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Risque hémorragique sous anticoagulants : Vers une prise en charge personnalisée

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RISQUE HEMORRAGIQUE SOUS ANTICOAGULANTS

Vers une prise en charge personnalisée.

Thèse soutenue publiquement le 20 novembre 2017, par
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Résumé

Introduction. Devant les nombreux facteurs pouvant influencer le risque hémorragique des patients sous anticoagulant, le concept de médecine personnalisée pourrait avoir un impact favorable dans la prise en charge globale de ces patients.

Hypothèse et objectif. L'hypothèse de ce travail de thèse est que l'utilisation et l'analyse de registre de « vraie vie » pourrait permettre de définir des « profils » hémorragique de patient permettant une prise en charge personnalisée des patients.

Matériel et Méthode. Ce travail de thèse a utilisé deux registres de vraie vie, le registre RIETE (registre international multicentrique prospectif) et le registre RATED (registre monocentrique).

Résultats. Nous avons montré l'importance du recueil biologique dans l'analyse des accidents hémorragiques sous anticoagulants avec une perte plus élevée de facteurs de coagulation, lors d'hémorragie gastro-intestinales par rapport aux intracrâniennes sous AVK. A l'inverse, ce risque est diminué de moitié en cas de mutation du facteur V Leiden. Grâce au registre RIETE, nous nous sommes ensuite intéressés aux métrorragies sous anticoagulant (peu décrites dans la littérature) où seulement 0,17% des femmes présentaient des saignements utérins majeurs. Nous avons par la suite montré que les patients fragiles ($\text{CrCl} \leq 50 \text{ mL / min}$, un âge ≥ 75 ans ou un poids corporel $\leq 50 \text{ kg}$) ont un risque deux fois plus élevé de saignement grave. Enfin, afin de montrer la complémentarité des registres de vraie vie et des données d'essais randomisés, nous nous sommes intéressés aux patients exclus de ces essais randomisés et avons montré également un risque hémorragique 4 fois plus élevé.

Conclusion. Ce travail de thèse a permis de démontrer l'intérêt de travailler non pas toutes hémorragies confondues mais hémorragies par hémorragies, avec un intérêt de réalisation de registres prospectifs de vraie vie avec la mise en œuvre de bio-banque permettant une analyse plus personnalisée de la prise en charge des patients.

Abstract

Introduction. Given many risk factors that may influence the risk of hemorrhage under anticoagulant therapy, the concept of personalized medicine could have a favorable impact in the overall management of these patients.

Hypothesis and objective. The hypothesis of this thesis is that the use and analyze of "real life" registries could allow to define hemorrhagic "profiles" allowing a personalized management of the patients.

Material and method. This thesis work has used two real life registries, the RIETE registry (international, multicentric and prospective register) and RATED (monocentric register).

Results. We showed the importance of biological database in the analysis of hemorrhagic events under anticoagulants with a higher loss of coagulation factors in gastrointestinal bleeding compared with intracranial bleeding under AVK. Conversely, this bleeding risk is two times lower in case of factor V Leiden mutation. Thanks to the RIETE registry, we were interested in abnormal uterine bleeding under anticoagulant therapy (few studies in the literature) with major uterine bleeding only for 0.17% of women. Then, we showed that fragile patients ($\text{CrCl} \leq 50 \text{ mL / min}$, $\text{age} \geq 75 \text{ years}$ or $\text{body weight} \leq 50 \text{ kg}$) have a 2-fold higher risk for major bleeding. Finally, in order to show the complementarity between data from real life registries and randomized trial, we assessed patients normally excluded from these randomized trials and also showed a 4-fold higher bleeding risk in these excluded patients.

Conclusion. This thesis work allowed us to demonstrate the interest of working not only on overall hemorrhages but on each type of hemorrhage separately, with a particular interest to create real life prospective registries with the implementation of bio-bank allowing a more personalized analysis of the intake of patients.

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Abbréviations

WF : facteur de Willebrand

ADP : adénosine diphosphate

TFPI : Tissue Factor Pathway Inhibitor

KHPM : kinogène de haut poids moléculaire

HNF : Héparine Non Fractionnée

HBPM : Héparine de Bas Poids Moléculaire

PM : Poids Moléculaire

AVK : Anti-Vitamine K

VKORC1 : vitamine K époxyde réductase

FA : Fibrillation Atriale

INR : International Normalized Ratio

AOD : Anticoagulants Oraux Directs

CNAM : Caisse Nationale d'Assurance Maladie

SNIIRAM : Système National d'Information Inter-régions de l'Assurance Maladie

PMSI : Programme de Médicalisation des Systèmes d'Information

AMM : autorisation de mise sur le marché

MTEV : maladies thrombo-emboliques veineuse

AVC : accidents vasculaires cérébraux

EP : Embolie pulmonaire

TVP : thrombose veineuse profonde

CES1 : carboxylesteras 1

ClCr ou VCreat: Clearance de la créatinine

HAS : Haute Autorité de Santé

ISTH : International Society on Thrombosis and Haemostasis

RIETE : Registro Informatizado Enfermedad TromboEmbolica

RATED : Registry of patient with Antithrombotic agents admitted to an Emergency

DepartmentCRF

CRF : Case Report Form

FVL : facteur V Leiden

PTM : prothrombine G20210A

RR : Risque Relatif

OR : Odds Ratio

HR : Hazard Ratio

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I. Introduction

L'analyse des accidents hémorragiques sous anticoagulants fait intervenir différents facteurs que sont l'hémostase, la molécule incriminée, les différentes interactions médicamenteuses pouvant être mise en jeu et enfin le profil propre du patient avec les différents facteurs de risque hémorragique. Dans l'introduction, nous nous attacherons donc à essayer de décrire les connaissances actuelles sur ces différents paramètres intervenant dans la genèse d'un accident hémorragique sous anticoagulant en ayant bien conscience que ces facteurs peuvent s'interpénétrer.

I.1 Accidents hémorragiques aux anticoagulants

Tous les anticoagulants peuvent induire des hémorragies aux conséquences potentiellement mortelles, en particulier au début de la prise du traitement ¹⁻³. Le risque de complications hémorragiques est corrélé à l'intensité de l'anticoagulation ³.

I.1.1 Epidémiologie

Le saignement sous AVK représente la première cause d'hospitalisation iatrogène en France (soit environ 17 000 par an) soit 13% des hospitalisations pour effet indésirable. ⁴ L'étude EMIR, réalisée en 2007, a retrouvé un résultat similaire : 12,3% des hospitalisation pour effet indésirable sont liées aux AVK.⁵ L'Enquête Nationale sur les Evènements Indésirables Graves liés aux soins retrouvait que 1/3 de ces évènements

était attribuable aux AVK. Le rapport de la 8^{ème} conférence de l'American College of Chest Physicians retrouvait des taux annuels d'hémorragie majeure dans les différentes études variant selon la définition de l'hémorragie majeure, les médicaments associés et le type d'étude.⁶ Les hémorragies fatales sont estimées entre 0.3% et 1%⁷⁻¹⁰ avec en première ligne les hémorragies intracrâniennes.¹¹

Les AOD ont montré une réduction significative du risque d'hémorragie fatale et d'hémorragie intracrânienne¹². Le dabigatran prescrit chez des patients avec une TVP, a un effet non inférieur à la coumadine¹ et présente un plus faible risque de saignement¹³. Il en est de même pour le rivaroxaban¹.

Dans plusieurs études chez des patients atteints de FA, les AOD apparaissent comme non inférieurs à la warfarine dans la réduction du risque d'AVC ou de MVTE. Le dabigatran (à 150mg) et l'apixaban ont une efficacité supérieure à la warfarine dans la diminution du risque d'AVC et de MVTE, sans augmenter le risque de saignement majeur ou d'hémorragie intracrânienne¹⁴. Il a été montré que l'effet de l'apixaban était supérieur à celui de la warfarine dans la prévention des pathologies citées précédemment. L'apixaban entraînerait moins de saignement et aurait un taux de mortalité plus faible que la warfarine¹⁵. On note également une meilleure compliance pour les AOD par rapport aux AVK¹⁵.

Les principaux essais ayant permis ces conclusions sont les études RE-LY^{16,17}, RECOVER-1 et 2^{18,19}, RE-SONATE et RE-MEDY²⁰ pour le dabigatran, les études ROCKET²¹, EINSTEIN²² pour le rivaroxaban, l'étude ARISTOTLE²³, AVERROES²⁴, AMPLIFY²⁵ pour l'apixaban et les études HOKUSAI²⁶, ENGAGE²⁷ pour l'edoxaban. Ces études de non-infériorité ont toutes été réalisées *versus* warfarine. Ces essais ont permis de montrer la non infériorité voire la supériorité des AOD par rapport aux AVK dans la prévention des AVC et des embolies dans la fibrillation atriale et le traitement des thromboses veineuses profondes et des embolies pulmonaires. Cependant, concernant le risque de saignement majeur en général, la plupart de ces essais n'ont pas permis d'atteindre une infériorité significative des AOD comparativement aux AVK. Ainsi, seules

les études ARISTOTLE²³ et RE-LY^{16,17} ont permis de mettre en évidence une diminution significative du risque relatif de saignement majeur.

I.1.2 Types et Localisation

Les études princeps sur les AODs ont permis de montrer une importante diminution du risque d'hémorragie intracrânien^{16,21,23} et un probable sur-risque d'hémorragies gastro-intestinales des AOD comparativement aux AVK^{16,21}.

Concernant les hémorragies intracrâniennes, il semblerait que les principaux facteurs de risques seraient l'hypertension artérielle, le traumatisme crânien ou encore les maladies cérébrovasculaires^{28,29}.

De plus, toutes les hémorragies intracrâniennes ne sont pas identiques (spontanée-traumatique)³⁰, de même pour les hémorragies digestives (hautes-basses, ulcère-cancer-angiodysplasie)³¹.

I.1.3 Score de risque hémorragique

Certains facteurs de risque hémorragiques ont été identifiés pour les AVK par le biais de nombreuses études (Tableau 1). Les principaux facteurs de risque hémorragique sous AVK identifiés sont : l'insuffisance hépatique, l'insuffisance rénale, l'hypertension artérielle, l'existence d'un cancer, l'alcoolisme chronique, le sexe féminin, l'insuffisance cardiaque, le diabète et l'existence de lésions susceptibles de saigner notamment au niveau gastro-intestinal^{6,32-38}. Ces différents facteurs sont repris dans les différents scores prédictifs de risque hémorragique. Les scores prédictifs suivants sont utilisés dans la pratique courante pour l'ACFA : HAS-BLED, HEMORR2HAGES et ATRIA.³⁹⁻⁴¹ Ces trois scores sont validés et sont recommandés pour évaluer le risque hémorragique, mais ont montré une faible précision dans le cadre de MTVE. Par conséquent dans le cadre d'une MTVE, il existe d'autres scores prédictifs : Kuijer et Riete.^{42,43} Ces scores ont été

évalués dans des études rétrospectives et manquent de validation externe. Tous ces scores ont été évalués sous AVK. Une étude récente dont l'objectif était de déterminer un score prédictif d'hémorragie chez les patients traités au long cours (après 30 jours d'utilisation) sous anticoagulant oraux (Warfarin et Dabigatran étexilate) pour une MTVE, a permis de définir un score utilisable pour les patients sous AVK et AOD : le score VTE-BLEED.⁴⁴

Tableau 1 : Score prédictif des risques hémorragiques (Tiré de l'étude de Klok F et al.)⁴⁵

Score	Kuijer ⁴²	Riete ⁴³	Hemorrhages ⁴¹	HAS BLEED ⁴⁰	ATRIA ³⁹
Items (Points)	- Age > 60 ans (1.6) - Sexe Féminin (1.3) - Cancer actif (2.2)	- Hémorragie récente (2) - Insuffisance rénale (1.5) - Anémie (1.5) - Age > 75 ans (1) - Cancer actif (1) - Embolie pulmonaire (1)	- Maladie rénale ou hépatique (1) - Alcoolisme (1) - Cancer actif (1) - Age >75 ans (1) - Thrombopénie ou fonction plaquettaire altérée (1) - Antécédent d'hémorragie (1) - Hypertension non contrôlée (1) - Anémie (1) - Facteurs génétiques (1) - Risque de chute, maladie neurologique ou psychiatrique (1) - Antécédent d'AVC (1)	- HTA (1) - Dysfonction rénale (1) - Dysfonction hépatique (1) - AVC (1) - Antécédents d'hémorragie (1) - INR labile (1) - Age > 65 ans (1) - Alcoolisme (1) - Prise de drogues (1)	- Anémie (3) - Insuffisance rénale majeure (3) - > 75 ans (2) - Antécédents d'hémorragie (1) - HTA (1)
<i>Risque hémorragique</i>					
Bas	0 points	0 points	0-1 points	0 points	0-3 points
Intermédiaire	1-3 points	1-4 points	2-3 points	1-2 points	4 points
Elevé	>3 points	>4 points	>3 points	>2 points	>4 points

De plus, pour les AVK, l'INR semble être un déterminant important du risque hémorragique puisqu'on note une augmentation linéaire de risque lorsque l'INR dépasse 3 avec un facteur multiplicatif de 20 à 30 lorsque cette INR est au-delà de 4⁴⁶⁻⁴⁹. Ainsi, pour les recommandations françaises, un INR supérieur à 5 est considéré comme le seuil au-delà duquel le risque hémorragique augmente significativement et donc nécessite une réversion.⁵⁰

Certaines études ont également repéré des facteurs de risque signant une certaine fragilité des patients avec un sur-risque hémorragique comme l'insuffisance rénale^{33,34,51,52}, un âge avancé⁵³ ou un contexte polyopathologique à risque de polymédication favorisant les interactions médicamenteuses^{33,54-57}. Le bon usage des AOD est une préoccupation majeure. Dans une étude réalisée par la CNAM, il apparaît que, sur la totalité des patients ayant débuté un traitement par AOD, 28,6% étaient dans une situation à risque avec une altération de la fonction rénale ou hépatique, une absence de surveillance de la fonction rénale chez des patients âgés de plus de 80 ans, la présence d'une pathologie valvulaire ou une co-prescription pouvant majorer le risque hémorragique.⁵⁸

I.2 La coagulation

La coagulation joue un rôle important dans le maintien de l'intégrité vasculaire et dans la protection contre le saignement en cas d'atteinte tissulaire. Ce rôle primordial passe par la mise en jeu de différentes interactions entre les protéines adhésives de la paroi endothéliale (hémostase primaire) et par une succession de cascades protéolytiques déclenchées par un stimulus initiateur (hémostase secondaire)⁵⁹⁻⁶¹.

I.2.1 Hémostase primaire

Lors d'une brèche vasculaire, le tissu endothélial est mis à nu. La vasoconstriction est le premier phénomène mis en place. Elle permet de réduire le débit sanguin au niveau de la brèche vasculaire et ainsi réduire, voire arrêter, le processus hémorragique.

Secondairement, au niveau de l'atteinte tissulaire, les plaquettes pourront interagir avec le collagène et le facteur Willebrand (WF). Les plaquettes ainsi activées émettent des molécules chimiques (adénosine diphosphate ou ADP, sérotonine, thromboxane A2)

permettant de recruter d'autres plaquettes au niveau de l'atteinte vasculaire et d'augmenter la vasoconstriction.

Lors de ce processus, les plaquettes modifient leur apparence passant de discoïdale à sphérique et émettent des pseudopodes favorisant leur étalement au niveau de l'atteinte vasculaire. Ce mécanisme augmente l'expression de la GPIIb-IIIa active qui permet par sa liaison au fibrinogène, et par l'agrégation des plaquettes entre elles, de former le clou plaquettaire (Figure 1).⁵⁹⁻⁶¹

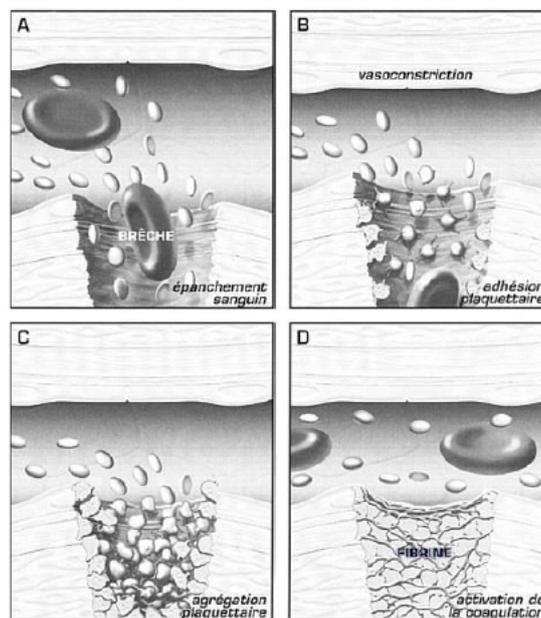


Figure 1: hémostase primaire (D'après B.Boneu et JP.Cazenave)⁶²

I.2.2 Hémostase secondaire

I.2.2.1 Voie extrinsèque

Cette voie a pour principale objectif l'augmentation de l'activité de la voie intrinsèque en générant du facteur X sous sa forme activée (FXa). Deux facteurs entrent en jeu de manière unique dans cette voie : le facteur III (facteur tissulaire) et le facteur VII. Lorsque le facteur III est activé, il se lie au facteur VII permettant son activation (Facteur Xa) et la

formation du complexe facteur tissulaire-facteur VII. Ce complexe agira par la suite sur le facteur IX ou X. Le facteur X activé permettra d'établir un contrôle (positif ou négatif) sur le complexe facteur tissulaire-facteur VII. Ce facteur Xa s'associe ensuite au TFPI (Tissue Factor Pathway Inhibitor) une protéine plasmatique. Ce complexe ainsi créé inhibe le facteur III et permet ainsi l'action du Facteur Xa sur le complexe facteur tissulaire-facteur VII permettant de cliver le facteur VII en VIIa permettant d'augmenter son activité.

I.2.2.2 Voie intrinsèque

Cette voie met en jeu le facteur d'Hageman (facteur XII), le facteur XI, la prékallicroïne et le kinogène de haut poids moléculaire (KHPM). La première étape de cette voie est la liaison du facteur XII à la surface sous endothéliale exposée au niveau de la lésion tissulaire. Le complexe prékallicroïne-KHPM interagit également au niveau de la surface de lésion tissulaire à proximité du facteur XII permettant de l'activer (facteur XIIa, chaîne légère du facteur XII). Ce dernier va alors activer la prékallicroïne. Le facteur XII restant au contact de la surface endothéliale atteinte permettra d'activer également le facteur XI. Le KHPM se liera également au facteur XI afin de faciliter l'activation du processus. A la fin la voie intrinsèque permet d'activer le facteur X (Facteur Xa) grâce à un complexe constitué par les facteurs IX, VII, le calcium et des phospholipides (Figure 2).⁵⁹⁻⁶¹

I.2.2.3 Voie commune

La voie intrinsèque et la voie extrinsèque conduisent toutes les deux à produire du facteur Xa, première protéine de la voie commune qui permettra la production de thrombine (Facteur IIa). Cette dernière entraîne la conversion du fibrinogène en fibrine par sa protéolyse et le relargage du fibrinopeptide A. Un second peptide, le fibrinopeptide B, est ensuite clivé par la thrombine créant des monomères de fibrines qui vont se polymériser et former un gel insoluble. Cette fibrine polymérisée est alors stabilisée par une transaminase (Facteur XIIIa) produite par l'action de la thrombine sur le facteur XIII.

Un agrégat se forme alors entre la fibrine insoluble et les plaquettes agrégées permettant le blocage de la lésion vasculaire prévenant d'autres saignements (Figure 2).⁵⁹⁻⁶¹

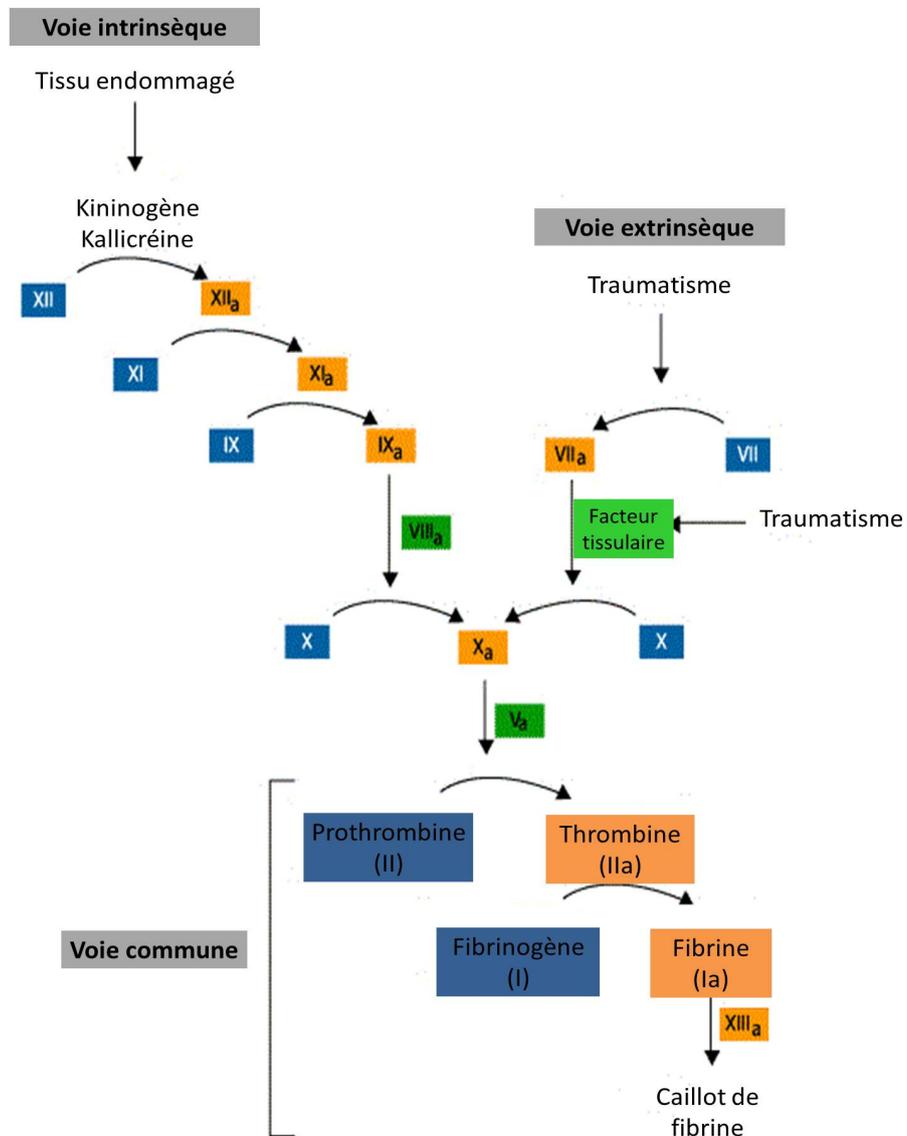


Figure 2 : L'hémostase secondaire (cascade de la coagulation)⁶³

I.3 Anticoagulants

Les anticoagulants font partis des antithrombotiques généralement utilisés pour le traitement et la prévention primaire (et/ou secondaire) dans diverses indications cardiovasculaires.⁶⁴ Les deux principales indications des anticoagulants sont la Fibrillation Atriale et la Maladie Thrombo-Embolique Veineuse^{2,65}.

I.3.1 Héparine Non Fractionnée : HNF

Cette classe est constituée par l'Héparine[®] et la Calciparine[®]. Ces héparines sont constituées d'un enchaînement linéaire de glucosamine et d'acide glycuronique. L'héparine entraîne une modification de structure de l'antithrombine facilitant ainsi l'inactivation de la thrombine par l'antithrombine et donc ses interactions avec les facteurs Iia, IXa, Xa, XIa et XIIa. L'inhibition de la thrombine entraîne la suppression des boucles de rétrocontrôle positif des facteurs V et VII empêchant ainsi sa production.

I.3.2 Héparine de Bas Poids Moléculaire : HBPM

Les HBPM sont obtenues à partir de l'héparine non fractionnée (Poids Moléculaire (PM) de 5000 à 30000 Daltons (Da)) afin d'obtenir une chaîne plus légère d'un PM de 2000 à 10000 Da. En effet, les chaînes de PM au-dessus de 5400 Da inhibent le facteur Xa et la thrombine, alors que celles de PM en-dessous de 5400 Da n'inhibent que le Xa permettant une effet pharmacologique plus prédictible avec une variabilité réduite et donc un espoir de réduction du risque thrombo-embolique et hémorragique avec des doses fixes sans suivi biologique par rapport aux HNF.^{1,60}

I.3.3 Anti-Vitamine K : AVK

Dérivés soit de la coumarine (Sintrom[®] et Coumadine[®]), soit d'indanedione (Préviscan[®]), ces anticoagulants sont administrés par voie orale et agissent par inhibition compétitive de la vitamine K au niveau de l'hépatocyte. En effet, la vitamine K est indispensable à la synthèse des facteurs II, VII, IX, X, et des protéines C et S. Dans l'organisme, l'acide glutamique, l'oxygène et le dioxyde de carbone peuvent être convertis en acide γ -carboxyglutamique. Cet acide aminé est l'un des composants des facteurs II, VII, IX et X. Ce processus de conversion nécessite de la vitamine K sous forme réduite, qui devient par la suite oxydée. Cette vitamine K oxydée est convertie en vitamine K puis de nouveau en vitamine K réduite. Ces deux réactions sont catalysées par une enzyme : la vitamine K époxyde réductase (VKORC1). Les AVK inhibent l'activité de cette enzyme^{1,60} (Figure 3).

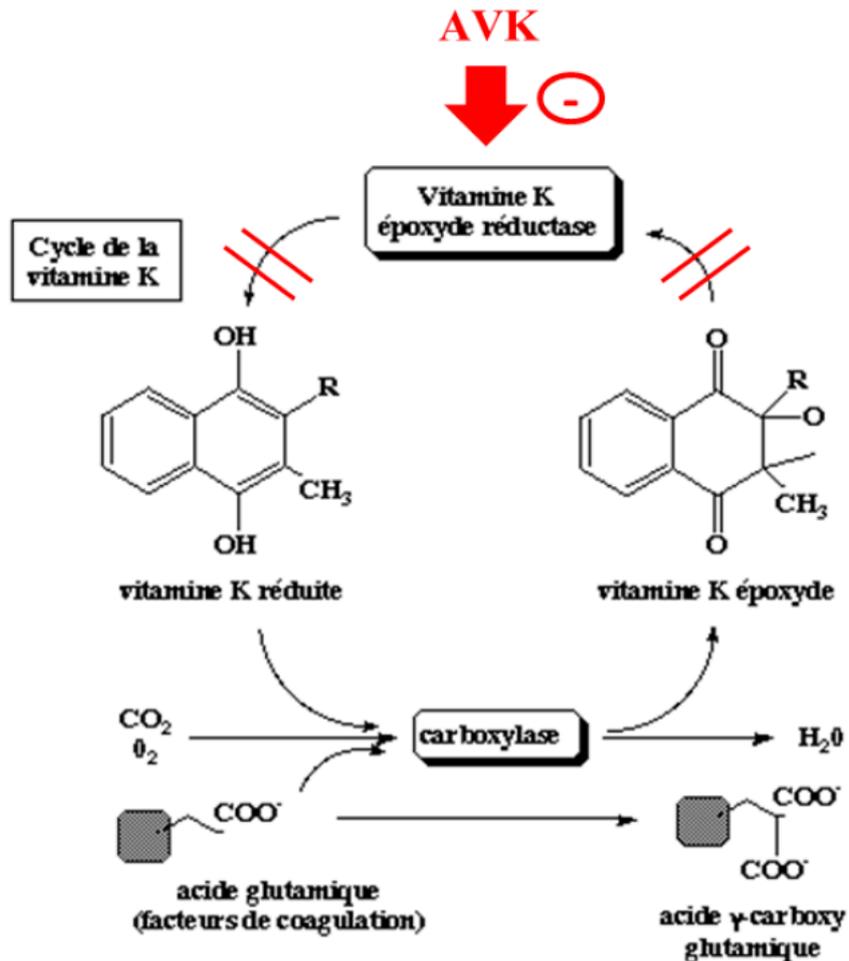


Figure 3: Mécanisme d'action des AVK (tiré de le Bonniec)⁶⁶

Si, les AVK sont très efficaces en termes de prévention des AVC chez les patients en FA, ils présentent certains inconvénients ¹⁵, comme la survenue d'hémorragies pouvant conduire au décès ⁶⁷.

Du fait d'une demi-vie différente selon l'AVK, d'une variabilité génétique du métabolisme (au niveau hépatique par les cytochromes P450 et notamment le CYP2C9), d'une quantité variable de vitamine K dans l'alimentation, d'une fenêtre thérapeutique étroite et de plusieurs interactions médicamenteuses, ce type de traitement nécessite une surveillance biologique ^{1,16}, par la mesure de l'INR (International Normalized Ratio). Ce suivi biologique est nécessaire pour éviter une insuffisance thérapeutique avec un risque de formation de *thrombus*, ou au contraire une anticoagulation excessive, qui augmente

le risque de saignement ¹³. Ces inconvénients entraînent un taux important d'interruption de traitement chez les patients prenant des AVK avec, de fait, une anticoagulation inadéquate ¹⁶.

La warfarine est l'AVK qui a été le mieux évalué car il s'agit du plus prescrit au niveau mondial, notamment dans les pays anglo-saxons.^{68,69} En France, la fluindione est l'AVK majoritairement prescrit représentant 85% des prescriptions d'AVK au troisième trimestre 2013, contre 9% pour la warfarine et 6% pour l'acénocoumarol.⁷⁰

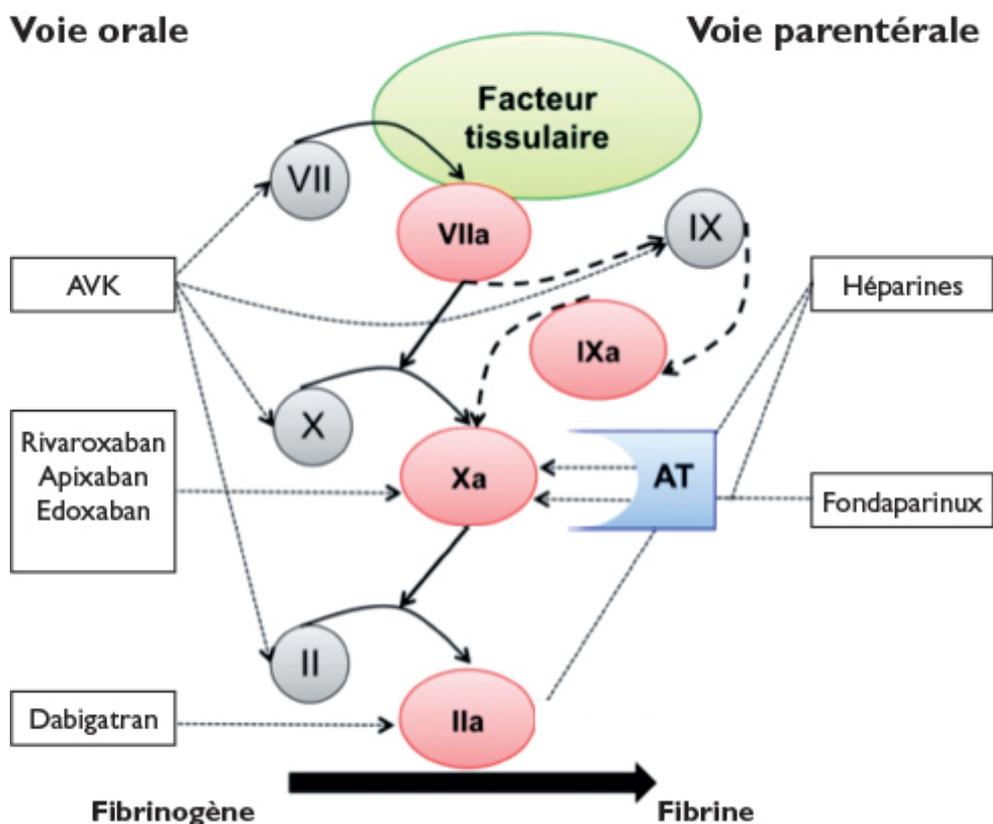
I.3.4 Anticoagulants Oraux Directs : AOD

Cette classe de médicament est en constante augmentation, depuis leur apparition sur le marché français en 2008, en termes de prescriptions. Ils pourraient remplacer dans le futur l'association HBPM et AVK chez les patients présentant une MVTE ou une fibrillation atriale (FA) avec, à l'heure actuelle, plus de 50% du marché dans ces deux indications en France ⁷¹.

