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Epidémiologie et facteurs de risque des complications artérielles chez les patients atteints de maladie veineuse thromboembolique

Steve Noumegni

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L'UNIVERSITE
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Biologie Santé

Spécialité : Epidémiologie, Analyse de Risque, Recherche Clinique

Par **Steve NOUMEGNI**



Epidémiologie et facteurs de risque des complications artérielles chez les patients atteints de maladie veineuse thromboembolique

Thèse présentée et soutenue à Brest, le 07 Juin 2022

Unité de recherche : Inserm, UMR 1304 (GETBO)

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Université de Bretagne Occidentale



Groupe d'Étude de la Thrombose
de Bretagne Occidentale

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PRELIMINAIRES

DEDICACE

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« Reposes en paix Karine, reposes en paix chère Maître »

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LISTE DES ABREVIATIONS

AOD	Anticoagulant oraux direct
AOMI	Artériopathie oblitérante des membres inférieurs
ATE	<i>Arterial thrombotic event</i> / Evènement artériel thrombotique
AVC	Accident vasculaire cerebral (aux)
AVK	Antivitamine K
CVDT	<i>Cardiovascular Death</i> / Mortalité cardiovasculaire
EP	Embolie pulmonaire
HBPM	Héparine de bas poid moléculaire
HR	<i>Hazard Ratio</i>
IC	Intervalle de confiance
MACE	<i>Major Adverse Cardiovascular Event</i> / Evènement cardiovasculaire majeur indésirable
MALE	<i>Major Adverse Limb Event</i> / Evènement majeur indésirable des membres
MVTE	Maladie veineuse thromboembolique
RR	Risque relatif / <i>Relative risk</i>
RRI	Risque relatif incident, (<i>Incidence risk ratio</i> , IRR)
SCA	Syndrome coronarien aigu
TVP	Thrombose veineuse profonde

RESUME

Contexte : Des études issues de la littérature récente ont montré que les affections cardiovasculaires en général sont plus fréquentes chez les patients atteints de maladie thromboembolique veineuse (MTEV) que dans la population générale ; cependant, les facteurs de risque des affections cardiovasculaires dans cette population de patients atteints de MVTE restent très peu explorés, de même que l'impact potentiel sur ces affections, du traitement anticoagulant utilisé pour la MVTE.

Méthodologie : Nous avons effectué après revue de littérature extensive, l'analyse des données d'une cohorte prospective multicentrique en utilisant principalement des modèles de risque compétitif. Notre premier objectif était d'identifier les facteurs de risques des événements cardiovasculaires majeurs indésirables et des événements majeurs indésirables des membres après MVTE en général. Le deuxième objectif était de déterminer les facteurs de risque d'événements artériels thrombotiques après MVTE non provoquée et après MVTE associée au Cancer. Le troisième objectif était de déterminer les facteurs de risque des décès cardiovasculaires après toute MVTE. Et le dernier objectif était de déterminer l'impact potentiel du traitement anticoagulant initié pour MVTE sur le risque de survenue des événements cardiovasculaires majeurs indésirables. Tous les événements composant ces critères de jugement ont été adjudiqués.

Résultats : De façon générale, la revue de littérature avec méta-analyses nous ont permis de confirmer le surrisque d'affection cardiovasculaire artérielle chez les patients atteints de MVTE par rapport à la population générale. Pour l'analyse de la cohorte, 4940 patients ont été retenus, avec une moyenne d'âge de 64.6 ans, et dont 46.9% étaient de sexe masculin. Nos analyses principales ont montré d'une part, que les facteurs de risque d'affections cardiovasculaires artérielles après MVTE incluent certains facteurs de risque cardiovasculaires connus en population générale tel que l'âge, certaines comorbidités, et des facteurs liés aux caractéristiques de la MVTE tel que le caractère non provoqué ; et d'autre part que l'anticoagulation pour MVTE influence le risque d'affections cardiovasculaires majeures ultérieures avec un risque moindre chez les patients traités par AOD et chez ceux traités plus de 3 mois, même si ces résultats restent à être confirmés par des essais cliniques randomisés.

Conclusion : Les facteurs de risques d'affections cardiovasculaires artérielles après MVTE incluent des facteurs de risque cardiovasculaires classiques, et des caractéristiques de la MVTE. Le traitement anticoagulant pour MVTE influencerait l'incidence de ces affections.

SUMMARY

Background: Studies from the recent literature have shown that arterial cardiovascular diseases are more common in patients with venous thromboembolic disease (VTE) than in the general population; however, risk factors of these arterial cardiovascular diseases in patients with VTE remain little explored, as well as the potential impact of anticoagulant therapy used for VTE on the risk of these diseases.

Methods: After an extensive literature review, we analyzed data from a multicenter prospective cohort using mainly competitive risk models. Our first objective was to identify the risk factors of major adverse cardiovascular events (MACE) and major adverse limbs events (MALE) that occurred after any VTE. The second objective was to determine the risk factors for arterial thrombotic events (ATE) after unprovoked VTE and after Cancer-associated VTE. The third objective was to determine the risk factors for cardiovascular death (CVDT) after any VTE. And the last objective was to determine the potential impact of anticoagulant treatment initiated for VTE on the risk of occurrence of MACE. All events composing the outcomes have been adjudicated.

Results: The literature review with meta-analyses allowed us to confirm that there is an increased risk of arterial cardiovascular events in patients with VTE, as compared to the general population. For the cohort analysis, 4940 patients were included, with a mean age of 64.6 years, of which 46.9% were male. Our main findings showed on the one hand, that the risk factors for arterial cardiovascular events after VTE include certain classic cardiovascular risk factors known in the general population such as age, some comorbidities, and factors related to the characteristics of VTE such as the unprovoked VTE; and on the other hand that anticoagulation for VTE influences the risk of subsequent arterial cardiovascular events with a lower risk in patients treated with DOAC and in those treated for more than 3 months, even if these results need to be confirmed by randomized trials.

Conclusion: Risk factors for arterial cardiovascular events after VTE include classic cardiovascular risk factors and characteristics of VTE. Anticoagulant treatment introduced for VTE may influence the incidence of these conditions.

Chapitre I :

INTRODUCTION

1) Contexte et justification

La maladie veineuse thromboembolique (MVTE), qui comprend la thrombose veineuse profonde (TVP), et l'embolie pulmonaire (EP), est un problème majeur de santé publique de par sa fréquence, sa mortalité et sa morbidité considérables [1,2]. En effet, elle représente la troisième cause de décès par maladies cardiovasculaires dans la population générale, après les crises cardiaques et les accidents vasculaires cérébraux [3]. Par ailleurs, malgré tous les efforts déployés pour combattre la MVTE ces dernières années, son incidence est estimée à environ 0,1 à 0,2 pour 100 personnes-années en Europe et aux États-Unis [4,5].

La relation entre la survenue de MVTE et l'augmentation du risque de complications artérielles ultérieures a été rapportée dans plusieurs études ; et ce, en considérant uniquement les événements ischémiques / thrombotiques artériels pris individuellement, ou en considérant toutes les complications artérielles très souvent regroupés en critères composites comme événements cardiovasculaires majeurs indésirables (MACE, pour *Major Adverse Cardiovascular Events*) et / ou événements indésirables majeurs des membres (MALE, pour *Major Adverse Limbs Events*) et / ou événement thrombotiques artériels (ATE, pour *Arterial Thrombotic Events*) [6,7]. Si l'association entre la survenue des événements cardiovasculaires artériels et l'augmentation du risque de MVTE est largement consensuelle depuis de nombreuses années, peut-être parce que les maladies artérielles conduisent généralement à une hospitalisation, et donc temporellement à l'immobilisation qui est un facteur établi MVTE, l'association entre la survenue de MVTE et l'augmentation du risque de complications artérielles ultérieures a été pendant longtemps hypothétique [8–10].

Cependant, sur la base de nombreuses études récentes et même de certaines méta-analyses, l'augmentation du risque de complications cardiovasculaires artérielles dans la population des patients ayant fait une MVTE par rapport à la population générale est aujourd'hui établi [6,11–13]. Il est important de noter qu'il a été démontré que ce surrisque de complications artérielles en général, ainsi que celui de MACE et MALE en particulier, est plus important chez les patients atteints de MVTE non provoquée et chez les patients atteints de MVTE liée au cancer [14,15]. Contrairement à la population générale où les facteurs de risque d'évènements cardiovasculaires artériels sont bien connus, ces derniers sont mal identifiés dans la population de sujets atteints de MVTE. Pour essayer palier à ce manque, quelques études se sont données pour objectif de comprendre les raisons de ce surrisque de complications cardiovasculaires artérielles chez les patients atteints de MVTE et en sont arrivées à la conclusion selon laquelle

les événements thrombotiques veineux et artériels auraient certains facteurs de risque communs [15,16]. Si ces résultats soutenus par une récente méta-analyse ont mis en évidence l'hypothèse que les thromboses artérielles et veineuses pourraient être la manifestation d'une même maladie, il existe très peu d'études de cohorte prospectives à grande taille d'échantillon qui se sont intéressées à cette question [17].

Ainsi, la question des facteurs de risque de MACE, de MALE ou d'ATE dans la population globale de patients atteints de MVTE et dans des sous-groupes de patients atteints de MVTE non provoquée ou de MVTE associée au cancer, reste très peu explorée. De plus, les quelques études de cohorte prospectives disponibles dans la littérature actuelle, qui ont déterminé les facteurs de risque de complications artérielles chez les patients atteints de MVTE, ont ignoré pour la majorité d'entre eux, l'impact potentiel du risque compétitif lié aux décès non causés aux événements d'intérêt [16,17]. Dans le but d'apporter des éléments de réponse à ces questions cruciales pour la pratique clinique, et de mieux prévenir les affections cardiovasculaires artérielles chez les patients atteints de MVTE, une détermination de l'incidence exacte de ces affections et des facteurs prédictifs de leurs survenues dans une importante cohorte prospective, en utilisant une méthodologie rigoureuse, s'avère indispensable. Nous avons à cet effet mené cette étude intitulée :

« Epidémiologie et facteurs de risque des complications artérielles chez les patients atteints de maladie veineuse thromboembolique ».

2) Question de recherche

Quels sont les facteurs de risque de survenue des complications artérielles chez les patients atteints de MVTE ?

3) Hypothèse de recherche

Il existerait plusieurs facteurs cliniques, biologiques, thérapeutiques ou environnementaux non identifiés en population générale qui favorisent la survenue de complications artérielles (ATE, MACE, ou MALE) chez les patients atteints de MVTE.

4) Objectifs

4.1) Objectif principal

1. Déterminer les facteurs de risque des MACE et des MALE chez les patients de MVTE.

4.2) Objectifs secondaires

2. Déterminer les facteurs de risque des évènements thrombotique ou ischémique (ATE) chez les patients atteints de MVTE non provoquée et chez les patients atteints de MVTE liée au cancer.
3. Déterminer les facteurs de risque de décès cardiovasculaires (CVDT, pour *cardiovascular death*) chez les patients atteints de MVTE.
4. Déterminer l'influence potentiel du traitement anticoagulant introduit pour la MVTE sur le risque de survenu des MACE.

Chapitre 2 :

REVUE DE LA LITTÉRATURE

Cette section s'articule autour de la présentation de 3 articles scientifiques que nous avons rédigé et publié à l'issue de la revue de littérature ayant précédé nos analyses principales. Nous présentons à chaque fois un résumé en langue française suivi de l'article complet dans la version acceptée pour publication. Il s'en suivra une synthèse générale. Les numérotations des références bibliographiques sont ajustées à l'ensemble de ce document et ne correspondent donc pas aux numérotations retrouvées dans la version publiée de chaque article mais les références sont exactement les mêmes. De même les mises en forme ont été modifiées pour des besoins d'adéquation avec l'ensemble de ce document et pourraient ne pas correspondre aux mises en forme exactes des articles publiés, toutefois le contenu est exactement le même. Le plan de présentation est le suivant :

- Fréquence et incidence des événements artériels chez les patients atteints de MVTE comparativement à la population générale : revue de littérature et méta-analyse des études de cohorte
- Facteurs de risque des événements artériels chez les patients atteints de MVTE : revue de littérature et méta-analyse
- Mortalité cardiovasculaire chez les patients atteints de MVTE : revue de littérature et méta-analyse des études de cohorte prospective
- Synthèse générale de la revue de littérature.

A. Article de revue 1 : fréquence et incidence des événements artériels après MVTE

Cet article a été publié dans le journal *Thrombosis Research* le 15 Mai 2021 et est référencé sous : « Noumegni SR, Hoffmann C, Tromeur C, et al. Frequency and incidence of arterial events in patients with venous thromboembolism compared to the general population: A systematic review and meta-analysis of cohort studies. *Thromb Res.* 2021 May 15;203:172–85. » Référence N° : 12.

I. RESUME

Rationnel : Les données récentes de la littérature ont émis l'hypothèse que les patients atteints de maladie veineuse thromboembolique (MVTE) ont un risque augmenté de développer des événements artériels ischémiques ou thrombotiques que la population générale. Cependant, des données résumant l'épidémiologie des événements artériels chez les patients atteints de MVTE en comparaison à la population générale indemne de MVTE sont manquants.

Méthodologie : Nous avons effectué une revue systématique avec méta-analyse de la littérature récente. Les bases de données PubMed, EMBASE et Cochrane ont été consultées pour des articles publiés entre le 1er janvier 2000 et le 31 décembre 2020. Les études éligibles étaient des études de cohorte observationnelles publiées en langue anglaise et rapportant des événements artériels ischémiques chez les patients atteints de MVTE. Les paramètres d'intérêt et leurs intervalles de confiance à 95 % ont été obtenus grâce à une méta-analyse de modèles à effets aléatoires.

Résultats : Vingt-huit études portant sur 35 2014 patients ont été identifiées et incluses. La fréquence de tous les événements artériels était de 6,1 % (IC à 95 % : 3,7 - 9,1) chez les patients atteints de MVTE et était significativement plus élevée que les 5,0 % (IC à 95 % : 3,1 - 7,2) trouvée chez les témoins, avec un risque relatif (RR) de 1,20 (IC à 95 % : 1,01 - 1,44 ; $p = 0,0422$). L'incidence combinée de tous les événements artériels chez les patients atteints de MVTE était de 11,3 ‰ patient-année (IC à 95 % : 4,6 - 18,0) et était significativement plus élevée que les 9,2 ‰ patient-année (IC à 95 % : 2,0 - 16,4) obtenus chez les témoins (Rapport de risque d'incidence, RRI : 1,32 ; IC à 95 % : 1,08 - 1,61 ; $p = 0,0103$). La fréquence et l'incidence des événements artériels étaient également plus élevées chez les patients atteints de MTEV non provoquée que chez les patients atteints de MTEV provoquée (RR : 2,12 ; IC à 95 % : 1,38 - 3,24 ; $p = 0,0042$; et RRI : 2,26, IC à 95 % : 1,45 - 3,49 ; $p = 0,0032$).

Interprétation : La fréquence et l'incidence des événements artériels chez les patients atteints de MVTE sont considérablement plus élevées que dans la population générale. Des études ultérieures sont nécessaires pour mieux comprendre ces différences et réduire la morbidité associée à ces affections.

Mots-clés : maladie veineuse thromboembolique, événements artériels, fréquence, incidence, méta-analyse.

II. ARTICLE COMPLET

Frequency and incidence of arterial events in patients with venous thromboembolism compared to the general population: a systematic review and meta-analysis of cohort studies

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Frequency and incidence of arterial events in patients with venous thromboembolism compared to the general population: A systematic review and meta-analysis of cohort studies

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Summary

Background: Recent literature hypothesized that patients with venous thromboembolism (VTE) are at increased risk of developing arterial ischemic events than general population without VTE. However, data summarizing the epidemiology of arterial events among VTE population compared to the general population are lacking.

Methods: We conducted a systematic review and meta-analysis from current literature. PubMed, EMBASE, and Cochrane databases were searched between Jan 1, 2000, and December 31, 2020. Eligible studies were observational cohort studies published in English on arterial ischemic events in patients with VTE. Pooled effect size estimates and their 95% confidence intervals were obtained through random-effect models meta-analysis.

