patients), may be due to discrepancies in stroke and bleeding risks between cardiologic and septic patients. First, thrombotic and bleeding risks in the latter seem to be higher than those reported in cardiology wards [1,4–6,9]. Second, CHA₂DS₂-VASc and HAS-BLED clinical score used in ambulatory cardiology patients [4] are not validated in septic patients; thus, a majority of intensivists did not take into account these scores for therapeutic anticoagulation management. Third, the frequency and required time for left atrial thrombus formation are unknown in septic patients, as the notion of left atrial stunning risk that mandate prolonged therapeutic anticoagulation after cardioversion in cardiologic patient [10].

Our study has several limitations. First, the response rate was low, a fact that may introduce some potential bias. However, the number of answers received after a single mailing without any reminder or incentive was important, and respondent's characteristics were diverse (Supplemental Digital Content 1. Supplement Table 1). Second, since the questionnaire consisted of closed responses with a limited number of choices, we could not explore the complexity of real life practices. However, the case presented was inspired from the clinical scenario. Third, the survey was sent only to French-speaking intensivists, which limits the generalization of our results.

In conclusion, this practice survey confirms the complexity of clinical decisions regarding management of thrombotic and hemodynamic risks in septic patients with NOAF. Specific guidelines would require further investigations with randomised clinical trials aiming at assessing the best strategies in this setting.

Table 1
Survey on the management of new onset atrial fibrillation during septic shock.

Variables	Number (percentage)
Number of intensivists	356 (100)
<i>Hemodynamic management^a</i>	
First hemodynamic intervention ^b	
Correction of reversible triggers ^c	200 (56.2)
Correction of reversible triggers + Pharmacological cardioversion	121 (34)
Correction of reversible triggers + Ventricular rate control	29 (8.1)
Correction of reversible triggers + Electrical cardioversion	6 (1.7)
No intervention	0
Drug agent used for pharmacological cardioversion, n = 121	
Amiodarone	121 (100)
Beta blocker	0
Calcium blocker	0
Flecainide	0
Drug agent used to control ventricular rate, n = 29	
Amiodarone	19 (65.5)
Beta blocker	6 (20.7)
Digoxin	4 (13.8)
Calcium blocker	0
Administration modalities of drug agent, n = 150	
Enteral	39 (25.9)
Intravenous	111 (74.1)
<i>Therapeutic anticoagulation initiation^d</i>	
Time to therapeutic anticoagulation initiation	
Before any cardioversion, regardless of the duration of NOAF	77 (21.6)
If NOAF sustained >24 h	96 (27)
If NOAF sustained >48 h	156 (43.8)
Never	27 (7.6)
Time to therapeutic anticoagulation initiation in patients with CHA ₂ DS ₂ VASc ≥ 2	
Before any cardioversion, regardless of the duration of NOAF	101 (28.4)
If NOAF sustained >24 h	77 (21.6)
If NOAF sustained >48 h	120 (33.7)
Never	22 (6.2)
Don't know	36 (10.1)
Drug for initial therapeutic anticoagulation	
Intravenous unfractionated heparin	252 (70.8)
Subcutaneous low-molecular-weight heparin	93 (26.1)
Vitamin K antagonist	6 (1.7)
Subcutaneous calcium heparin	5 (1.4)
Non-vitamin K antagonist oral anticoagulants	0 (0)
<i>Therapeutic anticoagulation discontinuation</i>	
Time to stop therapeutic anticoagulation after successful cardioversion	
Immediately	60 (16.9)
24 h	40 (11.2)
48 h	61 (17.1)
7 days	48 (13.5)
4 weeks	147 (41.3)
Time to stop therapeutic anticoagulation after successful cardioversion in patients with CHA ₂ DS ₂ VASc ≥ 2	
Immediately	44 (12.3)
24 h	23 (6.5)
48 h	34 (9.6)
7 days	28 (7.9)
4 weeks	182 (51.1)
Don't know	45 (12.6)
Time to stop therapeutic anticoagulation after successful cardioversion in patients with HAS-BLED ≥ 3	
Immediately	87 (24.4)
24 h	45 (12.6)
48 h	63 (17.7)
7 days	38 (10.7)
4 weeks	58 (16.3)
Don't know	65 (18.3)
Time to stop therapeutic anticoagulation after successful cardioversion in patients with risk factors for bleeding in the critically-ill (invasive mechanical ventilation or acute renal failure or antiulcer medication)	
Immediately	98 (27.5)
24 h	44 (12.4)

Table 1 (continued)

Variables	Number (percentage)
48 h	42 (11.8)
7 days	36 (10.1)
4 weeks	96 (27)
Don't know	40 (11.2)

Abbreviations: CHA₂DS₂VASc, Congestive heart failure, Hypertension, Age ≥ 75 (doubled), Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74, Sex category (female); HAS-BLED, Hypertension, Abnormal renal and liver function (1 point each), history of Stroke, history of Bleeding, Labile INR in patients on warfarin, Elderly (age > 65 years), Drug or alcohol abuse (1 point each); ICU, intensive care unit; NOAF, new onset atrial fibrillation.