Les AOD ont fait l'objet d'une surveillance renforcée lors de leur mise en place avec la réalisation d'une étude en 2013 par le département d'études et de santé publique de la Caisse Nationale d'Assurance Maladie (CNAM).⁵⁸ Cette étude était basée sur les données du SNIIRAM (Système National d'Information Inter-régims de l'Assurance Maladie) chaînées avec les données du PMSI (Programme de Médicalisation des Systèmes d'Information), de 2010 à 2013, montrant une augmentation importante des prescriptions d'AOD au troisième trimestre 2012 correspondant à l'obtention de l'AMM des AOD dans la prévention du risque thromboembolique dans la fibrillation atriale. Sur cette période, environ 74 000 patients ont débuté un traitement par AOD, dont 30000 dans le cadre d'un switch d'un AVK vers un AOD. Par conséquent, on assistait à une réduction équivalente du nombre de nouvelles prescriptions d'AVK. Ainsi, en 2013, 30% des patients recevant des anticoagulants recevaient des AOD.

Le dabigatran (Pradaxa[®]) est un inhibiteur direct de la thrombine (facteur IIa) ¹. Il se lie directement au site catalytique de la thrombine, soit lorsque la thrombine est sous forme « libre » dans le plasma, soit lorsque celle-ci est liée à la fibrine (formation du thrombus). Le rivaroxaban (Xarelto[®]), l'apixaban (Eliquis[®]) et l'edoxaban (Lixiana[®]) sont des inhibiteurs directs du facteur Xa. Ces inhibiteurs ne bloquent pas seulement le facteur Xa libre au niveau de son site actif, ils l'inactivent également au sein du complexe de la prothrombinase qui est lié aux plaquettes (Figure 4) ⁶¹

Les AOD présentent divers avantages pharmacodynamiques. Ils sont tout d'abord administrés par doses fixes une ou deux fois par jour ^{1,13,61}. Ils ont un début et une fin d'action thérapeutique plus rapide que les AVK ⁶¹. Il n'y a pas de surveillance de la coagulation et peu d'interactions médicamenteuses ou alimentaires ^{13,15,61}. C'est pourquoi la décennie précédente a connu une explosion dans le développement clinique des AOD dans le but de compléter ou remplacer les AVK et les héparines dans la prévention et le traitement des MVTE ainsi que pour la prévention des AVC et le traitement des syndromes aigus coronariens ^{13,72}, et ainsi améliorer le ratio bénéfice/risque ⁶¹. Dans l'ensemble, les AOD semblent avoir une efficacité similaire et un risque plus faible de saignement que le traitement standard administré après un épisode aigu d'une MVTE ¹³. Au niveau de la thérapie à long terme l'utilisation des AOD permettrait de réduire le nombre de récurrences de MVTE et d'EP comparé au placebo, en particulier pour les patients avec un haut risque de saignement ¹³. Le nombre de patients qui ont d'abord été traités ou qui ont changés de traitement au profit des AOD ne cesse d'augmenter ⁷³.



*Figure 4 : Mécanisme d'action des antithrombotiques*⁷⁴

I.4 Facteurs impactant le niveau d'anticoagulation

I.4.1 Polymorphisme Génétique

Le polymorphisme génétique (en particulier au niveau de deux gènes) pourrait expliquer en partie la variabilité interindividuelle de la réponse aux AVK. Le premier gène code pour la vitamine K époxyde réductase (VKORC1) et le second pour le cytochrome CYP2C9. Certains allèles de ces gènes confèrent une hyperréactivité aux AVK entraînant une réponse plus rapide et une posologie nécessaire plus faible que chez les patients

possédant les allèles dits « sauvages ». ⁷⁵⁻⁷⁹ A contrario, certaines mutations du gène VKORC1 entraînent une résistance aux AVK. ^{80,81} La population française porte dans 10 à 23% des cas l'allèle muté CYP2C9*2 et dans 10 à 15% des cas l'allèle muté CYP2C9*3. Un seul allèle muté du CYP2C9 est nécessaire à la réduction du métabolisme des AVK. ⁸²⁻⁸⁴ La mutation de VKORC1 serait présente dans 16% de la population caucasienne. ⁸² La pertinence clinique de la réalisation de tests pharmacogénétiques incluant ces gènes a été démontré dans de nombreuses études et expliquerait près de 50 % de la variabilité interindividuelle de la réponse aux AVK. ^{76,85} Une étude avait d'ailleurs démontré l'intérêt de l'utilisation d'un algorithme basé sur l'utilisation de ces gènes avec une diminution du risque hémorragique ou embolique (HR =0.72 ; 95%IC : 0.53-0.97). ⁸⁶ Cependant, l'intérêt pharmaco-économique d'un génotypage de VKORC1 et CYP2C9 est actuellement encore controversé. ⁸⁷

Comme pour les AVK, les AODs sont également soumis à une certaine variabilité génétique. En effet, les AODs sont soumis à l'effet de la P-gp qui est codée par le gène ABCB1 (ATP-binding cassette, subfamily B, member 1) et qui peut être soumis à un polymorphisme à l'origine de ces variabilités sur l'efficacité. Ils sont métabolisés par les CYP3A4, pour lesquels aucune mutation cliniquement significative n'a encore été identifiée, et le CYP3A5, pour lequel certains variants alléliques entraîneraient des modifications d'effet. ⁸⁸ D'autres gènes candidats ont également été mis en évidence comme la CES1 (carboxylestérase 1) pour le dabigatran, le CYP2J2 pour les anti-Xa, les SULT1A1 et SULT1E1 pour l'apixaban. ^{89,90}

I.4.2 Interactions Médicamenteuses

Compte-tenu d'une marge thérapeutique étroite et des effets indésirables potentiellement graves, le praticien doit se préoccuper particulièrement des nombreuses interactions médicamenteuses avec les AVK. Plusieurs mécanismes d'interactions médicamenteuses

ont été décrites pour la warfarine principalement mais peuvent être étendues aux autres AVK.⁹¹⁻⁹³ Le tableau 2 reprend ces différentes interactions.⁹²

Tableau 2 : Traitements et aliments à forte probabilité d'interaction avec les AVK⁹²

Causalité	Potentialisateur	Inhibiteur
Haute probabilité	Acetaminophen	Barbituates
	Alcohol (if concomitant liver disease)†	Carbamazepine†
	Amiodarone†	Chlordiazepoxide†
	Anabolic steroids†	Cholestyramine†
	Boldo-fenugreek Cimetidine†	Etodolac‡ (N = 18)
	Ciprofloxacin‡ (n = 34)	Griseofulvin†
	Citalopram‡(n=12)	Mercaptopurine
	Clofibrate†	Mesalamine
	Cotrimoxazole†	Nafcillin†
	Diltiazem‡ (n = 20)	Ribavirin
	Entacapone‡(n=12)	Rifampin†
	Erythromycin†	Sucralfate†
	Fenofibrate	Trazodone
	Fish oil	High vitamin K content foods/enteral feeds†
	Fluconazole†	Large amounts of avocado
	Isoniazid†	
	Mango	
	Metronidazole†	
	Miconazole oral gel†	
	Miconazole vaginal suppositories	
	Omeprazole†	
	Phenylbutazone†	
	Piroxicam†	
	Propafenone†	
	Propranolol†	
	Quilnggao	
	Sertraline‡(n = 12)	
	Sulfipyrazone (biphasic with later inhibition)†	
	Voriconazole‡(n=17)	
	Zileuton‡	

†Data de review de 1994.⁹⁴ ‡Médicaments et aliments dont l'évidence est basée sur des essais randomisés et contrôlés avec entre parenthèse le nombre de patients inclus

Les interactions médicamenteuses des AODs semblent moins importantes que celles avec les AVK. Cependant, ces interactions semblent dépendre de deux cibles : celle mettant en jeu la P-gp et celle concernant le CYP3A4.⁹⁵⁻⁹⁷ Les principales interactions médicamenteuses avec le dabigatran sont représentés dans le Tableau 3 et celles avec le Rivaroxaban ou l’apixaban dans le Tableau 4.

Tableau 3 : Interactions médicamenteuses cliniquement significatives avec le Dabigatran

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Médicaments	Aire sous la courbe des concentrations plasmatiques	Recommandations
Kétoconazole Ciclosporine Itraconazole Tacrolimus	Augmentation 150%	Contre-indication Absolue
Amiodarone Quinidine Vérapamil	<u>Augmentation de 60%</u> <u>Augmentation de 50%</u> <u>Augmentation de 70-150%</u>	Réduction de dose
Clarithromycine	<u>Augmentation de 2%</u>	Surveillance
Rifampicine Millepertuis Carbamazépine Phénytoïne	<u>Diminution de 70%</u>	A éviter

Tableau 4 : Interactions médicamenteuses cliniquement significatives avec le Rivaroxaban et l'Apixaban ⁷⁴

Médicaments	Aire sous la courbe des concentrations plasmatiques		Recommandations
	Rivaroxaban	Apixaban	
Kétoconazole Ritonavir Antiprotéase Itraconazole Voriconazole Posaconazole	Augmentation 160% Augmentation 150%	Augmentation de 100%	A éviter
Clarithromycine Erythromycine Diltiazem	Augmentation 50% Augmentation 30%	Augmentation 40%	Aucune recommandation
Rifampicine Millepertuis Carbamazépine Phénytoïne	Diminution de 50%	Diminution de 54%	Précautions d'emploi

I.4.3 Autres facteurs

I.4.3.1 Fonction Rénale

La fonction rénale est un paramètre important de surveillance à mettre en place dans le suivi thérapeutique des patients sous anticoagulants étant donné la prépondérance de l'élimination urinaire.

Ainsi, pour les AVK, une insuffisance rénale sévère définie par un Clcreat < 20 ml/min peut entraîner un déséquilibre thérapeutique.⁵¹

De même, pour les AOD, la fonction rénale doit être évaluée avant l'initiation du traitement. En effet, le Dabigatran est éliminé pour 85% sous forme inchangée dans les urines avec une exposition au traitement de 2.7 et 6 en cas, respectivement, d'insuffisance rénale modérée ou sévère.⁹⁸ Pour le Rivaroxaban, l'augmentation des concentrations plasmatiques sera de 1.4, 1.5 et 1.6 en cas, respectivement, d'une insuffisance rénale légère, modérée ou sévère.⁹⁶ L'élimination rénale du rivaroxaban n'est que de 33% sous forme active mais il faudra tout de même une adaptation posologique en cas d'insuffisance rénale modérée ou sévère.⁹⁶ Pour l'Apixaban, l'augmentation des concentrations plasmatiques est de 16%, 29% et 44% en cas, respectivement, d'une insuffisance rénale légère, modérée ou sévère.⁹⁷ L'élimination rénale de l'Apixaban n'est que de 25% entraînant une adaptation posologique uniquement en cas d'insuffisance rénale sévère. Un exemple des adaptations de posologies d'AOD à réaliser en cas d'insuffisance rénale dans l'indication de la fibrillation atriale est représenté dans Tableau 5.

Tableau 5: Recommandations des posologies d'AOD selon la fonction rénale lors de la prévention des AVC et embolies systémiques dans la Fibrillation atriale.⁷⁴

	CICr I 15 ml/min	CICr 15 à 30 ml/min	CICr 30 à 50 ml/min	CICr L 50 ml/min
Dabigatran	Contre-indiqué	Contre-indiqué	150 mg 2 x/jour ou 110 mg 2 x/jour b	150 mg 2 x/jour
Rivaroxaban	Contre-indiqué	15 mg/jour	15 mg/jour	20 mg/jour
Apixaban	Contre-indiqué	2,5 mg 2 x/jour	5 mg 2 x/jour ou 2,5 mg 2 x/jour c	5 mg 2 x/jour

CICr : clairance de la créatinine ; a peu de données cliniques, utiliser avec prudence ; b pour les patients à risque élevé de saignement : âge M 80 ans, traitement par vérapamil, association de plusieurs facteurs de risque hémorragiques ; c pour les patients à risque élevé de saignement : âge M 80 ans ou poids m 60 kg

I.4.3.2 Age

L'âge semble être un facteur de variabilité fréquemment retrouvé avec une augmentation du taux d'hémorragie grave selon l'âge (13.8% pour les patients de plus de 80 ans vs. 4.75% pour les moins de 80 ans).⁹⁹

En effet, pour les AVK, un âge supérieur à 75 ans semble clairement majorer le risque d'hémorragie intra-crânienne.¹⁰⁰ De plus, pour un même niveau d'anticoagulation, les posologies d'AVK nécessaire chez le sujet âgé semblent plus faible.^{101,102}

Concernant les AODs, l'âge semble augmenter l'exposition du dabigatran par rapport aux patients jeunes de 40 à 60% nécessitant une adaptation de la posologie chez les sujets de plus de 75 ans.⁹⁵ Une étude menée chez les sujets âgés de plus de 65 ans, montrait une aire sous la courbe du dabigatran augmentée d'un facteur de 1,7 chez les femmes et de 2 chez les hommes comparativement aux sujets jeunes.⁹⁸ De même, les patients âgés, sous rivaroxaban ou apixaban, semblent présenter une augmentation des concentrations plasmatiques de 30 à 50% sans qu'une adaptation posologique ne soit nécessaire en fonction de l'âge.^{97,103}

I.4.3.3 Poids extrêmes

Un poids inférieur à 60 kg semble diminuer la concentration résiduelle des AODs de 20 à 30%. Si, pour le dabigatran et le rivaroxaban, aucune adaptation posologique n'est nécessaire, pour l'apixaban il est requis de diminuer la posologie en cas de poids inférieur à 60 kg si d'autres facteurs de risque sont associés.⁹⁷

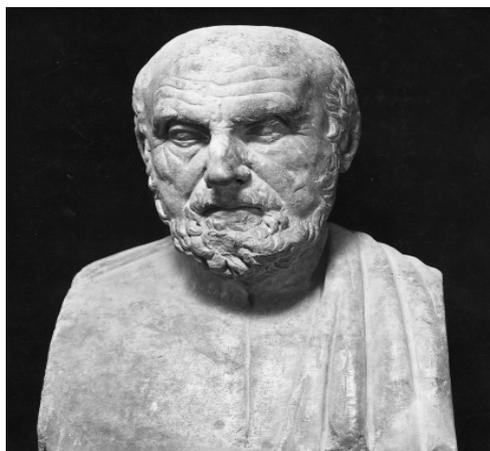
I.5 Médecine personnalisée

Devant ces nombreux facteurs pouvant influencer le risque hémorragique chez des patients sous anticoagulants oraux, le concept de médecine personnalisée pourrait avoir un impact favorable dans la prise en charge globale de ce type de patients. Le principe serait qu'il y a différents profils de patients comme différents profils d'hémorragies et qu'on ne peut appliquer des règles généralistes alors même que chaque cas est unique.

Hippocrate (**Figure 5**), né en 460 avant. J.-C. dans l'île de Cos et mort en 370 av. J.-C. à Larissa, est un médecin grec du siècle de Périclès, mais aussi un philosophe, et traditionnellement considéré comme le « père de la médecine », était un partisan de la médecine personnalisée. Il a notamment écrit sur «l'individualité» de la maladie et l'importance de la prescription de médicaments «différents» pour les patients «différents», il a déclaré : « *Il est beaucoup plus important de savoir quelle personne a la maladie, plutôt que de savoir quelle maladie a la personne* ». Hippocrate a également évalué plusieurs facteurs, tels que : la stature, l'âge et la constitution d'un patient, ainsi que la période de l'année pour aider à prendre ses décisions lorsqu'il prescrivait des traitements.

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Figure 5 : Buste d'Hippocrate



Le principe de la médecine personnalisée moderne a débuté avec les découvertes réalisées dans les domaines de la génétique, de la pharmacogénétique et génomique. Ce principe de personnalisation pourrait permettre la réduction des effets secondaires sévères de plus en plus nombreux et coûteux. En effet, les articles publiés sur ce sujet ont fortement augmenté ces dernières années grâce notamment à la médecine moléculaire, au diagnostic moléculaire et aux besoins médicaux réels.¹⁰⁵ Un rapport de la Fondation européenne de la science a d'ailleurs souligné que la médecine dite « personnalisée » sera amenée à jouer un rôle de plus en plus important dans le système de santé futur car elle représente « *une nouvelle approche pour classier, comprendre, traiter et prévenir les maladies sur la base de données et d'information prenant en compte les différences biologiques et environnementales entre les individus* ».¹⁰⁶ Face à cette promesse de faire de chaque traitement un traitement unique à chaque patient, certains rappellent que la médecine personnalisée serait également « *une capacité accrue de classer les individus en sous-groupes qui diffèrent dans leur susceptibilité de contracter une maladie donnée ou de répondre à une thérapie spécifique* ».¹⁰⁷ Certains spécialistes préfèrent d'ailleurs parler de « médecine stratifiée » du fait que l'approche moléculaire n'apporte qu'un complément d'information aux autres facteurs de risque utilisés permettant de dire que la génomique n'est pas suffisante.¹⁰⁸⁻¹¹⁰ Finalement, le principe de médecine personnalisée est souvent décrit comme « le bon patient avec le bon traitement à la bonne dose et au bon moment ».

II. Hypothèse et objectifs

II.1 Hypothèse

Comme nous l'avons vu précédemment les accidents hémorragiques sous anticoagulants sont des événements peu fréquents, pouvant être dus à des interactions médicamenteuses ou à d'autres facteurs, qu'ils soient génétiques ou cliniques, inhérents au patient. La compréhension de ces événements et de ces différents facteurs hémorragiques nécessite l'utilisation de registres avec un nombre important de patients pour permettre une analyse conduisant à une médecine, ou thérapeutique, personnalisée.

Le challenge le plus difficile reste à appliquer les résultats de cette médecine personnalisée pour améliorer la prise en charge des patients au niveau clinique. En effet, de nombreux praticiens ne sont pas prêts à intégrer les tests génétiques dans leur pratique quotidienne. Cette conclusion tient au fait qu'il n'y a pas encore de méthode précise permettant d'appliquer ces données pour améliorer les traitements. Une des pistes pour intégrer cette médecine personnalisée serait donc le versant « stratifié » de cette médecine par l'identification de sous-groupes de patients pouvant bénéficier d'un traitement adapté, personnalisable en fonction de différents facteurs cliniques facilement identifiable par le praticien dans sa pratique quotidienne.

Or, les données méthodologiques utilisées en recherche clinique sont basées sur les essais cliniques randomisés et contrôlés considérés comme la meilleure méthodologie pour montrer l'efficacité et la sécurité d'un traitement.¹¹¹ Les méta-analyses, souvent basées sur ces essais cliniques randomisés et contrôlés, participent à la conception d'une structuration du raisonnement clinique par l'Evidence Based Medicine. Or depuis quelques années, cette vérité, même issue d'une très bonne méthodologie, semble être

remise en doute.¹¹² Ainsi, certaines recommandations issues de l'Evidence Based Medicine nous ont éloigné de la problématique d'une prise en charge du patient dans sa globalité car ces recommandations ne prennent pas en compte les problématiques fréquentes liées à la poly-pathologie et la comorbidités des patients issue du vieillissement de la population.¹¹³ A ce titre les décideurs (notamment pour l'accord de mise sur le marché d'un produit) souhaite de plus en plus des informations issues de la vraie vie afin de créer une complémentarité entre ces données de vraie vie et les données issues des essais randomisés.¹¹⁴ Ces données de vie réelle sont toutes les données collectées en dehors des essais randomisés et contrôlés.¹¹⁵ L'ISPOR (International Society for Pharmacoeconomics and Outcomes Research, www.ispor.org) distingue ainsi les registres et cohortes, les bases de données administratives, les données complémentaires des essais randomisés, les essais pragmatiques, les enquêtes de santé et les données informatisées issues du dossier patient.

En effet, si nous prenons l'exemple de la maladie thrombo-embolique veineuse, les aspects contemporains de sa présentation, de sa prise en charge et des événements sont sous-étudiés. Les études épidémiologiques publiées sont généralement limitées par la petite taille, l'âge des données^{116,117} ou le manque de données cliniques détaillées.^{118,119} Les essais cliniques sont confrontés à la nécessité de fournir une base de donnée adéquate, avec des problèmes éthiques et de faisabilité limitant le recrutement de certains patients présentant certaines particularité importantes comme une instabilité hémodynamique ou des risques hémorragiques trop important,¹²⁰ et une sous-représentation de nombreux sous-groupes clés (comme les personnes âgées, les patientes enceintes, et ceux qui ont un risque élevé de saignement) qui limitent la validité et la généralisation des résultats.¹²¹ Ces constatations ont entraînés un besoin impératif grandissant pour les preuves apportées par de grandes cohortes de patients sans critères d'exclusions importants.¹²² Une information en temps réel permettant de caractériser la présentation, le profil des facteurs de risque, le traitement et les résultats

des patients peut donner une information sur les pratiques ; prévenir les dommages inutiles et apporter des hypothèses nouvelles pour la recherche future afin d'améliorer la qualité et les résultats.¹²³⁻¹²⁶

De même, il est à noter que les sites hémorragiques retrouvés dans la vraie vie semblent différents de ceux issus des études princeps des anticoagulants avec une sous-évaluation de ces « outcomes » hémorragiques du fait d'une sur-sélection des patients. Ceci vient également du fait de définitions différentes concernant les hémorragiques graves selon qu'elles soient nationales (HAS 2008)^{127,128} ou internationales (ISTH)¹²⁹.

De plus, le terme d'hémorragie cliniquement pertinente (« Clinically relevant non major bleeding ») introduit récemment dans de nombreux essais cliniques n'a pas été clairement défini et peut également entraîner une confusion lors de l'analyse et de l'interprétation des résultats du fait de critères différents selon les essais.¹³⁰

L'hypothèse de ce travail de thèse est que l'utilisation et l'analyse de registre de « vraie vie » sur le thème des accidents hémorragiques sous anticoagulants pourrait permettre de définir des « profils » de patient concernant ce risque hémorragique. L'identification de certains profils de patients permettrait ainsi de pouvoir envisager une prise en charge des patients n'ont pas généraliste mais personnalisée.

II.2 Objectifs

L'objectif de ce travail de thèse était donc d'évaluer différents profils cliniques de patients en ce qui concerne leur risque hémorragique ainsi que différents profils hémorragiques en s'aidant de deux registres de vraie vie, le registre RIETE et le registre RATED.

III. Matériels et Méthodes

III.1 Le registre RATED (Registry of patient with Antithrombotic agents admitted to an Emergency Department)

Ce registre RATED est un registre monocentrique, observationnel créé au sein du service des urgences adultes du CHU de Clermont-Ferrand et en cours depuis janvier 2014, incluant les patients consécutifs sous antithrombotique à leur admission au sein des urgences et ce quel que soit le motif d'admission (NCT02706080)¹³¹

Les praticiens du service et investigateurs mettent en œuvre tous les efforts nécessaires à l'inclusion de ces patients consécutifs lors de leur prise en charge médical. Toutes les données sont recueillies dans un CRF électronique inclus dans le dossier patient informatisé sur le logiciel Urqual (**Figure 8**). Les données suivantes sont recueillis de manière systématiques : présentation clinique, caractéristiques cliniques du patient à son arrivée, antécédents, facteurs de risque hémorragique communément décrit dans la littérature (âge, antécédents d'hémorragie digestive, antécédents d'AVC, insuffisance rénale, anémie, thrombopénie, insuffisance hépatique, cancer, hypertension artérielle, démence, alcool)¹³², la réalisation d'une imagerie, les données biologiques à l'arrivée du patient, le type d'antithrombotique (indication, durée de traitement, molécule et dose) et les traitements associés.

Figure 8 : Capture d'écran du CRF électronique du registre RATED

RATED

Administratif

Date et heure arrivée aux urgences: 25/11/2015 10:57

Identité patient: [REDACTED]

Tel patient: [REDACTED]

Poids du patient: [REDACTED]

Médecin traitant: Recherche

Mode d'entrée au BE (GAM): URGENCE ACCID VOIE PUBLIQUE

Type d'admission au BE (GAM): [REDACTED]

Mode de transport au BE (GAM): 10POMPIER

Prise en Charge durant le Transport: (PARAMED) PEC Para-Médicalisé

Admission

Motif(s) de la Consultation: (0503) suspicion de traumatisme crânié sans perte de connaissance

Score de gravité: [REDACTED]

Hémorragie: Oui Non

Type d'accident hémorragique: [REDACTED]

Antécédents

Infarctus du myocarde	Oui <input type="radio"/> Non <input type="radio"/>	Insuffisance hépatocellulaire	Oui <input type="radio"/> Non <input type="radio"/>
Hypertension artérielle	Oui <input type="radio"/> Non <input type="radio"/>	Cancer	Oui <input type="radio"/> Non <input type="radio"/>
Diabète	Oui <input type="radio"/> Non <input type="radio"/>	Arythmie par fibrillation auriculaire	Oui <input type="radio"/> Non <input type="radio"/>
Ulcère gastroodéal	Oui <input type="radio"/> Non <input type="radio"/>	Accident Vasculaire Cérébral	Oui <input type="radio"/> Non <input type="radio"/>
Hémorragie digestive	Oui <input type="radio"/> Non <input type="radio"/>	Démence	Oui <input type="radio"/> Non <input type="radio"/>
Exogénose	Oui <input type="radio"/> Non <input type="radio"/>	Hémorragie sous Anti-Thrombotique	Oui <input type="radio"/> Non <input type="radio"/>
Insuffisance coronarienne	Oui <input type="radio"/> Non <input type="radio"/>	MTEV	Oui <input type="radio"/> Non <input type="radio"/>
Autres ATCD	[REDACTED]	Artériopathie	Oui <input type="radio"/> Non <input type="radio"/>

Autres ATCD: [REDACTED]

Constantes hémodynamiques

Glasgow: 15

Spontanée: (4) Spontanée

Adaptée: (5) Adaptée

A la demande: (6) A la demande

Biologie

Accès restab		Accès restab	
Créatininémie (micromol/l)	[REDACTED]	Plaquettes (GR)	[REDACTED]
Urée (mmol/l)	[REDACTED]	Hématocrite (%)	[REDACTED]
CRP (mg/l)	[REDACTED]	Hémoglobine (g/l)	[REDACTED]
PCT (microg/l)	[REDACTED]	Facteur V	[REDACTED]
Troponine (ng/ml)	[REDACTED]	Facteur II	[REDACTED]
Taux prothrombine(%)	[REDACTED]	Facteur X	[REDACTED]
Temps céphaline activée (ratio)	[REDACTED]	INR	[REDACTED]
Fibrinogène(g/dl)	[REDACTED]	Dosage Pondéral Nouv Anticoag (ng/ml)	[REDACTED]
D-Dimère (microg/ml)	[REDACTED]	Protidémie (g/l)	[REDACTED]
Bilirubine libre (U/L)	[REDACTED]	ASAT (U/L)	[REDACTED]
ALAT (U/L)	[REDACTED]	GGT (U/L)	[REDACTED]
Phosphate alcaline (U/L)	[REDACTED]	VGM (en FI)	[REDACTED]

Prise en charge

Nb culot globulaires reçus: [REDACTED]

Nb de concentrés plaquettaire reçus: [REDACTED]

Nb de plasma frais reçus: [REDACTED]

Complexe pro-thrombinique reçu: Oui Non

Felba reçu: Oui Non

Vitamine K reçu: Oui Non

Embolisation: Oui Non

Modif TT antithrombotique: Oui Non

Imagerie

Image	Réalisation	Injection	Date Heure
Scanner abdomino-pelvien	Oui <input type="radio"/> Non <input type="radio"/>	Oui <input type="radio"/> Non <input type="radio"/>	[REDACTED]
Scanner cérébral	Oui <input type="radio"/> Non <input type="radio"/>	Oui <input type="radio"/> Non <input type="radio"/>	[REDACTED]
Echographie Abdominale	Oui <input type="radio"/> Non <input type="radio"/>	Oui <input type="radio"/> Non <input type="radio"/>	[REDACTED]
Echographie cardiaque	Oui <input type="radio"/> Non <input type="radio"/>	Oui <input type="radio"/> Non <input type="radio"/>	[REDACTED]
Scanner thoracique	Oui <input type="radio"/> Non <input type="radio"/>	Oui <input type="radio"/> Non <input type="radio"/>	[REDACTED]

III.2 Le registre RIETE (Registro Informatizado Enfermedad TromboEmbolica)

Ce registre est un registre prospectif multicentrique et international en cours (NCT02832245), conçu pour répondre à la nécessité de données de vraie vie non disponibles à l'aide de données représentatives provenant de plusieurs centres. Lancé en Espagne en 2001, RIETE compte actuellement 179 centres dans 24 pays et a inscrit plus de 72 000 patients (**Figure 6**). RIETE a contribué à caractériser le modèle de présentation et les événements lors de la MTEV, y compris dans l'analyse de différents sous-groupes. RIETE a récemment été élargi pour recueillir des données sur les résultats à long terme et a élargi son critère d'inclusion pour inscrire d'autres formes de thrombose veineuse (comme la thrombose des veines cérébrales et la thrombose veine splanchnique) (**Figure 7**). La plate-forme RIETE est également utilisée pour mener des études d'efficacité comparatives pragmatiques, y compris des essais randomisés. Les étapes futures porteraient sur la collaboration avec des centres supplémentaires à travers le monde et sur les efforts visant à assurer la qualité et l'expansion du registre. En conclusion, RIETE est un vaste registre permanent de patients atteints de MTEV et d'autres conditions thrombotiques. Ses résultats pourraient être utiles pour améliorer notre compréhension de l'épidémiologie, les modes de soins et les événements des patients atteints de maladie thrombotique. Plusieurs des études obtenues ont permis de mieux comprendre l'épidémiologie^{133,134}, des modes de traitement courants,^{135,136} et des résultats^{137,138} de patients atteints de MTEV et des sous-groupes cliniques clés non étudiés¹³⁹⁻¹⁴¹.

Dans ce registre, les complications hémorragiques ont été classées comme « majeures » si elles étaient déclarées comme telle et nécessitaient une transfusion

de deux unités de sang ou plus, ou rétro-péritonéales, rachidiennes ou intracrâniennes, ou lorsqu'elles entraînaient le décès. Les saignements non majeurs ont été définis comme tout saignement manifeste nécessitant une assistance médicale mais ne remplissant pas les critères de saignement majeur. Les saignements mortels ont été définis comme tout décès survenant dans les 10 jours suivant un épisode de saignement majeur, en l'absence d'une autre cause de décès.

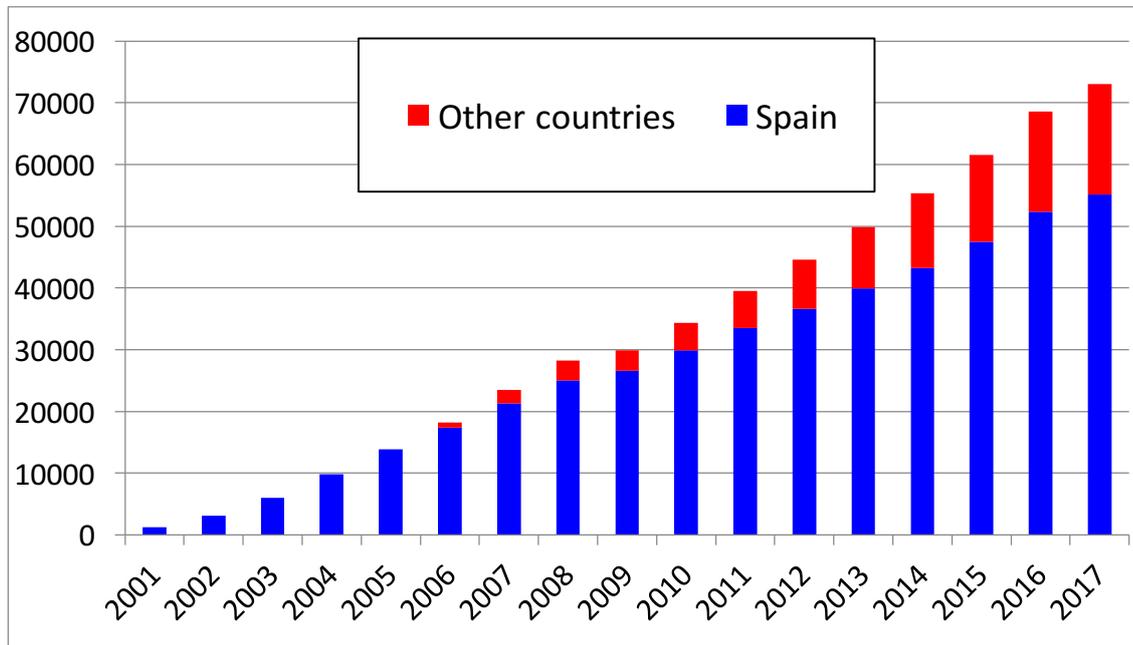
Compte-tenu du nombre important de profils cliniques rencontrés chez les patients sous anticoagulants du fait de patients polypathologiques, nous nous sommes concentrés sur l'analyse de certains profils particuliers illustrant l'importance du site hémorragique ou de certains facteurs cliniques.