Findings: Twenty-eight observational studies enrolling 352014 patients were identified and included. The pooled frequency of all arterial events was 6.1 % (95 % CI: 3.7- 9.1) in patients with VTE and was significantly higher than the pooled frequency of 5.0 % (95 % CI: 3.1 - 7.2) found in controls, with a pooled risk ratio (RR) of 1.20 (95 % CI: 1.01 - 1.44; $p = 0.0422$). The pooled incidence of all arterial events in patients with VTE was 11.3 ‰ per patient-year (95 % CI: 4.6 - 18.0), and was significantly higher than the 9.2 ‰ per patient-year (95 % CI: 2.0 - 16.4) obtained in controls (Incidence risk ratio, IRR: 1.32; 95 % CI: 1.08 - 1.61; $p = 0.0103$). The pooled frequency and pooled incidence of arterial events were also higher in patients with unprovoked VTE than in patients with provoked VTE (RR: 2.12; 95 % CI: 1.38 - 3.24; $p = 0.0042$; and IRR: 2.26, 95 % CI: 1.45 - 3.49; $p = 0.0032$).

Interpretation: The frequency and incidence of arterial events in patients with VTE are considerably higher than in the general population, without VTE. Further studies are urgently needed to understand these differences and reduce the burden related to these diseases.

Keywords: venous thromboembolism, arterial event, frequency, incidence, meta-analysis.

Research in context**Evidence before this study**

Venous thromboembolism (VTE) is frequent in patients with arterial diseases, generally because of acute illness, and immobilization related to hospitalization. Many patients with venous thromboembolism developed arterial thrombotic complications, but it is not clear whether this population is at higher risk of arterial events than the general population without VTE. We searched for relevant cohort studies including patients with VTE reporting on at least one arterial ischemic event (including myocardial infarction or other acute coronary syndrome, ischemic stroke or transient ischemic attack, major adverse limb event, mesenteric ischemia and any other arterial ischemic event) in MEDLINE, EMBASE, and Cochrane Library, with emphasis on studies including a control group, without VTE. We used the search terms: venous thromboembolism, venous thrombosis, pulmonary embolism, myocardial ischemia (MI), coronary artery disease, arterial occlusive disease, brain ischemia, intracranial embolism and thrombosis, stroke, peripheral arterial disease (PAD), and mesenteric ischemia, with relevant medical subject headings (MeSH) or keywords. One previous review and meta-analysis on the topic was done in 2010, but the authors included few studies, and only compared the incidence of arterial events in patients with unprovoked (which was higher than in control group) and provoked VTE (control group). VTE might have an independent effect on the occurrence of arterial events in patients with VTE, with a higher risk in patients with unprovoked VTE. However, the overall and accurate evidence supporting this hypothesis is uncertain.

Added value of this study

This meta-analysis of observational cohorts' studies confirmed that the risk of arterial events is significantly higher in patients with VTE, than in the general population without VTE, and in patients with unprovoked VTE compared to patients with provoked VTE.

Implications of all the available evidence

Based on our current meta-analysis and previous literature, there is an urgent need for implementation of comprehensive and effective strategies to prevent arterial events in patients with VTE, with specific attention for patients with unprovoked VTE. Further studies are also needed to understand the reason of this over-risk.

Introduction

Despite considerable progress constantly made in the prevention and treatment of cardiovascular diseases, they remain an important public health problem, as they are responsible of about 17.9 million death each year [18]. Myocardial infarction and stroke account for four out of five cardiovascular disease deaths and therefore constitute the leading majority of these conditions [19]. Venous thromboembolism (VTE) represents the third most common cause of death from cardiovascular diseases after heart attacks and stroke [3]. After considering arterial ischemic events and venous thromboembolism (VTE) as two separate diseases for a while, several studies highlighted a possible relationship between these two entities in recent literature [3,14].

Growing evidence is supporting an association between the occurrence of VTE, particularly unprovoked ones, and the risk of future arterial ischemic events [6,7]. For example, a retrospective study including 2154 patients with unprovoked VTE and 4308 controls concluded in 2017 reported that patients with VTE, particularly males, suffered from a 1.86-fold risk of major adverse cardiovascular events (including acute coronary syndrome and stroke), as compared to controls [15]. If the majority of recently published studies are along these lines, it is no less true that there are conflicting data. In fact, a population-based case-control and cohort study including 1177 patients with VTE and 1495 controls concluded in 2014 concluded that VTE is not a predictor of MI and that myocardial infarction (MI) is not an independent risk factor for VTE [20]. While a large retrospective cohort study including 41259 patients with VTE and published in 2020, reported that after adjusting for multiple conventional cardiovascular risk factors, provoked VTE, compared with unprovoked VTE, was significantly associated with an increased hazard for major adverse cardiovascular events including stroke, myocardial infarction, and unstable angina (HR, 1.4; 95% CI, 1.1-1.7) [14].

So, are patients with VTE really at increased risk of arterial ischemic events than the general population? Are patients with unprovoked VTE really at increased risk of arterials ischemic events as compared to those with provoked VTE? These are several questions, which deserve to be answered by summarizing data from current literature while waiting for results of further cohort studies. To fill this critical gap, we conducted a systematic review and meta-analysis, with the objective to determine the frequency and incidence of arterial events in patients with VTE, compared to the general population (controls without VTE), and in patients with unprovoked VTE, compared to patients with provoked VTE.

Methods

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines served as the template for reporting the present review[21]. The protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the following registration number: CRD42021238103.

Eligibility criteria

We included all population-based original research articles on human cohort studies involving adults and reporting on at least one of the following arterial ischemic events in patients with VTE: myocardial infarction or other acute coronary syndrome, ischemic stroke or transient ischemic attack, major adverse limb event (including peripheral arterial disease, acute limb ischemia, revascularization procedure, or limb amputation), mesenteric ischemia and any other arterial ischemic event. The minimum follow-up for studies included in meta-analysis of incidence was three months. In our review, VTE included deep vein thrombosis (DVT), pulmonary embolism (PE), and superficial venous thrombosis (SVT).

We excluded commentaries, editorials, reviews, studies lacking primary data or with incomplete methods description. Studies that did not report the number of events or patient-time values or the incidence of arterial events in patients with VTE were also excluded.

Search strategy to identify relevant studies

We performed a comprehensive literature search in Medline/PubMed, Excerpta Medica Database (EMBASE), and Cochrane databases, which was complemented by hand searches of bibliographies, to identify eligible studies published in English language between January 1, 2000 and December 31, 2020. We used a combination of the following terms: venous thromboembolism, venous thrombosis, pulmonary embolism, myocardial ischemia (MI), coronary artery disease, arterial occlusive disease, brain ischemia, intracranial embolism and thrombosis, stroke, peripheral arterial disease (PAD), and mesenteric ischemia, with relevant medical subject headings (MeSH) or keywords. The main search strategy conducted in EMBASE is presented in **supplementary file 1** for illustration, and **Figure 1** gives a summary of the studies' selection process.

Two investigators independently identified articles and sequentially screened their titles and abstracts for eligibility. Full texts of potentially eligible articles were acquired and assessed to retain studies to be included. Disagreements when existing were solved by consensus. For

duplicate publications, only the most comprehensive report including the largest sample size was retained.

Supplementary file 1: EMBASE search strategy

	Search	Results
#1	('vein thrombosis'/exp OR 'vein thrombosis' OR 'lung embolism':ab,ti OR 'deep vein thrombosis':ab,ti OR 'superficial venous thrombosis':ab,ti) AND 'venous thromboembolism':ab,ti AND [2000-2020]/py	13184
#2	('cardiovascular disease'/exp OR 'cardiovascular disease' OR 'major adverse cardiac event':ab,ti OR 'major adverse limb event':ab,ti OR 'cardiovascular death':ab,ti OR 'peripheral occlusive artery disease'/exp OR 'peripheral occlusive artery disease' OR 'artery disease'/exp OR 'artery disease' OR 'heart infarction'/exp OR 'heart infarction' OR 'acute coronary syndrome'/exp OR 'acute coronary syndrome' OR 'peripheral vascular disease'/exp OR 'peripheral vascular disease' OR 'cerebrovascular accident'/exp OR 'cerebrovascular accident' OR 'mesenteric ischemia'/exp OR 'mesenteric ischemia') AND [2000-2020]/py	3325546
#3	#1 AND #2	13170
#4	#3 Limited to <ul style="list-style-type: none"> - Observational studies, - Comparative studies, - Original research articles or meta-analysis, - Humans, - English language, and - Period between January 2000 and December 31st 2020. 	2817

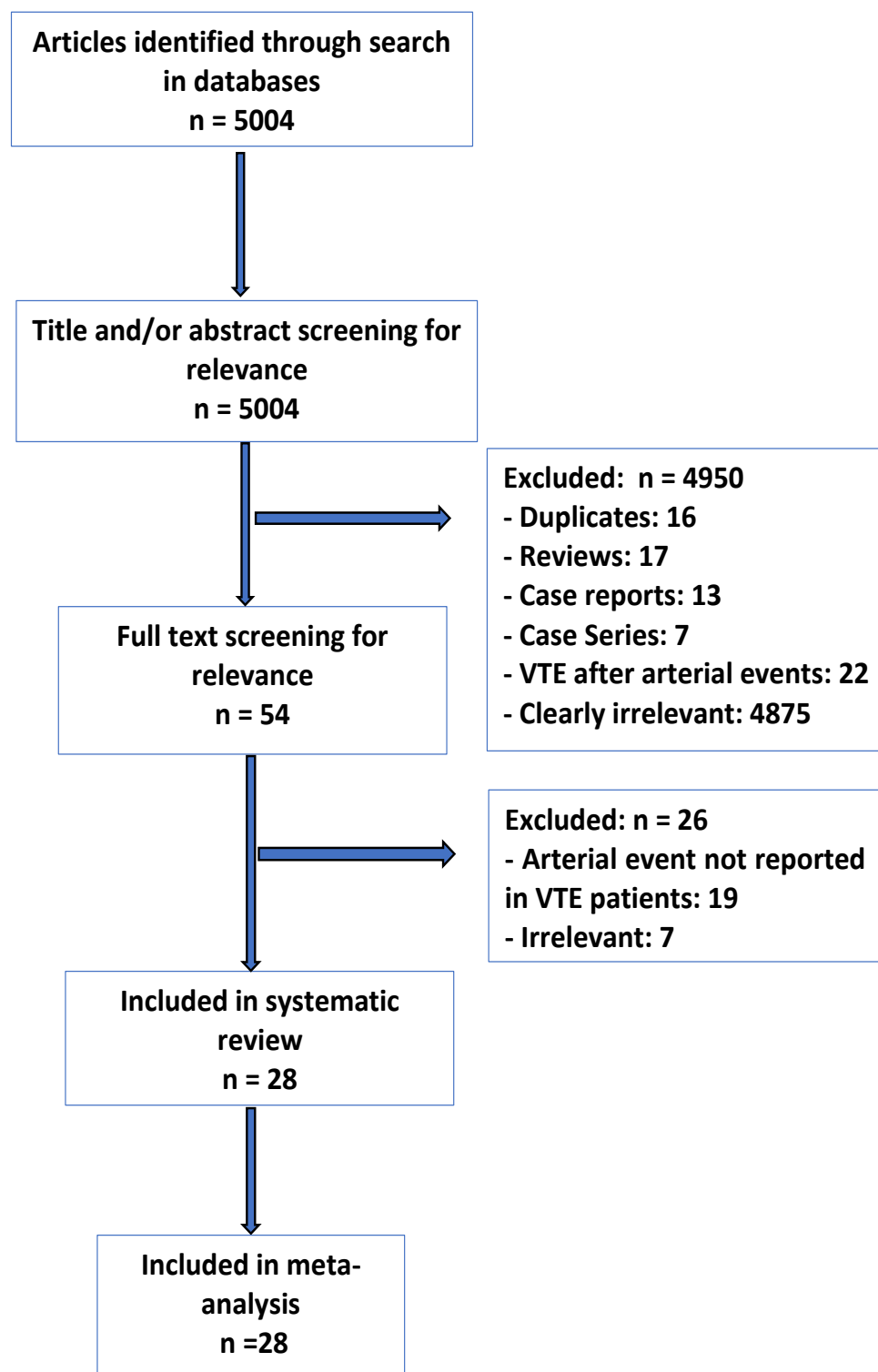


Figure 1: Flow chart of studies' selection

Data extraction

We used a standardized data extraction sheet to report information on study design, sample size (total number of patients with venous thromboembolism), type of VTE (PE, DVT, or SVT), mean or median age, number of men, outcomes, number of new arterial events, incidence rate or patient-time estimates and median/mean duration of anticoagulant therapy. When not directly provided, an approximate patient-time value was calculated either from the number of participants and overall follow-up (when there was no lost to follow-up), or from the incidence rate and the number of new events. We used primary data (number of patients with VTE, number of outcomes, and number of patient-time), to calculate the crude frequency or the crude incidence rate of arterial events in patients with VTE (all, provoked, and unprovoked), and controls. Data were extracted by one investigator (SN) and a second investigator (CH) double-checked extracted data for accuracy, with disagreements between authors being reconciled through discussion. Search results were compiled using the citation management software Zotero version 5.0.77.

Appraisal of the quality of included studies

Methodological quality and risk of bias of included studies were assessed using an adapted version of the Newcastle-Ottawa quality assessment scale (NOS) for evaluation of the quality of observational studies [22]. The NOS is formulated by a star allocation system, assigning a maximum of nine stars for the risk of bias in three areas: selection of study groups, comparability of groups, and ascertainment of the outcome of interest. There is no validation study that provides a cut-off for interpretation of this score, despite the fact that many authors consider a score equal to, or higher than 7 to define high-quality studies. We, therefore, considered a score from zero to three stars for low-quality studies (high risk of bias), four to six stars for fair-quality studies (moderate risk of bias), and seven to nine stars for high-quality studies (low risk of bias), respectively. Details of stars allocation per category in each included study are presented in **supplementary file 2**.

Data synthesis and statistical analysis

Data were analyzed using the “meta”, “dmetar”, and “metaphor” packages of the statistical software R, version 3.6.2. Forest plots were drawn to visualize the combined frequency and incidence of arterial events in patients with VTE and the extent of heterogeneity between studies. All effect sizes including frequency, incidence rate, risk ratio (RR), and incidence risk

ratio (IRR) were reported with their 95% confidence intervals (CI) and 95% prediction intervals for some.

Owing to the clinical differences across patients included in the studies (difference of outcome definition, difference of clinical presentation, and possible misclassification of positive and negative outcome), random-effects meta-analysis was used to pooled effect sizes (frequency, incidence, RR, and IRR) [23]. This was done using the inverse variance method for frequency and incidence, while the Mantel-Haenszel method was used for the meta-analysis of RR and IRR. In order to keep the effect of studies with extremely small or extremely large effect size on the overall estimates to a minimum for meta-analysis of frequency, stabilization of variance of studies was done using the Freeman-Tukey double arc-sine transformation [24]. Heterogeneity was assessed using the χ^2 test on Cochrane's Q statistic and quantified by calculating the I^2 which values greater than 60–70% indicate the presence of substantial heterogeneity [25]. In order to assess possible publication bias, we used funnel plots and Egger's test, with a p-value < 0.10 considered statistically significant [19]. generally, a p-value < 0.05 characterized statistically significant results in our analysis.

Sensitivity analyses

After calculating the crude overall pooled frequency and incidence rate of all arterial events in patients with VTE, we did sensitivity analyses including only studies with a low risk of bias to assess the robustness of our findings. We also calculated the overall pooled frequency and incidence of arterial events excluding studies with patients suffering from SVT. We did a subgroup analysis comparing values in prospective and retrospective studies, and comparing results according to the median duration of follow-up, the mean/median age (> 50, ≤ 50 years) and the duration of anticoagulant therapy (1-6 months, > 6 months).