^a in a patient with NOAF, heart rate at 140 bpm, mean arterial pressure at 65 mmHg, norepinephrine at 2 mg/h.

^b within 24 h of NOAF onset.

^c as fluid resuscitation, correction of potassium and magnesium.

^d in patients with NOAF during septic shock eligible for cardioversion (no contraindication to therapeutic anticoagulation).

Authors' contribution

VL and AMD conceived and designed the study. VL and AMD created the survey. FB, MF and GV contributed to survey creation (piloted the survey before release). VL and AMD acquired, analysed and interpreted the data. VL and AMD drafted the original manuscript. All authors revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Declaration of Competing Interest

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VL receives advisory board fees from Amomed unrelated with the present study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcrr.2020.09.025>.

References

- [1] Boriani G, Fauchier L, Aguinaga L, Beattie JM, Blomstrom Lundqvist C, Cohen A, et al. European Heart Rhythm Association (EHRA) consensus document on management of arrhythmias and cardiac electronic devices in the critically ill and post-surgery patient, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society

- (APHRS), Cardiac Arrhythmia Society of Southern Africa (CASSA), and Latin American Heart Rhythm Society (LAHRS). *Europace* 2019;21:7–8. <https://doi.org/10.1093/europace/euy110>.
- [2] Seemann A, Boissier F, Razazi K, Carreaux G, de Prost N, Brun-Buisson C, et al. New-onset supraventricular arrhythmia during septic shock: prevalence, risk factors and prognosis. *Ann Intensive Care* 2015;5:27. <https://doi.org/10.1186/s13613-015-0069-5>.
- [3] Klein Klouwenberg PMC, Frencken JF, Kuipers S, Ong DSY, Peelen LM, van Vught LA, et al. Incidence, predictors, and outcomes of new-onset atrial fibrillation in critically ill patients with sepsis. A cohort study. *Am J Respir Crit Care Med* 2017;195:205–11. <https://doi.org/10.1164/rccm.201603-0618OC>.
- [4] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;18:1609–78. <https://doi.org/10.1093/europace/euw295>.
- [5] Brown RB, Klar J, Teres D, Lemeshow S, Sands M. Prospective study of clinical bleeding in intensive care unit patients. *Crit Care Med* 1988;16:1171–6. <https://doi.org/10.1001/jamacardio.2016.2181>.
- [7] Guenancia C, Binquet C, Laurent G, Vinault S, Bruyère R, Prin S, et al. Incidence and predictors of new-onset atrial fibrillation in septic shock patients in a medical ICU: data from 7-day Holter ECG monitoring. *PLoS One* 2015;10:e0127168. <https://doi.org/10.1371/journal.pone.0127168>.
- [8] Vieillard-Baron A, Boyd J. Non-antiarrhythmic interventions in new onset and paroxysmal sepsis-related atrial fibrillation. *Intensive Care Med* 2018;44:94–7. <https://doi.org/10.1007/s00134-017-4986-7>.
- [9] Airaksinen KEJ, Grönberg T, Nuotio I, Nikkinen M, Ylitalo A, Biancari F, et al. Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. *J Am Coll Cardiol* 2013;62:1187–92. <https://doi.org/10.1016/j.jacc.2013.04.089>.
- [10] Black IW, Fatkin D, Sagar KB, Khandheria BK, Leung DY, Galloway JM, et al. Exclusion of atrial thrombus by transesophageal echocardiography does not preclude embolism after cardioversion of atrial fibrillation. A multicenter study. *Circulation* 1994;89:2509–13. <https://doi.org/10.1161/01.CIR.89.6.2509>.

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Supplemental Digital Content 1. Supplement Table 1. Characteristics of respondents

Characteristics of respondents	Number (percentage) or Median (interquartile range)
<i>Number of intensivists</i>	356 (100)
<i>Type of institution, n (%)</i>	
University Hospital	159 (44.7)
Non University Public Hospital	152 (42.7)
Private Hospital	40 (11.2)
Other institution	5 (1.4)
<i>Type of ICU (md=2)</i>	
Mixed	227 (64.1)
Medical	97 (27.4)
Surgical	30 (8.5)
<i>Number of beds in Intensive care unit (md=3)</i>	20 (15-24)
<i>Number of admissions per year (md=7)</i>	
<500	33 (9.5)
500 – 1000	172 (49.3)
>1000	144 (41.2)
<i>Medical status (md=2)</i>	
Hospital practitioner	234 (66.1)
University professor	26 (7.4)
Assistant	56 (15.8)
Resident	38 (10.7)
<i>Primary specialty (md=3)</i>	
Anaesthesia	141 (40)
Pneumology	47 (13.3)
Internal medicine	42 (11.9)
Intensive care	37 (10.5)
Cardiology	29 (8.2)
Emergency	29 (8.2)
Nephrology	17 (4.8)
Other	11 (3.1)
<i>Years of experience (md=4)</i>	8 (3-16)

Abbreviation: md, missing data