Figure 6 : Représentation des centres participants à RIETE en 2001 et 2017

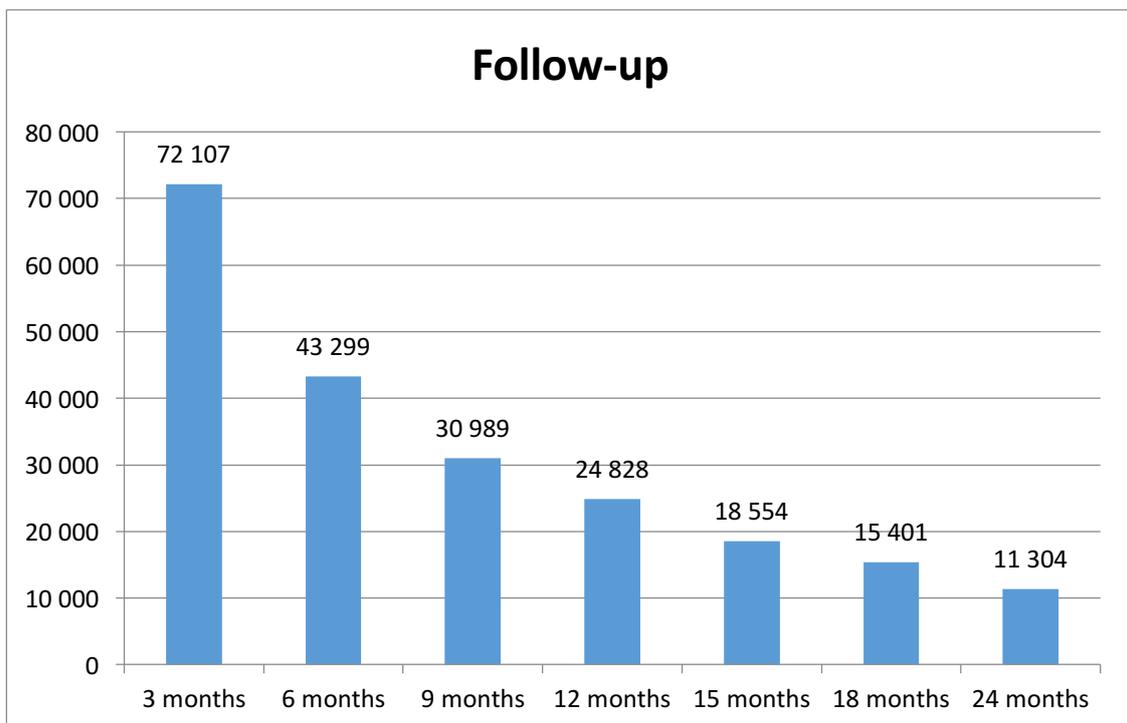


Figure 7 : Nombre cumulé de patients inclus au fil des années (A) et nombre de données disponibles concernant la durée de suivi (B)

A)



B)



IV. Résultats

IV.1 Caractéristiques des patients présentant une hémorragie sous anticoagulant

IV.1.1 Exemple à partir d'un registre monocentrique

Nous présentons ici un exemple de données apportées par un registre monocentrique (RATED) qui présente l'avantage d'avoir un recueil de certains paramètres biologiques que le registre RIETE ne pouvait fournir. Ci-dessous, nous avons pu utiliser un item particulier de ce registre comme la L-Thyroxine afin d'évaluer l'impact de ce traitement sur le risque hémorragique des patients sous AVK.

Assessment of the Impact of L-Thyroxine Therapy on Bleeding Risk in Patients Receiving Vitamin K Antagonists (Clinical Drug Investigation, Annexe 6)¹³¹

Dans cette étude, nous avons réalisé une analyse des patients sous AVK inclus dans le registre RATED entre janvier 2014 et juin 2015. Nous avons ainsi pu avoir une description des patients sous AVK ayant présenté une hémorragie à leur arrivée aux urgences. L'hémorragie grave était définie par les critères ISTH¹²⁹ (entraînant le décès, saignement dans un organe critique, saignement nécessitant la transfusion de 2 ou plus de culots globulaires).

Nous avons pu recruter 1454 patients sous AVK dont 83 (5.7%) hémorragies graves. Cette étude nous a permis de décrire les caractéristiques de la population sous AVK en générale (**Tableau 6**) en montrant une population âgée (77.6 +/- 13.4 ans) dont 85% des patients avaient plus de 65 ans avec une créatininémie élevée (109.9 +/- 93.6 $\mu\text{mol/l}$). Nous avons également pu décrire les caractéristiques des patients ayant présentés une hémorragie sous AVK montrant que 87% des patients avaient plus de 65 ans avec une prédominance des femmes (54.2%) et un HASbled > 3 dans 31% des cas. Nous avons également pu analyser le type d'hémorragie grave et non grave (**Tableau 7**) intéressant, respectivement, 5.7% (N=83) et 15.5% (N=225) de la population avec seulement 35 (2.4%) patients ayant une hémorragie gastro-intestinale et 10 (0.7%) patients ayant une hémorragie intracrâniennes.

- Discussion et conclusion

Nous notons, dans nos limites d'étude, le caractère observationnel du registre qui ne permettait que de générer des hypothèses et non des conclusions fortes. Pour ces raisons, les résultats ne permettaient pas d'apporter une décision thérapeutique forte pour le clinicien. De plus, le caractère monocentrique du registre, s'il permettait une certaine homogénéité des pratiques, ne permettait pas de généraliser les résultats à d'autres centres de soin. Cependant le registre RATED fournit des informations précieuses et des idées du fait de sa population de patients non sélectionnée, contrairement aux conditions rigoureusement contrôlées des études cliniques randomisées. Il peut donc aider à identifier des facteurs associés à un bon ou mauvais pronostic, fournir également des renseignements de situations cliniques de vie réelle, qui peut être précieux pour la réalisation de futurs essais cliniques randomisés.

Tableau 6 : Caractéristiques clinico-biologiques des patients sous AVK (N=1454) et de ceux ayant présenté une hémorragie sous AVK (N=83)

	Total (N =1454)	Total (N =83)
Age, mean ± sd	77.6±13.4	78.3±13.3
Age > 65 years, n (%)	1231 (85)	72 (86.7)
Male gender, n (%)	738 (50.7)	38 (45.8)
SBP (mmHg), mean ± sd	139.8±27.1	133.1±29.1
Type of VKA		
Acenocoumarol, n (%)	126 (8.7)	8 (9.6)
Warfarin, n (%)	308 (21.2)	24 (28.9)
Fluindione, n (%)	982 (67.5)	49 (59.0)
Indication of VKA		
Atrial fibrillation, n (%)	522 (35.9)	30 (50.8)
VTE, n (%)	151 (10.4)	12 (20.3)
Mechanical valve, n (%)	77 (5.3)	5 (8.5)
Stroke, n (%)	42 (2.9)	3 (5.1)
Ischemic heart disease, n (%)	87 (6.0)	6 (10.2)
Other, n (%)	74 (5.1)	3 (5.1)
Concomitant disease		
Hypertension, n (%)	775 (53.3)	44 (56.4)
Coronary syndrome, n (%)	235 (16.2)	12 (15.6)
Myocardial Infarct, n (%)	206 (14.2)	11 (14.3)
Stroke, n (%)	232 (15.9)	12 (15.9)
Cancer, n (%)	194 (13.3)	15 (19.7)
Chronic alcoholism, n (%)	58 (4.0)	4 (5.2)
Diabetes, n (%)	347 (23.9)	19 (24.4)
Gastrointestinal ulcer, n (%)	37 (2.5)	3 (3.9)
Gastrointestinal bleeding, n (%)	13 (0.9)	1 (1.3)
Dementia, n (%)	101 (6.9)	9 (12.0)
Laboratory values at admission		
Creatinine (µmol/l), mean ± sd	109.9±93.6	91.8±41.3
INR, mean ± sd	3.4±2.4	4.5±6.2
Platelet (G/l), mean ± sd	237.2±88.6	256.4±95.1
Hb (g/dl), mean ± sd	12.9±2.3	11.4±3.1
Anemia, n(%)	442 (30.4)	38 (45.8)
HASBLED, mean ± sd	1.97±1.02	1.92±1.02
HASBLED >= 3, n (%)	369 (25.4)	22 (31.0)

Abbreviations: SBP, Systolic Blood Pressure; VKA, vitamin K antagonist; VTE, venous thromboembolism; sd, standard deviation, INR: international normalized ratio

Tableau 7 : Type d'hémorragies graves et non graves survenues sous AVK

	Total N =1454
Hémorragie, n (%)	225 (15.5)
Gastrointestinal bleeding, n (%)	35 (2.4)
Intracranial bleeding, n (%)	10 (0.7)
Intramuscular bleeding, n (%)	27 (1.9)
Nosebleed, n (%)	58 (4.0)
Others, n (%)	79 (5.4)
Major bleeding, n (%)	83 (5.7)

IV.1.2 Intérêt de la biologie

Le fait que les données biologiques soient plus facilement recueillies dans un registre monocentrique, nous a permis de nous intéresser aux données biologiques jouant un rôle dans l'hémostase d'un patient sous anticoagulant et pouvant influencer le risque hémorragique. Or, les anticoagulants ont un impact direct sur les facteurs de coagulation (facteurs II, VII, IX et X pour les AVK et Xa pour les AOD entre autre). Il nous est donc apparu important de mesurer la valeur de ces facteurs afin d'analyser l'éventuel impact sur les événements hémorragiques.

Comparison of blood coagulation factors between patients with gastrointestinal or intracranial bleeding under vitamin K antagonist (European Journal of Internal Medicine, Annexe 1)¹⁵⁵

Cette étude nous a permis d'analyser la perte des facteurs de coagulation en comparant des patients présentant une spoliation sanguine importante sous anticoagulants (hémorragie digestives) *versus* des patients avec une spoliation sanguine moins importante (hémorragie intracrânienne). En effet, ces deux types d'hémorragie sont reversées à l'heure actuelle de la même manière, sans prise en compte de la spoliation en facteur de coagulation, par concentré de complexe prothrombinique (25UI/kg ou selon INR) en association avec de la vitamine K.¹⁵²⁻¹⁵⁴

L'effet du traitement par AVK sur les niveaux de facteur procoagulant est bien connu, entraînant une diminution de FII, FVII, FIX, FX et des protéines C et S, mais aucune diminution du fibrinogène, du FV, du FVIII, du FXI ou de l'antithrombine. Cependant, seules quelques études ont étudiées les facteurs de coagulation lors d'accidents hémorragiques sous AVK et une compréhension plus claire des pertes de facteurs de coagulation propres à chaque type de saignement nous permettra d'optimiser les traitements de réversion actuellement recommandés en les adaptant au type de saignement et au volume de sang perdu. Avec cette étude, nous avons cherché à comparer les niveaux de facteurs de coagulation sanguine chez les patients recevant des AVK et présentant des saignements gastro-intestinaux ou intracrâniens graves.

Dans cette étude rétrospective, nous avons analysé les patients de plus de 18 ans, traités par AVK, reversés par PCC hémorragie digestive ou une hémorragie intracrânienne et admis dans notre service d'urgence du 1^{er} janvier 2010 au 31 décembre 2011.

- Résultats

155 patients ont été inclus dans cette étude : 88 avec un saignement gastro-intestinal et 67 avec un saignement intracrânien (**Tableau 10**). L'INR moyen avant réversion était de 4,67 +/- 3,11 pour le groupe saignement gastro-intestinal et de 2,88 +/- 1,89 pour le groupe saignement intracrânien, avec une différence statistiquement significative ($p < 0,001$). Nous avons également observé une différence significative concernant le TCA entre les patients atteints de saignements gastro-intestinaux et ceux atteints de saignements intracrâniens, respectivement, $1,98 \pm 0,93$ et $1,56 \pm 0,54$ respectivement ($p < 0,001$). Les niveaux FII, FV et FX ont également été significativement plus faibles chez les patients admis pour un saignement gastro-intestinal.

Tableau 10. Niveau des facteurs de coagulation des patients présentant une hémorragie intracrânienne ou gastro-intestinale sous AVK.

	Intracranial bleedings (n=67)	Gastrointestinal bleedings (n=88)	p-value
Demographic characteristics			
Male, n (%)	40 (59.7%)	42 (47.7%)	0.14
Age, years, mean (standard deviation)	77.6 (10.7)	79.0 (19.2)	0.39
INR. n			
Global mean \pm SD	2.88 \pm 1.89	4.67 \pm 3.11	<0.001
Mechanical valve mean \pm SD(n)	2.3 \pm 0.3 (2)	3.9 \pm 2.1 (11)	0.299
No Mechanical Valve mean \pm SD(n)	2.9 \pm 1.92 (63)	4.8 \pm 3.2 (73)	<0.001
aPTT ratio. n			
mean \pm SD	1.56 \pm 0.54	1.98 \pm 0.93	<0.001
Blood coagulation factors. n			
Factor II (%)	19.6 \pm 10.7	11.6 \pm 7.3	0.009
Factor V (%)	107.7 \pm 26.7	91.1 \pm 23.8	0.030
Factor X (%)	10.7 \pm 5.30	6.5 \pm 8.6	0.028
Fibrinogen (g/L). n	66	87	0.74
mean \pm SD	4.41 \pm 1.25	4.33 \pm 1.48	

- Discussion et conclusion

Les résultats de cette étude suggèrent que la perte de sang total, comprenant les globules rouges et les facteurs de coagulation sanguins, est plus élevée chez les patients atteints de saignements gastro-intestinaux graves par rapport à ceux atteints de saignements intracrâniens sous AVK. Nous avons observé, dans le groupe de

saignement gastro-intestinal, des niveaux inférieurs de facteurs dépendants de la vitamine K (FII, FVII, FIX et FX), avec des INR plus élevés, ne pouvant être causés uniquement par l'effet de l'anticoagulation puisque le facteur V (un facteur indépendant de la vitamine K) était également inférieur. La diminution du facteur V peut être expliquée par le fait que le saignement gastro-intestinal peut ne pas être symptomatique pendant une longue période avant que le patient ne devienne symptomatique, avec des micro-saignements et une perte de sang, alors que les symptômes du saignement intracrânien se manifestent immédiatement.

Nos résultats ont soulevé des doutes quant à la gestion de la réversion, telle qu'elle est actuellement proposée, car nous pensons qu'un taux d'INR normalisé peut ne pas être suffisant pour évaluer l'impact sur la mortalité.

Sarode et al. a montré que, même si la réduction de l'INR était plus rapide avec le PCC qu'avec le plasma frais congelé, il n'y avait aucune différence dans l'hémostase effective ou le décès quelle que soit la catégorie de saignement.¹⁵⁶ Ainsi, éviter tout retard avant la réversion est l'une des solutions pour le saignement intracrânien.¹⁵⁷ Alors que pour les saignements gastro-intestinaux, la solution pourrait être une thérapie plus agressive avec une hémostase plus rapide, ou, du fait de la diminution significative des facteurs dépendants et indépendants de la vitamine K, une correction d'autres facteurs de la coagulation à l'aide de plasma frais congelé, en raison de la perte sanguine, ou avec des facteurs de coagulation activés (FVIIa ou FEIBA) ou d'autres composés présentant des effets pro-hémostatiques.¹⁵⁸

Outcome of patients with venous thromboembolism and Factor V Leiden or Prothrombin 20210 carrier mutations during the course of anticoagulation (The American Journal of Medicine, Annexe 2)¹⁵⁹

Cette étude s'est intéressée aux patients porteurs d'un facteur V Leiden ou d'une mutation sur la prothrombin 20210 et son impact sur le risque hémorragique.

Les individus atteints de la mutation du facteur V Leiden (FVL) ou de la prothrombine G20210A (PTM) présentent un risque plus élevé de développer une MTEV. Ces mutations sont fréquemment recherchées chez les patients présentant une MTEV et sont donc communément recueillies dans le registre multicentrique RIETE. Cependant, l'influence de ces polymorphismes sur les différents événements du patient au cours du traitement anticoagulant n'a pas été systématiquement explorée et notamment son impact sur les événements hémorragiques.

Dans cette étude, nous nous sommes intéressés aux patients inclus dans le registre RIETE qui avaient bénéficiés de tests de thrombophilie et de l'impact sur les événements hémorragiques de la présence d'une mutation du facteur V Leiden (FVL), d'une mutation du prothrombin 20210G-A (PTM) ou d'aucun de ces polymorphismes.

- Résultats

Au cours du traitement anticoagulant, 154 ont eu des saignements majeurs (47 hémorragies digestives, 28 hémorragies intracrâniennes, 11 rétro péritonéales), 291 ont présenté des saignements non majeurs et 151 sont décédés (**Tableau 11**). Par rapport aux patients non porteurs de mutation, ceux avec une mutation du FVL avaient un taux de saignement majeur (RR: 0,32; IC à 95%: 0,16 à 0,59) et non majeurs (RR: 0,46; IC à 95%: 0,30-0,68) significativement plus faible. Les patients avec une mutation PTM ont

également montré un taux de saignement majeur significativement plus faible par rapport aux non-porteurs (RR: 0,49; IC à 95%: 0,27-0,84), mais avaient un taux similaire d'événements hémorragiques non majeurs (RR: 0,78; IC à 95%: 0,54- 1.10).

Tableau 11. Evénements hémorragiques survenant durant le traitement anticoagulant.

	FVL carriers		PTM carriers		Non-carriers	
	N	N per 100 patient-years	N	N per 100 patient-years	N	N per 100 patient-years
Patients, N	1,384		1,115		7,640	
Events,						
Major bleeding	10	0.67 (0.34-1.19) [‡]	13	1.03 (0.57-1.71) [†]	131	2.09 (1.75-2.47)
Gastrointestinal	2	0.13 (0.02-0.44) [†]	4	0.31 (0.10-0.76)	41	0.65 (0.47-0.87)
Haematoma	2	0.13 (0.02-0.44) [*]	3	0.23 (0.06-0.64)	31	0.49 (0.34-0.69)
Cerebral	3	0.20 (0.05-0.54)	2	0.16 (0.03-0.52)	23	0.36 (0.24-0.54)
Retroperitoneal	1	0.07 (0.00-0.33)	0	-	10	0.16 (0.08-0.28)
Haemopericardias	0	-	0	-	4	0.06 (0.02-0.15)
Non-major bleeding	25	1.70 (1.12-2.47) [‡]	36	2.91 (2.07-3.98)	230	3.72 (3.26-4.23)
Gastrointestinal	4	0.27 (0.08-0.64) [*]	10	0.79 (0.40-1.41) _‡	51	0.81 (0.61-1.05)
Urinary	2	0.13 (0.02-0.44) [‡]	4	0.31 (0.10-0.76) [*]	54	0.85 (0.65-1.11)
Haematoma	5	0.33 (0.12-0.74)	4	0.31 (0.10-0.76)	38	0.60 (0.43-0.82)
Menorrhagia	3	0.20 (0.05-0.55)	2	0.16 (0.03-0.52)	20	0.32 (0.20-0.48)
Death	13	0.86 (0.48-1.44) [†]	11	0.86 (0.45-1.49) [†]	127	2.00 (1.68-2.37)
Bleeding	1	0.07 (0.00-0.33)	0	-	9	0.14 (0.07-0.26)
Cerebral	0	-	0	-	4	0.06 (0.02-0.15)
Gastrointestinal	1	0.07 (0.00-0.33)	0	-	2	0.03 (0.01-0.10)

Differences between FVL carriers or PTM carriers and non-carriers: * p < 0.05; † p < 0.01; ‡ p < 0.001

L'analyse multivariée a confirmé que les porteurs de la mutation FVL (mais pas les transporteurs de PTM) présentaient un risque plus faible pour le saignement majeur (rapport de risque [HR]: 0,50; IC à 95%: 0,25-0,99) et pour les saignements non majeurs (HR: 0,66; 95% CI: 0,43-1,01) comparativement aux non-transporteurs. (Tableau 12).

Tableau 12. Analyse multivariée sur les évènements thromboembolique, hémorragiques et les décès.

	VTE recurrences	Major bleeding	Non-major bleeding
Clinical characteristics,			
Age >50 years	-	-	1.56 (1.16-2.11)
Underlying diseases,			
CrCl levels <60 mL min	-	1.52 (1.02-2.27)	1.45 (1.09-1.92)
Recent major bleeding	2.80 (1.35-5.80)	-	
Anemia	-	2.45 (1.72-3.48)	1.35 (1.03-1.75)
Risk Factors for VTE,			
Unprovoked	Ref.	Ref.	Ref.
Cancer with metastases	2.84 (1.66-4.84)	1.73 (1.06-2.82)	-
Cancer without metastases	1.62 (1.09-2.40)	-	-
Transient risk factors	0.61 (0.44-0.85)	-	-
Initial VTE presentation,			
Symptomatic PE	-	1.50 (1.06-2.12)	1.41 (1.11-1.79)
Thrombophilia testing,			
Non-carriers	Ref.	Ref.	Ref.
FVL carriers	1.16 (0.82-1.64)	0.50 (0.25-0.99)	0.66 (0.43-1.01)
PTM carriers	1.00 (0.68-1.48)	0.75 (0.42-1.34)	1.10 (0.77-1.57)

L'évaluation du résultat chez les patients doublement hétérozygotes pour FVL, PTM et homozygote pour FVL ou PTM, n'a révélé aucune différence de résultat par rapport aux non-porteurs. Seul le sous-groupe de patients hétérozygotes pour FVL ou PTM a eu un taux de saignement majeur significativement plus faible par rapport aux non-porteurs (Tableau 13).

Tableau 13. Evénements survenant durant le traitement anticoagulant dans différents sous-groupe de thrombophilie. Les résultats sont exprimés en nombre d'événements pour 100 patients années.

	N	Age	VTE recurrences		Major bleeding	
Non-carriers	7,640	56.4±18.4	181	2.95 (2.54-3.41)	131	2.09 (1.75-2.47)
Heterozigous FVL	1,326	50.2±17.9 [‡]	41	2.99 (2.18-4.02)	10	0.70 (0.36-1.26) [‡]
Heterozigous PTM	970	50.7±17.4 [‡]	25	2.43 (1.61-3.53)	9	0.84 (0.41-1.55) [†]
Heterozigous FVL and PTM	106	47.1±17.2 [‡]	5	3.14 (1.15-6.97)	2	1.21 (0.20-3.99)
Homozygous FVL	58	47.4±15.6 [‡]	0	-	0	-
Homozygous PTM	39	47.1±17.4 [†]	1	2.58 (0.13-12.7)	2	5.56 (0.93-18.4)

[†]p <0.05; [‡]p <0.01; ^{‡‡}p <0.001

Abbreviations: FVL, Factor V Leiden; PTM, prothrombin mutation; VTE, venous thromboembolism.

- Discussion et conclusion

La plupart des recommandations publiées avant 2008 sur le traitement antithrombotique ont recommandé d'effectuer un test de thrombophilie chez des patients atteints de MTEV avec des situations cliniques particulières, comme un premier épisode de MTEV spontanée, un âge inférieur à 50 ans ou MTEV récurrente au cours d'un traitement anticoagulant.^{160,161} Cependant, les dernières recommandations n'étaient pas en faveur de ces tests puisqu'ils ne semblaient pas apporter de valeur ajoutée à la gestion des patients.^{153,162,163} Nos résultats, obtenus à partir d'une grande série de patients consécutifs atteints de MTEV, révèlent que dans la vie réelle, un patient sur 6-7 atteint de MTEV a subi des tests de thrombophilie. Le risque de saignement doit être pris en compte pour décider si le traitement anticoagulant doit être prolongé au-delà de trois mois. Nos résultats suggèrent que certains patients atteints de MTEV pourraient vraisemblablement bénéficier de ces tests, puisque les porteurs de thrombophilie se sont révélés avoir un risque de saignement plus faible durant le traitement anticoagulant comparativement aux non-porteurs.

IV.2 Particularité du site hémorragique : exemple des métrorragies

Malheureusement, même s'il est plus aisé de recueillir les données biologiques des patients inclus dans un registre monocentrique, le nombre réduit de patients inclus et donc d'événements hémorragiques sous anticoagulant ne nous permettait pas d'analyser spécifiquement un site hémorragique en particulier.

Nous souhaitons nous intéresser à un type d'hémorragie peu décrit dans la littérature que sont les métrorragies sous anticoagulants. Ce type d'hémorragie est souvent peu décrit du fait d'un manque de puissance, résultant d'un faible nombre de cas. Le registre RIETE, du fait d'un nombre de patient inclus important, nous permet cette approche des hémorragies « rares ». En effet, le fait de se focaliser sur un seul type d'hémorragie mais issu d'un registre de données prospectif et international (RIETE) avec la réalisation d'un suivi des patients, nous a permis d'améliorer la richesse de nos données.

Uterine bleeding during anticoagulation in women with venous thromboembolism (Thrombosis Research, Annexe 3)¹⁴²

Les saignements utérins anormaux sous anticoagulants sont fréquents chez les patientes sous anticoagulants¹⁴³⁻¹⁴⁵ mais la littérature décrit peu leur fréquence, leurs caractéristiques cliniques, leur délai de survenue ou la sévérité du saignement^{143,146,147}.

Dans cette étude, le saignement utérin majeur a été défini comme un saignement manifeste qui nécessitait une transfusion de deux unités ou plus de sang ou ayant entraîné le décès. Le saignement utérin non majeur cliniquement pertinent a été défini comme tout saignement nécessitant une intervention médicale (hospitalisation, chirurgie ou procédure interventionnelle, une imagerie diagnostic, test de laboratoire ou évaluation spécialisée) et / ou arrêt du traitement, et ne répondant à aucun des critères de saignement majeur. Nous avons comparé les caractéristiques cliniques, la durée, les

résultats au cours des 30 premiers jours et la prise en charge des anticoagulants après saignement chez les femmes présentant un saignement utérin par rapport à celles présentant des saignements majeurs dans d'autres sites.

En octobre 2016, 31 951 femmes avec une MTEV ont été recrutées dans RIETE. Durant le traitement anticoagulant, 53 (0.17%; IC 95%: 0.13-0.21) ont développé des saignements utérins majeurs, 118 (0.37%; IC 95%: 0.31-0.44) avaient des saignements utérins non majeurs cliniquement pertinents et 948 (2.97% IC 95%: 2,79-3,16) ont subi des saignements majeurs dans d'autres sites. Leur âge moyen était respectivement de 56 ± 17 , 52 ± 20 et 75 ± 14 ans (**Tableau 8**). Les femmes atteintes de saignement utérin (majeur ou non majeur) étaient de 10 ans plus jeunes que celles qui ne saignaient pas et 20 ans plus jeunes que celles atteintes de saignements majeurs dans d'autres sites. 51% des femmes atteintes de saignements utérins majeurs et 23% de celles atteintes de saignements non majeurs avaient un cancer, principalement (63%) utérin. On notait chez les femmes ayant des saignements utérins majeurs (mais pas chez celles avec un saignement non-majeur) la présence plus fréquente d'une anémie (72%), d'un nombre élevé de plaquettes (19%) ou des saignements majeurs récents (11%) lors du diagnostic de MTEV comparativement à celles présentant des saignements majeurs dans d'autres sites ou une absence de saignement.

Tableau 8: Caractéristiques des patients selon la sévérité et le site de saignement au cours du traitement anticoagulant.

	Major uterine bleeding	Non-major uterine bleeding	Major bleeding in other sites	No major bleeding
Patients, N	53	118	948	30,832
Clinical characteristics,				
Mean age (years ±SD)	56±17 [‡]	52±20 [‡]	75±14 [‡]	67±19
Age <35 years	4 (7.5%)	23 (19%) [‡]	27 (2.8%) [‡]	2,736 (8.9%)
Age 35-50 years	17 (32%) [‡]	44 (37%) [‡]	35 (3.7%) [‡]	3,672 (12%)
Age >50 years	32 (60%) [‡]	51 (43%) [‡]	886 (93%) [‡]	24,424 (79%)
Body weight (kg±SD)	77±20 [*]	78±21 [‡]	69±15 [†]	71±15
Associated conditions,				
Cancer	27 (51%) [‡]	27 (23%)	272 (29%) [‡]	6,145 (20%)
Uterine	19 (36%) [‡]	15 (13%) [‡]	26 (2.7%) [*]	515 (1.7%)
Metastatic cancer	15 (56%)	9 (33%)	127 (47%)	2,606 (42%)
Pregnancy/puerperium	3 (5.7%)	4 (3.4%)	3 (0.32%) [‡]	820 (2.7%)
Anemia	38 (72%) [‡]	51 (43%)	479 (51%) [‡]	10,980 (36%)
PIC <100,000/μL	0	3 (2.5%)	34 (3.6%) [‡]	600 (1.9%)
PIC >450,000/μL	10 (19%) [‡]	6 (5.1%)	62 (6.5%) [‡]	1,160 (3.8%)
CrCl levels <60 ml/min	13 (25%) [‡]	26 (22%) [‡]	638 (67%) [‡]	14,616 (47%)
Recent major bleeding	6 (11%) [‡]	7 (5.9%) [*]	47 (5.0%) [‡]	645 (2.1%)
Initial VTE presentation,				
Pulmonary embolism	30 (57%)	72 (61%)	595 (63%) [‡]	16,421 (53%)

Comparisons between women who bled vs. those that did not bleed: p < 0.05; [†]p < 0.01; [‡]p < 0.001.

Abbreviations: SD, standard therapy; PIC, platelet count; CrCl, creatinine clearance; VTE, venous thromboembolism.

Parmi les 53 femmes atteintes de saignements utérins majeurs, 26% ont présenté le saignement durant la première semaine de traitement anticoagulant, 19% entre le 8^{ème} et le 30^{ème} jour, 26% entre le 31^{ème} et le 90^{ème} jour et 28% au-delà du 90^{ème} jour (**Tableau 9**). Parmi les 118 femmes atteintes de saignements utérins non majeurs, les proportions étaient respectivement de 13%, 20%, 26% et 41%.

Tableau 9: Temps de survenue de l'événement hémorragique selon le site et la sévérité du saignement.

	Major uterine bleeding	Non-major uterine bleeding	Major bleeding In other sites
Patients, N	53	118	948
Time elapsed from index VTE,			
Mean days (±SD)	74±108	130±200	137±358
Median days (IQR)	32 (7-121)	71 (19-143)	22 (7-105)
Day 0 to Day 7	14 (26%)	15 (13%) [†]	240 (25%)
Day 8 to Day 30	10 (19%)	24 (20%) [*]	288 (30%)
Day 31 to Day 90	14 (26%)	31 (26%) [*]	165 (17%)
Beyond Day 90	15 (28%)	48 (41%) [†]	255 (27%)

Comparisons between women with uterine bleeding vs. those who bled in other sites: * p < 0.05; † p < 0.01; ‡ p < 0.001.

Abbreviations: VTE, venous thromboembolism; SD, standard therapy; IQR, inter-quartile range.

- Discussion et conclusion

Les saignements utérins anormaux chez les femmes recevant un traitement anticoagulant pour MTEV peuvent avoir un impact significatif sur leur qualité de vie physique, sociale et émotionnelle.^{144,148,149} Nos données, obtenues à partir d'une grande série de femmes consécutives recevant un traitement anticoagulant pour VTE, révèlent que ce saignement utérin n'est pas aussi commun. Seule 1 femme sur 603 (0,17%) a présenté un saignement utérin majeur (qui représentent 5,3% de tous les saignements majeurs) et 1 sur 270 (0,37%) présente un saignement utérin non majeur.

Cette étude présente cependant certaines limites. Tout d'abord, RIETE est un registre observationnel, et nos résultats servent à générer des hypothèses. Ainsi, nos données sont inutiles pour décider de la meilleure stratégie thérapeutique pour ces femmes. En outre, il n'y a pas d'arbitrage externe des événements (y compris le saignement majeur), qui sont signalés par les médecins. Cependant, certaines études antérieures ont montrées que les données jugées par le praticien en charge du patient correspondent généralement bien à l'évaluation des résultats par adjudication.^{150,151} Deuxièmement, les

patients de la base de données RIETE ont été sélectionnés dans plusieurs pays. La variabilité des pratiques dans différents pays pourrait affecter les résultats de l'étude. Par exemple, le dosage et le schéma thérapeutique peuvent varier en fonction du modèle thérapeutique de chaque pays, du processus sous-jacent de la maladie et / ou de la présence ou de l'absence de cancer. En outre, une variété de praticiens a introduit des données dans le registre, ce qui peut entraîner certaines inexactitudes dans les données rapportées. Cependant, le registre RIETE donne un aperçu de l'histoire naturelle de la MTEV avec une population de patients non sélectionnée, contrairement aux conditions rigoureusement contrôlées des études cliniques randomisées.

IV.3 Particularité des patients

Nous avons vu précédemment que certains sites hémorragiques présentent certaines particularités, cliniques mais également biologiques, pouvant influencer le devenir ou la prise en charge d'un saignement sous anticoagulant. Il serait intéressant de pouvoir identifier des patients à risque de saignement du fait de traits cliniques communs avant la survenue d'un événement hémorragique grave. Pour cela nous nous sommes intéressés à deux types de population fréquemment peu étudiés dans les essais cliniques randomisés que sont les patients « fragiles » et les patients présentant certains « critères d'exclusions habituellement retrouvés dans ces essais ».