Supplementary file 2: Assessment of methodological quality of included studies with the Newcastle-Ottawa quality assessment scale for cohort studies

Authors	Selection				Comparability	Outcome			Number of stars/Risk of Bias
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Le Moigne et al.	*	*	*	- not sure	- no description of any match process or multivariate adjustment	*	- not reported	*	5 / Moderate
Brenner et al.	*	- no control group	*	*	- no control group	*	*	- no statement	5 / Moderate
De Miguel-Díez et al.	*	*	*	*	**	*	*	- no statement	8 / Low
Hu et al.	*	- no control group	*	*	- no control group	*	*	- no statement	5 / Moderate
Chang et al.	*	*	*	*	**	*	*	*	9 / Low
Bilora et al.	*	*	*	*	**	*	*	*	9 / Low
Vindis et al.	*	*	*	- not sure	**	*	*	- 25% lost to follow-up	7 / Low
Ljungqvist et al.	*	*	*	*	**	*	*	*	9 / Low
Pasha et al.	*	*	*	*	**	*	*	*	9 / Low
Cannegieter et al.	*	*	*	*	**	*	*	- no statement	8 / Low
Madridano et al.	*	- no control group	*	*	- no control group	*	*	- no statement	5 / Moderate
Lind et al.	*	*	*	- not sure	*	*	*	- no statement	6 / Low
Barsoum et al.	*	*	*	*	**	*	*	*	9 / Low
Laliberté et al.	*	- no control group	*	*	- no control group	*	*	- no statement	5 / Moderate

Goliszek et al.	- Participants selected from a group of patients	- no control group	*	- not sure	- no control group	*	- not reported	- no statement	2 / High
Doyen et al.	*	*	*	- not sure	- no description of any match process or multivariate adjustment	*	- not reported	- no statement	4 / Moderate
Roach et al.	*	*	*	*	**	*	*	- no statement	8 / Low
Verso et al.	*	- no control group	*	*	- no control group	*	*	- no statement	5 / Moderate
Roshani et al.	*	*	*	*	*	*	*	- no statement	7 / Low
Prandoni et al.	*	*	*	*	**	*	*	*	9 / Low
Klok et al.	*	*	*	*	**	*	*	*	9 / Low
Huerta et al.	*	*	*	*	**	*	*	- no statement	8 / Low
Spencer et al.	*	*	*	*	**	*	*	- no statement	8 / Low
Sorensen et al.	*	*	*	*	**	*	*	- no statement	8 / Low
Linnemann et al.	*	- no control group	*	- not sure	- no control group	*	- not reported	- no statement	3 / High
Bova et al.	*	*	*	*	**	*	*	*	9 / Low
Prandoni et al.	*	*	*	*	**	*	*	*	9 / Low
Becattini et al.	*	- no control group	*	*	- no control group	*	*	- no statement	5 / Moderate

Thresholds for interpretation of the Newcastle-Ottawa scales used in our study.

Good quality > Low risk of bias: 7-9

Fair quality > Moderate risk of bias: 4-6

Poor quality > High risk of bias: 0-3

Results

Studies selection and general characteristic of included studies

Initially, a total of 5004 records were identified. After elimination of duplicates, screening titles and abstracts, 4950 papers were found irrelevant and excluded. Full texts of the remaining 54 papers were deeply screened for eligibility, among which 26 were excluded. Overall, 28 studies were found eligible and included in the meta-analysis. They were published between 2005 and 2019 and were all cohorts including 13 prospective [20,26–37] and 15 retrospective studies [6,7,11,15,16,38–47]. All studies reported frequency or incidence of arterial ischemic events in patients with VTE, but only 14 studies reported data in a control group without VTE. The number of participants with VTE varied between 41 and 177885 per study, with a total of 352014 patients among all included studies; and the percentage of males varied between 0 and 51.8%. Median or mean follow-up was reported for 17 studies and varied between 7.3 months and 10 years; while the overall follow-up period was reported for 7 studies and varied between 12 months and 20 years. Median duration of anticoagulant therapy was reported only in 7 studies and varied between 3.1 months and 13.9 months. **Table 1** gives the general characteristic of each included study and participants.

Methodological quality and heterogeneity

Of the included studies, 18 (64%) had low [6,7,11,15,20,28,29,32–36,38,40,41,44,45,47], 8 (29%) moderate [16,26,27,31,37,39,42,43], and 2 (7%) high risk of bias in their methodological quality [30,46]. There was substantial heterogeneity for all analysis of frequency and incidences in the VTE population compared to controls without VTE, but not in analysis comparing unprovoked and provoked VTE population. However, generally, there was no publication bias for the majority of analysis (p-values of the Egger test reported in table 2,3,4 and 5).

Frequency of arterial events in patients with VTE and control population

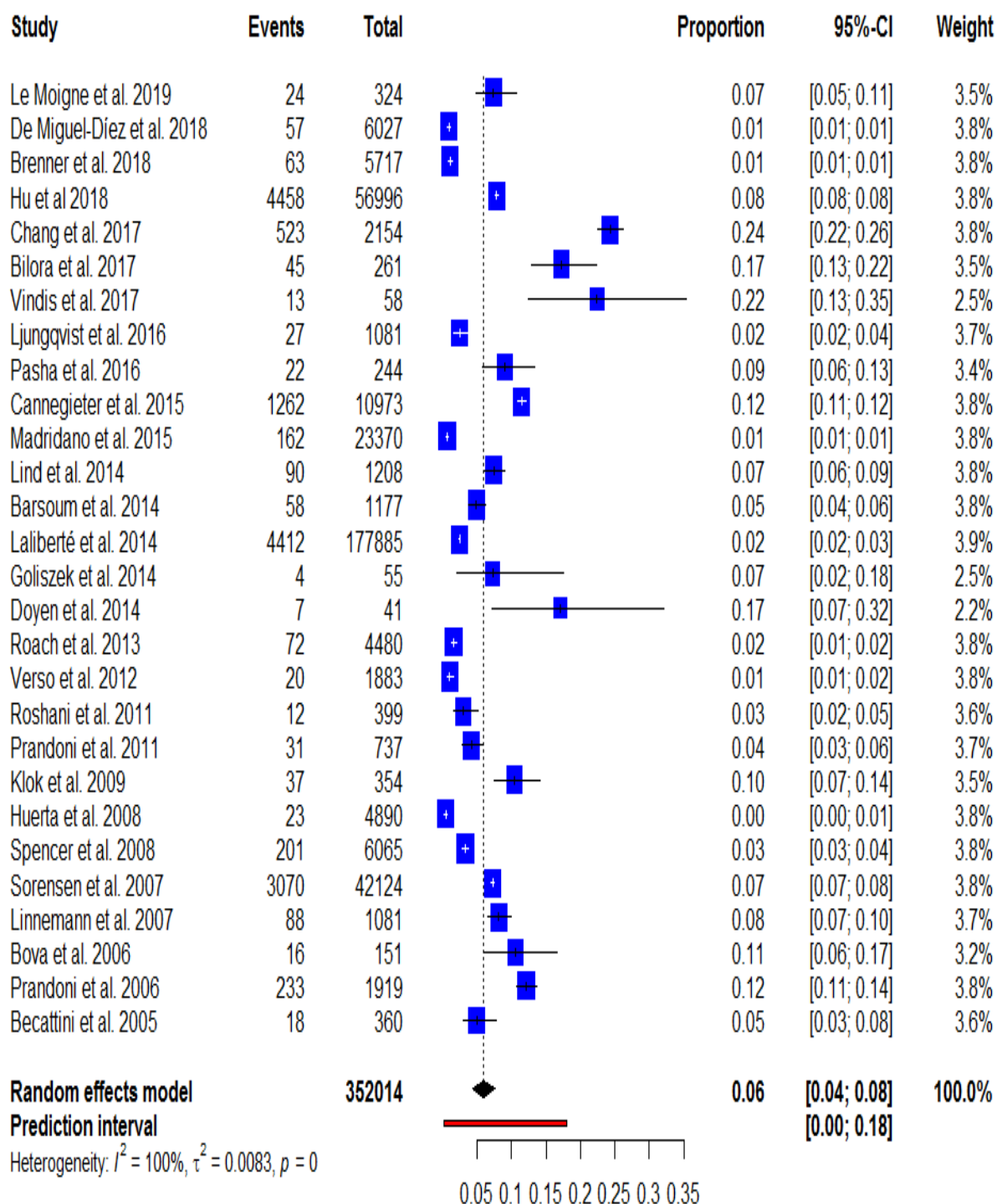
The overall pooled frequency of all arterial events in patients with VTE was 6.0 % (28 studies, 352014 patients, 95 % CI: 4.3 - 7.7; $I^2 = 99.7\%$) (**Figure 2**), and the overall pooled frequency of all arterial events in controls was 5.0 % (14 studies, 830294 patients, 95 % CI: 3.1 - 7.2; $I^2 = 99.9\%$). The funnel plot suggested no publication bias for the estimation of the overall frequency of arterial events among patients with VTE, and this was confirmed by the results of Egger's test (p = 0.1877).

The overall pooled frequency of myocardial infarction/acute coronary syndrome was 2.4 % (20 studies, 292325 patients, 95 % CI: 1.6 - 3.4; $I^2 = 99.3\%$) in patients with VTE, and 2.5 % (11 studies, 824518 patients, 95 % CI: 1.5 - 3.7; $I^2 = 99.8\%$) in controls. While the overall pooled frequency of stroke/transient ischemic attack was 3.2 % (21 studies, 159147 patients, 95 % CI: 1.8 - 5.1; $I^2 = 99.6\%$) in patients with VTE, and 1.8 % (8 studies, 767580 patients, 95 % CI: 0.9 - 2.9; $I^2 = 99.8\%$) in controls.

Comparison of frequency of arterial events in patients with VTE and controls

In studies including controls without VTE, the frequency of arterial events in patients with VTE (6.1%, 95% CI: 3.7- 9.1, 14 studies, $I^2 = 99.4\%$) was significantly higher than in controls population (**Table 2**), with an overall pooled RR of 1.20 (14 studies, 95 % CI: 1.01 - 1.44; $I^2 = 93.5\%$, $p = 0.0422$) (**Figure 3**); there was no publication bias ($p = 0.1032$). The same tendency was present despite non-significant p-values while comparing only frequencies of myocardial infarction/acute coronary syndrome and ischemic stroke/transient ischemic attack in patients with VTE and controls, with respective RR of 1.17 (11 studies, 95 % CI: 0.87 - 1.57; $p = 0.2577$) and 1.17 (8 studies, 95 % CI: 0.89 - 1.54; $p = 0.1983$) (**Table 2**). Definitions of cases of VTE and controls in each study with these two groups are given in **Table 3**.

Considering patients with provoked or unprovoked VTE only compared to controls, the frequency of all arterial events in patients with unprovoked was significantly higher than in control population, with a pooled RR of 1.57 (8 studies, 95 % CI: 1.13 - 2.20; $I^2 = 93.2\%$, $p = 0.0151$) ; while there was no significant difference comparing the frequency of arterial events in patients with provoked VTE and controls (RR: 0.91, 5 studies, 95 % CI: 0.47 - 1.80; $I^2 = 89.5\%$, $p = 0.7237$).



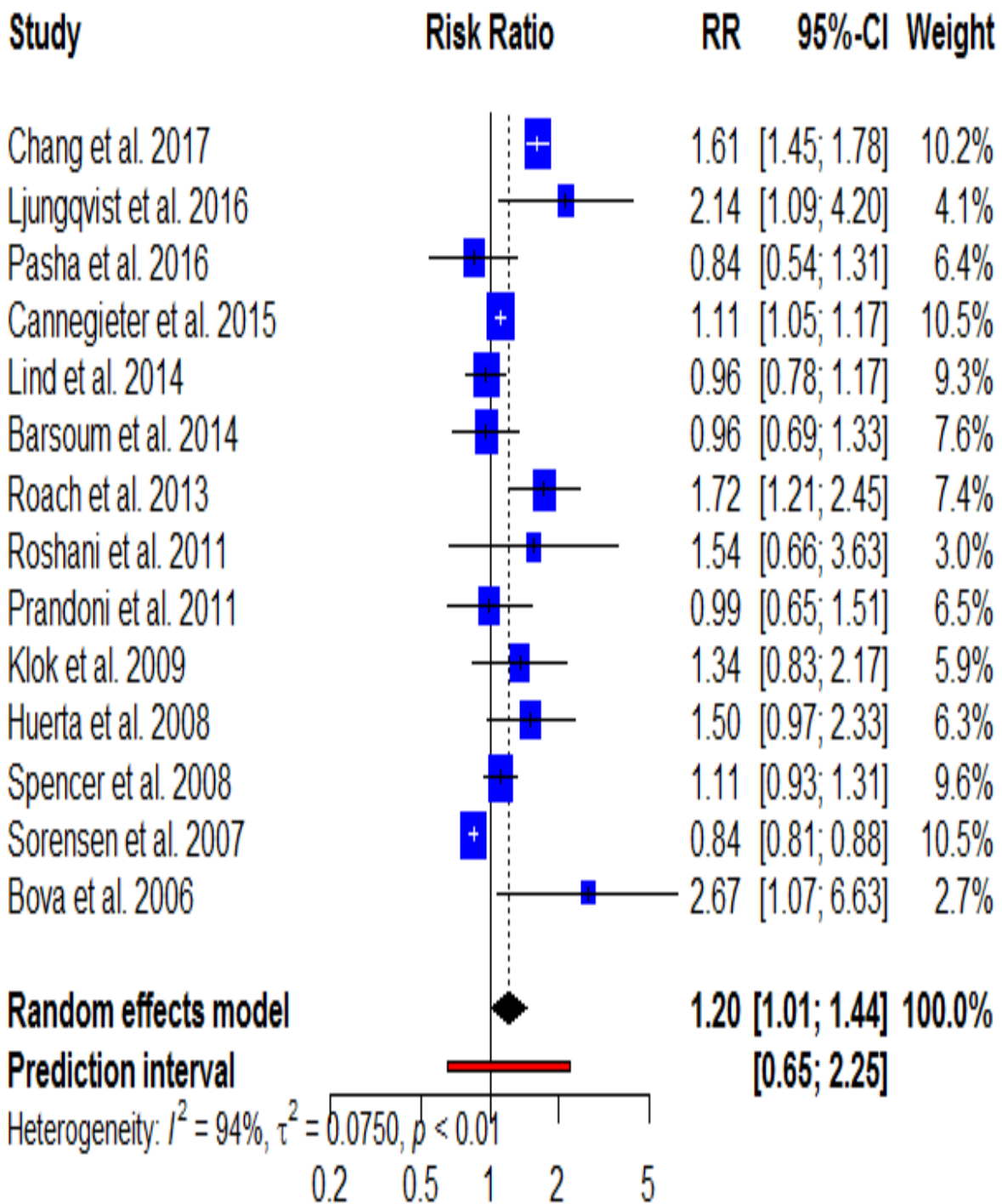
- CI: confidence interval

Figure 2: Frequency of all arterial event in patients with venous thromboembolism.

Table 2: Comparison of pooled frequency of arterial events between VTE and control populations

Outcomes	Pooled frequency in patients with VTE (%) 95% CI	Pooled frequency in controls (%) 95% CI	RR (95% CI)	Number of studies	p-value (random effects models)	p-value (Eggers' test)	I^2 , RR meta-analysis
All arterial events	6.1 (3.7- 9.1)	5.0 (3.1 - 7.2)	1.20 (1.01 - 1.44)	14	0.0422	0.1032	93.5%
MI/ACS	2.9 (1.8 - 4.3)	2.5 (1.5 - 3.7)	1.17 (0.87 - 1.57)	11	0.2577	0.0418	85.5%
Stroke/TIA	2.4 (1.1 - 4.2)	1.8 (0.9 - 2.9)	1.17 (0.89 - 1.54)	8	0.1983	0.3198	77%

- VTE: venous thromboembolism, MI: myocardial infarction, ACS: acute coronary syndrome, TIA: transient ischemic attack, - RR: risk ratio, CI: confidence interval



- CI: confidence interval

Figure 3: Risk ratio related to comparison of frequencies of arterial events in patients with venous thromboembolism and controls.

Table 3. Definition of cases of venous thromboembolism and controls in studies with these two groups

First author, year	Definition of cases	Definition of controls
Chang, 2017	Patients with a diagnosis of deep venous thrombosis (ICD-9-CM codes 453.8) and PE (ICD-9-CM codes 415.1).	Randomly selected patients who were not diagnosed with VTE any time before their assigned index date (2 control patients for every VTE patients). Controls were matched to patients with VTE using the propensity score matching approach for age, sex, and chronic cardiovascular risk factors.
Ljungqvist, 2016	Women with a first episode of deep vein thrombosis (DVT) in the lower limb or a pulmonary embolism (PE). The diagnosis of VTE was objectively verified by venography or Doppler ultrasound for DVT-patients and by CT-scan or ventilation-perfusion scintigraphy for PE.	Randomly selected from the Swedish population register and matched to the cases by age.
Pasha, 2016	Patients with a first acute deep-vein thrombosis. The diagnosis of proximal DVT was based on non-compressibility in the popliteal, femoral, and iliac veins on color ultrasonography.	Patients in whom a first proximal DVT was clinically suspected but ruled out by a serial color ultrasonography or single ultrasonography with a normal D-dimer test.
Cannegieter, 2015	Individuals with a first recorded diagnosis of SVT (inpatients and patients treated in hospital outpatient clinics) based on ICD, 8th revision (ICD-8), and ICD-10 codes.	For each patient in the SVT cohort, 50 SVT-free general population cohort members were selected from persons alive on the date of the SVT diagnosis (index date) and matched by age and gender.