IV.3.1 Les patients Fragiles

Clinical outcomes during anticoagulant therapy in fragile patients with venous thromboembolism (Research and Practice in Thrombosis and Haemostasis, Annexe 4)¹⁶⁴

Au cours des dernières années, un certain nombre d'anticoagulants oraux directs (AOD) ont été développés pour le traitement de la MTEV. Leur utilisation a été associée à un taux inférieur de saignement grave par rapport à la thérapeutique standard.^{22,165-167,26} Les analyses en sous-groupes de ces essais cliniques randomisés ont donné certains résultats prometteurs, en particulier pour les patients « fragiles », définis comme ceux ayant des niveaux de clairance de la créatinine (CrCl) ≤ 50 mL / min, un âge ≥ 75 ans ou un poids corporel ≤ 50 kg.^{22,167-169} Par conséquent, il existe des raisons de penser que les patients « fragiles » atteints de MTEV pourraient être considérés comme des candidats idéaux pour une thérapie à long terme avec des AOD.¹⁶⁷⁻¹⁷⁰

Afin d'analyser l'impact sur les accidents hémorragiques de ces patients « fragiles » dans la vraie vie, nous avons analysé ces patients à partir du registre RIETE en incluant les patients consécutifs recrutés à partir de janvier 2013 (l'année où le premier AOD a été approuvé pour les patients atteints de MTEV).

- Résultats

Au cours des 3 premiers mois de traitement anticoagulant, les patients « fragiles » ont un risque plus élevé de saignement grave (2,6% contre 1,4%, OR: 1,86; IC à 95%: 1,47-2,36) que les « non fragiles » (**Tableau 14**). Les patients « fragiles » ont également eu un risque plus élevé de décès toutes causes confondues (9,2% contre 3,5%, OR: 2,82; IC à 95%: 2,44 à 3,25) et d'hémorragies fatales (0,35% contre 0,19%; OR: 1,83; IC 95%: 0,97-3,44) par rapport aux « non fragiles ».

Tableau 14. Événements survenant durant les 3 premiers mois d'anticoagulation chez les patients fragiles vs. non-fragile avec MTEV.

	Fragile (6,260)	Non fragile (8,819)	Crude OR (95%CI)	Adjusted OR (95%CI)
Major bleeding	162 (2.6%)	124 (1.4%)	1.86 (1.47-2.36)	1.41 (1.10-1.80)
<i>Sites of major bleeding</i>				
Gastrointestinal	54 (0.86%)	31 (0.35%)	2.47 (1.58-3.84)	1.84 (1.16-2.92)
Cerebral	20 (0.32%)	21 (0.24%)	1.34 (0.73-2.48)	-
Haematoma	32 (0.51%)	6 (0.07%)	7.55 (3.15-18.1)	5.05 (2.05-12.4)
Retroperitoneal	16 (0.26%)	11 (0.12%)	2.05 (0.95-4.42)	-
Death	574 (9.2%)	305 (3.5%)	2.82 (2.44-3.25)	2.02 (1.75-2.33)
Fatal Bleeding	22 (0.35%)	17 (0.19%)	1.83 (0.97-3.44)	-
Cerebral	8 (0.13%)	6 (0.07%)	1.88 (0.65-5.42)	-
Gastrointestinal	4 (0.06%)	3 (0.03%)	1.88 (0.42-8.40)	-
Retroperitoneal	5 (0.08%)	1 (0.01%)	7.05 (0.82-60.3)	-

Abbreviations: CI, confidence intervals; OR, odds ratio; CI, confidence intervals.

Variables included in the multivariable analysis for major bleeding: fragile, gender, active cancer, chronic lung disease, recent major bleeding, anaemia, abnormal platelet count and initial VTE presentation (DVT or PE).

Variables included in the multivariable analysis for death: fragile, gender, active cancer, recent surgery, recent immobilization, prior VTE, chronic lung

Lors de l'analyse séparée des résultats, le risque de saignements majeurs chez les patients pesant <50 kg était similaire au risque des « non fragiles », chez les patients âgés de plus de 75 ans, il était légèrement (mais significativement) plus élevé et chez ceux ayant une CrCl <50 mL / min, il était trois fois plus élevé que chez les « non fragiles » (Tableau 15).

Table 15. Taux d'hémorragies graves selon la présence d'un âge ≥75 ans, d'une CrCl ≤50 mL/min et/ou d'un poids ≤50 kg.

	N	Major bleeding	
		N (%)	OR (95%CI)
Non fragile	8,819	124 (1.4%)	Ref.
Age ≥75 years only	2,967	62 (2.1%)	1.5 (1.1-2.0)
CrCl ≤50 mL/min only	521	23 (4.4%)	3.2 (2.0-5.0)
Body weight ≤50 kg only	183	2 (1.1%)	0.8 (0.1-2.6)
Age ≥75 years and CrCl ≤50 mL/min	2,235	60 (2.7%)	1.9 (1.4-2.6)
Age ≥75 years and body weight ≤50 kg	51	1 (2.0%)	1.4 (0.1-7.3)
CrCl ≤50 mL/min and weight ≤50 kg	42	2 (4.8%)	3.5 (0.6-12.4)
All three conditions	261	12 (4.6%)	3.4 (1.8-6.0)

Abbreviations: CrCl, creatinine clearance; VTE, venous thromboembolism; OR, odds ratio; CI, confidence intervals; Ref., reference.

- Discussion et conclusion

Nos résultats, obtenus à partir d'une grande série de patients consécutifs atteints de MTEV, révèlent que dans la vie réelle, 42% des patients étaient fragiles avec un risque plus élevé de saignement majeur que les non fragiles.

Nos données confirment que l'utilisation d'un traitement anticoagulant entraîne un risque plus élevé de saignement chez les personnes âgées et chez les personnes atteintes d'insuffisance rénale, comme cela a déjà été rapporté.¹⁷¹⁻¹⁷⁵

Ce groupe de patients fragiles a été détecté, par des analyses en sous-groupes, dans les essais randomisés princeps avec des critères d'inclusion très strictes. Or ces critères d'exclusion correspondent fréquemment à des patients considérés comme ayant un risque de saignement plus élevé. Afin de vérifier si ces patients généralement exclus présentaient effectivement un sur-risque hémorragique nous avons souhaité les étudier en situation de vraie vie.

IV.3.2 Critères d'Exclusion

Real-Life use of anticoagulants in venous thromboembolism with focus on patients with exclusion criteria for direct oral anticoagulants (Clinical Pharmacology & Therapeutics, Annexe 5)¹⁷⁶

Dans cette étude nous souhaitons nous intéresser aux données complémentaires que pouvaient apporter les registres de vraie vie par rapport aux essais randomisés. En effet, les recommandations actuelles sur le traitement antithrombotique, basée sur les preuves provenant d'essais randomisés, recommandent l'utilisation du dabigatran, rivaroxaban, apixaban ou edoxaban comme traitement à long terme chez les patients atteints de MTEV.¹⁷⁷ La réduction du risque de MTEV récurrentes avec les AOD est semblable à la réduction du risque avec l'héparine de faible poids moléculaire (LMWH) et les antagonistes de la vitamine K (VKA) alors que le risque de saignement (et en particulier le saignement intracrânien) est inférieur avec les AOD comparativement aux AVK.^{22,165-169} Cependant, ces essais princeps appliquaient des critères d'exclusion stricts, visant à exclure les patients dont le risque présumé de saignement était élevé. Or, dans la vie réelle, 1 patient sur 4 recevant un traitement anticoagulant à long terme n'aurait pas été admissible dans ces essais, et ces patients ont un taux plus élevé de saignements majeurs.^{34,178-184}

A partir du registre RIETE, nous avons analysé les patients présentant certains de ces critères d'exclusion à partir de janvier 2013 (moment où la prescription d'AOD a été autorisée).

Afin de définir les critères d'exclusion de notre étude, nous avons cherché les essais princeps à partir desquelles l'indication de l'utilisation des AOD, chez les patients atteints de MTEV, avait été basée.^{22,165-167} Les critères d'exclusion variaient légèrement de l'une à l'autre de ces études, mais en général, les patients étaient exclus s'ils avaient : 1) un

cancer nécessitant plus de 6 mois de thérapie par HBPM ou avec une durée de vie de 3 à 6 mois ; 2) des niveaux de clairance de la créatinine (ClCr) <30 mL / min (<25 mL / min dans un essai) ; 3) un risque élevé de saignement ; 4) maladie du foie cliniquement significative ou ; 5) une grossesse. Pour l'étude en cours, nous avons considéré comme critères d'exclusion l'un des éléments suivants : 1) cancer métastatique ; 2) Niveaux de ClCr <30 ml / min ; 3) nombre de plaquettes <100 000 / μ L ; 4) des saignements majeurs récents (<30 jours avant) ; 5) insuffisance hépatique chronique (définie comme une cirrhose hépatique prouvée par biopsie ou ASAT ou ALAT > 3 fois la normale supérieure) et 6) la grossesse.

- Résultats

De janvier 2013 à novembre 2016, 18 853 patients atteints de MTEV ont été recrutés. Dans l'ensemble, 3 578 patients (19%) avaient au moins l'un des critères d'exclusion prédéfinis. Parmi ceux-ci, 3177 patients (89%) avaient un critère d'exclusion, 369 (10%) en avaient deux et 32 patients (0,89%) avaient trois critères d'exclusion ou plus. L'âge moyen des patients ayant au moins un critère d'exclusion était de $69,7 \pm 16,5$, tandis que pour ceux sans critères d'exclusion, il était de $63,4 \pm 17,2$ ans ($p < 0,001$). Au cours du traitement anticoagulant (moyenne, 176 ± 151 jours), les patients ayant des critères d'exclusion avaient un taux plus élevé de saignement majeur (HR : 4,10 ; IC 95%: 3,38-4,96), décès tout-cause (HR : 9,47; IC à 95%: 8,46-10,6) ou saignement fatal (HR : 6,07 ; IC 95%: 3,56-10,4) que ceux sans critère d'exclusion (**Tableau 16**).

Tableau 16. Taux d'incidence des hémorragies graves durant le traitement anticoagulant selon la présence ou l'absence des critères d'exclusion.

	Any exclusion criteria		No exclusion criteria		Hazard ratio (95%CI)
	N	Events per 100 patient-years	N	Events per 100 patient-years	
Patients, N		3,578		15,275	
Mean days of therapy (±SD)		143±159		184±185	<0.001
Median days (IQR)		99 (32-190)		125 (86-228)	<0.001
Major bleeding	181	12.9 (11.2-14.9)	243	3.16 (2.78-3.58)	4.10 (3.38-4.96)
Death	828	58.1 (54.3-62.2)	476	6.14 (5.61-6.71)	9.47 (8.46-10.6)
Fatal bleeding	29	2.04 (1.39-2.88)	26	0.34 (0.22-0.48)	6.07 (3.56-10.4)
Metastatic cancer, N		1,732		17,121	
Major bleeding	90	14.8 (12.0-18.1)	334	3.94 (3.53-4.38)	3.76 (2.96-4.72)
CrCl levels <30 mL/min, N		1,020		17,833	
Major bleeding	51	12.3 (9.24-16.0)	373	4.30 (3.88-4.75)	2.85 (2.11-3.80)
PIC <100,000/μL, N		453		18,400	
Major bleeding	25	14.1 (9.31-20.5)	399	4.48 (4.06-4.94)	3.14 (2.05-4.63)
Recent major bleeding, N		380		18,473	
Major bleeding	28	19.6 (13.2-27.9)	396	4.43 (4.01-4.88)	4.42 (2.96-6.39)
Chronic liver failure, N		268		18,585	
Major bleeding	14	12.9 (7.36-21.2)	410	4.56 (4.14-5.02)	2.83 (1.60-4.69)
Pregnancy, N		126		18,727	
Major bleeding	1	2.03 (0.10-10.0)	423	4.68 (4.25-5.14)	0.43 (0.02-2.15)

Abbreviations: SD, standard deviation; IQR, interquartile range; VTE, venous thromboembolism; PE, pulmonary embolism; CrCl, creatinine clearance; PIC, platelet count; CI, confidence intervals.

Au cours du traitement initial (**Tableau 17**), les patients sous rivaroxaban avaient un taux de saignement majeur significativement plus faible que ceux sous HNF (HR : 0,18; IC à 95%: 0,03-0,64) et un taux non significativement inférieur à ceux sous HBPM (HR : 0,39; 95% CI: 0,06-1,30). L'analyse multivariée a confirmé le taux plus faible de saignements majeurs chez les patients sous rivaroxaban comparativement à ceux sous HNF (HR ajustée : 0,18 ; IC à 95% : 0,04-0,79).

Tableau 17. Hémorragies graves à la phase initiale du traitement anticoagulant. Les résultats sont exprimés en événements pour 100 patients années.

	LMWH	UFH	Rivaroxaban	Apixaban
Major bleeding,				
Metastatic cancer	13.3 (10.6-16.6)	68.0 (33.2-124.7) [†]	7.19 (0.36-35.5)	-
CrCl levels <30 mL/min	12.1 (8.83-16.1)	14.5 (5.89-30.3)	-	-
PIC <100,000/μL	10.6 (6.24-16.8)	58.9 (21.6-130.7) [†]	13.4 (0.67-66.0)	-
Recent major bleeding	19.9 (12.8-29.6)	25.8 (8.19-62.2)	-	-
Chronic liver failure	11.2 (5.90-19.5)	-	-	-
Pregnancy	2.11 (0.11-10.4)	-	-	-
Any exclusion criteria	11.8 (10.0-13.9)	26.2 (16.6-39.3)[†]	4.60 (0.77-15.2)	-
2 exclusion criteria	23.7 (15.1-35.6)	50.1 (8.40-165.5)	-	-
≥3 exclusion criteria	21.3 (1.06-104.8)	347.9 (17.4-1,715.6)	-	-
No exclusion criteria	3.23 (2.81-3.70)	5.66 (3.41-8.88)[*]	1.85 (1.11-2.90)[*]	2.89 (0.14-14.2)

Comparisons between patients on LMWH therapy vs. other drugs: *p <0.05; †p <0.01.

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; CrCl, creatinine clearance; PIC; platelet count.

Au cours du traitement à long terme, les patients sous rivaroxaban présentaient un taux inférieur de saignement majeur (HR : 0,44 ; IC 95% : 0,27-0,71) comparativement aux patients sous HBPM (**Tableau 18**). Cependant, sur l'analyse multivariée, cette différence a disparu : HR ajusté : 0,41 (IC 95% : 0,15-1,15) pour les saignements majeurs. Ils ont également un taux similaire de saignement majeur comparativement à ceux sous AVK (HR : 0,78 ; IC à 95%: 0,49-1,21).

Tableau 18. Hémorragies graves durant le traitement anticoagulant à long terme. Les résultats sont exprimés en événements pour 100 patients années.

	LMWH	VKA	Rivaroxaban	Apixaban
Major bleeding,				
Metastatic cancer	12.2 (9.45-15.6)	15.5 (7.57-28.5)	-	-
CrCl levels <30 mL/min	14.8 (9.08-23.0)	7.18 (4.39-11.1)*	-	-
PIC <100,000/μL	15.7 (8.52-26.7)	4.79 (1.52-11.6)*	17.7 (2.96-58.4)	-
Recent major bleeding	24.1 (14.7-37.3)	4.83 (0.81-16.0)*	6.29 (0.31-31.0)	14.2 (0.71-69.8)
Chronic liver failure	23.5 (10.9-44.7)	3.16 (0.53-10.4)†	14.1 (0.71-69.8)	-
Pregnancy	2.42 (0.12-11.9)	-	-	-
Any exclusion criteria	12.9 (10.5-15.6)	7.11 (5.00-9.82)†	4.85 (1.54-11.7)	4.98 (0.25-24.6)
2 exclusion criteria	25.4 (15.3-39.8)	4.87 (0.24-24.03)	-	-
≥3 exclusion criteria	24.8 (1.24-122.4)	-	-	-
No exclusion criteria	4.51 (3.55-5.65)	2.38 (1.96-2.86)‡	1.61 (1.01-2.45)	3.30 (1.21-7.31)

Comparisons between patients on LMWH therapy vs. other drugs: *p <0.05; †p <0.01; ‡p <0.001.

Abbreviations: LMWH, low-molecular-weight heparin; VKA, vitamin K antagonists; CrCl, creatinine clearance; PIC; platelet count

- Discussion et conclusion

Nos données, obtenues à partir d'une grande série de patients consécutifs atteints de MTEV, révèlent que dans la vie réelle, un patient sur cinq avait au moins l'un des critères d'exclusion retrouvés dans les essais randomisés pivot des AOD.^{178-180,182-184} Comme attendu, les patients ayant des critères d'exclusion avaient un taux 4 fois plus élevé de saignements majeurs (et un taux de saignement fatal 6 fois plus élevé) que ceux sans critères d'exclusion, comme reporté dans la littérature.¹⁸⁵⁻¹⁸⁷ Dans notre série, un taux accru de saignements majeurs a été retrouvé chez les patients atteints de cancer métastatique, d'une ClCr <30 mL / min, d'une thrombopénie, d'un antécédent de saignements majeurs récents et chez ceux atteints d'insuffisance hépatique, mais pas chez les femmes enceintes.

Les données de PREFER ont également révélé que l'utilisation des AOD était moins probable chez les patients souffrant d'insuffisance rénale ou de risque accru de saignement.^{188,189} Nos résultats confirment que les AOD ont été utilisés chez quelques patients avec des critères d'exclusion (3,2% pour le traitement initial et 6,2% pour le traitement à long terme), ce qui semble paradoxal puisque son utilisation a été associée à moins de saignement dans les essais randomisés.^{22,165-167,26,169} Il semble plus rentable de prescrire des médicaments plus sûrs chez les patients présentant un risque accru de saignement.¹⁹⁰ Compte tenu du petit nombre de patients ayant des critères d'exclusion recevant du rivaroxaban (104 pour la thérapie initiale, 151 à long terme), nous pouvons seulement émettre l'hypothèse que le rivaroxaban peut être une bonne alternative au traitement standard chez les patients ayant ces critères d'exclusion.

En résumé, les patients atteints de MTEV avec des critères d'exclusion ne sont pas rares dans la vie réelle (19% dans notre cohorte) avec des événements hémorragiques plus importants que ceux sans ces critères. L'utilisation des AOD est rare chez ces patients, mais nos données suggèrent qu'elle peut être au moins aussi sûre que le traitement standard.

V. Conclusion et Perspectives

V.1 Perspectives

Après des débuts relativement lents, la médecine personnalisée, ou de façon plus réaliste la médecine stratifiée, semble arriver incessamment à notre portée. En effet, cette médecine pouvant être liée aussi bien au diagnostic qu'à la prévention, prend de l'ampleur et les patients paraissent de plus en plus ouverts à l'utilisation d'outils diagnostics prédictifs. Malheureusement, l'utilisation de ces outils de diagnostics notamment génomiques entraîne certaines réticences notamment éthiques, réglementaires ou légales freinant leur utilisation. De multiples efforts dans les deux technologies que sont le développement et l'application biologique, se sont produits, et un nombre croissant de chercheurs et de médecins partagent cette vision. Hood et al. a d'ailleurs qualifié cette approche de "P4 Medicine" pour la médecine prédictive, préventive, personnalisée et participative.¹⁹¹

Dans ce contexte, l'utilisation de registre de vraie vie semblent pouvoir apporter une autre voie à cette médecine personnalisée ou stratifiée par l'utilisation de la révolution digitale par le biais des big-datas.

Dans le cadre des hémorragies sous anticoagulants, notre travail de thèse a permis de montrer différentes voies futures pour l'étude et la prise en charge personnalisée de ces accidents hémorragiques sous anticoagulants qui représentent la première cause d'hospitalisation iatrogène en France (soit environ 17 000 par an) soit 13% des hospitalisations pour effet indésirable.⁴

L'une des pistes serait de travailler par site hémorragique et non plus toutes hémorragies

confondues. En effet, tous les sites hémorragiques ne présentent pas le même volume de perte de sanguine, le même pronostic de survie, le même mécanisme déclenchant ou ni les mêmes facteurs de risque. Ainsi, le taux de mortalité associé à un saignement graves peut varier entre 10 et 60%, en particulier en cas d'hémorragie intracrânienne, particulièrement la première semaine suivant le début de l'hémorragie.¹⁹²⁻¹⁹⁴ D'autant plus, qu'il existe des différences entre les AOD et les AVK¹⁹⁵ voire même d'un AOD à l'autre concernant le risque hémorragique.¹⁹⁶

Une plus-value pourrait être également apportée par l'analyse biologique des patients sous anticoagulants. Nous avons montré que selon le site hémorragique les pertes sanguines n'étaient pas identiques avec notamment des pertes en facteurs de coagulation différentes (hémorragies intracrâniennes vs. Hémorragies digestives) pouvant impacter la réussite de la prise en charge de réversion recommandée.⁵⁰ Ceci amène à penser que des stratégies de réversion adaptées au site hémorragique, prenant en compte le site hémorragique et donc le volume sanguin perdu, et adaptées aux données biologiques concernant les facteurs de coagulation, pourrait permettre d'améliorer le pronostic des patients.

De même, une analyse biologique des patients sous anticoagulants à la recherche de caractéristiques biologiques pouvant prédire un sur-risque hémorragique ou un sous-risque hémorragique pourrait être une perspective intéressante à l'avenir. Ainsi, nous avons montré que pour les patients sous anticoagulants dans le cadre d'une MTEV, la mutation des facteurs V Leiden et de la prothrombin sont non seulement un facteur de Thrombophilie bien connu mais également un facteur de sous-risque hémorragique chez ses patients porteurs.

Les caractéristiques clinico-biologiques des patients sont d'ailleurs souvent prises en compte dans les différents scores hémorragiques utilisés en pratique courante par le clinicien.^{45,197,198} Nous avons d'ailleurs démontré l'importance de la prise en compte de ces facteurs de risque notamment dans la population des « fragiles » qui présentaient un risque hémorragique accru. Paradoxalement, ces patients à haut risque hémorragiques

sont souvent exclus des études pragmatiques réalisés pour la mise en place des nouvelles thérapeutiques anticoagulantes. Malheureusement, ces différents scores hémorragiques permettant d'identifier ces patients à risque ne sont pas spécifiques d'un site hémorragique en particulier. Or il serait probablement intéressant d'identifier des patients à risque pour un site hémorragique et non à risque pour un autre permettant ainsi de lui proposer la thérapeutique la mieux adaptée.

L'utilisation des registres nous est apparu pertinente dans le cadre de cette recherche sur la personnalisation clinique de la thérapeutique. C'est ainsi que nous avons initié, durant cette thèse, le registre RATED, au service des urgences adultes du CHU de Clermont-Ferrand. Ce registre était basé avant tout sur le traitement anticoagulant et non pas sur le type de pathologie ou indication car l'événement hémorragique est avant tout la conséquence d'un traitement survenant chez un patient avec un terrain propice ou non à sa survenue. Le but futur étant de rentrer dans la personnalisation de la prise en charge du risque hémorragique par la mise en place de registres prospectifs incluant une évaluation de la biologie et du devenir des patients. Ceci pourra, par exemple, passer par la réalisation d'une bio-banque au sein d'un registre multicentrique prospectif et international déjà établi comme le registre RIETE, mais le principal facteur limitant, du fait de sa dimension européenne et mondiale, sera l'obtention d'un financement européen ou par le biais de sociétés savantes comme l'ISTH ou l'ESC.

V.2 Conclusions

Ce travail de thèse a permis de démontrer l'intérêt de travailler non pas toutes hémorragies confondues mais hémorragies par hémorragies car certains sites semblent différents les uns des autres. Cette approche pourrait permettre de prendre en charge différemment ces accidents hémorragiques sous anticoagulants que ce soit sur le plan de

la prédiction du risque hémorragique ou de la réversion des accidents hémorragiques. Ceci nous conduit à penser que la création de registres prospectifs de vraie vie avec la mise en œuvre de bio-banque pour l'analyse des éléments biologiques pourraient permettre à terme de garantir une analyse plus personnalisée de la prise en charge des patients que ce soit à l'initiation du traitement ou lors de la réversion des accidents hémorragiques.

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VII. Annexes

VII.1 Annexe 1: « Comparison of blood coagulation factors between patients with gastrointestinal or intracranial bleeding under vitamin K antagonist » (SIGAPS B, IF : 2.591)



Letter to the Editor

Comparison of blood coagulation factors between patients with gastrointestinal or intracranial bleeding under vitamin K antagonists


Keywords:

Serious bleeding
VKA
Blood coagulation factors
Gastrointestinal bleeding
Intracranial bleeding

Vitamin K antagonists (VKAs) are the most commonly-used anticoagulant treatments for the prevention of thrombotic and embolic events related to atrial fibrillation, venous thromboembolism (VTE), and prosthetic heart valve. The incidence of major bleedings has been estimated at 7%, and that of fatal bleedings at 1% [1]. The primary bleeding complications observed in patients receiving long-term VKA therapy are either gastrointestinal (30–60% of cases) or cerebral (17–30%) [2,3]. The current guidelines recommend administering four-factor PCC (4 F-PCC) rather than FFP to reverse VKA-induced coagulopathy in patients suffering from major VKA-associated bleedings, while optimal dosage protocols have not yet been clearly defined, thus differing widely [4–7]. The effect of VKA treatment on procoagulant factor levels is well-known, causing a decrease in FII, FVII, FIX, FX, and proteins C and S, yet no decrease in fibrinogen, FV, FVIII, FXI, or in antithrombin. However, only a few studies have investigated blood coagulation factors in bleeding events under VKAs, and a clearer understanding of the coagulation factor losses specific to each bleeding type would enable us to optimize currently-recommended treatments by adapting them to bleeding type and lost blood volume. With this study, we sought to compare the levels of blood coagulation factors in patients receiving VKAs and exhibiting serious gastrointestinal or intracranial bleeding.

We carried out a retrospective study on patients hospitalized in the emergency ward of the Clermont-Ferrand University Hospital from January 1st 2010 to December 31st 2011. We included all patients over 18 years old, treated with VKAs, admitted to the emergency unit for serious gastrointestinal or intracranial bleeding events, and receiving PCC reversal therapy according to the unit reversal protocol (Kanokad® Laboratoire LFB Biomédicaments, Courtaboeuf [91], France). Patients exhibiting bleeding events with another anticoagulant combined with VKAs were excluded from analysis. The eligible patients were screened in a comprehensive manner according to the list provided by the central pharmacy for each PCC request within the hospital. Data was retrieved from patient's medical records and anonymously collected with the administrative authorization of the Clermont-Ferrand University Hospital. All statistical tests were two-sided, with statistical significance set at $p < 0.05$.

In total, 272 patients were administered PCC due to bleeding events under VKAs during the study period, 155 of whom were enrolled in this study (88 with gastrointestinal bleeding and 67 with intracranial bleeding).

Table 1 presents the patient characteristics and coagulation factor levels prior to reversal. The average patient age was 78.4 ± 10.4 years, with a male-to-female gender ratio of 1.12. The mean international normalized ratio (INR) assessed in the initial report prior to reversal was 4.67 ± 3.11 for the gastrointestinal bleeding group and 2.88 ± 1.89 for the intracranial bleeding group, with a statistically-significant difference ($p < 0.001$). In the intracranial bleeding group, 24 patients (35.8%) exhibited head trauma and 36 (53.7%) spontaneous hemorrhage, with no difference observed in INR ratio.

We also observed a significant difference in the aPTT prolongation between patients with gastrointestinal bleeding and those with intracranial bleeding, recording ratios of 1.98 ± 0.93 and 1.56 ± 0.54 , respectively ($p < 0.001$). The FII, FV, and FX levels were also significantly lower in patients referred for gastrointestinal bleeding.

The mean time between the patient first being seen and diagnosis of the hemorrhage was approximately $2 \text{ h}57 \pm 3 \text{ h}58$, with no significant difference observed between groups ($2 \text{ h}37 \pm 4 \text{ h}22$ for gastrointestinal bleeding versus $3 \text{ h}25 \pm 3 \text{ h}19$ for intracranial bleeding).

With regard to reversal, the mean vitamin K dose administered and timing of administration did not differ between gastrointestinal bleeding and intracranial bleeding patients ($9.22 \pm 1.83 \text{ mg}$ and $55 \text{ min} \pm 2 \text{ h}31$ versus $9.03 \pm 2.04 \text{ mg}$ and $42 \text{ min} \pm 1 \text{ h}17$, respectively). The administered PCC doses were higher in the gastrointestinal bleeding group ($24.60 \text{ UI/kg} \pm 4.10$ versus $22.29 \text{ UI/kg} \pm 4.66$, respectively; $p = 0.001$), with no difference observed in the delay between diagnosis and administration ($1 \text{ h}22 \pm 1 \text{ h}44$ versus $1 \text{ h}15 \pm 1 \text{ h}29$ for gastrointestinal bleeding patients and intracranial bleeding patients, respectively). Overall, the post-reversal INR values were similar, namely 1.26 ± 0.24 for gastrointestinal bleeding patients and 1.19 ± 0.18 for intracranial bleeding patients.

A total of 132 patients (85.1%) were admitted to a conventional ward, 11 (7.1%) to an intensive care unit (ICU), six (3.9%) were discharged, and six (3.9%) died. The number of deceased patients at 1 week then 1 month and six months later, was five (5.7%), 10 (11.4%), and 15 (17.0%) for gastrointestinal bleeding patients and 17 (25.4%), 24 (35.8%), and 32 (47.8%) for intracranial bleeding patients. These numbers were significantly higher in intracranial bleeding patients at each time point ($p = 0.001$).

The study findings suggest that the loss of whole blood, including both red blood cells and blood coagulation factors (both those with vitamin K-influenced synthesis and not), is greater in patients with serious gastrointestinal bleeding as opposed to those with intracranial bleeding under VKA therapy. Our hypothesis is based on the results recorded for red blood cell loss, with a lower mean hemoglobin level for gastrointestinal bleeding patients. By the same token, in the gastrointestinal bleeding group, we measured lower levels of vitamin K-dependent factors (FII, FVII, FIX, and FX) yet higher INRs, which could not be caused

Table 1
Population characteristics and levels of blood coagulation factors and target INR before reversal in patients under VKAs admitted for intracranial bleeding and serious gastrointestinal bleeding.

	Intracranial bleedings (n = 67)	Gastrointestinal bleedings (n = 88)	p-Value
Demographic characteristics			
Male, n (%)	40 (59.7%)	42 (47.7%)	0.14
Age, years, mean (standard deviation)	77.6 (10.7)	79.0 (19.2)	0.39
Weight, kg, mean (standard deviation)	72.4 (14.5)	70.8 (15.8)	0.53
Creatinine level (μmol/l), mean ± SD	138.8 ± 148.8	121.7 ± 112.1	0.46
Cockcroft-Gault creatinine clearance (ml/min), mean ± SD	56.3 ± 32.3	55.8 ± 33.5	0.9
Medical history			
Cardiac, n (%)	38 (56.7%)	61 (69.3%)	0.11
Diabetes-dysthyreosis, n (%)	13 (19.4%)	23 (26.1%)	0.32
Neoplastic, n (%)	12 (17.9%)	23 (26.1%)	0.22
Neurological (cerebral stroke), n (%)	14 (20.9%)	14 (15.9%)	0.42
Renal (chronic kidney failure), n (%)	3 (4.5%)	16 (18.2%)	0.01
Pulmonary, n (%)	4 (6.0%)	9 (10.2%)	0.34
Vascular, n (%)	6 (9.0%)	9 (10.2%)	0.79
Other diseases, n (%)	1 (1.5%)	1 (1.1%)	1.00
Antiplatelet therapy			
VKA type			
Fluindione (Previscan®), n (%)	46 (68.7%)	54 (61.4%)	0.13
Acenocoumarol (Sintrom®), n (%)	12 (17.9%)	12 (13.6%)	
Warfarin (Coumadin®), n (%)	3 (4.5%)	15 (17.0%)	
Unavailable, n (%)	6 (9.0%)	7 (8.0%)	
Indication for VKA therapy			
AF, n (%)	51 (76.1%)	56 (63.6%)	0.184
VTE, n (%)	10 (14.9%)	12 (13.6%)	
Mechanical valve prosthesis, n (%)	2 (3.0%)	11 (12.5%)	
Other, n (%)	1 (1.5%)	4 (4.5%)	
Unavailable, n (%)	3 (4.5%)	5 (5.7%)	
INR, n			
Global mean ± SD	2.88 ± 1.89	4.67 ± 3.11	<0.001
Mechanical valve mean ± SD (n)	2.3 ± 0.3 (2)	3.9 ± 2.1 (11)	0.299
No mechanical valve mean ± SD (n)	2.9 ± 1.92 (63)	4.8 ± 3.2 (73)	<0.001
aPTT ratio, n			
Mean ± SD	1.56 ± 0.54	1.98 ± 0.93	
Blood coagulation factors, n			
Factor II (%)	19.61 ± 10.71	11.68 ± 7.32	0.009
Factor V (%)	107.78 ± 26.72	91.07 ± 23.82	0.030
Factor X (%)	10.72 ± 5.30	6.56 ± 8.63	0.028
Fibrinogen (g/L), n	66	87	0.74
Mean ± SD	4.41 ± 1.25	4.33 ± 1.48	

In the Medical history: Cardiac (represent coronary syndrome, high blood pressure, valve disease, pacemaker), pulmonary (represent COPD and/or chronic respiratory failure), vascular (represent Obliterating arteriopathy of the lower limbs, abdominal aortic aneurysm, iliac aortic aneurysm). VKA: vitamin K antagonist; AF: atrial fibrillation; VTE: venous thromboembolism; SD: standard deviation; aPTT: activated partial thromboplastin time; n: number of patients; INR: international normalized ratio.

solely by the effect of anticoagulation, as FV (a vitamin K independent factor) levels were also lower. The decrease in FV can be explained by the fact that gastrointestinal bleeding can go unreported for long periods of time before the patient becomes symptomatic, with microbleeding and blood loss, while the symptoms of intracranial bleeding manifest immediately.