- VTE: venous thromboembolism, PE: pulmonary embolism, - DVT: deep venous thrombosis, - SVT: superficial venous thrombosis, - ICD: international classification of disease, CM: clinical modification.

Table 3 Continued

First author, year	Definition of cases	Definition of controls
Lind, 2014	Objectively verified symptomatic VTE events. VTE diagnosis was verified when typical clinical symptoms of VTE were combined with confirmatory diagnostic test results (ultrasound, venography, echocardiography, ventilation-perfusion lung scan, or computed tomography scan), or when autopsy verified VTE	Patients without VTE. No more details.
Barsoum, 2014	Olmsted County residents with a first lifetime objectively-diagnosed DVT or PE.	One to two age- (\pm one year) and sex-matched Olmsted County residents who had an episode of medical care within \pm one year of the VTE case event date and whose medical record number was closest to the case's medical record number were selected as controls as previously described.
Roach, 2013	Patients aged 18 to 70 years with a first deep vein thrombosis (DVT) or pulmonary embolism.	Partners of patients were invited to participate as controls if they were aged 18 to 70 years and had no history of VT (partner controls). Additional controls were recruited by random digit dialing (RDD controls)
Roshani, 2011	Patients with documented VTE	First-degree relatives of the patients with a history of VTE
Prandoni, 2011	Patients 18 years of age or older who had acute symptomatic isolated SVT of the lower extremities at least 5 cm long, as confirmed by standardized compression ultrasonography.	Subjects matched with cases for age (\pm 3 years) and sex, who had no history of cancer and had not experienced either venous (including SVT) or arterial thromboembolic disorders before the beginning of the observation. The controls were recruited in a 2:1 ratio from the general population of LEOGRA study, ongoing in northern Italy.

- VTE: venous thromboembolism, PE: pulmonary embolism, - DVT: deep venous thrombosis.

Table 3 Continued

First author, year	Definition of cases	Definition of controls
Klok, 2009	Patients with proven PE. The diagnosis of PE was based on either a positive CT angiogram or a ventilation perfusion scintigraphy indicating a high probability for PE.	The control cohort consisted of patients in whom PE was clinically suspected but ruled out by either an unlikely probability (Wells rule ≤ 4 points) in combination with a normal D-dimer test or a CT scan without signs of PE, followed by a 3-month follow-up period without the occurrence of subsequent symptomatic VTE.
Huerta, 2008	Patients with first recorded diagnosis of VTE (diagnosis confirmed in 94% of cases).	Individuals without a VTE diagnosis, randomly sampled from the same source population (as cases) and matched by age, sex and calendar year to the VTE cohort.
Spencer, 2008	Patients aged 20–64 years with a primary diagnosis of DVT or PE identified from the Canadian Institute for Health Information database. Potential subjects were identified using the most responsible diagnosis of a DVT or PE (ICD-9 codes 451.1, 451.2, 451.8, 451.9, 453.1, 453.2, 453.8, 453.9, and 415.1).	Matched population controls were identified randomly from the same database as cases (Canadian Institute for Health Information) using hospital discharge abstracts from the same time period (1991–1995). All population controls were matched in a 2:1 fashion (i.e., two controls for every one patient with unprovoked VTE) on the basis of a series of criteria.
Sorensen, 2007	Patients with first recorded inpatient hospital discharge diagnosis of lower limb deep venous thrombosis, or pulmonary embolism, or both in all Danish residents aged at least 40 years	For each patient in the venous thromboembolism cohort, five population controls were randomly chosen from the entire registry, matched for sex, age, and municipality of residence. Each control was required to be alive on the date the corresponding case person was first hospitalized with venous thromboembolism.
Bova, 2006	Patients aged 18 years or older with an objectively documented first episode of deep venous thrombosis or pulmonary embolism. Objective diagnosis of pulmonary embolism included a high-probability ventilation/perfusion lung scintigraphy, an abnormal pulmonary angiography, or an abnormal spiral computed tomography of the chest. The diagnosis of deep venous thrombosis was obtained by compression ultrasonography.	For each patient with idiopathic VTE we randomly selected a control subject, matched for sex and age (in five-year age groups), from the database of two of the local family physicians who began their practice before 1998.

- VTE: venous thromboembolism, PE: pulmonary embolism, - DVT: deep venous thrombosis, - CT: computerized tomography

Incidence of arterial events in patients with VTE and control population

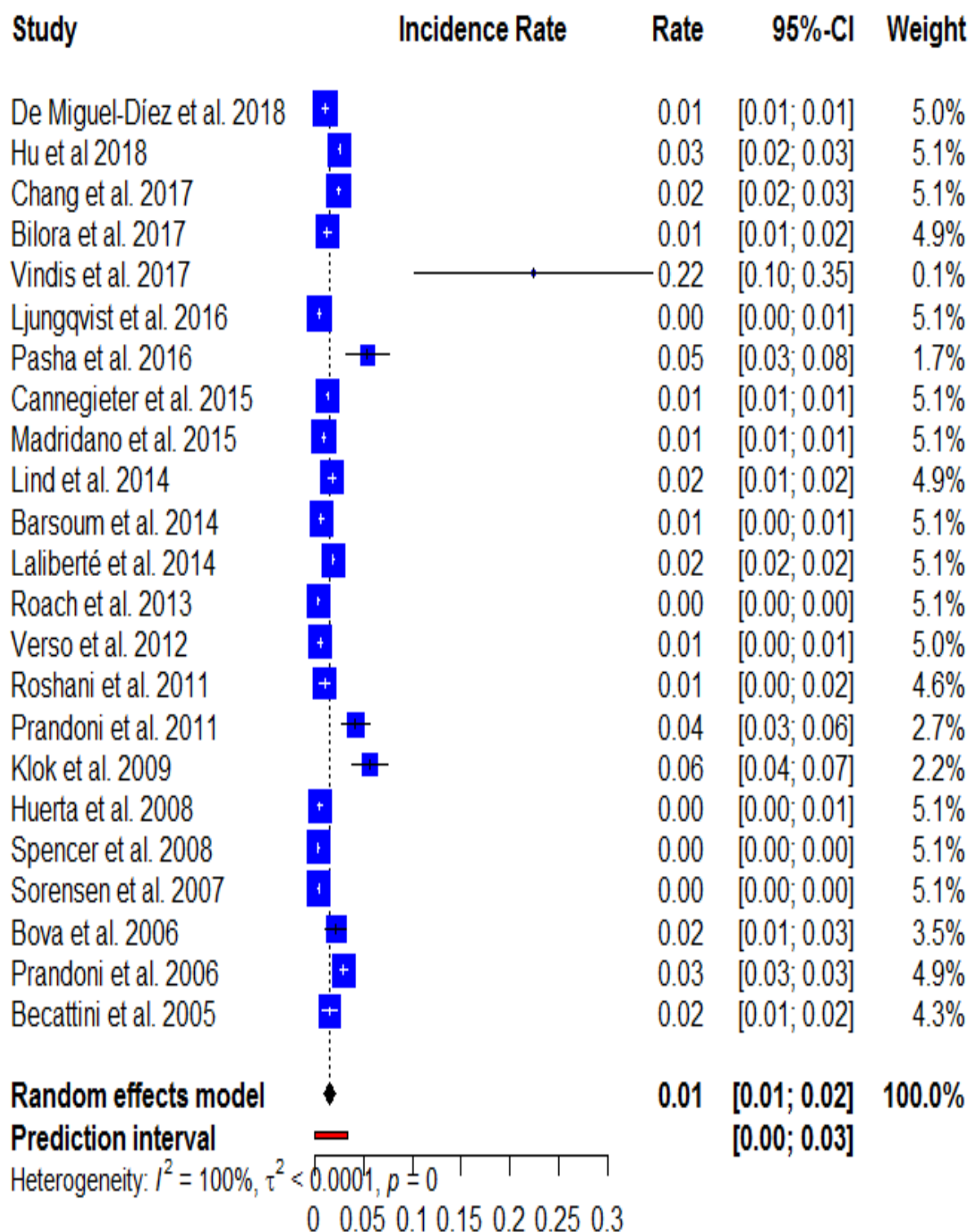
The overall pooled incidence of all arterial events in patients with VTE was 15.0 per 1000 patient-years (23 studies, 1525248 patient-years, 95 % CI: 8.9 - 21.0; $I^2 = 99.7\%$) (**Figure 4**), and the overall pooled incidence of all arterial events in controls was 9.2 per 1000 patient-years (14 studies, 9690407 patient-years, 95 % CI: 2.0 - 16.4; $I^2 = 99.9\%$). The funnel plot suggested no publication bias for the estimation of the overall incidence rate of arterial events among patients with VTE (**supplementary file S3**).

The overall pooled incidence of myocardial infarction/acute coronary syndrome was 6.7 per 1000 patient-years (16 studies, 1329673 patient-years, 95 % CI: 3.8 - 9.5; $I^2 = 99.6\%$) in patients with VTE, and 3.5 per 1000 patient-years (10 studies, 9630679 patient-years, 95 % CI: 1.5 - 5.5; $I^2 = 99.5\%$) in controls. Considering stroke/transient ischemic attack only, the overall pooled incidence was 6.7 per 1000 patient-years (15 studies, 1184431 patient-years, 95 % CI: 1.3 - 12.2; $I^2 = 99.7\%$) in patients with VTE, and 3.1 per 1000 patient-years (7 studies, 9435621 patient-years, 95 % CI: 0.0 - 6.3; $I^2 = 100\%$) in controls.

Comparison of incidence of arterial events in patients with VTE and controls

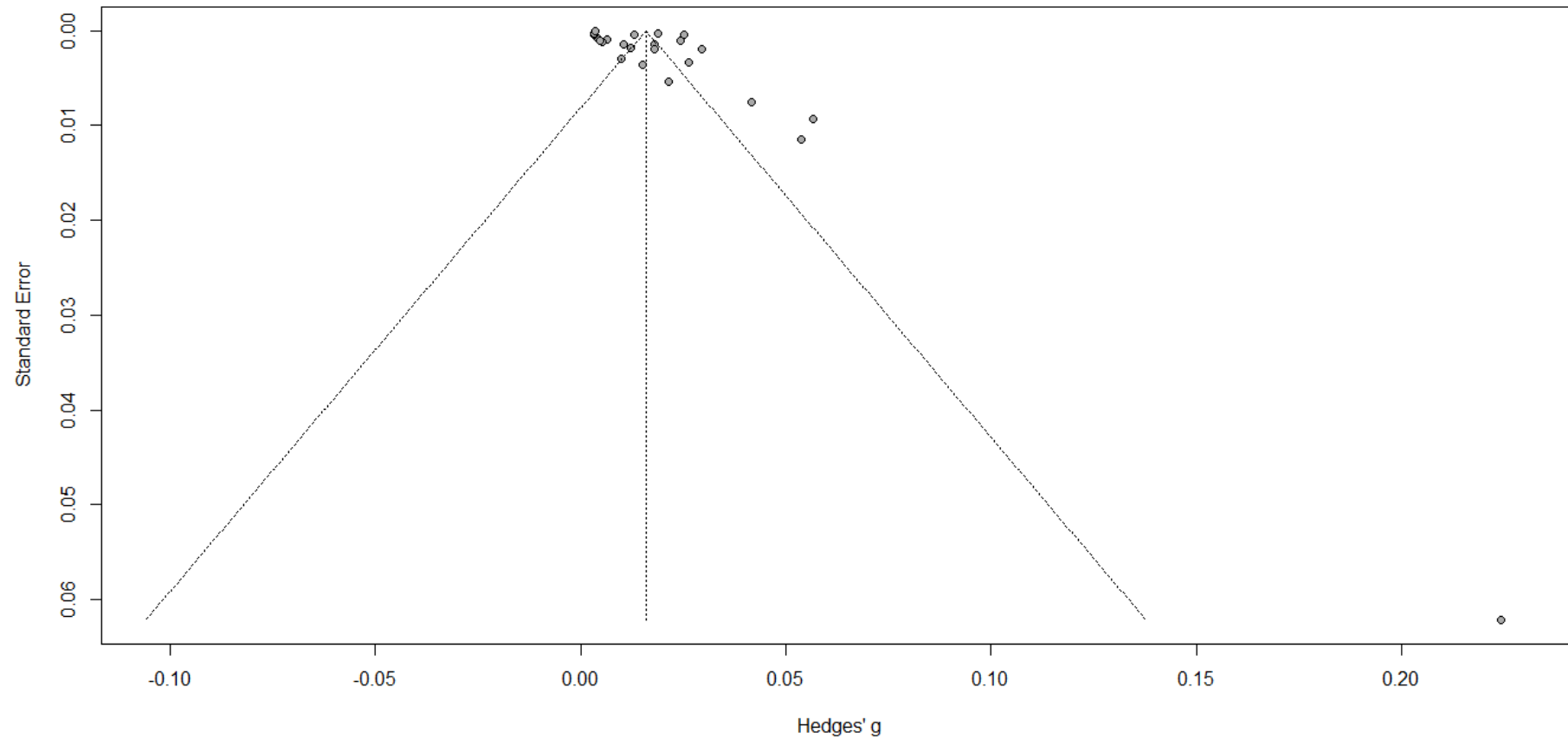
In studies with control groups, the incidence of arterial events in patients with VTE (11.3‰ per patient-year, 95% CI: 4.6 - 18.0, 14 studies; $I^2 = 98.9\%$) was significantly higher than in controls (**Table 4**), with an overall pooled IRR of 1.32 (14 studies, 95 % CI: 1.08 - 1.61; $p = 0.0103$, $I^2 = 95.9\%$) (**Figure 5**); there was no publication bias ($p = 0.1216$). The same tendency was present despite non-significant p-values while comparing only incidence rates of myocardial infarction/acute coronary syndrome and ischemic stroke/transient ischemic attack in patients with VTE and control, with respective IRR of 1.31 (10 studies, 95 % CI: 0.97 - 1.77; $p = 0.0708$) and 1.39 (7 studies, 95 % CI: 0.96 - 2.01; $p = 0.0751$) (**Table 4**). Definitions of cases of unprovoked and provoked VTE in each study with these two groups are given in **Table 5**.

Considering patients with provoked or unprovoked VTE only compared to controls, the incidence of all arterial events in patients with unprovoked was significantly higher than in control population, with a pooled IRR of 1.61 (8 studies, 95 % CI: 1.13 - 2.30; $I^2 = 92.5\%$, $p = 0.0162$); while there was no significant difference comparing the incidence of arterial events in patients with provoked VTE and controls (IRR: 0.85, 5 studies, 95 % CI: 0.44 - 1.67; $I^2 = 87.8\%$, $p = 0.5523$).



- CI: confidence interval

Figure 4: Incidence rates of arterial events in patients with venous thromboembolism.

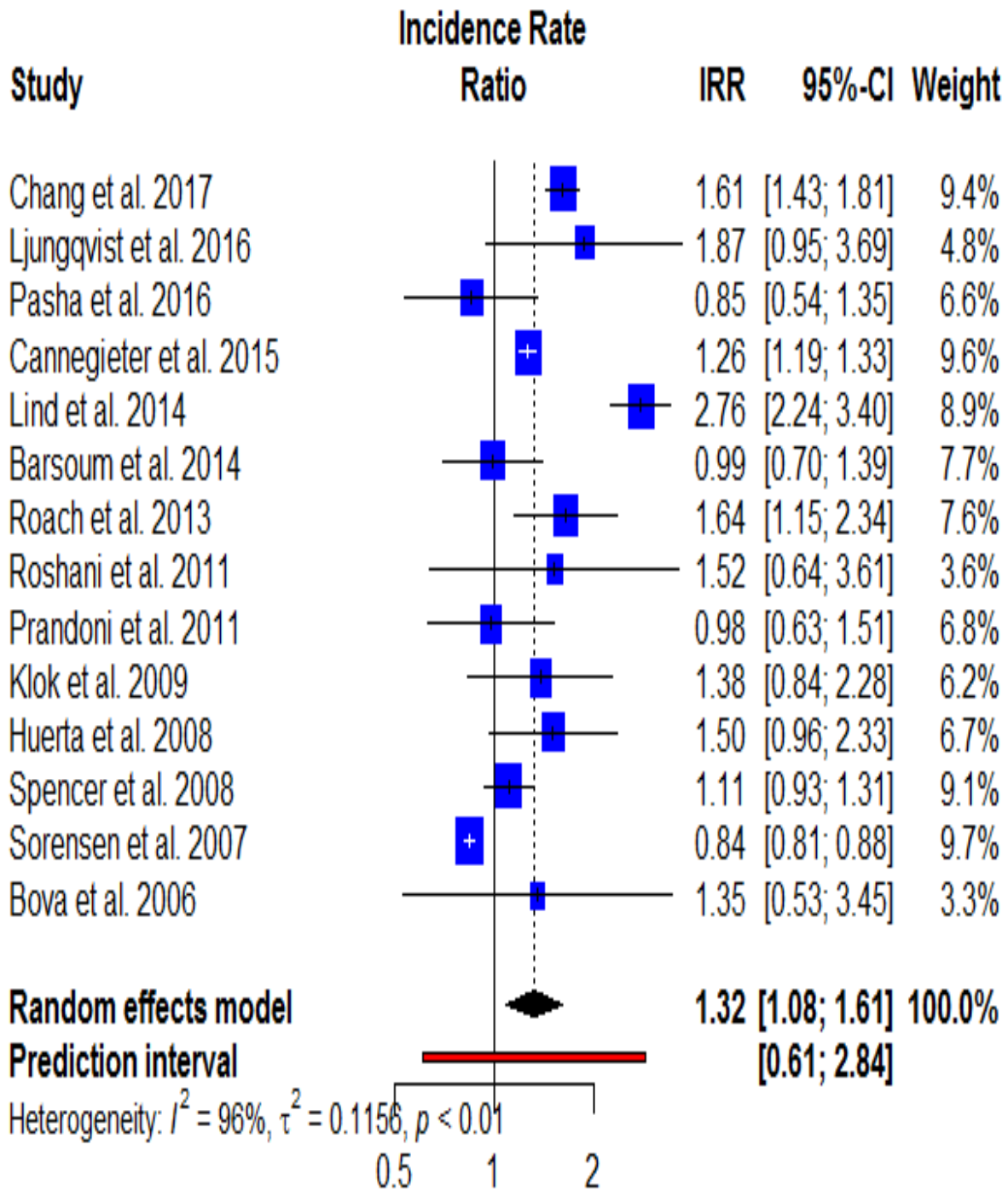


Supplementary file S3: Funnel plot to assess publication bias for meta-analysis of incidence of arterial events in patients with venous thromboembolism

Table 4: Comparison of pooled incidence of arterial events between patients with VTE and controls.

Outcomes	Pooled incidence in patients with VTE (%) 95%CI	Pooled incidence in controls (‰) 95%CI	IRR (95% CI)	Number of studies	p-value (random effects models)	p-value (Eggers' test)	I ² , IRR meta-analysis
All arterial events	11.3 (4.6 - 18.0)	9.2 (2.0 - 16.4)	1.32 (1.08 - 1.61)	14	0.0103	0.1216	95.9%
MI/ACS	4.8 (2.3 - 7.3)	3.5 (1.5 - 5.5)	1.31 (0.97 - 1.77)	10	0.0708	0.0730	94.1%
Stroke/TIA	4.2 (0.5 - 8.0)	3.1 (0.0 - 6.3)	1.39 (0.96 - 2.01)	7	0.0751	0.4300	93%

- VTE: venous thromboembolism, MI: myocardial infarction, ACS: acute coronary syndrome, TIA: transient ischemic attack, - IRR: incidence rate ratio, CI: confidence interval



- CI: confidence interval

Figure 5: Incidence risk ratio related to comparison of incidence rates of arterial events in patients with venous thromboembolism and controls.

Table 5. Definition of cases of unprovoked and provoked venous thromboembolism in studies with these two groups

First author, year	Definition of cases of unprovoked VTE	Definition of cases of provoked VTE
Bilora, 2017	Idiopathic VTE, no more precision	Secondary VTE, no more precision
Ljungqvist, 2016	VTE without provoking risk factor	VTE provoked by either surgery / cast or hormonal treatment
Pasha, 2016	VTE occurring in the absence of risk factors that included: active malignancy, immobility for more than 3 days or a recent long flight (at least 4 h), recent surgery or fracture of lower extremity, pregnancy or peri-partum period, hormone replacement therapy, and the use of oral contraception	VTE occurring after one of the following risk factors: active malignancy, immobility for more than 3 days or a recent long flight (at least 4 h), recent surgery or fracture of lower extremity, pregnancy or peri-partum period, hormone replacement therapy, and the use of oral contraception
Roach, 2013	VTE without provoking risk factors that included surgery, malignancy, immobilization, hormone use, and pregnancy	VTE after one of the following provoking risk factors: surgery, malignancy, immobilization, hormone use, and pregnancy
Klok, 2009	VTE occurring in the absence of risk factors, that included: active malignancy, immobility more than 3 days or recent long flight, recent surgery or fracture of extremity, pregnancy or peripartum period, hormone replacement therapy, and use of oral contraception	VTE occurring after one of the following risk factors: active malignancy, immobility more than 3 days or recent long flight, recent surgery or fracture of extremity, pregnancy or peripartum period, hormone replacement therapy, and use of oral contraception

- VTE: venous thromboembolism.

Table 5 Continued

First author, year	Definition of cases of unprovoked VTE	Definition of cases of provoked VTE
Sorensen, 2007	Cases of VTE without provoking risk factors	VTE with a diagnosed malignancy before or within 90 days after the thrombotic event in the hospital registry, and those with a discharge diagnosis of fracture, surgery, trauma, or pregnancy within 90 days before the hospitalization for venous thromboembolism
Prandoni, 2006	VTE without provoking risk factor	VTE occurring after one of the following risk factors: recent trauma, recent surgery, medical disease, hormonal treatment, pregnancy, collagenopathies, puerperium, or thrombophilia
Becattini, 2005	Idiopathic VTE	VTE occurring after a transient risk factors that included: recent trauma with or without bone fracture, recent surgery or childbirth, prolonged immobilization (i.e., lasting more than 7 days), or during the use of oral contraceptives or pregnancy

- VTE: venous thromboembolism.

Frequency of arterial events in patients with unprovoked and provoked VTE

The overall pooled frequency of all arterial events in patients with unprovoked VTE was 10.7 % (11 studies, 41493 patients, 95 % CI: 6.7 - 15.4; $I^2 = 99.0\%$), and the overall pooled frequency of all arterial events in patients with provoked VTE was 4.2 % (8 studies, 17694 patients, 95 % CI: 2.5 - 6.3; $I^2 = 94.4\%$).

Considering myocardial infarction/acute coronary syndrome only, the overall pooled frequency was 5.0 % (8 studies, 37259 patients, 95 % CI: 3.5 - 6.7; $I^2 = 93.7\%$) in patients with unprovoked VTE, and the 1.8 % (6 studies, 15050 patients, 95 % CI: 1.0 - 2.8; $I^2 = 75.3\%$) in patients with provoked VTE. While the overall pooled frequency of ischemic stroke/transient ischemic attack was 3.6 % (7 studies, 31194 patients, 95 % CI: 2.2 - 5.2; $I^2 = 82.5\%$) in patients with unprovoked VTE, and 1.7 % (6 studies, 15050 patients, 95 % CI: 1.1 - 2.6; $I^2 = 69.2\%$) in patients with provoked VTE.

Comparison of frequency of arterial events in patients with unprovoked and provoked VTE

The frequency of arterial events in patients with unprovoked VTE was significantly higher than in patients with provoked VTE, overall pooled RR: 2.12 (8 studies, 95 % CI: 1.38 - 3.24; $p = 0.0042$, $I^2 = 49\%$); there was no publication bias ($p = 0.5227$). This was also the case while comparing only frequencies of myocardial infarction/acute coronary syndrome and ischemic stroke/transient ischemic attack in these two populations, with respective RR of 2.38 (6 studies, 95 % CI: 1.13 - 4.99; $p = 0.0298$) and 1.94 (6 studies, 95 % CI: 1.35 - 2.79; $p = 0.0057$) (**Table 6**). It is important to note that in the 8 studies reporting data in patients with provoked unprovoked VTE, the pooled proportion of patients with provoked VTE was 53.0 % (95 % CI: 41.1 - 64.8), and the pooled proportion of patients with unprovoked VTE was 47.0 % (95 % CI: 35.1 - 58.9).

Incidence of arterial events in patients with unprovoked and provoked VTE

The overall pooled incidence of all arterial events in patients with unprovoked VTE was 12.6 per 1000 patient-years (11 studies, 686986.9 patient-years, 95 % CI: 4.2 - 21.1; $I^2 = 98.2\%$), and the overall pooled incidence of all arterial events in patients with provoked VTE was 5.4 per 1000 patient-years (8 studies, 285100.8 patient-years, 95 % CI: 0.0 - 10.8; $I^2 = 91.4\%$).

The overall pooled incidence of myocardial infarction/acute coronary syndrome in patients with unprovoked VTE was 3.8 per 1000 patient-years (6 studies, 648918.3 patients-years, 95 % CI: 0.9 - 6.6; $I^2 = 82.6\%$), and in patients with provoked VTE, the overall pooled incidence of myocardial infarction/acute coronary syndrome was 1.5 per 1000 patient-years (3 studies, 265688 patient-years, 95 % CI: 1.2 - 1.7; $I^2 = 0\%$). Considering only stroke/transient ischemic attack, the overall pooled incidence was 3.1 per 1000 patient-years (5 studies, 588261.7 patient-years, 95 % CI: 0.1 - 6.1; $I^2 = 67.9\%$) in patients with unprovoked VTE, and 1.0 per 1000 patient-years (4 studies, 266188 patient-years, 95 % CI: 0.1 - 1.8; $I^2 = 19.8\%$) in patients with provoked VTE.

Table 6: Comparison of pooled frequency of arterial events between patients with unprovoked and patients with provoked VTE

Outcomes	Pooled frequency in patients with unprovoked VTE (%) 95% CI	Pooled frequency in patients with provoked VTE (%) 95% CI	RR (95% CI)	Number of studies	p-value (random effects models)	p-value (Eggers' test)	I^2 , RR meta-analysis
All arterial events	10.4 (6.2 - 15.4)	4.2 (2.5 - 6.3)	2.12 (1.38 - 3.24)	8	0.0042	0.5227	49%
MI/ACS	5.3 (3.4 - 7.6)	1.8 (1.0 - 2.8)	2.38 (1.13 - 4.99)	6	0.0298	0.4395	31%
Stroke/TIA	3.7 (2.2 - 5.6)	1.7 (1.1 - 2.6)	1.94 (1.35 - 2.79)	6	0.0057	0.4780	0%

- VTE: venous thromboembolism, MI: myocardial infarction, ACS: acute coronary syndrome, TIA: transient ischemic attack, - RR: risk ratio, CI: confidence interval

Comparison of incidence of arterial events in patients with unprovoked and provoked VTE

The incidence of arterial events in patients with unprovoked VTE was significantly higher than in patients with provoked VTE, with an overall IRR of 2.26 (8 studies, 95 % CI: 1.45 - 3.49; $p = 0.0032$, $I^2 = 65\%$); there was no publication bias ($p = 0.2048$). This was also the case while comparing only incidence rates of myocardial infarction/acute coronary syndrome and stroke/transient ischemic attack, with respective IRR of 2.07 (3 studies, 95 % CI: 1.04 - 4.09; $p = 0.0448$) and 1.85 (4 studies, 95 % CI: 1.60 - 2.14; $p = 0.0009$) (Table 7).

Table 7: Comparison of pooled incidence of arterial events between patients with unprovoked and patients with provoked VTE

Outcomes	Pooled incidence in patients with unprovoked VTE (‰) 95%CI	Pooled incidence in patients with provoked VTE (‰) 95%CI	IRR (95% CI)	Number of studies	p-value (random effects models)	p-value (Eggers' test)	I^2 , IRR meta-analysis
All	12.7 (0.0 - 25.6)	5.4 (0.0 - 10.8)	2.26 (1.45 - 3.49)	8	0.0032	0.2048	65%
MI/ACS	4.5 (0.0 - 13.5)	1.5 (1.2 - 1.7)	2.07 (1.04 - 4.09)	3	0.0448	0.6808	15%
Stroke/TIA	2.8 (0.0 - 6.6)	1.0 (0.1 - 1.8)	1.85 (1.60 - 2.14)	4	0.0009	0.6119	0%

- VTE: venous thromboembolism, MI: myocardial infarction, ACS: acute coronary syndrome, TIA: transient ischemic attack, - IRR: incidence rate ratio, CI: confidence interval

Added to these results, we calculated the pooled frequency (0.4%; 95% CI: 0.1 - 0.8; $n = 8$ studies, $I^2 = 93.6\%$) and incidence (0.8‰ per patient-year; 95% CI: 0.4 - 1.1; $n = 5$ studies; $I^2 = 0\%$) of MALE in patients with VTE, but there was no statically significant difference between

these data and those abstained in controls; (data on frequency and incidence of MALE in controls, as well as data on RR and IRR for comparison of VTE and controls not shown).

We also calculated the overall pooled frequency and incidence of arterial events in patients with PE with or without DVT (frequency from 6 studies: 4.4%, 95% CI: 1.4 - 8.9, $I^2 = 99.4\%$; incidence from 6 studies: 7.1‰ per patient-year, 95%CI: 0.8-13.4, $I^2 = 93.1\%$) and DVT only (frequency from 7 studies: 5.5%, 95% CI: 1.9 - 10.8, $I^2 = 99.6\%$; incidence from 7 studies: 7.2‰ per patient-year, 95% CI: 2.8-11.5, $I^2 = 92.2\%$) only, but there was no statistically significance difference between these groups (RR: 1.03, 6 studies, 95% CI: 0.75 -1.42, $I^2 = 67.2\%$; IRR: 1.02, 6 studies, 95% CI: 0.71 -1.46, $I^2 = 68.7\%$) even when considering only incidence and prevalence of MI or stroke (data not shown).

Sensitivity and subgroup analyses

The overall pooled frequency of arterial events in patients with VTE, excluding studies on patients with SVT was 5.8% (26 studies, 95% CI: 4.2 - 7.5, $I^2 = 99.6\%$), and the pooled incidence was 14.3 per 1000 patient-years (21 studies, 95% CI: 8.0 - 20.7, $I^2 = 99.7\%$).

The overall pooled frequency of arterial events in patients with VTE after meta-analysis including only studies with low risk of bias in their methodological quality was 7.0% (18 studies, 95% CI: 4.6 - 9.8, $I^2 = 99.4\%$), and the pooled incidence was 12.8 per 1000 patient-years (18 studies, 95% CI: 6.7 - 18.9, $I^2 = 98.8\%$).

The overall pooled frequency of arterial events in patients with VTE after meta-analysis including only prospective cohort studies was 6% (13 studies, 95% CI: 3.4 - 9.1, $I^2 = 98.2\%$), and the pooled incidence was 16.5 per 1000 patient-years (9 studies, 95% CI: 11.0 - 31.9, $I^2 = 96.9\%$). While the overall pooled frequency of arterial events in patients with VTE after meta-analysis including only retrospective cohort studies was 6% (15 studies, 95% CI: 3.9 - 8.4, $I^2 = 99.8\%$), and the pooled incidence was 14.0 per 1000 patient-years (14 studies, 95% CI: 8.4 - 19.7, $I^2 = 99.8\%$). There was no statistically significant difference in subgroup analysis comparing the pooled frequency in prospective cohort studies with the pooled frequency in retrospective cohort studies (Q-test for between subgroup heterogeneity = 0.01, $p = 0.9112$). This was also the case while comparing the pooled incidence of arterial events in patients with VTE between these two groups of studies (Q = 0.12, $p = 0.7323$).

The pooled frequency of all arterial events in studies with median duration of anticoagulant therapy between 1 and 6 months was 9.2% (3 studies, 95% CI: 0.8 - 24.6, $I^2 = 99.5\%$), and we

obtained 3.4 % (4 studies, 95% CI: 1.3 - 6.3, $I^2 = 98.6\%$) in studies with median duration of anticoagulant therapy > 6 months, but subgroups analysis does not display statistically significant difference between these results ($Q = 1.26$, $p = 0.2610$). This was also the case comparing incidence rates (not shown) of arterial events in these two group of studies ($Q = 1.14$, $p = 0.2850$).

The pooled frequency of all arterial events varied with the median follow-up duration ($Q = 72.99$, $p < 0.0001$); indeed, we obtained 0.9% for median follow-up < 1 year (3 studies, 95% CI: 0.6 - 1.2, $I^2 = 81.8\%$), 5.8% for 1-5 years (7 studies, 95% CI: 1.7 - 11.9, $I^2 = 98.8\%$), 6.9% for 5-10 years (7 studies, 95% CI: 2.7 - 12.8, $I^2 = 99.6\%$), and 9.6% for > 10 years (3 studies, 95% CI: 6.6 - 12.1, $I^2 = 92.2\%$). This result was not confirmed in subgroup analysis of incidence rates ($Q = 1.33$, $p = 0.7227$).