Our findings have raised doubts about reversal management, such as it is currently proposed, as we believe that a normalized INR ratio may not be enough to evaluate impact on mortality. Sarode et al. demonstrated that even if the INR reduction was quicker with PCC than with fresh frozen plasma, there was no difference in effective hemostasis or death for any category of bleeding [8]. Avoiding any delay before reversal is one of the solutions for intracranial bleeding (subgroup analysis), as demonstrated in the EHPAK study, where the thromboembolic event value reversed during the first 8 h, although even faster would be better [9]. For gastrointestinal bleedings, the solution could be a more

aggressive therapy with faster hemostasis or, given that we reported significant decrease in both the vitamin K-dependent and independent factors, by correcting other coagulation factors using fresh frozen plasma, due to the blood loss, or with activated coagulation factors (FVIIa or FEIBA) or other compounds exhibiting pro-hemostatic effects [10].

To our knowledge, no study has ever before specifically examined variations in the different blood coagulation factors in the event of serious bleedings under VKAs, in particular concerning gastrointestinal bleedings. Given the retrospective nature of this study, some data was unavailable, as not provided in the medical records. The missing data rate was especially high for blood coagulation FII, FV, and FX levels.

Our results now require confirmation in a prospective study due to potential confounding factors. In conclusion, patients with gastrointestinal bleedings appear to suffer greater loss of blood coagulation factors than those with intracranial bleedings.

Conflict of interest

F. Moustafa reports receiving personal fees from Bayer and non-financial support from Sanofi-aventis. S. Laporte has received fees for board membership from Bayer and for consultancy from Leo Pharma, and financial support for travel expenses from Boehringer Ingelheim and Procter & Gamble.

P. Mismetti has received fees for board membership from Bayer, Boehringer Ingelheim, Daichi and Pfizer, consultancy honoraria from Pfizer, and financial support for travel expenses from AstraZeneca. J. Schmidt has received fees for board membership from Bayer, Daichi, Lilly and Pfizer, and personal fees from Biomerieux, Boehringer Ingelheim, Sanofi, and Novartis.

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VII.2 Annexe 2: « Outcome of patients with venous thromboembolism and Factor V Leiden or Prothrombin 2010 carrier mutations during the course of anticoagulation » (SIGAPS A; IF : 5.61)

Accepted Manuscript



Outcome of patients with venous thromboembolism and Factor V Leiden or Prothrombin 20210 carrier mutations during the course of anticoagulation

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Clinical Research Study

Outcome of patients with venous thromboembolism and Factor V Leiden or Prothrombin 20210 carrier mutations during the course of anticoagulation

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And the RIETE Investigators*

**A full list of the RIETE investigators is given in the appendix*

Running title: Venous thromboembolism outcome in factor V Leiden carriers on anticoagulants

Abstract**Abstract**

Background: Individuals with factor V Leiden or prothrombin G20210A mutations are at a higher risk to develop venous thromboembolism. However, the influence of these polymorphisms on patient outcome during anticoagulant therapy has not been consistently explored.

Methods: We used the RIETE database to compare rates of venous thromboembolism recurrence and bleeding events occurring during the anticoagulation course in factor V Leiden carriers, prothrombin mutation carriers and non-carriers.

Results: Between 03.2001 and 12.2015, 10139 patients underwent thrombophilia testing. Of these, 1384 were factor V Leiden carriers, 1115 prothrombin mutation carriers and 7640 non-carriers. During the anticoagulation course, 160 patients developed recurrent deep vein thrombosis and 94 – pulmonary embolism (16 died); 154 had major bleeding (10 died) and 291 had non-major bleeding. On multivariable analysis, factor V Leiden carriers had a similar rate of venous thromboembolism recurrence (adjusted hazard ratio [HR]: 1.16; 95%CI: 0.82-1.64), half the rate of major bleeding (adjusted HR: 0.50; 95%CI: 0.25-0.99) and a non-significantly lower rate of non-major bleeding (adjusted HR: 0.66; 95%CI: 0.43-1.01) than non-carriers. Prothrombin mutation carriers and non-carriers had a comparable rate of venous thromboembolism recurrence (adjusted HR: 1.00; 95%CI: 0.68-1.48), major bleeding (adjusted HR: 0.75; 95%CI: 0.42-1.34) and non-major bleeding events (adjusted HR: 1.10; 95%CI: 0.77-1.57).

Conclusions: During the anticoagulation course, factor V Leiden carriers had a similar risk for venous thromboembolism recurrence and half the risk for major bleeding compared to non-carriers. This finding may contribute to decision-making regarding anticoagulation duration in selected factor V Leiden carriers with venous thromboembolism.

Keywords: thrombophilia, anticoagulant therapy, venous thromboembolism, bleeding

Funding source: None

Introduction

Factor V Leiden and prothrombin 20210G-A mutations are the most common genetic causes of thrombophilia in Caucasian population (1, 2). Carriers of these mutations are at an increased risk to develop acute venous thromboembolism, particularly in the presence of concomitant risk factors such as estrogen use, pregnancy, surgery or immobility (3, 4). However, the influence of factor V Leiden and prothrombin 20210G-A mutations on the natural history of venous thromboembolism is still a matter of debate (5). In the past, some studies suggested that venous thromboembolism patients with factor V Leiden or prothrombin 20210G-A mutations were at an increased risk for venous thromboembolism recurrence after discontinuing anticoagulant therapy (6-9), influencing the American College of Chest Physicians (ACCP) guidelines recommendation that these patients should receive anticoagulant therapy for 6-12 months and their suggestion of indefinite therapy (10). However, subsequent research led to a change in the more recent ACCP guidelines and the presence of hereditary thrombophilia was no longer taken into consideration when the duration of anticoagulant therapy was determined (11-13).

Moreover, it has also been suggested that factor factor V Leiden and prothrombin 20210G-A mutations may contribute to an evolutionary advantage by reducing the risk of life-threatening bleeding, such as during childbirth, warfare, or other high risk activities (14, 15). A number of studies have suggested that these mutations may be associated with a significantly lower bleeding rate in patients with hemophilia (16-18), and a decreased hemorrhagic risk in patients undergoing surgery (19, 20).

The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) Registry is an ongoing, multicenter, international (Spain, Belgium, Canada, Czech Republic, Ecuador, France, Greece, Israel, Italy, Latvia, Portugal, Republic of Macedonia and Switzerland) observational registry of consecutive patients with objectively confirmed acute venous thromboembolism. Data from this registry have been used to evaluate outcomes after acute venous thromboembolism, such as the frequency of recurrent venous thromboembolism, bleeding and

mortality, and risk factors for these outcomes (21-23). The aim of the current study was to compare the rate of symptomatic venous thromboembolism recurrence and bleeding events during the course of anticoagulant therapy in factor V Leiden carriers, prothrombin 20210G-A mutation carriers and non-carriers.

Patients and Methods

Inclusion criteria

Consecutive patients with acute, symptomatic, objectively proven venous thromboembolism were enrolled in RIETE. For this analysis, only patients undergoing thrombophilia tests were considered. All patients provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements. This analysis was approved by the Ethics Committees of the UZ Gasthuisberg Hospital in Leuven, Belgium (B70721111790) and the Hospital Clinic of Barcelona, Spain (Reg. HCB/2015/0386).

Physicians participating in the RIETE registry made all efforts to enroll consecutive patients. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The coordinating center assigned patients with a unique identification number to maintain patient confidentiality and was responsible for all data management.

Study design

Although thrombophilia testing was not routinely performed in RIETE, in those patients who were tested the analyses were performed according to the protocol of each participating hospital. Only patients tested for thrombophilia who were found to have factor V Leiden, prothrombin 20210G-A mutation or none of these polymorphisms were included in this study. We excluded from the study all the patients with other thrombophilic states. In particular, patients with protein C or protein S deficiencies, those with antithrombin deficiency and those with antiphospholipid syndrome were not included in the analysis. We compared their clinical characteristics, laboratory findings, treatment and outcome during the course of anticoagulant therapy. The major outcome was

the rate of symptomatic, objectively confirmed venous thromboembolism and bleeding complications occurring during the course of anticoagulation. Bleeding complications were classified as 'major' if they were overt and required a transfusion of two units of blood or more, or were retroperitoneal, spinal or intracranial, or when they were fatal. Non-major bleeding was defined as any overt bleed requiring medical assistance but not filling the criteria for major bleeding. Each episode of clinically suspected pulmonary embolism or deep vein thrombosis was investigated by ultrasonography, contrast venography, ventilation-perfusion lung scanning, computerized tomographic pulmonary angiography scan or conventional contrast pulmonary angiography as appropriate. Fatal pulmonary embolism, in the absence of autopsy, was defined as any death appearing within 10 days after symptomatic pulmonary embolism diagnosis, in the absence of any alternative cause of death. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death.

Baseline variables

The following parameters are routinely recorded in RIETE: patient's baseline characteristics; clinical status including any coexisting or underlying conditions; risk factors for venous thromboembolism; laboratory data; treatment received upon venous thromboembolism diagnosis (drugs, doses and duration) and the outcome during the course of anticoagulant therapy. Immobilized patients were defined as non-surgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for ≥ 4 days in the 2-month period prior to venous thromboembolism diagnosis. Surgical patients were defined as those who underwent a surgical intervention in the 2 months prior to venous thromboembolism. Recent bleeding was defined as a major bleeding episode < 30 days prior to venous thromboembolism.

Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). Patients were followed-up for at least 3 months in the outpatient clinic. During each visit, any signs or symptoms suggesting symptomatic venous thromboembolism

recurrence or bleeding complications were noted. Each episode of clinically suspected recurrent venous thromboembolism was investigated by repeat compression ultrasonography, ventilation-perfusion lung scanning, computerized tomographic pulmonary angiography scan or conventional contrast pulmonary angiography, as appropriate. Most outcomes were classified as reported by the clinical centers. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

Data collection and monitoring

The primary investigator ensured a consecutive enrollment of qualified patients. The data collected were recorded electronically using the RIETE report form accessible to each of the participating hospitals and medical offices and were submitted securely to the central coordinating center. Data were encrypted to ensure confidentiality and security and patients were assigned a unique number by the study's coordinating center. Quality measures were utilized regularly and electronically documented to expose errors or inconsistencies.

Statistical analysis

We used Student's t test and X^2 test (or Fisher's exact test where appropriate) to compare continuous or categorical variables. Then, we carried out a multivariable analysis through a logistic regression model trying to identify independent predictors for venous thromboembolism recurrence and for major- and non-major bleeding during the course of anticoagulant therapy. Covariates entering in the model were selected by a significance level of $p < 0.10$ on univariable analysis, or by a well-known association reported in the literature. SPSS software (version 20, SPSS Inc. Chicago, Illinois) was used for the statistical management of the data, and a two-sided $p < 0.05$ was considered to be statistically significant.

Results

From March 2001 to March 2016, 64690 venous thromboembolism patients were recruited into the registry. Of these, 10139 (16%) were tested for thrombophilia: 1384 patients were positive for factor V Leiden and 1115 were

positive for prothrombin 20210G-A mutation. Carriers of either factor V Leiden or prothrombin 20210G-A mutations were younger and with slight male predominance compared to non-carriers (Table I). They were less likely to have chronic heart failure, lung disease, renal insufficiency or anemia, but more frequently were users of hormonal therapy or pregnant than non-carriers. Additionally, factor V Leiden carriers (but not prothrombin 20210G-A mutation carriers) were less likely to have recent major bleeding, surgery or immobilization and pulmonary embolism at baseline (compared to deep vein thrombosis alone) than non-carriers. Among patients initially presenting with pulmonary embolism, factor V Leiden carriers were less likely to have severe symptoms associated with their pulmonary embolism (i.e., hypotension, hypoxemia or tachycardia) than non-carriers and scored lower in PESI (pulmonary embolism severity index) and RIETE scores(24, 25).

The majority of patients in all the three subgroups (89%, 90% and 86%, respectively) received initial therapy with low molecular weight heparin (LMWH), at similar daily doses, transitioned immediately to vitamin K antagonists (VKA) (Table II). Notably, the duration of anticoagulation was longer in carriers of factor V Leiden or prothrombin 20210G-A mutation than in non-carriers (397±508 days per 100 patient-years in factor V Leiden carriers, 420±502 days in prothrombin 20210G-A mutation carriers and 303±377 days in non-carriers; $p < 0.001$).

During the course of anticoagulant therapy, 160 patients developed deep vein thrombosis recurrence, 94 pulmonary embolism recurrence, 154 had major bleeding (gastrointestinal tract $n=47$, brain $n=28$, retroperitoneal $n=11$), 291 presented with non-major bleeding and 151 died (Table III). Compared with non-carriers, factor V Leiden carriers had a similar rate of venous thromboembolism recurrence (rate ratio [RR]: 0.96; 95%CI: 0.68-1.33) and a significantly lower rate of major bleeding (RR: 0.32; 95%CI: 0.16-0.59) and non-major bleeding (RR: 0.46; 95%CI: 0.30-0.68). Prothrombin 20210G-A mutation carriers had a comparable rate of venous thromboembolism recurrence (RR: 0.86; 95%CI: 0.58-1.24) and a lower rate of major bleeding (RR: 0.49; 95%CI:

0.27-0.84), but their rate of non-major bleeding was similar to that observed in non-carriers (RR: 0.78; 95%CI: 0.54-1.10).

On multivariable analysis, factor V Leiden carriers had a similar rate of venous thromboembolism recurrences (adjusted hazard ratio [HR]: 1.16; 95%CI: 0.82-1.64), half the rate of major bleeding (adjusted HR: 0.50; 95%CI: 0.25-0.99) and a non-significantly lower rate of non-major bleeding (adjusted HR: 0.66; 95%CI: 0.43-1.01) compared to non-carriers. Both prothrombin 20210G-A mutation carriers and non-carriers had a similar rate of venous thromboembolism recurrences (adjusted HR: 1.00; 95%CI: 0.68-1.48), major bleeding (adjusted HR: 0.75; 95%CI: 0.42-1.34) and non-major bleeding (adjusted HR: 1.10; 95%CI: 0.77-1.57) (Table IV).

The assessment of patients with double heterozygosity for factor V Leiden and prothrombin 20210G-A mutations, or with homozygosity for factor V Leiden or prothrombin 20210G-A mutation did not reveal any measurable difference in the outcome compared with non-carriers, but there were only 203 patients in this category (Table V).

Discussion

Most guidelines of antithrombotic therapy issued before 2008 recommended performing thrombophilia testing in venous thromboembolism patients with specific clinical conditions, including a first episode of spontaneous venous thromboembolism, age under 50 years or recurrent venous thromboembolism during the course of anticoagulant therapy(5, 10). However, the latest guidelines did recommend against such testing, since it did not provide added value for patient management(11-13, 26). Our findings, obtained from a large series of consecutive patients with venous thromboembolism, demonstrated that in real life one in every 6-7 patients with venous thromboembolism did undergo thrombophilia testing, and that factor V Leiden or prothrombin 20210G-A mutation carriers did receive anticoagulant therapy for longer periods of time than non-carriers. We failed to find a measurable difference in the rate of venous thromboembolism recurrence during the course of anticoagulant therapy, but factor V Leiden carriers did bleed significantly less.

We consistently found a lower rate of bleeding in factor V Leiden carriers than in non-carriers: they had a decreased rate of major bleeding immediately prior to venous thromboembolism (odds ratio: 0.30; 95%CI: 0.12-0.63), and during the course of anticoagulation they had a lower rate of major bleeding (RR: 0.32; 95%CI: 0.16-0.59) and non-major bleeding (RR: 0.46; 95%CI: 0.30-0.68) relative to non-carriers. This lower risk of bleeding was confirmed on multivariable analysis, after adjusting for potentially confounding variables. Thus, our findings suggest that the presence of factor V Leiden mutation should be considered in future studies aiming to identify venous thromboembolism patients at risk for bleeding during the course of anticoagulant therapy. We also found that factor V Leiden carriers less likely presented with pulmonary embolism at baseline compared with non-carriers (as already reported)(27-31). These findings might suggest against the benefit from prolonging anticoagulation in factor V Leiden carriers. However, we found no differences in the rate of pulmonary embolism recurrence between the three subgroups.

We failed to find a lower rate of bleeding in prothrombin 20210G-A mutation carriers. Their rate of major bleeding prior to the baseline venous thromboembolism and their rate of non-major bleeding during the course of anticoagulant therapy were similar to those in non-carriers. They certainly had a lower rate of major bleeding during the course of anticoagulant therapy (RR: 0.49; 95%CI: 0.27-0.84), but any difference disappeared on multivariable analysis. We also failed to find any difference in the outcome of patients heterozygous for both mutations or in those who were homozygous. Most likely, this absence of differences could be attributed to the small number of patients in each subgroup.

Our study has several limitations that should be addressed. Testing for thrombophilia was performed according to the protocol of each participating hospital, which could cause a bias. However, the proportion of patients found to harbor these polymorphisms in our series was similar to that reported in several prospective studies (8, 32, 33). Of note, unlike the careful patient selection that characterizes some prospective studies performed in academic centers, our

patient population reflects routine, unmonitored medical practice involving a broad spectrum of patients with venous thromboembolism. The RIETE registry provides data on the management of patients with venous thromboembolism in a real-world situation with an unselected patient population. To that end, it may help to identify factors associated with patient outcomes. However, as an observational database, RIETE is not designed to answer questions regarding the efficiency of thrombophilia testing. Data from the registry are hypothesis-generating and provide feedback from real-world clinical situations which may be of help when designing new randomized clinical studies.

In summary, factor V Leiden carriers had half the risk for major and non-major bleeding during the course of anticoagulant therapy as did non-carriers. This finding can contribute to the evaluation of risk and benefit of prolonged secondary venous thromboembolism prevention in patients with venous thromboembolism.

Conflict of interest statement: The authors have no conflicts to declare.

Author Contributions:

Inna Tzoran: Conception and design, critical revision of the article for important intellectual content, final approval of the article

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Table I. Clinical characteristics and treatment according to thrombophilia testing

	FVL carriers	PTM carriers	Non-carriers
Patients, N	1,384	1,115	7,640
Clinical characteristics			
Age (mean years±SD)	50±18	50±17	56±18
Age >50 years	669 (48%)	536 (48%)	4,707 (62%)
Gender (male)	750 (54%)	597 (54%)	3,822 (50%)
Body weight (mean kg±SD)	78±16	78±16	77±16
Underlying diseases			
Chronic heart failure	23 (1.7%)	23 (2.1%)	373 (4.9%)
Chronic lung disease	88 (6.4%)	64 (5.7%)	766 (10%)
CrCl levels <60 mL/min	163 (12%)	131 (12%)	1,631 (21%)
Recent major bleeding	6 (0.43%)	21 (1.9%)	111 (1.5%)
Anaemia	207 (15%)	226 (20%)	1,894 (25%)
Concomitant medications			
Antiplatelets	100 (7.2%)	91 (8.2%)	805 (11%)
Risk factors for VTE			
Surgery	107 (7.7%)	125 (11%)	887 (12%)
Immobility ≥4 days	200 (14%)	179 (16%)	1,400 (18%)
Estrogen therapy (N=1,173)	195 (31%)	162 (31%)	816 (21%)
Pregnancy/puerperium (N=299)	53 (8.4%)	53 (10%)	193 (5.1%)
Cancer	86 (6.2%)	92 (8.3%)	807 (11%)
Prior VTE	347 (25%)	215 (19%)	1,200 (16%)
Initial VTE presentation,			
Pulmonary embolism	463 (33%)	536 (48%)	3,829 (50%)
<i>In patients with PE,</i>			
SBP levels <90 mm Hg	3 (0.65%)	15 (2.8%)	139 (3.6%)
Heart rate >110 per minute	77 (17%)	110 (21%)	937 (25%)
Sat O ₂ <90%	25 (9.6%)	63 (20%)	755 (30%)
<i>Prognostic scores,</i>			
PESI <65 points	243 (52%)	262 (49%)	1,230 (32%)
sPESI <1 point	300 (65%)	325 (61%)	1,779 (46%)
RIETE <1 point	247 (53%)	263 (49%)	1,344 (35%)

Abbreviations: FVL, Factor V Leiden; PTM, prothrombin mutation; SD, standard deviation; CrCl, creatinine clearance; VTE, venous thromboembolism; SBP, systolic blood pressure; PESI, pulmonary embolism severity index; sPESI, simplified PESI score; CI, confidence intervals

Table II. Therapeutic strategies

	FVL carriers	PTM carriers	Non-carriers
Patients, N	1,384	1,115	7,640
Initial therapy,			
Low-molecular-weight heparin	1,231 (89%)	1,007 (90%)	6,538 (86%)
Mean LMWH doses (IU/Kg/day)	178±40	179±38	180±37
Unfractionated heparin	66 (4.8%)	66 (5.9%)	657 (8.6%)
Fondaparinux	46 (3.3%)	17 (1.5%)	158 (2.1%)
Rivaroxaban	18 (1.3%)	3 (0.27%)	78 (1.0%)
Thrombolytics	15 (1.1%)	20 (1.8%)	170 (2.2%)
Vena cava filter	28 (2.0%)	23 (2.1%)	155 (2.0%)
Long-term therapy,			
Vitamin K-antagonists	1,102 (80%)	898 (81%)	5,985 (78%)
Low-molecular-weight heparin	212 (15%)	187 (17%)	1,341 (18%)
Mean LMWH doses (IU/Kg/day)	149±44	149±47	149±48
Rivaroxaban	45 (3.3%)	20 (1.8%)	176 (2.3%)
Duration of therapy,			
Mean days (±SD)	397±508	420±502	303±377
Median days (IQR)	229 (146-398)	246 (166-411)	199 (132-349)

Abbreviations: FVL, Factor V Leiden; PTM, prothrombin mutation; LMWH, low-molecular-weight heparin; IU, international units; SD, standard deviation; IQR, interquartile range.

Table III. Clinical outcome during the course of anticoagulant therapy

	FVL carriers		PTM carriers		Non-carriers	
	N	N per 100 patient-years	N	N per 100 patient-years	N	N per 100 patient-years
Patients, N	1,384		1,115		7,640	
Events,						
Recurrent DVT	25	1.69 (1.12-2.46)	17	1.36 (0.82-2.13)	118	1.90 (1.58-2.27)
Recurrent PE	16	1.08 (0.64-1.72)	14	1.11 (0.63-1.82)	64	1.02 (0.79-1.29)
Recurrent VTE	41	2.83 (2.06-3.80)	31	2.52 (1.75-3.54)	182	2.95 (2.54-3.41)
Major bleeding	10	0.67 (0.34-1.19) [‡]	13	1.03 (0.57-1.71) [†]	131	2.09 (1.75-2.47)
Gastrointestinal	2	0.13 (0.02-0.44) [‡]	4	0.31 (0.10-0.76)	41	0.65 (0.47-0.87)
Haematoma	2	0.13 (0.02-0.44) [‡]	3	0.23 (0.06-0.64)	31	0.49 (0.34-0.69)
Cerebral	3	0.20 (0.05-0.54)	2	0.16 (0.03-0.52)	23	0.36 (0.24-0.54)
Retroperitoneal	1	0.07 (0.00-0.33)	0	-	10	0.16 (0.08-0.28)
Haemopericardias	0	-	0	-	4	0.06 (0.02-0.15)
Non-major bleeding	25	1.70 (1.12-2.47) [‡]	36	2.91 (2.07-3.98)	230	3.72 (3.26-4.23)
Gastrointestinal	4	0.27 (0.08-0.64) [‡]	10	0.79 (0.40-1.41)	51	0.81 (0.61-1.05)
Hematuria	2	0.13 (0.02-0.44) [‡]	4	0.31 (0.10-0.76) [*]	54	0.85 (0.65-1.11)
Haematoma	5	0.33 (0.12-0.74)	4	0.31 (0.10-0.76)	38	0.60 (0.43-0.82)
Menorrhagia	3	0.20 (0.05-0.55)	2	0.16 (0.03-0.52)	20	0.32 (0.20-0.48)
Death	13	0.86 (0.48-1.44) [†]	11	0.86 (0.45-1.49) [†]	127	2.00 (1.68-2.37)
Pulmonary embolism	1	0.07 (0.00-0.33)	3	0.23 (0.06-0.64)	12	0.19 (0.10-0.32)
Bleeding	1	0.07 (0.00-0.33)	0	-	9	0.14 (0.07-0.26)
Cerebral	0	-	0	-	4	0.06 (0.02-0.15)
Gastrointestinal	1	0.07 (0.00-0.33)	0	-	2	0.03 (0.01-0.10)

Differences between FVL carriers or PTM carriers and non-carriers (reference):

*p < 0.05; †p < 0.01; ‡p < 0.001

Abbreviations: FVL, Factor V Leiden; PTM, prothrombin mutation; IQR, interquartile range; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Table IV. Multivariable analyses for VTE recurrences, major bleeding or death during the course of anticoagulant therapy.

	VTE recurrences	P value	Major bleeding	P value	Non-major bleeding	p_value
Clinical characteristics,						
Age >50 years	0.73 (0.55-1.01)	0.054	1.43 (0.92-2.23)	0.112	1.57 (1.16-2.12)	0.003
Underlying diseases,						
CrCl levels <60 mL min	1.01 (0.71-1.44)	0.944	1.52 (1.02-2.28)	0.040	1.45 (1.09-1.93)	0.011
Recent major bleeding	2.80 (1.35-5.81)	0.005	1.64 (0.66-4.11)	0.287	1.79 (0.94-3.43)	0.079
Anemia	1.28 (0.95-1.72)	0.110	2.45 (1.72-3.48)	0.000	1.35 (1.03-1.75)	0.028
Concomitant medications,						
Antiplatelets	1.30 (0.90-1.89)	0.164	0.99 (0.58-1.69)	0.966	0.93 (0.62-1.40)	0.733
Risk Factors for VTE,						
Unprovoked	Reference	0.000	Reference	0.157	Reference	0.408
Cancer with metastases	2.84 (1.67-4.84)	0.000	1.39 (0.61-3.19)	0.432	0.93 (0.46-1.87)	0.831
Cancer without metastases	1.60 (1.08-2.38)	0.020	1.73 (1.06-2.82)	0.029	1.17 (0.78-1.75)	0.453
Transient risk factors	0.61 (0.44-0.85)	0.003	1.05 (0.70-1.56)	0.824	1.25 (0.95-1.64)	0.114
Initial VTE presentation,						
Symptomatic PE	1.12 (0.87-1.45)		1.50 (1.06-2.12)	0.021	1.41 (1.11-1.79)	0.005
Thrombophilia testing,						
Non-carriers	Reference	0.659	Reference	0.111	Reference	0.114
FVL carriers	1.16 (0.82-1.64)	0.363	0.50 (0.25-0.99)	0.042	0.66 (0.43-1.01)	0.054
PTM carriers	1.00 (0.68-1.48)	0.974	0.75 (0.42-1.34)	0.327	1.10 (0.77-1.57)	0.599

Abbreviations: VTE, venous thromboembolism; CrCl, creatinine clearance; PE, pulmonary embolism; FVL, Factor V Leiden; PTM, prothrombin mutation.

Table V. Clinical outcome during the course of anticoagulant therapy in some subgroups of patients with thrombophilia. Results expressed as number of events per 100 patient-years

	N	Age	VTE recurrences		Major bleeding	
Non-carriers	7,640	56.4±18.4	181	2.95 (2.54-3.41)	131	2.09 (1.75-2.47)
Heterozigous FVL	1,326	50.2±17.9 [‡]	41	2.99 (2.18-4.02)	10	0.70 (0.36-1.26) [‡]
Heterozigous PTM	970	50.7±17.4 [‡]	25	2.43 (1.61-3.53)	9	0.84 (0.41-1.55) [‡]
Heterozigous FVL and PTM	106	47.1±17.2 [‡]	5	3.14 (1.15-6.97)	2	1.21 (0.20-3.99)
Homozygous FVL	58	47.4±15.6 [‡]	0	-	0	-
Homozygous PTM	39	47.1±17.4 [‡]	1	2.58 (0.13-12.7)	2	5.56 (0.93-18.4)

Comaprison between non-carriers and other subgroups: [‡]p <0.05; [†]p <0.01; [‡]p <0.001

Abbreviations: FVL, Factor V Leiden; PTM, prothrombin mutation; VTE, venous thromboembolism

Highlights

- During anticoagulation, the risk of major bleeding was 50% lower in factor V Leiden carriers
- During anticoagulation, factor V Leiden presence did not affect venous thromboembolism recurrence risk
- Factor V Leiden presence should be considered in decision-making on anticoagulation duration

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APPENDIX

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VII.3 Annexe 3: « Uterine bleeding during anticoagulation in women with venous thromboembolism (SIGAPS D, IF : 2.32)



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Uterine bleeding during anticoagulation in women with venous thromboembolism

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Uterine bleeding
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Venous thromboembolism
A real-life study

ABSTRACT

Background: Women presenting with uterine bleeding during the course of anticoagulant therapy for venous thromboembolism (VTE) present a difficult therapeutic dilemma due to the absence of evidence-based recommendations.

Methods: We used the RIETE (Registro Informatizado Enfermedad TromboEmbólica) database to assess the clinical characteristics of women presenting with uterine bleeding during anticoagulation for VTE, its frequency, time course, management and 30-day outcomes.

Results: As of October 2016, 31,951 women with VTE were recruited in RIETE. During the course of anticoagulant therapy, 53 (0.17%) developed major uterine bleeding, 118 (0.37%) non-major uterine bleeding and 948 (2.97%) had major bleeding in other sites. Median time elapsed from VTE to bleeding was: 32, 71 and 22 days, respectively. Mean age was: 56 ± 17 , 52 ± 20 and 75 ± 14 years, respectively. Women with major uterine bleeding more likely had cancer (51%), anemia (72%), raised platelet count (19%) or recent major bleeding (11%) at VTE presentation than those in the other subgroups. During the first 30 days after bleeding, 17%, 1.7% and 31% of women died, respectively. Of 11 women with uterine bleeding who died, 9 (82%) had cancer, two (18%) died of bleeding and one (9.1%) died of pulmonary embolism after discontinuing anticoagulation.

Conclusions: Uterine bleeding during the course of anticoagulation for VTE is not uncommon and mostly affects young women. Those with cancer, anaemia, raised platelet count or recent bleeding at baseline are at an increased risk for uterine bleeding during anticoagulation.

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1. Introduction

Abnormal uterine bleeding is a relatively common complication in women receiving anticoagulant therapy for venous thromboembolism (VTE) [1–3]. In the literature, there is scarce information on its frequency, the clinical characteristics of these women, the time course and the severity of bleeding [1,4,5]. Most of the published information came from randomized clinical trials with strict inclusion and exclusion criteria, and limited follow-up [6]. Thus, although randomized clinical trials provide high-level evidence on the effi-

cacy and safety of therapeutic interventions, they generally involve well-defined study populations that exclude complex patients and do not provide data on the management of bleeding [1,7,8]. This is important since uterine bleeding in women receiving anticoagulant therapy for VTE presents a dilemma because the potential benefits of anticoagulation must be weighed against the risk of inducing re-bleeding.

RIETE (Registro Informatizado Enfermedad TromboEmbólica) is a multicenter, ongoing, international (Spain, Belgium, Czech Republic, France, Greece, Israel, Italy, Latvia, Republic of Macedonia, Switzerland, United States, Canada, Ecuador and Venezuela enroll patients) observational registry of consecutive patients with symptomatic, objectively confirmed, acute VTE (ClinicalTrials.gov identifier: NCT02832245). Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes [9–13].

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** A full list of RIETE investigators is given in the appendix.

Using the RIETE database, we retrospectively assessed the clinical characteristics of these women, the frequency and time course of bleeding, its management and the outcome within the first 30 days after bleeding.

2. Methods

2.1. Inclusion criteria

Consecutive patients with acute, symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) confirmed by objective tests (compression ultrasonography or contrast venography for DVT; helical CT-scan, ventilation–perfusion lung scintigraphy or angiography for PE) were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their legal power of attorney) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

Physicians participating in the RIETE registry made all efforts to enroll consecutive patients. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. To ensure the validity of the information entered into the database, one of the specially trained monitors visited each participating hospital and compared information in 25 to 50 randomly chosen patient records with the information entered into the RIETE database. For data quality assessment, monitors assessed 4,100 random records from all participating hospitals that included 1,230,000 measurements. These data showed a 95% overall agreement between the registered information and patient records. RIETE also used electronic data monitoring to detect inconsistencies or errors and attempted to resolve discrepancies by contacting the local coordinators.

2.2. Study design

We conducted a retrospective study that used prospectively collected data from consecutive patients enrolled in the RIETE registry. Major uterine bleeding was defined as an overt bleed that required a transfusion of two units or more of blood or was fatal. Clinically relevant non major uterine bleeding was defined as any bleeding requiring a medical intervention (hospitalization, surgery or interventional procedure, further diagnostic imaging, laboratory test or specialist evaluation) and/or treatment discontinuation, and not meeting any of the criteria for major bleeding. We compared the clinical characteristics of women with uterine bleeding during anticoagulation for VTE, its frequency, time course, management and 30-day outcomes vs. those in women presenting with major bleeding in other sites. We focused on the management of anticoagulant therapy after bleeding, not on other interventions (like surgery, hormonal therapy, etc.).

2.3. Baseline variables and definitions

The following parameters are routinely recorded in RIETE: patient's baseline characteristics; clinical status including any co-existing or underlying conditions; risk factors for VTE; diagnostics tools used for diagnosis; laboratory data; the treatment received upon VTE diagnosis (drugs, doses, regimen and duration); and the outcome during the course of anticoagulation. Age was divided in three categories (less than 35 years, 35 to 50 years and more than 50 years). Active cancer was defined as newly diagnosed cancer, metastatic cancer, or cancer that was being treated (i.e. surgery, chemotherapy, radiotherapy, support therapy). Anemia was defined as a hemoglobin content <13 g/dL for men and <12 g/dL for women.

2.4. Treatment and follow-up

Patients were managed according to the clinical practice of each participating centre (i.e., there was no standardization of treatment). Patients were followed-up during the course of therapy in the outpatient clinic or physician's office. During each visit, any signs or symptoms suggesting VTE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent VTE was investigated by repeat compression ultrasonography, lung scanning, helical-CT scan or pulmonary angiography, as appropriate. Most outcomes were classified as reported by the clinical centers. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

2.5. Statistical analysis

Categorical variables were compared using the chi-square test (two-sided) and Fisher's Exact Test (two-sided). Continuous variables were compared using Student t test. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were calculated, and a *p*-value <0.05 was considered to be statistically significant. Statistical analyses were conducted with SPSS for Windows Release 17.0 (SPSS, Inc).

2.6. Role of the funding source

The sponsors of the RIETE registry (Sanofi and Bayer) had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

As of October 2016, 31,951 women with VTE were recruited in RIETE. During the course of anticoagulant therapy, 53 (0.17%; 95% CI: 0.13–0.21) developed major uterine bleeding, 118 (0.37%; 95% CI: 0.31–0.44) had clinically relevant non major uterine bleeding and 948 (2.97%; 95% CI: 2.79–3.16) suffered major bleeding in other

Table 1
Clinical characteristics of the patients, according to severity and site of bleeding during the course of anticoagulant therapy.

	Major uterine bleeding	Non-major uterine bleeding	Major bleeding in other sites	No major bleeding in other sites
Patients, N	53	118	948	30,832
Clinical characteristics				
Mean age (years ± SD)	56 ± 17 [‡]	52 ± 20 [‡]	75 ± 14 [‡]	67 ± 19
Age <35 years	4 (7.5%)	23 (19%) [‡]	27 (2.8%) [‡]	2,736 (8.9%)
Age 35–50 years	17 (32%) [‡]	44 (37%) [‡]	35 (3.7%) [‡]	3,672 (12%)
Age >50 years	32 (60%) [‡]	51 (43%) [‡]	886 (93%) [‡]	24,424 (79%)
Body weight (kg ± SD)	77 ± 20*	78 ± 21 [‡]	69 ± 15 [‡]	71 ± 15
Associated conditions				
Cancer	27 (51%) [‡]	27 (23%)	272 (29%) [‡]	6,145 (20%)
Uterine	19 (36%) [‡]	15 (13%) [‡]	26 (2.7%) [*]	515 (1.7%)
Metastatic cancer	15 (56%)	9 (33%)	127 (47%)	2,606 (42%)
Pregnancy/puerperium	3 (5.7%)	4 (3.4%)	3 (0.32%) [‡]	820 (2.7%)
Anemia	38 (72%) [‡]	51 (43%)	479 (51%) [‡]	10,980 (36%)
PIC <100,000/μL	0	3 (2.5%)	34 (3.6%) [‡]	600 (1.9%)
PIC >450,000/μL	10 (19%) [‡]	6 (5.1%)	62 (6.5%) [‡]	1,160 (3.8%)
CrCl levels <60 ml/min	13 (25%) [‡]	26 (22%) [‡]	638 (67%) [‡]	14,616 (47%)
Recent major bleeding	6 (11%) [‡]	7 (5.9%) [*]	47 (5.0%) [‡]	645 (2.1%)
Initial VTE presentation				
Pulmonary embolism	30 (57%)	72 (61%)	595 (63%) [‡]	16,421 (53%)

Comparisons between women who bled vs. those that did not bleed: ^{*}*p* < 0.05; [‡]*p* < 0.01; [‡]*p* < 0.001.

Abbreviations: SD, standard therapy; PIC, platelet count; CrCl, creatinine clearance; VTE, venous thromboembolism.

Table 2
Time course and 30-day outcomes according to site and severity of bleeding.

	Major uterine bleeding	Non-major uterine bleeding	Major bleeding in other sites
Patients, N	53	118	948
Time elapsed from index VTE			
Mean days (± SD)	74 ± 108	130 ± 200	137 ± 358
Median days (IQR)	32 (7–121)	71 (19–143)	22 (7–105)
Day 0 to Day 7	14 (26%)	15 (13%) [†]	240 (25%)
Day 8 to Day 30	10 (19%)	24 (20%)*	288 (30%)
Day 31 to Day 90	14 (26%)	31 (26%)*	165 (17%)
Beyond Day 90	15 (28%)	48 (41%) [†]	255 (27%)
30-day outcomes			
Major re-bleeding	4 (7.5%)	2 (1.7%)	44 (4.6%)
Uterine	2 (3.8%) [†]	1 (0.85%)	0
Non-major re-bleeding	0	3 (2.5%)	11 (1.2%)
Uterine	0	1 (0.85%)	1 (0.11%)
Recurrent VTE	1 (1.9%)	1 (0.85%)	37 (3.9%)
Death	9 (17%)*	2 (1.7%) [†]	291 (31%)
Fatal pulmonary embolism	1 (1.9%)	0	12 (1.3%)
Fatal bleeding	2 (3.8%) [†]	0 [‡]	193 (20%)

Comparisons between women with uterine bleeding vs. those who bled in other sites: **p* < 0.05; [†]*p* < 0.01; [‡]*p* < 0.001.

Abbreviations: VTE, venous thromboembolism; SD, standard therapy; IQR, interquartile range.

sites. Their mean age was: 56 ± 17, 52 ± 20 and 75 ± 14 years, respectively (Table 1). Women with uterine bleeding (major or non-major) were over 10 years younger than those that did not bleed, and 20 years younger than those with major bleeding in other sites. Fifty-one percent of women with major uterine bleeding and 23% of those with non-major bleeding had cancer, mostly (63%) in the uterus. Women with major (but not those with non-major) uterine bleeding more likely had anemia (72%), raised platelet count (19%) or recent major bleeding (11%) at VTE presentation than those presenting with major bleeding in other sites or without bleeding.

Among 53 women with major uterine bleeding, 26% bled within the first week of anticoagulant therapy, 19% from Day 8 to Day 30, 26% from Day 31 to day 90 and 28% beyond Day 90 (Table 2). Among 118 women with non-major uterine bleeding the proportions were 13%, 20%, 26% and 41%, respectively. The proportion of women who re-bleed within the first 30 days was similar, but the mortality rate was half in women with major uterine bleeding than in those with major bleeding in other sites (17% vs. 31%, odds ratio: 0.46; 95% CI: 0.21–0.93).

Most bleeding episodes appeared during the course of therapy with vitamin K antagonists (VKA) or low-molecular-weight heparin (LMWH), as shown in Table 3. Women with cancer were more likely to be on LMWH than those without cancer (46% vs. 14%, *p* < 0.0001), and less likely to be on VKA (37% vs. 51%, *p* = 0.12) or direct oral anticoagulants (3.7% vs. 27%, *p* = 0.0004). Among women with uterine bleeding, anticoagulant therapy was definitely discontinued in 13 (25%) women with major bleeding and in 10 (8.5%) with non-major bleeding (*p* = 0.009). Anticoagulation was transiently discontinued in 9 (17%) women with major- and in 3 (2.5%) with non-major bleeding (*p* = 0.003). After uterine bleeding, most patients re-started anticoagulation with LMWH, at lower mean doses than before. Nine women with major bleeding (17%) and two (with non-major bleeding 1.7%) died within the first 30 days. Of these, 10 (91%) had cancer. Two women died of bleeding and one died of PE after discontinuing anticoagulant therapy.

4. Discussion

Abnormal uterine bleeding in women receiving anticoagulant therapy for VTE may have significant impact on their physical, social and emotional quality of life [2,14,15]. Our data, obtained from a large series of consecutive women receiving anticoagulant therapy

Table 3
Treatment at uterine bleeding, after its cessation and 30-day outcomes, according to the severity of bleeding and presence of cancer.

	Major bleeding		Non-major bleeding	
	cancer	no cancer	cancer	no cancer
Patients, N	27	26	27	91
Current therapy at bleeding				
Vitamin K antagonists	7 (26%)	11 (42%)	13 (48%)	49 (54%)
Low-molecular-weight heparin	14 (52%)	6 (23%)*	11 (41%)	10 (11%) [†]
Mean LMWH dose (IU/kg/day)	161 ± 45	157 ± 34	146 ± 58	157 ± 33
LMWH+VKA	1 (3.7%)	1 (3.8%)	0	0
Direct oral anticoagulants	1 (3.7%)	5 (19%)	1 (3.7%)	27 (30%) [†]
Unfractionated heparin	4 (15%)	2 (7.7%)	1 (3.7%)	2 (2.2%)
Fondaparinux	0	0	1 (3.7%)	2 (2.2%)
Thrombolytics	0	1 (3.8%)	0	1 (1.1%)
Therapy on bleeding				
Cessation of therapy	5 (18%)	8 (31%)	1 (3.7%)	9 (9.9%)
Transient discontinuation	4 (15%)	5 (19%)	1 (3.7%)	2 (2.2%)
Days without therapy (mean)	5.0 ± 4.1	9.1 ± 13	–	3.9 ± 2.8
Days without therapy (median)	4 (3–8)	4 (2–5)	–	4 (2–6)
Therapy after bleeding				
Low-molecular-weight heparin	17 (63%)	8 (31%)*	14 (52%)	22 (24%) [†]
Mean LMWH dose (IU/kg/day)	92 ± 55	146 ± 61	108 ± 55	120 ± 47
Vitamin K antagonists	1 (3.7%)	8 (31%)*	10 (37%)	42 (46%)
Direct oral anticoagulants	1 (3.7%)	2 (7.7%)	1 (3.7%)	18 (20%) [†]
Unfractionated heparin	3 (11%)	0	1 (3.7%)	0
Vena cava filter	4 (15%)	2 (7.7%)	4 (15%)	3 (3.3%)*
30-day outcomes				
Major re-bleeding	4 (15%)	0	1 (3.7%)	1 (1.1%)
Uterine	2 (7.4%)	0	1 (3.7%)	0
Non-major uterine bleeding	0	0	0	3 (3.3%)
Recurrent DVT	0	1 (3.8%)	0	0
Recurrent PE	1 (3.7%)	0	0	1 (1.1%)
Death	8 (30%)	1 (3.8%)*	2 (7.4%)	0
Fatal bleeding	2 (7.4%)	0	0	0
Fatal PE	1 (3.7%)	0	0	0

Comparisons between women with versus without cancer: **p* < 0.05; [†]*p* < 0.01; [‡]*p* < 0.001.

Abbreviations: LMWH, low-molecular-weight heparin; IU, international units; VKA, vitamin K antagonists; DVT, deep vein thrombosis; PE, pulmonary embolism.

for VTE, reveal that uterine bleeding is not that common. Only one in every 603 (0.17%) women presented with major uterine bleeding (accounting for 5.3% of all major bleeds), and one in every 270 (0.37%) presented with non-major uterine bleeding. However, one in every 6 women with major uterine bleeding (17%) died within the first 30 days, and this is important since many (40%) were aged <50 years, two died of the bleeding event and one died of PE appearing shortly after discontinuing anticoagulant therapy. Thus, its clinical relevance should not be underestimated.

Compared with women that did not bleed, women presenting with major uterine bleeding were more likely to have cancer, anaemia or raised platelet count at the index VTE presentation. These three conditions have been associated with an increased risk for bleeding in the literature [16–22], and suggest that early identification of women with VTE at increased risk for uterine bleeding during the course of anticoagulation might be feasible in the future.

Our study also shows that the management of major uterine bleeding in real life is rather heterogeneous, most likely due to the absence of evidence-based recommendations in the literature [23–25]. In our series, anticoagulation was stopped in 20%, transiently discontinued in 15% and modified in most. Besides, it was not modified in most women with non-major bleeding. The 30-day outcome was clearly worse in women with cancer. However, further studies are needed to more precisely identify women at an increased risk for re-bleeding and for VTE recurrences after discontinuing anticoagulant therapy.

The present study has potential limitations. First, RIETE is an observational registry, and our findings are hypothesis-generating. Thus, our data are of no help to decide the best therapeutic strategy

for these women. Moreover, there is no external adjudication of the events (including major bleed), which are reported by the doctors. However, some prior studies showed that adjudicated data usually match well with onsite outcome assessment [26–28]. Second, patients in the RIETE database were selected in several countries. The variability of practices in different countries could potentially affect the study outcomes. For instance, the dosing and regimen can vary according to each individual's country's pattern of practice, underlying disease process, and/or presence or absence of cancer. Furthermore, a variety of practitioners entered data into the registry, which may lend itself to potential inaccuracies in the data being reported. However, the RIETE registry provides insights into the natural history of VTE with an unselected patient population, in contrast to the rigorously controlled conditions of randomized clinical studies. It can, therefore, help to identify factors associated with better or worse outcomes, and provide feedback from real-world clinical situations, which may be valuable when designing new randomized clinical studies.

In summary, this is the first real-life study on the frequency, time course, clinical characteristics and severity of uterine bleeding occurring during the course of anticoagulation for VTE. These events are not common, but clinically relevant because they mostly affect young women. The existence of cancer, anaemia or raised platelet count at baseline should alert the clinician to be aware about an increased risk for bleeding.

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Conflict of interest statement

The authors declare that they have no relevant conflicts of interest with this manuscript.

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VII.4 Annexe 4: « Clinical outcomes during anticoagulant therapy in fragile patients with venous thromboembolism »

Clinical outcomes during anticoagulant therapy in fragile patients with venous thromboembolism

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Abstract

Background: Subgroup analyses from randomized trials suggested favorable results for the direct oral anticoagulants in fragile patients with venous thromboembolism (VTE). The frequency and natural history of fragile patients with VTE have not been studied yet.

Objectives: To compare the clinical characteristics, treatment and outcomes during the first 3 months of anticoagulation in fragile vs non-fragile patients with VTE.

Methods: Retrospective study using consecutive patients enrolled in the RIETE (Registro Informatizado Enfermedad TromboEmbolica) registry. Fragile patients were defined as those having age ≥ 75 years, creatinine clearance (CrCl) levels ≤ 50 mL/min, and/or body weight ≤ 50 kg.

Results: From January 2013 to October 2016, 15 079 patients were recruited. Of these, 6260 (42%) were fragile: 37% were aged ≥ 75 years, 20% had CrCl levels ≤ 50 mL/min, and 3.6% weighed ≤ 50 kg. During the first 3 months of anticoagulant therapy, fragile patients had a lower risk of VTE recurrences (0.78% vs 1.4%; adjusted odds ratio [OR]: 0.52; 95% confidence intervals [CI]: 0.37-0.74) and a higher risk of

*A full list of RIETE investigators is given in the Appendix.

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major bleeding (2.6% vs 1.4%; adjusted OR: 1.41; 95% CI: 1.10-1.80), gastrointestinal bleeding (0.86% vs 0.35%; adjusted OR: 1.84; 95% CI: 1.16-2.92), haematoma (0.51% vs 0.07%; adjusted OR: 5.05; 95% CI: 2.05-12.4), all-cause death (9.2% vs 3.5%; adjusted OR: 2.02; 95% CI: 1.75-2.33), or fatal PE (0.85% vs 0.35%; adjusted OR: 1.77; 95% CI: 1.10-2.85) than the non-fragile.

Conclusions: In real life, 42% of VTE patients were fragile. During anticoagulation, they had fewer VTE recurrences and more major bleeding events than the non-fragile.

KEYWORDS

anticoagulants, hemorrhage, mortality, recurrences, venous thromboembolism

Essentials

- Recent randomized trials suggested fewer bleeding events in fragile patients with VTE receiving DOACs.
- The frequency, clinical characteristics and outcome of these patients have not been reported in real life.
- Fragile patients with VTE had a higher risk for major bleeding or death and a lower risk for recurrences than non-fragile.

1 | INTRODUCTION

In recent years, a number of direct oral anticoagulants (DOACs) have been developed for the treatment of venous thromboembolism (VTE). Their use has been associated with a lower rate of major bleeding compared with standard therapy.¹⁻⁵ Hence, apixaban, rivaroxaban, dabigatran, and edoxaban have been approved for the treatment of patients with deep vein thrombosis (DVT) or pulmonary embolism (PE).⁶ Subgroup analyses from these randomized clinical trials have delivered further promising results, particularly for the so-called fragile patients, defined as those having creatinine clearance (CrCl) levels ≤ 50 mL/min, age ≥ 75 years, or body weight ≤ 50 kg.^{3-5,7} Hence, there are reasons to suggest that fragile patients with VTE could be considered ideal candidates for long-term therapy with DOACs.^{4,5,7,8} However, the proportion of fragile patients in real life, and their outcome during the course of anticoagulant therapy have not been thoroughly studied yet.

RIETE (Registro Informatizado Enfermedad TromboEmbólica) is a multicenter, ongoing, international (Spain, Belgium, Brazil, Canada, Czech Republic, Ecuador, France, Israel, Italy, Latvia, Republic of Macedonia, Switzerland, and the United States enroll patients) registry of consecutive patients with symptomatic, objectively confirmed, acute VTE (ClinicalTrials.gov identifier: NCT02832245).⁹⁻¹³ Since its inception in 2001, the aim of RIETE is to record data including the clinical characteristics, treatment patterns, and outcomes in patients diagnosed with VTE. Using the RIETE database, the current study compared the clinical characteristics, treatment, and outcomes during the first 3 months of anticoagulation in fragile vs non-fragile patients with acute VTE.

2 | PATIENTS AND METHODS

2.1 | Inclusion criteria

Consecutive patients presenting with symptomatic, acute DVT or PE confirmed by objective tests (compression ultrasonography or contrast

venography for DVT; helical CT-scan, ventilation-perfusion lung scintigraphy or angiography for PE) were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their legal power of attorney) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

Physicians participating in the RIETE registry made all efforts to enroll consecutive patients. Data were recorded onto a computer-based case-report form at each participating hospital and submitted to a centralized coordinating center through a secure website. To ensure the validity of the information entered into the database, one of the specially trained monitors visited each participating hospital and compared information in 25-50 randomly chosen patient records with the information entered into the RIETE database. For data quality assessment, monitors assessed 4100 random records from all participating hospitals, which included 1 230 000 measurements. These data showed a 95% overall agreement between the registered information and patient records. RIETE also used electronic data monitoring to detect inconsistencies or errors and attempted to resolve discrepancies by contacting the local coordinators.

2.2 | Study design

We conducted a cohort study that used consecutive patients enrolled in the RIETE registry. For this study, only patients recruited from January 2013 (the year when the first DOAC was approved for use in patients with VTE) were considered. Our aim was to compare the clinical characteristics, treatment, and outcomes in fragile vs non-fragile patients. The major outcome was the rate of VTE recurrences or major bleeding occurring during the first 3 months of anticoagulant therapy.

2.3 | Definitions

Fragile patients were defined as those having CrCl levels ≤ 50 mL/min, age ≥ 75 years, or body weight ≤ 50 kg.³ Immobilized patients were

TABLE 1 Clinical characteristics in 15 079 fragile and non-fragile patients with acute venous thromboembolism

	Non-fragile	Fragile	Age ≥ 75 y	Weight ≤ 50 kg	CrCl ≤ 50 mL/min
Patients, N	8819	6260	5514	537	3059
Clinical characteristics					
Age (y ± SD)	55 ± 14	80 ± 10 [‡]	82 ± 5.0	71 ± 2.0	81 ± 10
Gender (male)	5058 (57%)	2407 (38%) [‡]	2104 (38%)	73 (14%)	1030 (34%)
Body weight (kg ± SD)	81 ± 17	71 ± 14 [‡]	72 ± 14	47 ± 4.	67 ± 13
Risk factors for VTE					
Immobilization ≥ 4 d	1342 (15%)	1648 (26%) [‡]	1488 (27%)	165 (31%)	894 (29%)
Surgery	1097 (12%)	502 (8.0%) [‡]	406 (7.4%)	48 (8.9%)	228 (7.5%)
Cancer	1894 (21%)	1495 (24%) [‡]	1235 (22%)	164 (31%)	723 (24%)
Estrogen use	813 (9.2%)	222 (3.5%) [‡]	160 (2.9%)	53 (9.9%)	92 (3.0%)
Pregnancy/puerperium	172 (2.0%)	7 (0.11%) [‡]	0	4 (0.74%)	3 (0.10%)
None of the above	4353 (49%)	3004 (48%)	2731 (50%)	175 (33%)	1425 (47%)
Prior VTE	1352 (15%)	906 (14%)	821 (15%)	58 (11%)	419 (14%)
Underlying diseases					
Chronic heart failure	254 (2.9%)	775 (12%) [‡]	720 (13%)	56 (10%)	469 (15%)
Chronic lung disease	801 (9.1%)	1015 (16%) [‡]	904 (16%)	62 (12%)	495 (16%)
Recent major bleeding	170 (1.9%)	168 (2.7%) [‡]	132 (2.4%)	15 (2.8%)	82 (2.7%)
Blood tests					
Anemia	2492 (28%)	2514 (40%) [‡]	2116 (38%)	275 (51%)	1430 (47%)
Platelet count <150 000/μL	1083 (12%)	1036 (17%) [‡]	884 (16%)	70 (13%)	537 (18%)
Platelet count >450 000/μL	249 (2.8%)	185 (3.0%)	151 (2.7%)	35 (6.5%)	95 (3.1%)
CrCl levels (mL/min ± SD)	108 ± 50	54 ± 24 [‡]	55 ± 23	54 ± 38	36 ± 10
Initial VTE presentation					
Pulmonary embolism	4698 (53%)	3751 (60%) [‡]	3364 (61%)	280 (52%)	1853 (61%)

CrCl, creatinine clearance; SD, standard deviation; VTE, venous thromboembolism.

Comparisons between fragile and non-fragile patients: **P* < .05; [†]*P* < .01; [‡]*P* < .001. Anemia was considered in men with haemoglobin levels <13 g/dL or women with levels <12 g/dL.

defined as non-surgical patients who had been immobilized (ie, total bed rest with bathroom privileges) for ≥4 days in the 2-month period prior to VTE.¹² Surgical patients were defined as those who underwent a surgical intervention in the 2 months prior to VTE.¹¹ Active cancer was defined as newly diagnosed cancer, metastatic cancer, or cancer that was being treated (ie, surgery, chemotherapy, radiotherapy, support therapy).¹⁰ Recent bleeding was defined as any major bleeding episode <30 days prior to VTE.¹⁴ Bleeding events were classified as "major" if they were overt and required a transfusion of two units or more of blood, or were retroperitoneal, spinal, or intracranial, or when they were fatal. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death.¹⁴ Fatal PE, in the absence of autopsy, was defined as any death appearing within 10 days after symptomatic PE diagnosis, in the absence of any alternative cause of death.¹² Initial therapy was defined as any therapy administered during the first week in case of low-molecular-weight heparin (LMWH), unfractionated heparin, fondaparinux, or apixaban, and during the first 3 weeks in case of rivaroxaban. Long-term therapy was defined as any therapy administered after the end of initial therapy.

2.4 | Treatment and follow-up

Patients were managed according to each participating hospital's clinical practice, and there were no standardized or recommended duration of therapy or follow-up. All patients had to be followed-up for at least 3 months in the outpatient clinic or physician's office. During each visit, any signs or symptoms suggesting VTE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent VTE was investigated by repeat compression ultrasonography, lung scanning, helical-CT scan, or pulmonary angiography, as appropriate. Most outcomes were classified as reported by the clinical centers. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

2.5 | Statistical analysis

Clinical characteristics, risk factors, and initial VTE presentation were analyzed using descriptive statistics for continuous variables and frequency counts and percentages for categorical variables. Categorical

TABLE 2 Treatment strategies in fragile and non-fragile patients with acute venous thromboembolism

	Non-fragile	Fragile	Age ≥75 y	Weight ≤ 50 kg	CrCl ≤ 50 mL/min
Patients, N	8819	6260	5514	537	3059
Initial therapy					
LMWH	7288 (83%)	5493 (88%) [†]	4879 (88%)	472 (88%)	2660 (87%)
LMWH doses (IU/kg/d)	173 ± 43	172 ± 45	171 ± 44	187 ± 55	169 ± 47
Unfractionated heparin	382 (4.3%)	316 (5.0%)*	244 (4.4%)	26 (4.8%)	215 (7.0%)
Fondaparinux	317 (3.6%)	136 (2.2%) [‡]	124 (2.2%)	13 (2.4%)	56 (1.8%)
Rivaroxaban	534 (6.1%)	151 (2.4%) [‡]	134 (2.4%)	14 (2.6%)	44 (1.4%)
Apixaban	27 (0.31%)	17 (0.27%)	16 (0.29%)	1 (0.19%)	11 (0.36%)
Long-term therapy					
LMWH	2551 (29%)	1879 (30%)	1583 (29%)	242 (45%)	965 (32%)
LMWH doses (IU/kg/d)	153 ± 44	146 ± 45 [‡]	145 ± 43	159 ± 48	144 ± 46
Vitamin K antagonists	4415 (50%)	3401 (54%) [‡]	3069 (56%)	192 (36%)	1643 (54%)
Rivaroxaban	1452 (17%)	505 (8.4%) [‡]	456 (8.6%)	42 (8.4%)	172 (6.0%)
Apixaban	130 (1.5%)	93 (1.6%)	87 (1.6%)	7 (1.4%)	47 (1.6%)
Dabigatran	28 (0.32%)	21 (0.35%)	21 (0.40%)	2 (0.40%)	6 (0.21%)

CrCl, creatinine clearance; IU, international units; LMWH, low-molecular-weight heparin. Comparisons between fragile and non-fragile patients: * $P < .05$; [†] $P < .01$; [‡] $P < .001$.

variables were compared using the chi-square test (two-sided) and Fisher's exact test (two-sided). Continuous variables were compared using Student's *t* test. Odds ratios (OR) with 95% confidence intervals (CI), as well as *P*-values (Mann-Whitney test or *t* test for continuous variables and Cochran-Mantel-Haenszel tests for categorical variables) were presented for each variable analyzed. All outcomes were analyzed in the overall follow-up period (0-90 days). Univariate analysis was conducted yielding odds ratios with 95% CI, as well as *P*-values (Cochran-Mantel-Haenszel tests) for each outcome. Kaplan-Meier survival analysis was conducted to investigate the risk of outcomes in both subgroups for the overall period (0-90 days).

Cox proportional hazard models were used to compare the rates of VTE recurrences and major bleeding in the two subgroups during the 90-day follow-up period. Covariates included in the adjusted model were those for which a statistically significant difference (a threshold *P*-value of .1 was set to assess significance of differences) was found between the two subgroups, and a backward selection was used for the covariate selection in the multivariate model. For both Kaplan-Meier survival analyses and Cox regression analyses, if a patient did not have a study outcome of interest before the cut-off time of 90 days or if he died, then the time-to-event was censored. Statistical analyses were conducted with SPSS for Windows Release 20.0 (SPSS, Inc., Chicago, Illinois).

3 | RESULTS

From January 2013 to October 2016, 15 079 patients with acute VTE were recruited in RIETE. Of these, 6260 (42%) were fragile: 5514 (37%) were aged ≥75 years, 537 (3.6%) weighed ≤50 kg, and 3059 (20%) had CrCl levels ≤50 mL/min. Fragile patients were less likely to

be men (38% vs 57%) and more likely to have had recent immobility, cancer, chronic heart or lung disease, recent major bleeding, anemia, or abnormal platelet count than the non-fragile, but were less likely to have had recent surgery or estrogen use (Table 1). Fragile patients more likely presented initially with PE (with or without concomitant DVT) as compared with DVT alone (60% vs 53%).

Fragile patients more often received initial therapy with LMWH (88% vs 83%) or UFH (5.0% vs 4.3%), but less often fondaparinux (2.2% vs 3.6%) or rivaroxaban (2.4% vs 6.1%), as shown in Table 2. For long-term therapy, fragile patients more often received VKA (54% vs 50%) and less often rivaroxaban (8.4% vs 17%) than the non-fragile. The proportion of patients receiving apixaban or dabigatran was small and similar in both subgroups. Moreover, fragile patients on long-term LMWH therapy received lower mean daily doses per body weight than the non-fragile. Mean duration of therapy was slightly shorter in fragile than in non-fragile patients (207 ± 190 vs 214 ± 179 days, respectively; $P = .026$).

During the first 3 months of anticoagulant therapy, fragile patients had a lower risk of VTE recurrences (0.78% vs 1.4%; OR: 0.56; 95% CI: 0.40-0.78) and a higher risk of major bleeding (2.6% vs 1.4%; OR: 1.86; 95% CI: 1.47-2.36) than the non-fragile (Table 3). The risk of DVT recurrences was particularly lower (0.37% vs 0.90%; OR: 0.41; 95% CI: 0.26-0.65) while the risk of PE recurrences was non-significantly lower (0.43% vs 0.53%; OR: 0.81; 95% CI: 0.50-1.30). Fragile patients also had a higher risk of all-cause death (9.2% vs 3.5%; OR: 2.82; 95% CI: 2.44-3.25), fatal PE (0.85% vs 0.32%; OR: 2.68; 95% CI: 1.69-4.24), and fatal bleeding (0.35% vs 0.19%; OR: 1.83; 95% CI: 0.97-3.44) compared with non-fragile. In fragile patients, the risk of VTE recurrences was one-third the rate of major bleeding (49 vs 162 events, respectively) from the beginning of therapy (Figure 1). In non-fragile patients, both risks were similar (123 vs 124 events, respectively).

TABLE 3 Clinical outcomes during the first 3 months of anticoagulant therapy in fragile vs non-fragile patients with VTE

	Fragile	Non-fragile	Crude OR (95% CI)	Adjusted OR (95% CI)
Patients, N	6260	8819		
Events				
Recurrent VTE	49 (0.78%)	123 (1.4%)	0.56 (0.40-0.78)	0.52 (0.37-0.74)
Recurrent PE	27 (0.43%)	47 (0.53%)	0.81 (0.50-1.30)	–
Recurrent DVT	23 (0.37%)	79 (0.90%)	0.41 (0.26-0.65)	0.41 (0.25-0.67)
Major bleeding	162 (2.6%)	124 (1.4%)	1.86 (1.47-2.36)	1.41 (1.10-1.80)
Sites of major bleeding				
Gastrointestinal	54 (0.86%)	31 (0.35%)	2.47 (1.58-3.84)	1.84 (1.16-2.92)
Cerebral	20 (0.32%)	21 (0.24%)	1.34 (0.73-2.48)	–
Haematoma	32 (0.51%)	6 (0.07%)	7.55 (3.15-18.1)	5.05 (2.05-12.4)
Retroperitoneal	16 (0.26%)	11 (0.12%)	2.05 (0.95-4.42)	–
Death	574 (9.2%)	305 (3.5%)	2.82 (2.44-3.25)	2.02 (1.75-2.33)
Causes of death				
Pulmonary embolism	53 (0.85%)	28 (0.32%)	2.68 (1.69-4.24)	1.77 (1.10-2.85)
Initial PE	49 (0.78%)	23 (0.26%)	3.02 (1.84-4.96)	1.91 (1.14-3.20)
Recurrent PE	4 (0.06%)	5 (0.06%)	1.13 (0.30-4.20)	–
Bleeding	22 (0.35%)	17 (0.19%)	1.83 (0.97-3.44)	–
Cerebral	8 (0.13%)	6 (0.07%)	1.88 (0.65-5.42)	–
Gastrointestinal	4 (0.06%)	3 (0.03%)	1.88 (0.42-8.40)	–
Retroperitoneal	5 (0.08%)	1 (0.01%)	7.05 (0.82-60.3)	–
Respiratory insufficiency	44 (0.70%)	24 (0.27%)	2.59 (1.58-4.27)	–
Sudden, unexpected	16 (0.26%)	12 (0.14%)	1.88 (0.89-3.98)	–

CI, confidence intervals; DVT, deep vein thrombosis; OR, odds ratio; PE, pulmonary embolism; VTE, venous thromboembolism.