The pooled frequency of all arterial events in studies with mean/median age > 50 years was 7.1% (20 studies, 95% CI: 4.9 - 9.6, $I^2 = 99.7\%$), and was significantly higher than the 3.6% (6 studies, 95% CI: 2.0 - 5.5, $I^2 = 95.1\%$) obtained in studies with mean/median age equal or < 50 years ($Q = 5.58$, $p = 0.0181$). This tendency was confirmed in subgroup analysis of incidence rates (18.7 per 1000 patient-years, 17 studies, 95% CI: 11.8 - 25.7, $I^2 = 98.6\%$; vs 3.5 per 1000 patient-years, 4 studies, 95% CI: 1.8 - 5.2, $I^2 = 53.8\%$; $Q = 20.79$, $p < 0.0001$).

Discussion

We investigated the frequency and incidence of arterial ischemic events in patients with VTE with a comparison of results between the VTE population and the general population without VTE, as well as between patients with unprovoked VTE and patients with provoked VTE. This systematic review and meta-analysis confirmed that patients with VTE are at increased risk of arterial events than the general population and that patients with unprovoked VTE are at increased risk of arterial events than patients with provoked VTE.

The pooled frequency of arterial events in patients with VTE found after meta-analysis of all studies was 6%, and was similar to the frequency found after meta-analysis including only studies with a control group (6.1%). These numbers were very close to the ones found in sensitivity analyses after excluding studies on patients with SVT [41,44], and studies with moderate to high risk of bias. The pooled frequency of arterial events in the general population without VTE (controls), was 5.6 %. These data are on the same lines with many population-

based recently published studies, which reported a higher risk of arterial events in patients with VTE, as compared to controls without VTE [7,33,47]. Moreover, the comparison of frequency of arterial events in these two populations in our meta-analysis, led to an overall pooled RR of 1.20 with a statically significant p-value.

This tendency was also found while comparing the incidence of arterial events in patients with VTE and in controls, with statistically significant p-values. In fact, we found an overall pooled incidence of arterial events of 15.0 per 1000 patient-years in patients with VTE after meta-analysis of all included studies, and 11.3 per 1000 patient-years after meta-analysis of studies with a control group. This last number was significantly higher than the incidence found in control population without VTE (9.9 per 1000 patient-years), with an overall pooled incidence RR of 1.32. These results which highlighted the fact that patients with VTE are also at higher risk of future arterials ischemic events, than the general population over long terms follow-up, are in line with many recent population-based studies [6,11,48]. Several assumptions have been elucidated in literature concerning the possible reasons of this higher risk of arterial thrombotic events in patients with VTE compared to general population. Many authors suggested that venous and arterial thrombosis may share some common risk factors as obesity, metabolic syndrome and in some extend cancers; however, further studies on risk factors of arterials thrombotic events in patients with VTE are need to exactly clarify this question [14,49–51].

According to our results, the risk of arterials events is higher in patients with unprovoked VTE than in patients with provoked VTE. Indeed, we found respective frequencies and incidence of 10.4 %, and 12.7 per 1000 patient-years in patients with unprovoked VTE; and respective frequency and incidence of 4.2%, and 5.4 per 1000 patient-years in patients with provoked VTE. Comparison of theses number led to an overall pooled RR of 2.12 for frequencies, and an overall pooled IRR of 2.26, which were all statistically significant. These results are in line with a meta-analysis including four studies published in 2010 by Becattini *et al* [13]. In fact, the authors reported a weighted mean incidence of arterial cardiovascular events (including stroke and myocardial infarction) of 4.6 per 1000 patient-years and 3.5 per 1000 patient-years in patients with unprovoked and provoked VTE, respectively; with an incidence RR of 1.86 (95% CI: 1.19 to 2.89) [13]. Our results also highlighted significantly higher frequency and incidence of arterial events in patients with unprovoked VTE compared to controls, with a pooled RR of 1.57 and a pooled IRR of 1.61; while there was no significant

difference comparing the frequency and incidence of arterial events in patients with provoked VTE and controls. These results indicate the need for specific attention to patients with unprovoked VTE while dealing with the prevention of arterial ischemic events in patients with VTE.

Our systematic review and meta-analysis present some flaws. First, there was substantial heterogeneity for the great majority of our analysis, despite the use of appropriate techniques with random-effects models to calculate our effect size estimates; therefore, the results should be interpreted with caution. Second, there was a small number of studies included in the meta-analysis of some estimates, which could hamper the assessment of publication bias by the Egger' test used in our study as this test may lack the statistical power to detect bias when the number of studies is small [52]. Third, for selected studies, it is not possible to totally exclude the eventuality of bias in the diagnosis of some arterial events, because of concurrent illness. Fourth, despite the results shown in subgroup analysis, we were unable to accurately examine the role of anticoagulant therapy on the frequency and incidence of arterial events in patients with VTE, due to the lack of related data in the majority of included studies. Finally, it is important to note that a third of the 28 studies included in this review and meta-analysis, had a moderate to high risk of bias in their methodological quality, yielding once again the necessity to interpret the results with caution

Despite these limitations, to the best of our knowledge, this is the first meta-analysis focusing on the frequency and incidence of arterial ischemic events in patients with VTE, with comparison to the general population, and the second meta-analysis with more and updated studies that evaluated the incidence of arterial events in patients with unprovoked VTE, compared to patients with provoked VTE. Moreover, our synthesis of the relevant published articles from current literature provided strong evidence to support the fact that frequency and incidence of arterial events is higher in patients with VTE than in the general population and in patients with unprovoked VTE than in patients with provoked VTE. Even if the differences between groups highlighted in our study are really small and the associated risk very mild, we should keep in mind that cardiovascular diseases, essentially made of arterial diseases, remain the main cause of death worldwide, and any condition increasing the risk of these diseases, should be considered seriously. Therefore, our finding should have clinical implications for the prevention of arterial cardiovascular events in general, and in patients with VTE in particular.

Conclusions

This systematic review and meta-analysis confirmed that the risk of arterial events is significantly higher in patients with VTE than the general population without VTE, and in patients with unprovoked VTE compared to patients with provoked VTE. If further studies are warranted to understand this over-risk, for better prevention of these conditions, our findings already indicate the need for comprehensive and effective strategies to reduce the burden of arterial events in patients with VTE, with specific attention for patients with unprovoked VTE.

List of Abbreviations:

AMI: acute myocardial infarction

DVT: deep venous thrombosis

IRR: incidence rate ratio

MACE: major adverse cardiovascular event

MALE: major adverse limb event

RR: risk ratio

PE: pulmonary embolism

SVT: superficial venous thrombosis

VTE: venous thromboembolism

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Author's contributions: Conception, designing of the protocol: SN, FC, KL, CT. Literature search, studies selection, data extraction: SN, CH. Writing of the first draft: SN. Data management, data synthesis and analysis: SN. Critical revision: SN, CT, FC, KL, LB. Final revision and approval of the final version: All authors. Guarantor of the review: SN.

Availability of data: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

B. Article de revue 2 : facteurs de risque des événements artériels après MVTE

Cet article a été publié dans le journal *Thrombosis and Haemostasis* le 11 Juillet 2021 et est référencé sous : « *Noumegni SR, Hoffmann C, Tromeur C, et al. Risk Factors of Arterial Events in Patients with Venous Thromboembolism: A Systematic Review and Meta-Analysis. Thromb Haemost. 2021 Jul 11* » Référence N° : 17.

I. RESUME

Rationnel : Si des études récentes suggèrent que les événements artériels ischémiques chez les patients atteints de maladie veineuse thromboembolique (MVTE) sont plus fréquents que dans la population générale, il reste à déterminer si les patients atteints de MVTE présentent des facteurs de risque d'événements artériels différents des facteurs de risque classiques connus. Par cette revue systématique avec méta-analyse, nous avons voulu identifier les facteurs de risque d'événements artériels ischémiques chez les patients atteints de MVTE.

Méthodologie : Nous avons effectué des recherches dans les bases de données PubMed, EMBASE et Cochrane pour identifier les études publiées entre le 1er janvier 2000 et le 31 décembre 2020, rapportant les facteurs de risque d'événements artériels ischémiques chez les patients atteints de MVTE. Une méta-analyse de modèles à effets aléatoires a permis d'obtenir l'Hazard Ratio (HR) et l'intervalle de confiance (IC) à 95 % de chaque facteur de risque identifié.

Résultats : Nous avons examiné 1467 études, dont 18 ont finalement été incluses dans la revue systématique et 10 dans la méta-analyses. Les HR ajustés pour 9 facteurs ont été inclus dans la méta-analyse. Le sexe masculin (HR : 1,38 ; IC à 95 % : 1,28 - 1,49), le diabète (HR : 1,65 ; IC à 95 % : 1,28 - 2,12), l'hypertension (HR : 1,38 ; IC à 95 % : 1,04 - 1,84), l'antécédent d'événement athéro-thrombotique (HR : 3,22 ; IC à 95 % : 1,12 - 9,23), la maladie rénale chronique (HR : 1,41 ; IC à 95 % : 1,05 - 1,88), le cancer (HR : 1,72 ; IC à 95 % : 1,41 - 2,09) et la MVTE non provoquée (HR : 1,88 ; IC à 95 % : 1,37 - 2,57) sont les facteurs de risque d'événements artériels que nous avons identifiés dans la population de patient avec MVTE après méta-analyse.

Conclusion : Les facteurs de risque d'événements artériels chez les patients atteints de MVTE comprennent les facteurs de risque cardiovasculaire habituels et d'autres facteurs de risque liés à la MVTE tels que le cancer et le caractère non provoquée de la MVTE.

Mots-clés : événements artériels ; maladie cardiovasculaire ; maladie thromboembolique veineuse ; facteur de risque ; méta-analyse.

II. ARTICLE COMPLET

Risk factors of arterial events in patients with venous thromboembolism: a systematic review and meta-analysis of cohort studies

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Risk Factors of Arterial Events in Patients with Venous Thromboembolism: A Systematic Review and Meta-Analysis

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Abstract

Background: If recent studies suggested that arterial ischemic events in patients with venous thromboembolism (VTE) are more frequent than in the general population without VTE, whether patients with VTE have different risk factors of arterial events than classic known risk factors remain undefined. Through this systematic review and meta-analysis, we aimed to identify risk factors of arterial ischemic events in patients with VTE.

Methods: We searched PubMed, Embase, and Cochrane databases to identify studies published between Jan 1, 2000, and December 31, 2020, reporting risk factors of arterial ischemic events in patients with VTE. Random-effect models meta-analysis served to get the pooled hazard ratio (HR) and 95% confidence interval (CI) of each risk factor identified.

Results: We screened 1467 records of which 18 were finally included in systematic review and 10 in meta-analyses. Adjusted HRs for 9 factors were included in meta-analysis. Male gender (HR: 1.38; 95% CI: 1.28 - 1.49), diabetes (HR: 1.65; 95% CI: 1.28 - 2.12), hypertension (HR: 1.38; 95% CI: 1.04 - 1.84), previous atherothrombotic event (HR: 3.22; 95% CI: 1.12 - 9.23), chronic kidney disease (HR: 1.41; 95% CI: 1.05 - 1.88), cancer (HR: 1.72; 95% CI: 1.41 - 2.09), and unprovoked VTE (HR: 1.88; 95% CI: 1.37 - 2.57) were the identified risk factors of arterial events in VTE population after meta-analysis.

Conclusion: Risk factors of arterial events in patients with VTE include usual cardiovascular risk factors and other risk factors that are related to VTE such as cancer and unprovoked VTE.

Keywords: arterial events; cardiovascular disease; venous thromboembolism; risk factor; meta-analysis.

Introduction

Progress is constantly made in prevention and treatment of cardiovascular diseases in the general population, but these diseases remain an important public health concern, as they take about 17.9 million lives each year (31% of all death worldwide) [18]. Arterial ischemic events including myocardial infarction and stroke represent the majority of these conditions; as four out of five cardiovascular disease deaths are due to heart attacks and strokes [19].

Venous thromboembolism (VTE) represents the third leading cardiovascular disorder and the third most common cause of death from cardiovascular diseases after heart attacks and stroke [3]. The development of anticoagulant therapy, particularly with the arrival of direct oral anticoagulants has been a major landmark in the management of patients with VTE [10]. Type and duration of anticoagulation therapy in patients with VTE are mainly determined by specific risk factors of VTE which can be transient like recent surgery or persistent like cancer or thrombophilia [10]. These risk factors that can also be classified in major and minor categories, according to their predictive power for VTE, are different from traditional known risk factors of arterial events (tobacco, diabetes, hypertension, ...etc.); moreover, treatment of arterial ischemic events is primarily based on antiplatelet therapy, instead of anticoagulant therapy as in VTE [53,54].

For several years, many studies reported a link between arterial and venous diseases and this is almost evidence in 2021 [3,14]. What is not really clear according to available data is the direction of this association; are arterial diseases an independent predictor of VTE? or conversely, are VTE an independent predictor of arterial events? If answers to these questions are not yet clearly established, we know based on the current literature, that patients with VTE are at increased risk of arterial events compared to the general population (patients without VTE) and that some patients with stroke and myocardial infarction are at increased risk of VTE [8,9,13].

This could result of many interactions between independent risk factors of arterial ischemic events and independent risk factors of VTE or could in part be explained by the presence of common risk factors for both venous and arterial disease [49,50]. Based on the above, we can notice that the effective contribution of specific risk factors of VTE as well-known risk factors of arterials events to the development of arterial ischemic events in patients with VTE remain undefined and that the prevention of these events in patients with VTE may

require some specificities comparatively to the general population without VTE. Several studies have looked for risk factors of arterial events in patients with VTE, but data summarizing the results of these various published studies are lacking [15,16,34].

We performed this systematic review and meta-analysis with the aim to identify risk factors of arterial events in patients who had VTE. Particularly, we aimed to determine if there are specific risk factors for these arterial events in patients with VTE, other than the traditional known risk factors.

Methods

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines as template for reporting data of this review [21]. The protocol for this review was registered in the PROSPERO International Prospective Register of Systematic Reviews with the following registration number: CRD42021237207.

Inclusion criteria and exclusion criteria

We included all population-based original research articles on cohort studies published between January 1st 2000 and December 31th 2020, involving adults and reporting on at least one arterial ischemic event (myocardial infarction, ischemic stroke, peripheral arterial disease, acute limb ischemia, or mesenteric ischemia), and their risk factors in patients with venous thromboembolism. The minimum acceptable follow-up in studies to consider for meta-analysis was three months.

We excluded commentaries, editorials, reviews, and studies lacking primary data. Studies that did not report factors associated with arterial events with evidence of multivariate analysis (logistic regression, Cox proportional model, or any group comparison, adjusted to other cardiovascular risk factors), were excluded from the meta-analysis.

Search strategy and studies selection

A systematic literature review was performed to identify eligible studies published in English language through Medline/PubMed, Excerpta Medica Database (EMBASE), and Cochrane databases, that have evaluated risk factors of arterial events in patients with VTE. We used a combination of the following medical subject headings (MeSH): venous thromboembolism (VTE), venous thrombosis (VT), pulmonary embolism (PE), myocardial Ischemia (MI), coronary artery disease, arterial occlusive disease, brain ischemia, intracranial embolism and thrombosis, stroke, peripheral arterial disease (PAD), mesenteric ischemia, heart disease risk factors, cardiometabolic risk factors, and risk factor, with relevant complementary

keywords. The main search strategy conducted in PubMed/MEDLINE is presented in **supplementary file 1**, and the studies selection process is summarized in **Figure 1** by a flow chart.