Variables included in the multivariable analysis for VTE recurrence: fragile, active cancer, prior VTE, chronic heart failure, abnormal platelet count, and initial VTE presentation (DVT or PE).

Variables included in the multivariable analysis for major bleeding: fragile, gender, active cancer, chronic lung disease, recent major bleeding, anaemia, abnormal platelet count, and initial VTE presentation (DVT or PE).

Variables included in the multivariable analysis for death: fragile, gender, active cancer, recent surgery, recent immobilization, prior VTE, chronic lung disease, chronic heart failure, recent major bleeding, anaemia, abnormal platelet count, and initial VTE presentation (DVT or PE).

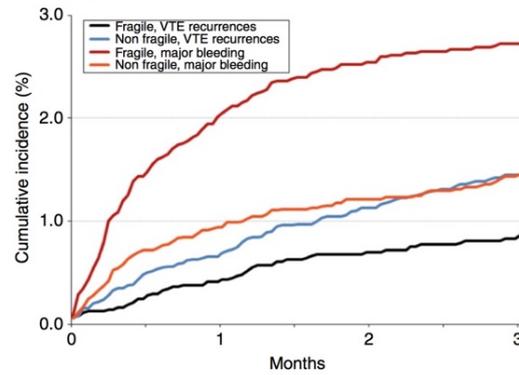
When separately analyzing outcomes, the risk of major bleeding in patients weighing <50 kg was similar to the risk in non-fragile, in patients aged ≥ 75 years it was slightly (but significantly) higher, and in those with CrCl levels <50 mL/min it was over 3-fold higher than in non-fragile (Table 4).

4 | DISCUSSION

The term "fragile" has been recently incorporated into the literature to include VTE patients who are elderly, renally impaired, or with low body weight.³ This term should not be confused with "frail," which usually refers to elderly people with reduced physiologic reserve associated with increased susceptibility to disability.¹⁵⁻¹⁹ Our findings, obtained from a large series of consecutive patients with VTE, reveal

that in real life 42% of patients were fragile, and that during the first 3 months of anticoagulant therapy they had half the risk of VTE recurrences and a higher risk of major bleeding than the non-fragile. Among fragile patients, the risk of VTE recurrences was much lower than the risk of major bleeding (49 vs 162 events). Among non-fragile patients, the risk of VTE recurrences and major bleeding were the same (123 vs 124 events, respectively). Thus, there are reasons to suggest that when choosing an anticoagulant therapy for fragile patients with VTE, safety is an important issue.

Recent randomized trials on patients with VTE provided indirect evidence on a number of advantages in fragile patients receiving DOACs.^{5,7,20} In the EINSTEIN-DVT and PE trials, the risk of major bleeding was much lower in fragile patients on rivaroxaban than in those on standard therapy (HR: 0.27; 95% CI: 0.13-0.54).⁷ This difference was not seen in non-fragile patients. In the HOKUSAI trial a



	Days	1	10	30	60	90
Fragile	VTE recurrences	5 (0.08%)	10 (0.16%)	26 (0.43%)	41 (0.7%)	49 (0.87%)
	Major bleeding	18 (0.29%)	74 (1.2%)	124 (2.05%)	152 (2.54%)	162 (2.72%)
Non-fragile	VTE recurrences	7 (0.08%)	31 (0.35%)	60 (0.69%)	97 (1.13%)	123 (1.45%)
	Major bleeding	10 (0.11%)	51 (0.58%)	82 (0.94%)	105 (1.21%)	124 (1.46%)

FIGURE 1 Cumulative incidence of venous thromboembolism (VTE) recurrence and major bleeding during the first 3 months of anticoagulant therapy in fragile vs non-fragile patients

	N	VTE recurrences		Major bleeding	
		N (%)	OR (95% CI)	N (%)	OR (95% CI)
Non-fragile	8819	123 (1.4%)	Ref.	124 (1.4%)	Ref.
Age ≥75 years only	2967	22 (0.7%)	0.5 (0.3-0.8)	62 (2.1%)	1.5 (1.1-2.0)
CrCl ≤50 mL/min only	521	6 (1.2%)	0.8 (0.3-1.8)	23 (4.4%)	3.2 (2.0-5.0)
Body weight ≤50 kg only	183	3 (1.6%)	1.2 (0.3-3.3)	2 (1.1%)	0.8 (0.1-2.6)
Age ≥75 years and CrCl ≤50 mL/min	2235	16 (0.7%)	0.5 (0.3-0.8)	60 (2.7%)	1.9 (1.4-2.6)
Age ≥75 years and body weight ≤50 kg	51	0	—	1 (2.0%)	1.4 (0.1-7.3)
CrCl ≤50 mL/min and weight ≤50 kg	42	1 (2.4%)	1.7 (0.1-9.0)	2 (4.8%)	3.5 (0.6-12.4)
All 3 conditions	261	1 (0.4%)	0.3 (0.01-1.4)	12 (4.6%)	3.4 (1.8-6.0)

TABLE 4 Rates of VTE recurrences and major bleeding, according to the presence of age ≥75 years, CrCl ≤50 mL/min and/or body weight ≤50 kg

CI, confidence intervals; CrCl, creatinine clearance; OR, odds ratio; Ref., reference; VTE, venous thromboembolism.

higher efficacy (defined as symptomatic recurrent venous thromboembolism) was found using edoxaban than with warfarin in fragile patients (2.5% vs 4.8%; $P = .04$), without any safety concern (11.0% vs 13.7%; $P = .87$).⁵ Unexpectedly, however, in our cohort rivaroxaban was less likely to be prescribed in fragile than in non-fragile patients,

both initially (2.4% vs 6.1%, respectively) and for long-term therapy (8.4% vs 17%).

Our data confirm that the use of anticoagulant therapy carries a higher risk to bleed than to recur in the elderly and in the renally impaired, as previously reported.^{14,21-25} During initial therapy with

LMWH, fragile patients weighing ≤ 50 kg received slightly higher (non-significantly) mean daily doses per body weight of LMWH compared with non-fragile patients. This might explain, at least in part, the higher risk of major bleeding in fragile patients. Moreover, since fragile patients had more underlying diseases, they probably used more drugs than the non-fragile patients. Thus, the increased risks of major bleeding during anticoagulation in fragile patients could be explained, at least in part, by these other drugs that might have potentiated the effect of the anticoagulant therapy. The similar risk for bleeding than for VTE recurrences in VTE patients weighing ≤ 50 kg has not been consistently reported.²⁶⁻²⁸ These findings suggest the potential benefit of tailored therapy for VTE according to clinical characteristics of the patients and warrant external validation.

The present study has a number of potential limitations. First, since RIETE is an observational registry (and not a randomized trial) our data are hypothesis-generating. They might be a useful basis for future controlled clinical trials comparing different therapeutic strategies, but we should be extremely cautious in suggesting changes in treatment strategies just because of uncontrolled registry data. Second, patients were not treated with a standardized anticoagulant regimen; treatment varied with local practice, and is likely to have been influenced by a physician's assessment of a patient's risk of bleeding. Finally, patients in the RIETE database resided in several different countries. The variability of practices in different countries could potentially affect the study outcomes. Furthermore, a variety of practitioners entered data into the registry, which may lend itself to potential inaccuracies in the data being reported. The main strengths of our observation are the high number of included patients, the strict diagnostic criteria and the reporting of objectively established outcomes (major bleeding and recurrent VTE). Additionally, the population-based sample we used describes the effects of anticoagulant therapy in "real-world" clinical care, as opposed to in a protocol-driven randomized trial, and enhances the generalizability of our findings.

In summary, in real life 42% of VTE patients were fragile, and these patients had fewer VTE recurrences and more major bleeding events during the course of anticoagulant therapy than the non-fragile. Randomized trials are warranted to confirm whether the use of DOACs could be safer than standard anticoagulant therapy in fragile patients with VTE.

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AUTHOR CONTRIBUTIONS

F. Moustafa contributed to the design, analysis, and interpretation of data, collected patients, and wrote the article. M. Giorgi-Pierfranceschi contributed to the interpretation of data, collected patients, and approved the final version of the article. P. Di Micco contributed to the interpretation of data, collected patients, and approved the final version of the article. E. Bucherini contributed to the interpretation of data, collected patients, and approved the final version of the article. A. Lorenzo contributed to the interpretation of data, collected patients, and approved the final version of the article. A. Villalobos contributed to the interpretation of data, collected patients, and approved the final version of the article. JA. Nieto collected patients and approved the final version of the article. B. Valero collected patients and approved the final version of the article. AL. Samperiz collected patients and approved the final version of the article. M. Monreal contributed to the design, analysis, and interpretation of data, collected patients, wrote the article, and obtained funding.

RELATIONSHIP DISCLOSURE

Dr. Moustafa has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals and Sanofi; has served as a speaker for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Daiichi-Sankyo and Sanofi; and has received grants from Sanofi, Bayer HealthCare and LFB. Dr. Monreal has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Leo Pharma, Pfizer, and Sanofi; has served as a speaker or a member of a speaker's bureau for Bayer Healthcare Pharmaceuticals, Daiichi-Sankyo, Leo Pharma, and Sanofi; and has received grants for clinical research from Sanofi and Bayer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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APPENDIX

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VII.5 Annexe 5: « Real-Life use of anticoagulants in venous thromboembolism with focus on patients with exclusion criteria for direct oral anticoagulants » (SIGAPS A, IF: 7.268)

Real-life use of anticoagulants in venous thromboembolism with focus on patients with exclusion criteria for direct oral anticoagulants.

DOACS in VTE patients excluded for trials

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Abstract

We assessed the real-life use of direct oral anticoagulants (DOACs) in patients with venous thromboembolism (VTE) and exclusion criteria for randomized trials. From 2013 to 2016, 3578 of 18853 patients (19%) had exclusion criteria. Irrespective of which anticoagulant was chosen, they had more VTE recurrences (hazard ratio [HR]: 3.10; 95%CI: 2.47-3.88), major bleeds (HR: 4.10; 95%CI: 3.38-4.96) and deaths (HR: 9.47; 95%CI: 8.46-10.6) than those without exclusion criteria. During initial therapy, no patient with exclusion criteria on DOACs (n=115) recurred, but those on rivaroxaban bled less often (adjusted HR: 0.18; 95%CI: 0.04-0.79) than those on unfractionated heparin (n=224) and similar to those (n=3,172) on low-molecular-weight heparin (LMWH). For long-term therapy, patients on rivaroxaban (n=151) had non-significantly fewer VTE recurrences (adjusted HR: 0.74; 95%CI: 0.08-1.32) and major bleeds (adjusted HR: 0.41; 95%CI: 0.15-1.15) than those on LMWH (n=2,071). The efficacy and safety of DOACs were similar to standard therapy.

Introduction

Current guidelines of antithrombotic therapy, based on the evidence from randomized trials, recommend the use of dabigatran, rivaroxaban, apixaban or edoxaban as long-term therapy in patients with venous thromboembolism (VTE).¹ The risk reduction of recurrent VTE with the direct oral anticoagulants (DOACs) is similar to the risk reduction with low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKA) while the risk of bleeding (and particularly intracranial bleeding) is less with the DOACs than with VKA therapy.²⁻⁷ However, the pivotal trials where their indication was based applied strict exclusion criteria, aimed to exclude patients with a presumed high risk of bleeding. In real-life, one in every 4 patients receiving long-term anticoagulant therapy would not have been eligible for these trials, and these patients have a higher rate of major bleeding.⁸⁻¹⁶

RIETE (Registro Informatizado Enfermedad TromboEmbólica) is a multicenter, ongoing, international (Spain, Belgium, Brazil, Canada, Czech Republic, Ecuador, France, Israel, Italy, Latvia, Republic of Macedonia, Switzerland, enroll patients) observational registry of consecutive patients with symptomatic, objectively confirmed, acute VTE (ClinicalTrials.gov identifier: NCT02832245). Since its inception in 2001, data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes.¹⁷⁻²² In the current study, we aimed to determine, within patients with VTE, the proportion of patient with at least one exclusion criterion for the trials where their indication was based and

compare the benefit/risk ratio (VTE recurrences and major bleeding) with DOACs vs. conventional therapy in these patients.

Results

From January 2013 to November 2016, 18,853 VTE patients were recruited. Their mean age was 65 ± 18 years; 9232 (49%) were male and 10,490 (56%) initially presented with PE (with or without associated DVT). Overall, 3,578 patients (19%) had at least one of the predefined exclusion criteria to be recruited in randomized trials: metastatic cancer 1,732 patients (48%); CrCl levels <30 mL/min 1,020 (29%); thrombocytopenia 453 (13%); recent major bleeding 380 (11%); chronic liver failure 268 (7.5%) and pregnancy 126 (3.5%). Of these, 3,177 patients (89%) had one exclusion criterion, 369 (10%) had two and 32 patients (0.89%) had three or more exclusion criteria. Mean age of patients with at least one exclusion criterion was 69.7 ± 16.5 , while in those without exclusion criteria was 63.4 ± 17.2 years, respectively ($p < 0.001$). During the course of anticoagulant therapy (mean, 176 ± 151 days), patients with exclusion criteria had a higher rate of VTE recurrences (hazard ratio [HR]: 3.10; 95%CI: 2.47-3.88), major bleeding (HR: 4.10; 95%CI: 3.38-4.96), all-cause death (HR: 9.47; 95%CI: 8.46-10.6), fatal PE (HR: 4.84; 95%CI: 3.15-7.42) or fatal bleeding (HR: 6.07; 95%CI: 3.56-10.4) than those without exclusion criteria (Table I).

Patients with exclusion criteria

Among 3,578 patients with exclusion criteria, LMWH was the most often used drug for initial therapy of VTE (89%), and UFH the second (6.3%). The use of

rivaroxaban (2.9%) or apixaban (0.3%) was much lower (Table II). Among 3,208 patients receiving long-term therapy, LMWH was again the most often used drug (65%), followed by VKA (29%), rivaroxaban (4.7%) and apixaban (1.3%). Interestingly however, VKA were the most often used drugs in patients with CrCl levels <30 mL/min (493 of 898 patients, 55%) or chronic liver failure (118 of 241 patients, 49%). Unexpectedly, 6 pregnant women were prescribed long-term therapy with rivaroxaban. For initial therapy, patients without exclusion criteria receiving LMWH were slightly older than those on DOACs: 69±16 vs. 68±18 years ($p < 0.05$). Among patients with at least one exclusion criterion, mean ages were: 65±18 vs. 58±18 years, respectively ($p < 0.01$). For long-term therapy, patients with no exclusion criteria receiving LMWH were slightly older than those on DOACs: 67±16 vs. 66±18 years ($p < 0.05$). Among patients with at least one exclusion criterion, mean ages were: 66±17 vs. 58±18 years, respectively ($p < 0.001$).

Of 31 patients with CrCl levels <30 mL/min receiving rivaroxaban for initial therapy, 19 (61%) received the recommended doses (30 mg daily) and 12 were prescribed lower doses. There also was one patient on apixaban, who received 10 mg daily. Of 39 patients with CrCl levels <30 mL/min receiving rivaroxaban for long-term therapy, 26 (67%) received the recommended doses (20 mg daily), 12 were prescribed lower than recommended doses and one patient received 30 mg daily. There were 17 patients on apixaban, and 12 (71%) received lower than recommended doses (5 mg daily).

During initial therapy, no patients receiving rivaroxaban (n=104) or apixaban (n=11) developed VTE recurrences (Table III). Patients on rivaroxaban had a significantly lower rate of major bleeding than those on UFH (hazard ratio [HR]: 0.18; 95%CI: 0.03-0.64) and a non-significantly lower rate than those on LMWH (HR: 0.39; 95%CI: 0.06-1.30). Multivariable analysis confirmed the lower rate of major bleeding in patients on rivaroxaban than in those on UFH (adjusted HR: 0.18; 95%CI: 0.04-0.79). There were too few patients on apixaban to establish comparisons. During long-term therapy, patients on rivaroxaban had a lower rate of VTE recurrences (HR: 0.25; 95%CI: 0.04-0.84) or major bleeding (HR: 0.44; 95%CI: 0.27-0.71) than those on LMWH (Table IV). On multivariable analysis however, these differences disappeared: adjusted HR: 0.74 (95%CI: 0.08-1.32) for VTE recurrences and 0.41 (95%CI: 0.15-1.15) for major bleeding. They also had a non-significantly lower rate of VTE recurrences (HR: 0.39; 95%CI: 0.06-1.40) and a similar rate of major bleeding (HR: 0.78; 95%CI: 0.49-1.21) than those on VKA. Interestingly, no patients with metastatic cancer (n=45) or with CrCl levels <30 mL/min (n=56) receiving DOACs for long-term therapy bled.

Patients without exclusion criteria

Among 15,275 patients without exclusion criteria, LMWH was the most often used drug for initial therapy of VTE (79%), then rivaroxaban (14%), UFH (3.8%), Fondaparinux (2.7%) and apixaban (0.73%). For long term therapy, VKA drugs were the most often used drugs (57%), then LMWH (24%), rivaroxaban ((17%), apixaban (2.5%) and dabigatran (0.5%).

During initial therapy, patients receiving rivaroxaban (n=2,125) had a lower rate of major bleeding than those on LMWH (HR: 0.57; 95%CI: 0.34-0.92) or UFH (HR: 0.33; 95%CI: 0.16-0.65). During long-term therapy, patients receiving rivaroxaban (n=2,348) had half the rate of VTE recurrences (HR: 0.44; 95%CI: 0.27-0.71) or major bleeding (HR: 0.57; 95%CI: 0.34-0.92) than those on LMWH, and similar rates than those on VKA.

Discussion

Our data, obtained from a large series of consecutive patients with acute VTE, reveal that in real life one in every five such patients had at least one of the exclusion criteria to be recruited in the pivotal randomized trials with DOACs.⁸⁻

¹⁴ Not unexpectedly, patients with exclusion criteria had a 4-fold higher rate of major bleeding (and a 6-fold higher rate of fatal bleeding) than those without exclusion criteria, as previously reported.²³⁻²⁵ In our series, this increased rate of major bleeding was found in patients with metastatic cancer, CrCl levels <30 mL/min, thrombocytopenia, recent major bleeding and in those with liver failure, but not in pregnant women. Moreover, patients with exclusion criteria also had a 3-fold higher rate of VTE recurrences (and a 4-fold higher rate of fatal PE) than those without exclusion criteria. This increased rate of VTE recurrences was only found in patients with metastatic cancer or thrombocytopenia (and marginally too in those with recent bleeding), and may likely be due to the use of lower than recommended doses of therapy because of the concern about bleeding.

Data from the PREFER in VTE registry also found that the use of DOACs was less likely in patients with renal insufficiency or at increased risk for bleeding.^{26,27} Our findings confirm that the DOACs were used in few patients with exclusion criteria (3.2% for initial therapy and 6.2% for long-term therapy), and this seems paradoxical since its use has been associated with less bleeding in randomized trials.^{2-5,7,28} It would seem to be more cost-effective to prescribe safer drugs in patients at increased risk for bleeding.²⁹ In our cohort, patients with exclusion criteria initially receiving rivaroxaban had fewer bleeds than those on UFH, and patients on long-term rivaroxaban had fewer VTE recurrences and fewer bleeds than those on long-term LMWH. However, given the small number of patients with exclusion criteria receiving rivaroxaban (104 for initial therapy, 151 for long-term), we can only hypothesize that rivaroxaban may be a good alternative to standard therapy in patients with these conditions. There were few patients with exclusion criteria receiving apixaban or dabigatran to make any comparison.

There is no evidence in the literature on the use of DOACs in VTE patients with metastatic cancer, but our preliminary data suggest that they may be effective and safe. Since there were only 45 patients with disseminated cancer receiving DOACs, we may only speculate about a similar safety compared with LMWH. As for renal insufficiency, one in every 18 patients (57 of 1,020, 5.6%) with CrCl levels <30 mL/min in our series was prescribed DOACs, and this is against the recommendations in the product label.³⁰⁻³³ However, none of these patients bled, thus suggesting that the DOACs might be at least as safe as VKA or LMWH in these patients. Unfortunately, randomized clinical trials to compare

the DOACs vs. standard therapy are not allowed in patients with severe renal insufficiency. Moreover, 6 pregnant women (4.8%) were prescribed rivaroxaban for long-term therapy, and the use of DOACs is formally contraindicated during pregnancy.¹ The ISTH issued a guidance document that recommended the immediate discontinuation of DOACs after confirmation of pregnancy.³⁴ We are unaware if any of these women had hypersensitivity to LMWH, if it was a medical mistake or choice, but there were no consequences on the new-born. Finally, a number of VTE patients in our cohort had recent major bleeding, liver insufficiency or thrombocytopenia. These patients were also excluded in most randomized trials of antithrombotic therapy.²⁻⁷ In our experience, LMWH was the most often used drug, both initially and for long-term therapy. In our experience, the use of DOACS in these patients was not associated with an increased rate of major bleeding.

RIETE provides data on the treatment of VTE in a real-world situation with an unselected patient population. Hence, it may provide insights into the natural history of VTE in patients that are not often included in randomized clinical trials, and help to identify factors associated with better or worse patient outcomes. However, as an observational study, RIETE is not designed to answer questions regarding the relative efficacy and safety of different drugs. In our series, since the sample of patients with exclusion criteria on DOACs was really small, the results are subject to uncertainty (as shown by the large confidence intervals). Moreover, patients were not treated with a standardized anticoagulant regimen; the duration of therapy varied with local practice, and is likely to have been influenced by a physician's assessment of a patient's risk of

bleeding. Data from registries are hypothesis-generating and provide feedback from real-world clinical situations which is invaluable when designing new randomized clinical studies. Strengths of the current analysis include that a large number of consecutive unselected patients were enrolled.

In summary, VTE patients with exclusion criteria are not uncommon in real life (19% in our cohort), and their outcome during the course of anticoagulation is worse than in those without exclusion criteria. The use of DOACs is rare in these patients, but our data suggest that they may be at least as safe as standard therapy (as it occurs in patients without exclusion criteria).

Methods

Inclusion criteria

Consecutive patients with acute deep vein thrombosis (DVT) or pulmonary embolism (PE) confirmed by objective tests (compression ultrasonography or contrast venography for DVT; helical CT-scan, ventilation-perfusion lung scintigraphy or angiography for PE) were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their legal power of attorney) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

Physicians participating in the RIETE registry made all efforts to enroll consecutive patients. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating

center through a secure website. To ensure the validity of the information entered into the database, one of the specially trained monitors visited each participating hospital and compared information in 25 to 50 randomly chosen patient records with the information entered into the RIETE database. For data quality assessment, monitors assessed 4,100 random records from all participating hospitals that included 1,230,000 measurements. These data showed a 95% overall agreement between the registered information and patient records. RIETE also used electronic data monitoring to detect inconsistencies or errors and attempted to resolve discrepancies by contacting the local coordinators.

Study design

We conducted a retrospective study of prospectively collected data from consecutive patients with acute VTE enrolled in the RIETE registry. Data were collected from January 2013 to September 2016, corresponding to the time when the prescription of DOACs was allowed. Our major outcome was the rate of VTE recurrences or major bleeding appearing during therapy with DOACs vs. conventional therapy (LMWH, unfractionated heparin [UFH] or Fondaparinux for initial therapy; LMWH or VKA for long-term therapy) in patients with at least one of the exclusion criteria in the trials where the DOACs demonstrated their efficacy and safety. Comparisons were made separately for initial and long-term therapy and for every DOAC.

We sought the pivotal trials where the indication for the use of DOACs in patients with VTE was based.²⁻⁵ The exclusion criteria slightly varied from each

other, but in general patients were excluded if they had: 1) cancer requiring over 6 months of LMWH therapy or with a life expectancy of 3-6 months; 2) creatinine clearance (CrCl) levels <30 mL/min (<25 mL/min in one trial); 3) a high risk of bleeding; 4) clinically significant liver disease or 5) pregnancy. For the current study, we considered as exclusion criteria any of the following: 1) metastatic cancer; 2) CrCl levels <30 mL/min; 3) platelet count at baseline <100,000/ μ L; 4) recent (<30 days before) major bleeding; 5) chronic liver failure (defined as biopsy proven liver cirrhosis or AST or ALT levels >3 times the upper normal range), and 6) pregnancy.

Baseline variables

The following parameters are routinely recorded in RIETE: patient's baseline characteristics; clinical status including any coexisting or underlying conditions; risk factors for VTE; diagnostics tools used for diagnosis; laboratory data at baseline; the treatment received upon VTE diagnosis (drugs, doses, regimen and duration) and the outcome during the course of anticoagulation. Active cancer was defined as newly diagnosed cancer, metastatic cancer, or cancer that was being treated (i.e. surgery, chemotherapy, radiotherapy, support therapy). Recent bleeding was defined as a major bleeding episode <30 days prior to VTE.

Treatment

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). The decision on the type and duration of therapy was left to the attending physicians. Patients were

followed-up during the course of therapy in the outpatient clinic or physician's office. During each visit, any signs or symptoms suggesting VTE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent VTE was investigated by repeat compression ultrasonography, lung scanning, helical-CT scan or pulmonary angiography, as appropriate.

Statistical Analysis

Categorical variables were compared using the chi-square test (two-sided) and Fisher's Exact Test (two-sided). Continuous variables were compared using Student t test. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were calculated. Incidence rates were calculated as cumulative incidence (events/100 patient-years) and compared using the hazard ratios. Cox proportional hazard models were used to compare the rates of VTE recurrences and major bleeding events occurring during initial and long-term therapy, separately. Crude and adjusted (HR) as well as their 95% CI were estimated. Covariates included in the adjusted model were those for which a statistically significant difference (a threshold p-value of 0.1 was set to assess significance of differences) was found between the different drugs, and a backward selection was used for the covariate selection in the multivariable model. Statistical analyses were conducted with SPSS for Windows Release 17.0 (SPSS, Inc).

Role of the funding source

The sponsors of the study (Sanofi and Bayer) had no role in study design, data collection, data analysis, data interpretation or writing of the report. The

corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Accepted Article

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Study Highlights

o What is the current knowledge on the topic?

Based on randomized trials, current guidelines recommend to treat venous thromboembolism (VTE) with direct oral anticoagulants (DOACs). However, randomized trials usually exclude patients at increased risk for bleeding.

o What question did this study address?

How common are patients with VTE and exclusion criteria for randomized trials, what was their outcome during anticoagulation and how often were prescribed DOACs?

o What this study adds to our knowledge ?

In real-life, 19% of VTE patients had exclusion criteria, and they had a higher rate of VTE recurrences or major bleeding than those without exclusion criteria.

The use of DOACs was rare in these patients (3.2% initially and 6.2% for long-term therapy), and their efficacy and safety were not better than standard therapy.

o How this might change clinical pharmacology or translational science

Patient

Randomized trials are needed on appropriate anticoagulant therapy for VTE in patients excluded from previous studies on NOACs.

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Disclosure

Dr. Moustafa has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals and Sanofi; has served as a speaker for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Daiichi-Sankyo and Sanofi; and has received grants from Sanofi, Bayer HealthCare and LFB.

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All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Author Contributions

F.M. and M.M. wrote the manuscript; F.M. and M.M. designed the research; F.M., R.P., P.D.M., J.G-M., R.Q., M-L.P., J.A.P., N.F., P.B., and M.M. performed the research; F.M., R.P., P.D.M., J.G-M., R.Q., M-L.P., J.A.P., N.F., P.B., and M.M. analyzed the data.

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APPENDIX

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Table I. Incidence rates of VTE recurrences and major bleeding during the course of anticoagulant therapy, according to the presence or absence of exclusion criteria.

	Any exclusion criteria		No exclusion criteria		Hazard ratio (95%CI)
	N	Events per 100 patient-years	N	Events per 100 patient-years	
Patients, N		3,578		15,275	
Mean days of therapy (\pm SD)		143 \pm 159		184 \pm 185	<0.001
Median days (IQR)		99 (32-190)		125 (86-228)	<0.001
VTE recurrences	118	8.51 (7.08-10.2)	210	2.75 (2.40-3.14)	3.10 (2.47-3.88)
Major bleeding	181	12.9 (11.2-14.9)	243	3.16 (2.78-3.58)	4.10 (3.38-4.96)
Death	828	58.1 (54.3-62.2)	476	6.14 (5.61-6.71)	9.47 (8.46-10.6)
Fatal PE	40	2.81 (2.03-3.78)	45	0.58 (0.43-0.77)	4.84 (3.15-7.42)
Fatal initial PE	31	2.18 (1.50-3.05)	41	0.53 (0.38-0.71)	4.11 (2.56-6.56)
Fatal recurrent PE	9	0.63 (0.31-1.16)	4	0.05 (0.02-0.12)	12.2 (3.83-45.7)
Fatal bleeding	29	2.04 (1.39-2.88)	26	0.34 (0.22-0.48)	6.07 (3.56-10.4)
Metastatic cancer, N		1,732		17,121	
VTE recurrences	82	13.9 (11.1-17.2)	246	2.92 (2.57-3.30)	4.77 (3.70-6.10)
Major bleeding	90	14.8 (12.0-18.1)	334	3.94 (3.53-4.38)	3.76 (2.96-4.72)
CrCl levels <30 mL/min, N		1,020		17,833	
VTE recurrences	12	2.88 (1.56-4.89)	316	3.67 (3.28-4.09)	0.78 (0.42-1.35)
Major bleeding	51	12.3 (9.24-16.0)	373	4.30 (3.88-4.75)	2.85 (2.11-3.80)
PIC <100,000/μL, N		453		18,400	
VTE recurrences	23	13.0 (8.43-19.2)	304	3.44 (3.07-3.84)	3.77 (2.42-5.67)
Major bleeding	25	14.1 (9.31-20.5)	399	4.48 (4.06-4.94)	3.14 (2.05-4.63)
Recent major bleeding, N		380		18,473	
VTE recurrences	10	7.02 (3.56-12.5)	318	3.58 (3.20-3.99)	1.96 (0.99-3.54)
Major bleeding	28	19.6 (13.2-27.9)	396	4.43 (4.01-4.88)	4.42 (2.96-6.39)
Chronic liver failure, N		268		18,585	
VTE recurrences	6	5.41 (2.19-11.2)	322	3.61 (3.23-4.02)	1.50 (0.60-3.14)
Major bleeding	14	12.9 (7.36-21.2)	410	4.56 (4.14-5.02)	2.83 (1.60-4.69)
Pregnancy, N		126		18,727	
VTE recurrences	0	-	328	3.65 (3.27-4.07)	-
Major bleeding	1	2.03 (0.10-10.0)	423	4.68 (4.25-5.14)	0.43 (0.02-2.15)

Abbreviations: SD, standard deviation; IQR, interquartile range; VTE, venous thromboembolism; PE, pulmonary embolism; CrCl, creatinine clearance; PIC, platelet count; CI, confidence intervals.

Table II. Use of drugs for initial- and for long-term therapy, according to the presence of exclusion criteria.