Supplementary file 1. PubMed search strategy

	Search	Results
#1	"Venous Thrombosis" [Tiab] OR "Pulmonary Embolism" [Tiab] OR "deep venous thrombosis" [Tiab] OR "superficial venous thrombosis" [Tiab] OR (("Pulmonary Embolism"[Mesh]) OR "Venous Thromboembolism"[Mesh]) OR "Venous Thrombosis"[Mesh]	117439
#2	"Cardiovascular Diseases"[Tiab] OR "major adverse cardiovascular event*" [Tiab] OR "major adverse limb event*" [Tiab] OR "cardiovascular death" [Tiab] OR "arterial complication*" [Tiab] OR "arterial disease*" [Tiab] OR "myocardial infarction" [Tiab] OR "acute coronary syndrome" [Tiab] OR "heart attack" [Tiab] OR "stroke" [Tiab] OR "peripheral arterial disease*" [Tiab] OR "Mesenteric Ischemia" [Tiab] OR (((((("Myocardial Ischemia" [Mesh]) OR "Coronary Artery Disease" [Mesh]) OR "Arterial Occlusive Disease*" [Mesh]) OR "Brain Ischemia" [Mesh]) OR "Intracranial Embolism and Thrombosis" [Mesh]) OR "Stroke" [Mesh]) OR "Peripheral Arterial Disease" [Mesh]) OR "Mesenteric Ischemia" [Mesh]	1001579
#3	"cardiovascular risk factor" [Tiab] OR "Cardiometabolic Risk Factors" [Tiab] OR ("Heart Disease Risk Factors" [Mesh]) OR "Cardiometabolic Risk Factors" [Mesh] OR "Risk Factor*" [Mesh]	853897
#4	#2 AND #3	130229
#5	# 1 AND #4	2233
# 6	#5 Limit to <ul style="list-style-type: none"> - Observational studies, - Comparative studies, - Original research articles or meta-analysis, - Humans, - English language, and - Period between January 1st 2000 and December 31st 2020. 	723

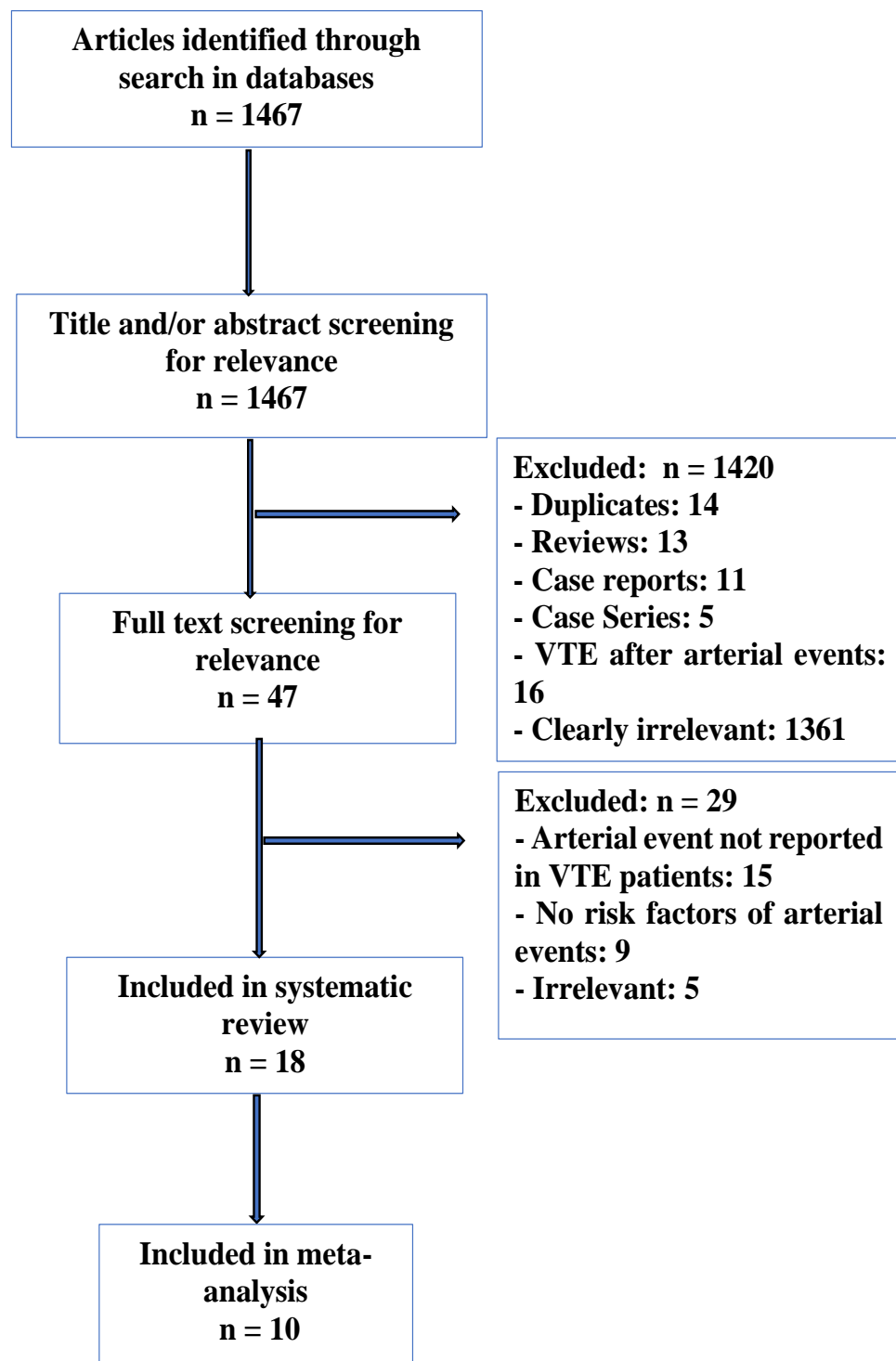


Figure 1: Flow chart of studies selection

Titles and abstracts of all identified articles from the literature search were independently screened by two investigators, and the full texts of potentially eligible articles were further evaluated for final inclusion. Disagreements, when exist, were resolved by discussion. For duplicate publications, only the most comprehensive report including the largest sample size was considered.

Appraisal of the quality of included studies

We evaluated included studies for methodological quality and risk of bias using an adapted version of the Newcastle-Ottawa quality assessment scale (NOS) for evaluation of the quality of observational studies [22]. The NOS is formulated by a star allocation system, assigning a maximum of nine stars for the risk of bias in three areas: selection of study groups, comparability of groups, and ascertainment of the outcome of interest. There is no validation study that provides a cut-off for interpretation of this score, despite the fact that many authors consider a score equal or higher to 7 to define high-quality studies. Therefore, in our review, we considered a score from zero to three stars for low-quality studies (high risk of bias), four to six stars for fair quality studies (moderate risk of bias), and seven to nine stars for high-quality studies (low risk of bias), respectively. Details of stars allocation per category in each included study are presented in **supplementary file 2**.

Data extraction

A standardized data extraction sheet was used to collect information on study design, sample size (total, number of patients with venous thromboembolism), type of VTE (PE, DVT, or VTE for the two), arterial outcomes, identified risk factors of arterial events, with their hazard ratios (HR) and 95% confident interval (CI) in multivariate analysis. We conducted a separate meta-analysis with a fixed-effects model to obtain the age-related HR in the Chang *et al.* study, as different HRs were reported for different age categories [15]. Mean or median follow-up was also reported as well as median duration of anticoagulant therapy. Data were extracted by one investigator (SN) and a second investigator (CH) double-checked extracted data for accuracy.

Data synthesis and statistical analysis

Search results were compiled using the citation management software Zotero version 5.0.77. Risk factors that were identified with a provided effect size of interest (multivariate HR and 95% CI) in at least two studies, were included in the meta-analysis. A random-effects model with inverse variance method was used to pool the logarithmic effect sizes of the

individual risk factors taking into account both the sampling error and between-study heterogeneity. Heterogeneity was assessed using the χ^2 test on Cochran's Q statistic and quantified by the I^2 value [55]. The I^2 statistic estimates the percentage of total variation across studies due to true between-study differences rather than chance and varies between 0 and 100%, with values greater than 60–70% generally indicating the presence of substantial heterogeneity [56]. Egger's test was used to detect the presence of publication bias, with a p-value < 0.10 considered statistically significant [52]. Data were analyzed using the “meta”, “dmetar” and “metaphor” packages of the statistical software R, version 3.6.2. A p-value < 0.05 characterized statistically significant results.

Supplementary file 2. Assessment of methodological quality of included studies with the Newcastle-Ottawa quality assessment scale for cohort studies

Authors	Selection				Comparability	Outcome			Number of stars/Risk of Bias
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Golemi et al.	- The query was restricted it to patients with data entry for the arterial outcomes	*	*	- not sure	*	*	*	- no statement	5 / Moderate
Le Moigne et al.	*	*	*	- not sure	- no description of any match process or multivariate adjustment	*	- not reported	*	5 / Moderate
Hu et al	*	- no control group	*	*	- no control group	*	*	- no statement	5 / Moderate
Bilora et al.	*	*	*	*	**	*	*	*	9 / Low
Chang et al.	*	*	*	*	**	*	*	*	9 / Low
Vindis et al.	*	*	*	- not sure	**	*	*	- 25% lost to follow-up	7 / Low
Ljungqvist et al.	*	*	*	*	**	*	*	*	9 / Low
Cannegieter et al.	*	*	*	*	**	*	*	- no statement	8 / Low
Madridano et al.	*	- no control group	*	*	- no control group	*	*	- no statement	5 / Moderate
Barsoum et al.	*	*	*	*	**	*	*	*	9 / Low
Doyen et al.	*	*	*	- not sure	- no description of any match process or multivariate adjustment	*	- not reported	- no statement	4 / Moderate
Goliszek et al.	- Participants selected from a group of patients	- no control group	*	- not sure	- no control group	*	- not reported	- no statement	2 / High
Laliberté et al.	*	- no control group	*	*	- no control group	*	*	- no statement	5 / Moderate

Lind et al.	*	*	*	- not sure	*	*	*	- no statement	6 / Low
Klok et al.	*	*	*	*	**	*	*	*	9 / Low
Spencer et al.	*	*	*	*	**	*	*	- no statement	8 / Low
Prandoni et al.	*	*	*	*	**	*	*	*	9 / Low
Becattini et al.	*	- no control group	*	*	- no control group	*	*	- no statement	5 / Moderate

Thresholds for interpretation of the Newcastle-Ottawa scales used in our study.

Good quality > Low risk of bias: 7-9

Fair quality > Moderate risk of bias: 4-6

Poor quality > High risk of bias: 0-3

Table 1. General characteristic of included studies

Authors, year	- Design - Follow-up if cohort.	Type of VTE	Number of patients with VTE	Arterial outcomes
Golemi, 2020	- Retrospective cohort - Overall follow-up: 10 years	VTE	41259	- MACE (stroke, MI, unstable angina) or - MALE (Major limb amputation)
Le Moigne, 2019	- Prospective cohort - Median/ mean follow-up: NP	VTE, all with PE	324	- Recent symptomatic or silent ischemic stroke
Hu, 2018	- Retrospective cohort - Mean follow-up: 3.11 years	VTE	56966	- Ischemic stroke
Bilora, 2017	- Retrospective cohort - Overall follow-up: 14 years	VTE	261	Symptomatic ATE including - AMI/angina - Stroke/TIA And - PAD

Chang, 2017	- Retrospective cohort, - Overall follow-up: 10 years	Unprovoked VTE	2154	- Acute coronary syndrome or - Stroke
Vindis, 2017	- Prospective cohort	VTE, all with PE	58	- New MRI ischemic brain lesions or - Stroke or TIA with no MRI finding
Ljungqvist, 2016	- Prospective cohort study, - Median follow-up: 6 years	VTE	1081	- MI - Ischemic stroke or - Cardiovascular mortality

- ATE: atherothrombotic event, - CVD: cardiovascular disease, MACE: major adverse - cardiovascular event, - MALE: major adverse limbs event, - AMI: acute myocardial infarction, - VTE: venous thromboembolism, PE: pulmonary embolism, - DVT: deep venous thrombosis, NR: not provided.

Table 1 continued:

Authors, year	- Design - Follow-up if cohort.	Type of VTE	Number of patients with VTE	Arterial outcomes
Cannegieter, 2015	- Retrospective cohort from registry, - Median follow-up: 7 years.	SVT	10973	- MI or - Ischemic Stroke
Madridano, 2015	- Retrospective cohort, from registry (RIETE), - Mean follow-up: 9.2 months	VTE	23370	ATE including - Ischemic stroke - MI - Limb amputation or - Mesenteric ischemia
Barsoum, 2014	- Prospective cohort study - Median follow-up: 7.3 years	VTE	1177	- MI

Doyen, 2014	- Prospective cohort - Median/mean follow-up: NP	VTE, all with PE	41	- Recent ischemic brain lesion
Goliszek, 2014	- Prospective cohort - Median/mean follow-up: NP	VTE all with PE	55	- Acute ischemic stroke
Laliberté, 2014	- Retrospective cohort - Median follow-up: 1.3 years	VTE	177885	- MI
Lind, 2014	- Retrospective cohort - Median follow-up: 12.2 years	VTE	1208	- MI, - Ischemic Stroke

- ATE: atherothrombotic event, - AMI: acute myocardial infarction, - VTE: venous thromboembolism, PE: pulmonary embolism, - DVT: deep venous thrombosis, - SVT: superficial venous thrombosis, NP: not provided.

Table 1 End

Authors, year	- Design - Follow-up if cohort.	Type of VTE	Number of patients with VTE	Arterial outcomes
Klok, 2009	- Prospective cohort - Median follow-up: 4.2 years	PE	354	Arterial event including: - MI clinically adjudicated - Stroke or transient ischemic attack - Claudication - Unstable angina - Carotid endarterectomy - Coronary artery bypass graft - Peripheral artery bypass or - Angioplasty

Spencer, 2008	- Retrospective cohort, - Overall follow-up: 10 years	unprovoked VTE	6065	- MI
Prandoni, 2006	- Prospective cohort, - Median follow-up: 48 months (unprovoked VTE) and 51 months (provoked VTE)	VTE	1919	Symptomatic ATE including: - Fatal and non-fatal AMI, Ischemic stroke and peripheral arterial disease - Fatal Heart failure from coronary artery disease and/or systemic hypertension
Becattini, 2005	- Prospective cohort, - Median follow-up: 38 months	PE	360	- MI - Stroke

- ATE: atherothrombotic event, - AMI: acute myocardial infarction, - VTE: venous thromboembolism, PE: pulmonary embolism, - DVT: deep venous thrombosis, - SVT: superficial venous thrombosis.

Results

General characteristic of selected studies

We screened 1467 records of which 18 studies that evaluated risk factors of arterial events in patients with VTE were identified, including 9 prospective cohorts [11,20,26,28,30,31,34,36,37] and 9 retrospective cohorts [7,14–16,39–42,45] (**Table 1**). They were all published between 2005 and 2020. The number of participants varies between 41 and 1919 participants for prospective cohort studies and between 261 and 177885 participants for retrospective cohort studies.

Median or mean follow-up was reported for 11 studies (5 prospective cohorts and 6 retrospective cohorts), while the overall follow-up period was reported for 4 retrospective cohort studies and 1 prospective cohort study. The median / mean follow-up period ranged from 38 months to 7.3 years for prospective cohort studies, and from 9.2 months to 10 years for retrospective cohort studies (**Table 1**). Median duration of anticoagulant therapy was reported only in 4 studies and ranged from 5.9 to 12 months [7,28,36,42].

Methodological quality of included studies and heterogeneity

Of studies included in systematic review, risk of bias in methodological quality was low in 10 (55.6%) studies, [7,11,15,20,28,34,36,40,41,45], moderate in 7 (38.9%) [14,16,26,31,37,39,42], and high in one (5.5%) [30]. There was substantial heterogeneity ($I^2 > 60\%$) for analysis concerning 5 risk factors (age, diabetes, hypertension, previous ATE, and chronic kidney disease) (**Figure 2**) but not for 4 risk factors (gender, unprovoked VTE, cancer and chronic lung disease) (**Figure3**).

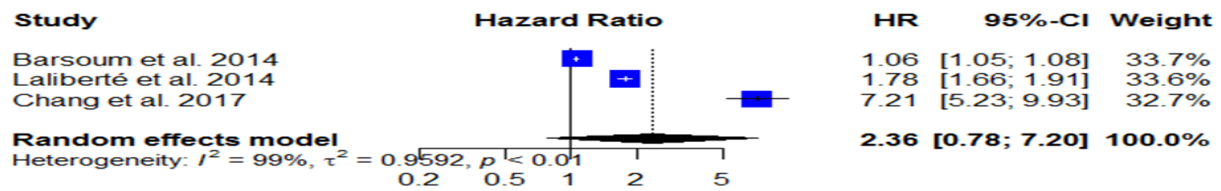
Identified risk factors of arterial events in patients with VTE

All identified risk factors of arterial events in patients with VTE are presented in **Table 2**, with their HR, or odds ratios, or relative risk and 95% CI. Of these, 9 risk factors of arterial events reported with adjusted HR were identified in at least two studies and included in the meta-analysis. After meta-analysis, risk factors of arterial events in patients with VTE included, male gender (HR: 1.38; 95% CI: 1.28 - 1.49; 3 studies), diabetes (HR: 1.65; 95% CI: 1.28 - 2.12; 5 studies), hypertension (HR: 1.38; 95% CI: 1.04 - 1.84; 3 studies), previous atherothrombotic event (HR: 3.22; 95% CI: 1.12 - 9.23, 2 studies), chronic kidney disease (HR:

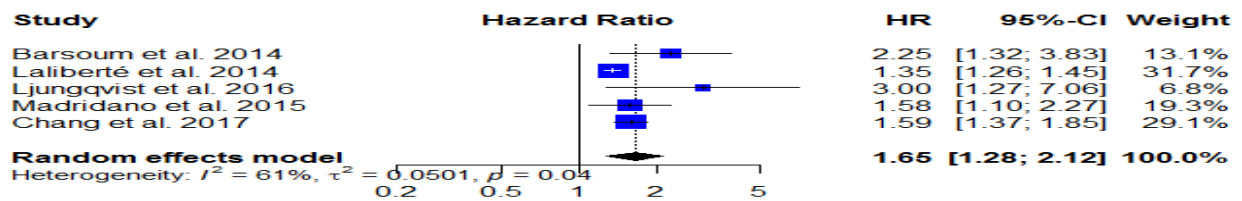
1.41; 95% CI: 1.05 - 1.88, 2 studies), cancer (HR: 1.72; 95% CI: 1.41 - 2.09; 2 studies), and unprovoked VTE (HR: 1.88; 95% CI: 1.37 - 2.57, 4 studies) (**Table 3**).