Initial therapy					
	LMWH	UFH	Rivaroxaban	Apixaban	Fondaparinux
Patients, N	15,208	812	2,229	123	481
Metastatic cancer	1,625 (11%)	54 (6.7%) [‡]	25 (1.1%) [‡]	1 (0.81%) [‡]	27 (5.6%) [‡]
CrCl levels <30 mL/min	864 (5.7%)	112 (14%) [‡]	31 (1.4%) [‡]	1 (0.81%) [‡]	12 (2.5%) [‡]
PIC <100,000/ μ L	373 (2.5%)	30 (3.7%) [*]	23 (1.0%) [‡]	3 (2.4%) [*]	24 (5.0%) [‡]
Recent major bleeding	300 (2.0%)	43 (5.3%) [‡]	21 (0.94%) [‡]	6 (4.9%) [*]	10 (2.1%)
Chronic liver failure	239 (1.6%)	13 (1.6%)	7 (0.31%) [‡]	2 (1.6%)	7 (1.5%)
Pregnancy	120 (0.79%)	4 (0.49%)	1 (0.04%) [‡]	0	1 (0.21%)
Any exclusion criteria	3,172 (21%)	224 (28%)[‡]	104 (4.7%)[‡]	11 (8.9%)[‡]	67 (14%)[‡]
2 exclusion criteria	324 (2.1%)	28 (3.4%) [*]	3 (0.13%) [‡]	1 (0.81%)	13 (2.7%)
\geq 3 exclusion criteria	25 (0.16%)	4 (0.49%)	1 (0.04%)	1 (0.81%)	1 (0.21%)
No exclusion criteria	12,036 (79%)	588 (3.8%)	2,125 (14%)	112 (0.73%)	414 (2.7%)
Long-term therapy					
	LMWH	VKA	Rivaroxaban	Apixaban	Dabigatran
Patients, N	5,455	8,998	2,499	401	81
Metastatic cancer	1,362 (25%)	124 (1.4%) [‡]	42 (1.7%) [‡]	3 (0.75%) [‡]	0
CrCl levels <30 mL/min	348 (6.4%)	493 (5.5%) [*]	39 (1.6%) [‡]	17 (4.2%)	1 (1.2%)
PIC <100,000/ μ L	201 (3.7%)	158 (1.8%) [‡]	23 (0.92%) [‡]	8 (2.0%)	1 (1.2%)
Recent major bleeding	205 (3.8%)	94 (1.0%) [‡]	36 (1.4%) [‡]	15 (3.7%)	2 (2.5%)
Chronic liver failure	107 (2.0%)	118 (1.3%) [‡]	13 (0.52%) [‡]	3 (0.75%)	0
Pregnancy	102 (1.9%)	9 (0.10%) [‡]	6 (0.24%) [‡]	0	0
Any exclusion criteria	2,071 (38%)	939 (10%)[‡]	151 (6.0%)[‡]	43 (11%)[‡]	4 (4.9%)[‡]
2 exclusion criteria	236 (4.3%)	52 (0.58%) [‡]	7 (0.28%) [‡]	3 (0.75%) [‡]	0
\geq 3 exclusion criteria	18 (0.33%)	5 (0.06%) [‡]	1 (0.04%) [*]	0	0
No exclusion criteria	3,384 (24%)	8,059 (57%)	2,348 (17%)	358 (2.5%)	77 (0.54%)

Comparisons between patients on LMWH therapy vs. other drugs: *p <0.05; [†]p <0.01; [‡]p <0.001.

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonists; CrCl, creatinine clearance; PIC; platelet count.

Table III. VTE recurrences and major bleeding during initial therapy, according to prescribed drugs. Results expressed as events per 100 patient-years and 95% confidence intervals.

	LMWH	UFH	Rivaroxaban	Apixaban
VTE recurrences,				
Metastatic cancer	14.2 (11.3-17.6)	22.3 (5.68-60.8)	-	-
CrCl levels <30 mL/min	3.09 (1.63-5.38)	2.29 (0.11-11.3)	-	-
PIC <100,000/ μ L	12.7 (7.87-19.5)	42.4 (13.5-102.3)	-	-
Recent major bleeding	7.18 (3.33-13.6)	6.55 (0.33-32.3)	-	-
Chronic liver failure	4.95 (1.81-11.0)	22.0 (1.10-108.6)	-	-
Pregnancy	-	-	-	-
Any exclusion criteria	8.73 (7.19-10.5)	10.8 (5.28-19.9)	-	-
2 exclusion criteria	16.3 (9.29-26.7)	24.5 (1.23-120.9)	-	-
\geq 3 exclusion criteria	-	-	-	-
No exclusion criteria	2.69 (2.31-3.12)	5.37 (3.18-8.53)[*]	1.96 (1.20-3.04)	-
Major bleeding,				
Metastatic cancer	13.3 (10.6-16.6)	68.0 (33.2-124.7) [†]	7.19 (0.36-35.5)	-
CrCl levels <30 mL/min	12.1 (8.83-16.1)	14.5 (5.89-30.3)	-	-
PIC <100,000/ μ L	10.6 (6.24-16.8)	58.9 (21.6-130.7) [†]	13.4 (0.67-66.0)	-
Recent major bleeding	19.9 (12.8-29.6)	25.8 (8.19-62.2)	-	-
Chronic liver failure	11.2 (5.90-19.5)	-	-	-
Pregnancy	2.11 (0.11-10.4)	-	-	-
Any exclusion criteria	11.8 (10.0-13.9)	26.2 (16.6-39.3)[†]	4.60 (0.77-15.2)	-
2 exclusion criteria	23.7 (15.1-35.6)	50.1 (8.40-165.5)	-	-
\geq 3 exclusion criteria	21.3 (1.06-104.8)	347.9 (17.4-1,715.6)	-	-
No exclusion criteria	3.23 (2.81-3.70)	5.66 (3.41-8.88)[†]	1.85 (1.11-2.90)[*]	2.89 (0.14-14.2)

Comparisons between patients on LMWH therapy vs. other drugs: *p <0.05; [†]p <0.01.

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; CrCl, creatinine clearance; PIC; platelet count.

Table IV. VTE recurrences and major bleeding during long-term therapy, according to prescribed drugs. Results expressed as events per 100 patient-years and 95% confidence intervals.

	LMWH	VKA	Rivaroxaban	Apixaban
VTE recurrences,				
Metastatic cancer	12.1 (9.34-15.5)	26.3 (15.0-43.1)*	4.12 (0.21-20.3)	93.4 (4.67-460.7)
CrCl levels <30 mL/min	4.07 (1.49-9.03)	2.40 (0.97-5.00)	-	-
PIC <100,000/ μ L	15.5 (8.39-26.3)	7.24 (2.94-15.1)	9.39 (0.47-46.3)	41.1 (2.06-202.9)
Recent major bleeding	9.26 (4.05-18.3)	4.96 (0.83-16.4)	-	15.3 (0.76-75.4)
Chronic liver failure	8.80 (2.24-23.9)	4.69 (1.19-12.8)	-	-
Pregnancy	-	-	-	-
Any exclusion criteria	9.78 (7.76-12.2)	6.14 (4.19-8.71)*	2.41 (0.40-7.96)	10.4 (1.75-34.4)
2 exclusion criteria	16.8 (8.85-29.2)	10.1 (1.70-33.5)	-	31.3 (1.57-154.6)
\geq 3 exclusion criteria	-	-	-	-
No exclusion criteria	4.21 (3.28-5.33)	2.40 (1.98-2.88)†	1.87 (1.22-2.76)	0.65 (0.03-3.21)
Major bleeding,				
Metastatic cancer	12.2 (9.45-15.6)	15.5 (7.57-28.5)	-	-
CrCl levels <30 mL/min	14.8 (9.08-23.0)	7.18 (4.39-11.1)*	-	-
PIC <100,000/ μ L	15.7 (8.52-26.7)	4.79 (1.52-11.6)*	17.7 (2.96-58.4)	-
Recent major bleeding	24.1 (14.7-37.3)	4.83 (0.81-16.0)*	6.29 (0.31-31.0)	14.2 (0.71-69.8)
Chronic liver failure	23.5 (10.9-44.7)	3.16 (0.53-10.4)†	14.1 (0.71-69.8)	-
Pregnancy	2.42 (0.12-11.9)	-	-	-
Any exclusion criteria	12.9 (10.5-15.6)	7.11 (5.00-9.82)†	4.85 (1.54-11.7)	4.98 (0.25-24.6)
2 exclusion criteria	25.4 (15.3-39.8)	4.87 (0.24-24.03)	-	-
\geq 3 exclusion criteria	24.8 (1.24-122.4)	-	-	-
No exclusion criteria	4.51 (3.55-5.65)	2.38 (1.96-2.86)†	1.61 (1.01-2.45)	3.30 (1.21-7.31)

Comparisons between patients on LMWH therapy vs. other drugs: *p <0.05; †p <0.01; ‡p <0.001.

Abbreviations: LMWH, low-molecular-weight heparin; VKA, vitamin K antagonists; CrCl, creatinine clearance; PIC; platelet count.

VII.6 Annexe 6 (autre publication): « Assessment of the Impact of l-Thyroxine Therapy on Bleeding Risk in patients Receiving Vitamin K Antagonist» (SIGAPS D, IF: 1.806)



Assessment of the Impact of L-Thyroxine Therapy on Bleeding Risk in Patients Receiving Vitamin K Antagonists

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Abstract

Background Several studies have suggested a link exists between L-thyroxine and the coagulation system, and, according to some drug interaction studies, L-thyroxine can potentiate the effect of warfarin. This study sought to assess whether thyroid hormone therapy could impact the risk of bleeding in patients receiving vitamin K antagonists (VKAs). **Methods** We conducted a monocentric, retrospective study on prospectively collected data from consecutive patients enrolled in the Registry of patient with AntiThrombotic agents admitted to an Emergency Department (RATED) database, and compared the hemorrhage rates (both major and nonmajor) of patients receiving treatment with and without L-thyroxine. Propensity score matching analysis was performed to reduce the differences between patients receiving L-thyroxine

and those not receiving L-thyroxine in order to reassess bleeding outcomes in patients receiving VKAs.

Results From January 2014 to June 2015, 1454 patients receiving VKAs were recruited into the RATED database. Overall, 187 patients (12.8%) received L-thyroxine. Patients receiving L-thyroxine were more likely to be female than those not receiving L-thyroxine (78.1 vs. 55%; $p = 0.015$), but less likely to have history of myocardial infarction (9.6 vs. 16.6%; $p = 0.022$) or higher creatinine levels (96.1 vs. 112.1 $\mu\text{mol/L}$; $p = 0.04$). After propensity score matching, bleeding outcomes were not significantly different between patients receiving L-thyroxine and those not receiving L-thyroxine.

Conclusions Our study revealed no evidence that L-thyroxine could increase bleeding risk in patients receiving VKAs. However, physicians must be aware that patients with thyroid disease receiving VKA therapy could have other drug interactions, particularly with amiodarone therapy. *ClinicalTrials.gov number* NCT02706080.

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Key Points

Nearly 13% of patients receiving VKAs also receive L-thyroxine.

Patients receiving L-thyroxine displayed higher rates of atrial fibrillation and higher rates of concomitant treatment with amiodarone than those not receiving L-thyroxine.

No evidence is available to suggest that L-thyroxine could increase bleeding risk in patients receiving VKAs, even after propensity analysis.

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1 Introduction

Vitamin K antagonists (VKAs) are the most common anticoagulant therapy used for the prevention and treatment of venous thromboembolic disease, the prevention of stroke and systemic embolism in nonvalvular atrial fibrillation, and prevention in mechanic valve replacement [1, 2]. Bleeding events are the most feared complication of VKA therapy. During treatment with VKAs, the incidence of major bleeding and fatal bleeding is estimated to be 2–5 and 0.5–1% per year, respectively [3–5]. Several risk factors for bleeding in patients receiving VKAs have been identified, which, together, create the bleeding risk score [6, 7]. However, no bleeding risk scoring system takes drug interactions into account, despite several therapies having been described as interfering with VKAs [8–11].

Recent studies have investigated the association between L-thyroxine and the coagulation system [12–14]. Although the mechanism behind this association is still unknown, thyroid disease does seem to affect hemostasis [15]. Indeed, high levels of free thyroxine (T4) have been found to enhance levels of Factor VIII, von Willebrand factor, fibrinogen, and Factor IX, thereby being a risk factor for venous thrombosis [13, 16, 17]. Hypermetabolic states induced by fever or hyperthyroidism amplify warfarin responsiveness, probably by increasing the catabolism of vitamin K-dependent coagulation factors [18, 19]. On the other hand, low factor VIII levels have been observed in patients with hypothyroidism, which is considered to be a risk factor for bleeding [20–22]. Moreover, the pharmacodynamics of VKAs could be impacted by T4 levels [23, 24]. Thus, although patients with thyroid diseases are not classified as having a disease that influences VKA treatment, L-thyroxine was classified as causing potential clinically relevant interactions with phenprocoumon, especially upon therapy initiation [12, 25, 26].

Given that L-thyroxine and warfarin are prescribed to numerous patients (1 in 300 Americans have hypothyroidism and 2.6 million exhibit atrial fibrillation) [27, 28], it is most likely that some will receive these drugs in combination. Moreover, hypothyroidism may increase the risk of atrial fibrillation, which, in turn, requires anticoagulation therapy [29, 30].

This study sought to assess whether thyroid hormonal therapy could impact the risk of bleeding in patients receiving VKAs.

2 Patients and Methods

2.1 Inclusion Criteria

Consecutive patients admitted to the emergency department of a university hospital, and receiving antithrombotic

treatment on admission, were enrolled in the Registry of patient with Antithrombotic agents admitted to an Emergency Department (RATED) database (NCT02706080). Patients (or their legal power of attorney) were informed of their personal data possibly being used, and provided informed consent. This study was approved by the Ethics Committee of the French Research Ethics Committee (CPP Sud-Est VI; IRB number: 00008526 – 2013/CE37).

RATED is a monocentric, still ongoing (from January 2014), observational registry of consecutive patients receiving antithrombotic drugs admitted to the Emergency Department of the Clermont-Ferrand University Hospital for any reason. The Emergency Department physicians made every effort to enroll consecutive patients during the patients' medical management. All data were recorded in the electronic case report forms from the hospital's patient records.

2.2 Study Design

This was a monocentric, retrospective study analyzing prospectively collected data from consecutive patients enrolled in the RATED registry from January 2014 to June 2015. For this study, only patients receiving VKAs were considered. We sought to compare both major and non-major hemorrhage rates of patients receiving L-thyroxine with those not receiving L-thyroxine. Both major and nonmajor bleeding was noticed at arrival in the emergency room and occurred in the outpatient setting. Major hemorrhage was defined by the following criteria: hemorrhage leading to death; symptomatic bleeding in a critical area or organ (intracranial, gastroduodenal, intramuscular, articular, or intraocular); and bleeding leading to transfusion of two or more units of whole blood or red cells [31].

2.3 Baseline Variables

The following parameters are routinely recorded in RATED: patient baseline characteristics; clinical presentation, including any coexisting or underlying conditions; bleeding risk factors described in the literature (age, previous stroke, previous gastrointestinal bleeding, renal failure, anemia, thrombocytopenia, liver disease, cancer, hypertension, dementia, or alcoholism) [32]; HAS-BLED score at arrival in the emergency room [10] and the use of antithrombotic therapy; use of computed tomography or echography; laboratory data at baseline; type of antithrombotic treatment (indication, time duration, drugs, and doses); and concomitant drugs.

2.4 Statistical Analysis

All analyses were performed using Stata software version 13 (StataCorp LLC, College Station, TX, US) and R

(<https://cran.r-project.org/>), with a two-sided error significance level set at 5%. The population was described using frequencies and percentages for categorical variables, and means with standard deviations or medians and interquartile range for quantitative parameters, according to statistical distribution (Shapiro–Wilk test for normality). For categorical variables, independent groups (e.g. bleeding: yes/no; L-thyroxine: yes/no) were compared using the Chi-squared test or Fisher's exact test; for quantitative variables, Student's *t* test was applied, replaced by the non-parametric Mann–Whitney test if the *t* test conditions were not met (normality and homoscedasticity determined using the Fisher–Snedecor test).

Finally, to more accurately compare outcomes of patients treated with L-thyroxine and those not treated with L-thyroxine, a propensity score analysis completed the other analyses. As the baseline characteristics of the two groups were unbalanced, we proposed propensity score matching as defined by Rosenbaum and Rubin [33]. The goal of developing propensity score-matched subsets was to account for potential confounding variables relating to the effects of L-thyroxine as patients were not randomly assigned to either the L-thyroxine or non-L-thyroxine groups in the RATED registry. The propensity score enables an observational nonrandomized study to be designed and analyzed that is able to mimic several particular characteristics of a randomized controlled trial. In particular, the propensity score is a balancing score, with the distribution of observed baseline covariates similar between two groups according to this score. The estimated propensity score is the predicted probability for use of L-thyroxine, derived from the fitted regression model (logistic regression) for each of the 1454 patients. Thus, in a set of subjects all producing the same propensity score, the distribution of observed baseline covariates will be the same between the two groups. The covariates included in the propensity score model were clinically relevant, and were determined according to univariate results. A total of nine variables found to correlate to bleeding risk were included in the model and were subsequently used to generate propensity scores. The nine variables used for matching were as follows: age, sex, past history of gastrointestinal ulcer, gastrointestinal bleeding, alcohol abuse, liver failure, cancer, stroke, and bleeding while receiving antithrombotic drugs. In line with several recommendations, we have proposed an approach based on the bootstrap method, a well-known resampling method for estimating the standard error of estimated statistics and constructing confidence intervals [34]. Following bootstrap simulation (2000 random), the odds ratio (OR) measured for each sweepstake was calculated and presented as described above in order to estimate

the risk of bleeding associated with L-thyroxine treatment.

3 Results

From January 2014 to June 2015, 1454 patients receiving VKAs were recruited into the RATED registry. Overall, 187 patients (12.8%) were taking L-thyroxine. Their clinical characteristics are provided in Table 1. Several differences were observed between patients receiving L-thyroxine and those not receiving L-thyroxine. In the former, VKAs were more commonly prescribed for atrial fibrillation (42.8 vs. 34.9% in those patients not receiving L-thyroxine) and less commonly prescribed for secondary prevention of stroke (0.5 vs. 3.2%). Specifically, patients receiving L-thyroxine were more likely to be women (OR 4.35, 95% CI 3.03–6.26) or to have hypertension (OR 1.43, 95% CI 1.05–1.96), with a higher systolic blood pressure on arrival (143.8 ± 28.4 vs. 139.3 ± 26.9). Furthermore, they were less likely to have a history of myocardial infarction (OR 0.53, 95% CI 0.31–0.91) than those not receiving L-thyroxine. Seventy-six (40.6%) patients receiving L-thyroxine had a thyroid-stimulating hormone (TSH) blood test (mean of 2.6 ± 2.5 UI/L) without significant difference between those with or without bleeding (2.8 ± 2.9 vs. 2.6 ± 2.5 UI/L; $p = 0.86$).

For concomitant drugs, amiodarone was prescribed two times more often (OR 3.1, 95% CI 1.2–7.9), and low-molecular-weight heparin (LMWH) three times more often (OR 3.1, 95% CI 1.2–7.9), in patients receiving L-thyroxine than those not receiving L-thyroxine (Table 2). For patients receiving amiodarone, no difference in the international normalized ratio (INR) rate was observed between those receiving L-thyroxine and those not receiving L-thyroxine (3.4 ± 1.7 vs. 3.5 ± 1.9 ; $p = 0.534$).

Major bleeding occurred for 83 patients, with 9 patients receiving L-thyroxine and 74 not receiving L-thyroxine. Their characteristics have been provided in Table 3. No statistically significant differences were observed between patients receiving and not receiving L-thyroxine.

Based on the total sample, the propensity score-matching algorithm produced 158 pairs of patients with similar propensity scores for the available and relevant demographic and comorbidity data. After propensity score matching, several differences were observed. Namely, patients receiving L-thyroxine displayed higher rates of atrial fibrillation (66.7 vs. 49.5%; $p = 0.026$) and higher rates of concomitant treatment with amiodarone (25.3 vs. 10.1%, $p < 0.001$) than those not receiving L-thyroxine. Patient bleeding outcomes have been summarized in Table 4 for the final propensity

Table 1 Patient characteristics without matching according to treatment with or without L-thyroxine

	Total [N = 1454]	L-Thyroxine [N = 187]	No L-thyroxine [N = 1267]	p value
Age, years [mean ± SD]	77.6 ± 13.4	78.9 ± 10.5	77.4 ± 13.8	0.14
>65	1231 (85)	166 (89)	1065 (84)	0.09
Male sex	738 (50.7)	41 (21.9)	697 (55.0)	<0.001
SBP, mmHg [mean ± SD]	139.8 ± 27.1	143.8 ± 28.4	139.3 ± 26.9	0.038
Type of VKA				
Acenocoumarol	126 (8.7)	12 (6.4)	114 (9.0)	0.24
Warfarin	308 (21.2)	41 (21.9)	267 (21.1)	0.79
Fluindione	982 (67.5)	131 (70.1)	851 (67.2)	0.43
Indication of VKA				
Atrial fibrillation	522 (35.9)	80 (42.8)	442 (34.9)	0.07
VTE	151 (10.4)	19 (10.2)	132 (10.4)	0.96
Mechanical valve	77 (5.3)	9 (4.8)	68 (5.4)	0.78
Stroke	42 (2.9)	1 (0.5)	41 (3.2)	0.03
Ischemic heart disease	87 (6.0)	6 (3.2)	81 (6.4)	0.09
Other	74 (5.1)	6 (3.2)	68 (5.4)	0.22
Concomitant disease				
Hypertension	775 (53.3)	114 (60.9)	661 (52.2)	0.02
Coronary syndrome	235 (16.2)	24 (12.8)	211 (16.6)	0.23
Myocardial infarction	206 (14.2)	16 (8.6)	190 (15.0)	0.02
Stroke	232 (15.9)	26 (13.9)	206 (16.3)	0.47
Cancer	194 (13.3)	26 (13.9)	168 (13.3)	0.76
Chronic alcoholism	58 (4.0)	6 (3.2)	52 (4.1)	0.6
Diabetes	347 (23.9)	45 (24.1)	302 (23.8)	0.87
Gastrointestinal ulcer	37 (2.5)	8 (4.3)	29 (2.3)	0.09
Gastrointestinal bleeding	13 (0.9)	3 (1.6)	10 (0.8)	0.22
Dementia	101 (6.9)	9 (4.8)	92 (7.3)	0.23
Laboratory values at admission [mean ± SD]				
Creatinine, μmol/l	109.9 ± 93.6	96.1 ± 48.1	112.1 ± 98.5	0.04
INR	3.4 ± 2.4	3.6 ± 2.4	3.3 ± 2.4	0.21
Platelet, g/l	237.2 ± 88.6	246.8 ± 87.5	235.8 ± 88.7	0.13
Hb, g/dl	12.9 ± 2.3	12.8 ± 2.1	12.9 ± 2.3	0.61
Anemia	442 (30.4)	47 (25.1)	395 (31.2)	0.09
HAS-BLED [mean ± SD]	1.97 ± 1.02	2.03 ± 0.96	1.96 ± 1.03	0.38
HAS-BLED ≥ 3	369 (25.4)	49 (26.2)	320 (25.2)	0.67

Data are expressed as n (%) unless otherwise specified

SBP systolic blood pressure, VKA vitamin K antagonist, VTE venous thromboembolism, SD standard deviation, INR international normalized ratio, Hb hemoglobin

score-matched samples, according to the matched L-thyroxine versus no L-thyroxine data. Finally, bleeding outcomes and major bleeding were statistically similar between patients receiving and not receiving L-thyroxine. However, a nonsignificantly higher rate of intracranial bleeding was observed in patients receiving L-thyroxine, and a nonsignificantly higher rate of gastrointestinal bleeding and nosebleeds was observed in those not receiving L-thyroxine.

4 Discussion

In our cohort, we found no differences in terms of bleeding outcomes between patients receiving L-thyroxine and those not receiving L-thyroxine, even after propensity score matching. This is one of the largest studies focusing on real-life drug interactions between VKAs and L-thyroxine. However, some differences were recorded between patients receiving L-thyroxine and those not receiving L-thyroxine.

Table 2 Concomitant drugs according to treatment with or without L-thyroxine

	Total [N = 1454]	L-Thyroxine [N = 187]	No L- thyroxine [N = 1267]	p value
Concomitant antiplatelets				
Aspirin	120 (8.25)	15 (8.02)	105 (8.29)	0.9
Clopidogrel	17 (1.2)	1 (0.53)	16 (1.26)	0.7
Both	3 (0.21)	0	3 (0.24)	–
Concomitant anticoagulants				
LMWH	14 (0.96)	5 (2.67)	9 (0.71)	0.01
UFH	5 (0.34)	2 (1.07)	3 (0.24)	0.13
Fondaparinux	1 (0.07)	0	1 (0.08)	–
Concomitant drugs				
Amiodarone	205 (14.1)	47 (25.1)	158 (12.5)	<0.001
β-Blockers	455 (31.3)	68 (36.4)	387 (30.5)	0.109
Diuretics	628 (43.2)	90 (48.1)	538 (42.5)	0.14
PPI	271 (18.6)	34 (18.2)	237 (18.7)	0.86
Digoxin	178 (12.2)	28 (15.0)	150 (11.8)	0.22
Statins	378 (26.0)	51 (27.3)	327 (25.8)	0.67
ARB 2	170 (11.7)	25 (13.4)	145 (11.4)	0.45
ACE inhibitor	233 (16.0)	27 (14.4)	206 (16.3)	0.53
Benzodiazepine	101 (6.9)	12 (6.42)	89 (7.02)	0.76
Calcium channel blockers	254 (17.5)	28 (15.0)	226 (17.8)	0.34

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LMWH low-molecular-weight heparin, UFH unfractionated heparin, PPI proton pump inhibitors, ARB 2 angiotensin II receptor blocker, ACE angiotensin-converting enzyme inhibitor

Patients receiving VKAs along with L-thyroxine were more often female and more often had hypertension or prior atrial fibrillation, and were thus more likely to have amiodarone as concomitant therapy.

The patients' hemostatic balance appeared very fragile, with many interacting factors, among which thyroid hormones had direct influence on primary and secondary hemostasis [13]. Several pharmacological studies have suggested that L-thyroxine could exert an impact on VKAs, thereby increasing the risk of bleeding and abnormal hemostasis [22, 35, 36]. However, the supposed pharmacodynamic interactions with warfarin are very poorly understood. In our cohort, we found no differences in terms of INR rates or platelet counts between patients receiving L-thyroxine and those not receiving L-thyroxine, nor did we reveal any difference in bleeding outcomes between the two patient groups. In line with our results, a recent case-control study failed to find any association between L-thyroxine therapy and hemorrhage risk in patients treated with warfarin [37].

In accordance with reports in the literature, patients receiving L-thyroxine were primarily female [38], and, as expected, they were also more likely to have suffered from atrial fibrillation [29, 30, 37]. Probably on account

of this, it was found amiodarone was more likely to be prescribed to patients receiving L-thyroxine than those not receiving L-thyroxine. However, it must be brought to mind that amiodarone can interfere with warfarin metabolism by competitively inhibiting the cytochrome P450 (CYP) enzymes CYP2C9 and CYP1A2, thereby increasing the drug's anticoagulant effect [24]. In addition, it has been reported that patients being started simultaneously on warfarin and amiodarone therapy have an enhanced pharmacodynamic response to warfarin therapy than those treated with warfarin alone [39]. However, as we had not recorded the time the different treatments were initiated, we do not know if amiodarone initiation occurred before, simultaneous to, or after anticoagulation initiation.

This study has certain limitations. First, as RATED is an observational registry, our findings may give rise to hypotheses rather than conclusions. For this reason, our results offer no help for the decision to select the best therapeutic strategy. It must also be taken into account that different practitioners entered data into the registry, which may have caused potential inaccuracies in the data reported. With respect to this, one should keep in mind that major bleeding outcomes were not notified by the

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Table 3 Characteristics of patients with major bleeds without matching according to treatment with or without L-thyroxine

	Total [N = 83]	L-Thyroxine [N = 9]	No L-thyroxine [N = 74]
Age, years [mean ± SD]	78.3 ± 13.3	76.1 ± 11.8	78.5 ± 13.5
>65	72 (86.7)	7 (77.8)	65 (87.8)
Male sex	38 (45.8)	1 (11.1)	37 (50.0)
SBP, mmHg [mean ± SD]	133.1 ± 29.1	128.5 ± 26.8	133.6 ± 29.5
Type of VKA			
Acenocoumarol	8 (9.6)	1 (11.1)	7 (9.5)
Warfarin	24 (28.9)	2 (22.2)	22 (29.7)
Fluindione	49 (59.0)	6 (66.7)	43 (58.1)
Indication of VKA			
Atrial fibrillation	30 (50.8)	1 (16.7)	29 (54.7)
VTE	12 (20.3)	3 (50.0)	9 (17.0)
Mechanical valve	5 (8.5)	1 (16.7)	4 (7.5)
Stroke	3 (5.1)	0	3 (5.7)
Ischemic heart disease	6 (10.2)	1 (16.7)	5 (9.4)
Other	3 (5.1)	0	3 (5.7)
Concomittant disease			
Hypertension	44 (56.4)	4 (50.0)	40 (57.1)
Coronary syndrome	12 (15.6)	1 (12.5)	11 (15.9)
Myocardial infarction	11 (14.3)	1 (12.5)	10 (14.5)
Stroke	12 (15.9)	0	12 (17.6)
Cancer	15 (19.7)	1 (12.5)	14 (20.6)
Alcohol	4 (5.2)	0	4 (5.8)
Diabetes	19 (24.4)	2 (25.0)	17 (24.3)
Gastrointestinal ulcer	3 (3.9)	0	3 (4.3)
Gastrointestinal bleeding	1 (1.3)	0	1 (1.5)
Dementia	9 (12.0)	1 (12.5)	8 (11.9)
Biology at admission [mean ± SD]			
Creatinine, µmol/l	91.8 ± 41.3	95.4 ± 46.5	91.4 ± 41.0
INR	4.5 ± 6.2	3.2 ± 2.1	4.6 ± 6.5
Platelet, g/l	256.4 ± 95.1	279.5 ± 112.4	253.4 ± 93.1
Hb, g/dl	11.4 ± 3.1	11.1 ± 3.6	11.4 ± 3.0
Anemia	38 (45.8)	3 (33.3)	35 (47.3)
HAS-BLED [mean ± SD]	1.92 ± 1.02	1.5 ± 1.06	1.98 ± 1.0
HAS-BLED ≥ 3	22 (31.0)	2 (25.0)	20 (31.7)

Data are expressed as n (%) unless otherwise specified

SBP systolic blood pressure, VKA vitamin K antagonist, VTE venous thromboembolism, SD standard deviation, INR international normalized ratio, Hb hemoglobin

clinician but were generated retrospectively based on the different components of the International Society of Thrombosis and Haemostasis (ISTH) definition in the patient records [31]. Second, less than half the patients receiving L-thyroxine exhibited normal mean values of TSH. Finally, more than two-thirds of patients received fluindione, the anticoagulant proven to most significantly interact with L-thyroxine [25]. This was not surprising as fluindione is the most common VKA in France, where it is regarded as an alternative to warfarin. Given that it is

not a racemic mixture, and due to its longer half-life, fluindione is often preferred for stabilizing INR levels [40]. However, the RATED registry provides valuable insights on account of its unselected patient population, in contrast to the rigorously controlled conditions of randomized clinical studies. It can therefore help identify factors associated with better or worse outcomes, while providing feedback from real-world clinical situations, which may be valuable for designing new randomized clinical studies.

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Table 4 Bleeding outcomes according to treatment with or without L-thyroxine before and after propensity score matching

	Total [N = 1454]	Full cohort			Matched cohort		
		L-Thyroxine [N = 187]	No L-thyroxine [N = 1267]	p value	L-Thyroxine [N = 158]	No L-thyroxine [N = 158]	p value
Hemorrhage	225 (15.5)	27 (14.4)	198 (15.6)	0.67	24 (15.2)	23 (14.6)	0.87
Gastrointestinal bleeding	35 (2.4)	2 (1.1)	33 (2.6)	0.30	2 (1.3)	4 (2.5)	0.41
Intracranial bleeding	10 (0.7)	2 (1.1)	8 (0.6)	0.37	2 (1.3)	1 (0.6)	0.56
Intramuscular bleeding	27 (1.9)	5 (2.7)	22 (1.7)	0.37	4 (2.5)	4 (2.5)	1.00
Nosebleed	58 (4.0)	5 (2.7)	53 (4.2)	0.32	5 (3.2)	7 (4.4)	0.56
Others	79 (5.4)	13 (6.9)	66 (5.2)	0.33	11 (6.9)	7 (4.4)	0.33
Major bleeding	83 (5.7)	9 (4.8)	74 (5.8)	0.57	8 (5.1)	10 (6.3)	0.63

Data are expressed as n (%)

5 Conclusions

Our study found no evidence that L-thyroxine therapy could increase bleeding risk in patients receiving VKAs. These results on ambulatory patients reassure that L-thyroxine can be used safely with VKAs. However, interactions are an independent risk factor for serious bleeding in patients receiving long-term warfarin therapy. Moreover, patients could be administered other concomitant drugs, such as amiodarone, known to interact with VKAs.

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Compliance with Ethical Standards

Conflict of interest Dr. Moustafa has served as a consultant for Bayer HealthCare Pharmaceuticals and Sanofi, has been a speaker for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Daiichi-Sankyo and Sanofi, and has received grants from Sanofi, Bayer HealthCare, and LFB. Dr. Schmidt has received payments for board membership from Bayer, Daiichi, Lilly, and Pfizer, as well as personal compensation from Biomerieux, Bohringer Ingelheim, Sanofi, and Novartis. Rémi Malhomme, Bruno Pereira, Alain Barres, Jennifer Saint-Denis, Frederic Dutheil, and Marie Batisse have no conflicts of interest relevant to the contents of this paper.

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