Egger's test was assessed for 5 risk factors and suggested possible publication bias for diabetes and unprovoked VTE, while, it was not statistically significant for age, gender, and hypertension (**Table 3**); however, it is limited by the small number of studies, as this test may lack the statistical power to detect bias when the number of studies is small [52].

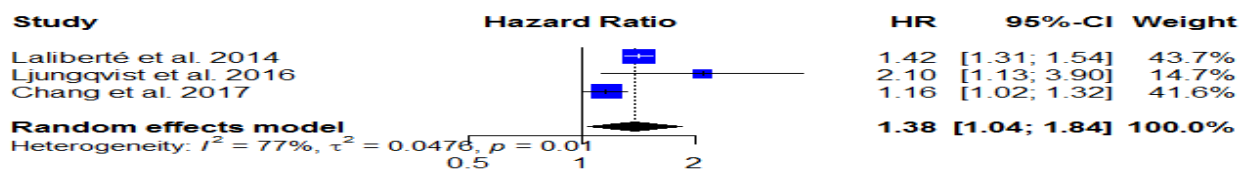
Age (older)



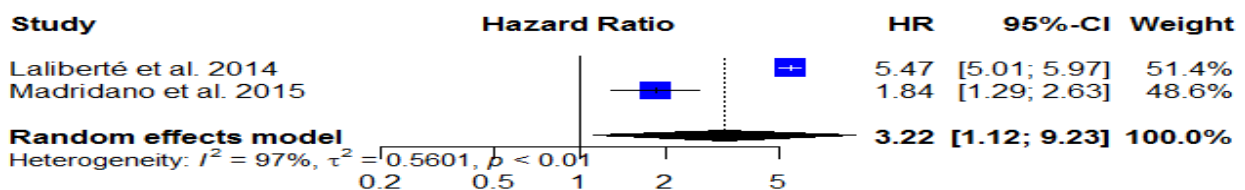
Diabetes



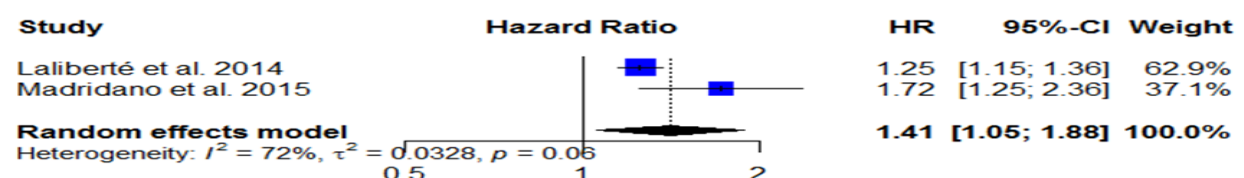
Hypertension



Previous atherothrombotic event



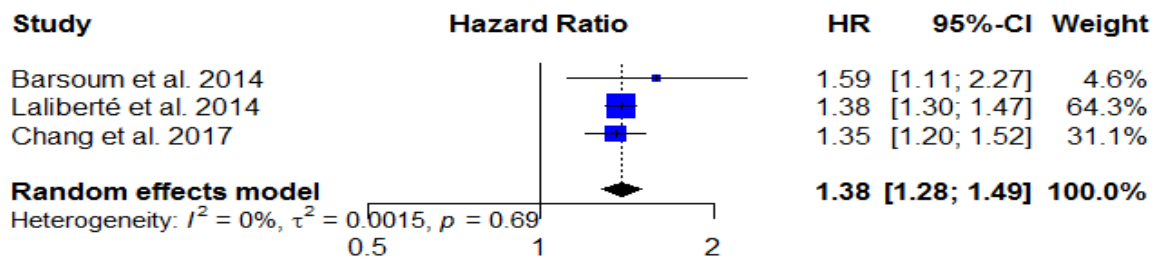
Chronic kidney disease



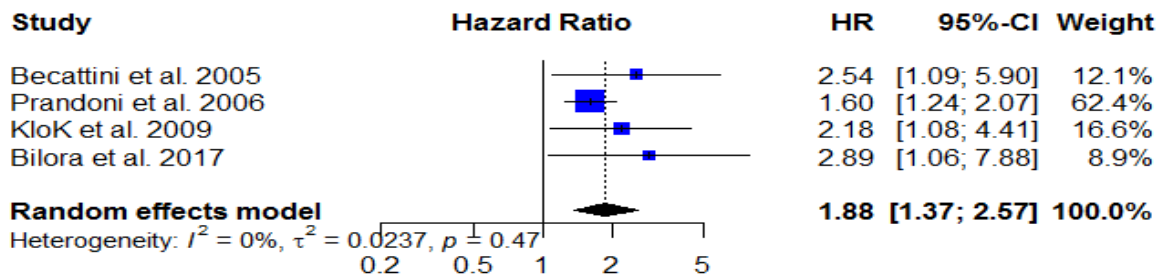
- HR: hazard ratio, - CI: confidence interval.

Figure 2: Arterial risk factors reported in meta-analysis with substantial heterogeneity.

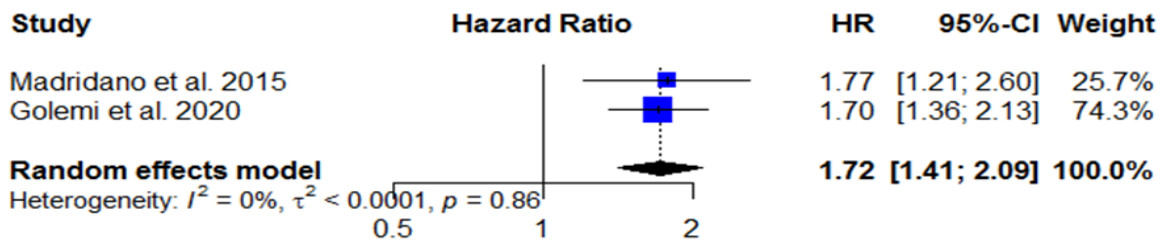
Gender (male)



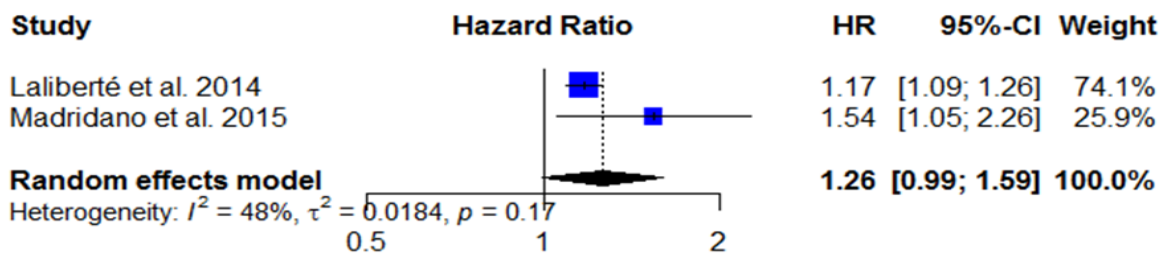
Unprovoked VTE



Cancer



Chronic lung disease



- HR: hazard ratio, - CI: confidence interval, - VTE: venous thromboembolism.

Figure 3: arterial risk factors reported in meta-analysis without substantial heterogeneity.

Table 2. Risk factors of arterial events in patients with VTE per included study

Authors, year	Risk factors	HR (95% CI)	Authors, year	Risk factors	HR (95% CI)
Golemi, 2020	- Cancer	1.7 (1.4 - 2.2)	Chang, 2017	- Age	7.29 (5.29 - 10.08)
	- Provoked VTE	1.39 (1.1 - 1.7)		- Gender (male)	1.35 (1.20 - 1.52)
	- Recent immobility	1.4 (1.1 - 1.8)		- Diabetes	1.59 (1.37 - 1.85)
		- Hypertension		1.16 (1.02 - 1.32)	
Le Moigne, 2019	- Patent foramen oval	Relative risk: 3.90 (1.62 - 8.67).	Bilora, 2017	- Unprovoked VTE	2.89 (1.06 - 7.88)
Hu, 2018	CHA2DS2-VASc score \geq 6	11.0 (9.24 - 13.0)	Vindis, 2017	Patent foramen oval	Odds Ratio: 4.6 (1.6 - 47.4)
Ljungqvist, 2016	- Diabetes	3 (1.3 - 7.2)	Cannegieter, 2015	- Gender (male)	NP
	- Hypertension	2.1 (1.1-3.8)			
	- PE vs DVT	2.8 (1.3 - 6.0)			
	- Smoking	3.0 (1.7-5.3)			
Madridano, 2015	- Cancer	1.77 (1.21 - 2.61)	Barsoum, 2014	- Age	1.06 (1.04 - 1.07)
	- Chronic lung disease	1.54 (1.05 - 2.26)			
	- Anemia	1.54 (1.11 - 2.14)		- Gender (male)	1.59 (1.1 - 2.27)
	- Prior artery disease	1.84 (1.29 - 2.64)			
	- Diabetes	1.58 (1.10 - 2.27)		- Diabetes	2.25 (1.32 - 3.83)
	- Renal insufficiency	1.72 (1.25 - 2.36)			

- VTE: venous thromboembolism, PE: pulmonary embolism, - DVT: deep venous thrombosis, NP: not provided, HR: hazard ratio, CI: confidence interval

Table 2 continued

Authors, year	Risk factors	HR (95% CI)	Authors, year	Risk factors	HR (95% CI)
Doyen, 2014	- Patent foramen ovale	NP	Goliszek, 2014	- Patent foramen ovale with right ventricle dysfunction	NP
Laliberté, 2014	- Age \geq 65	1.78 (1.66 - 1.91)	Lind, 2014	- Age < 65	NP
	- Hypertension	1.42 (1.31 - 1.51)		- Female gender	NP
	- Gender (male)	1.38 (1.30 - 1.47)		- PE vs DVT	NP
	- Diabetes	1.35 (1.26 - 1.45)			
	- Previous MI	5.47 (5.01 - 5.97)			
	- Chronic kidney disease	1.25 (1.15 - 1.37)			
	- Rheumatoid arthritis	1.26 (1.07 - 1.47)			
	- COPD	1.17 (1.07 - 1.26)			
	- Social risk factors (inadequate housing)	1.64 (1.13 - 2.39)			
Klok, 2009	- Unprovoked VTE	2.18 (1.1 - 4.5)	Spencer, 2008	- Age < 40 associated to unprovoked VTE	3.92 (1.65 - 9.35)
	- Prior arterial event	Odd Ratio: 3.10 (1.8 - 5.3)			
Prandoni, 2006	- Unprovoked VTE	1.6 (1.2 - 2.0)	Becattini, 2005	- Unprovoked VTE	2.54 (1.09 - 5.89)
	- Age	Relative risk: 1.9 (1.7 - 2.2)			
	- Male gender	Relative risk: 1.4 (1.1 - 1.9)			
	- Previous atherosclerotic	Relative risk: 2.5 (1.9 - 3.4)			

- VTE: venous thromboembolism, PE: pulmonary embolism, - DVT: deep venous thrombosis, COPD: Chronic obstructive pulmonary disease, NP: not provided, HR: hazard ratio, CI: confidence interval

Table 3. Pooled hazard ratio of risk factors of arterial events in patients with VTE

Risk factors	Number of studies	Pooled HR	95% CI	p-value (random effects models)	p-value (Eggers' test)
Age	03	2.36	0.78 - 7.20	0.1300	0.1248
Gender	03	1.38	1.28 - 1.49	< 0.0001	0.5629
Diabetes	05	1.65	1.28 - 2.12	< 0.0001	0.0283
Hypertension	03	1.38	1.04 - 1.84	0.0277	0.8923
Previous ATE	02	3.22	1.12 - 9.23	0.0295	-
Unprovoked VTE	04	1.88	1.37 - 2.57	< 0.0001	0.0021
Cancer	02	1.72	1.41 - 2.09	< 0.0001	-
Chronic kidney disease	02	1.41	1.05 - 1.88	0.0210	-
Chronic lung disease	02	1.26	0.99 - 1.59	0.0596	-

- ATE: atherothrombotic event, - VTE: venous thromboembolism, - HR: hazard ratio, - CI: confidence interval.

Discussion

This systematic review and meta-analysis showed that risk factors of arterial events in patients with VTE include known cardiovascular risk factors for arterial diseases and risk factors related to VTE characteristics. Included studies are all cohort studies, some with retrospective, and others with prospective collection of data; which in fact are ideal to evaluate risk factors.

Traditional cardiovascular risk factors identified in patients with VTE

Among established cardiovascular risk factors in the general population, male gender, hypertension, diabetes, and past history of arterial events, identified in this review and remaining after meta-analysis, are well known. Chronic kidney disease, a less evident cardiovascular risk factor in the general population was also reported by two studies and was significantly associated with arterial events after meta-analysis [16,42]. This highlighted the fact that, despite the peculiarity of VTE, patients with these conditions partly share common cardiovascular risk factors with the general population. There may exist common risk factors for venous and arterial disease as previously reported by some studies, citing older age, smoking, and adiposity or obesity, and metabolic syndrome [49,50,57]. Thus, these factors, which are well known in arterial diseases, have been shown to be also risk factors of VTE although most of them are less strongly associated with VTE than with arterial diseases; this hypothesis is supported by the fact that patients with some arterial diseases have been described to also be at increased risk of VTE [8,9,57].

Other risk factors of arterial event identified in VTE populations

In addition to classic cardiovascular risk factors, other risk factors of arterial events that were reported by at least one study include, cancer, unprovoked VTE versus provoked VTE, PE versus DVT, recent immobility, chronic lung diseases, anemia, rheumatoid arthritis, and social risk factor (inadequate housing). If some of these factors require confirmation by larger prospective studies, many of them were reported in more than one study and some, including cancer and unprovoked character of VTE, remained significantly associated with arterial events after meta-analysis, even if the mechanism leading to these associations remain to be investigated.

Cancer was reported as a risk factor for arterial events by three studies; with new diagnosis of cancer in a prospective cohort study including 360 PE patients, by Becattini *et al.* and cancer without precision in two retrospective cohort studies by Madridano *et al.* and by

Golemi *et al.* respectively with 23370 and 41259 VTE patients [14,37,42]. Cancer has been also reported by some authors as a possible risk factor for arterial events in the general population, and many hypotheses have been speculated on the pathophysiology of this implication [51,58,59]. Despite the potential association of cancer with the occurrence of arterial events in the general population, its association with the development of VTE is no longer to be demonstrated [60]. This could be one more argument to the fact that venous and arterial thrombotic diseases share some common risk factors. So, cancer should be an essential factor to consider in the prevention of arterial events in VTE populations.

The unprovoked character of VTE is henceforth well described in the literature as a risk factor for arterial events in patients with VTE and also reported in 5 studies included in our review, despite the fact that one retrospective cohort study reported contradictory results [14]. The unprovoked or provoked character of VTE is among the major factors that determine the duration of anticoagulant therapy [61]. Based on current recommendations on the management of VTE, patients with provoked VTE should be treated for 3 months, while patients with unprovoked VTE should receive indefinite treatment [61–63]. Considering these recommendations, we face a paradox if we suppose that anticoagulant therapy may play a role in the prevention of arterial ischemic events, as patients treated for shorter periods ultimately develop fewer events than those treated for a long time. Unfortunately, in the majority of studies included in our review, antithrombotic treatment was not extensively explored; yielding the necessity to investigate in further studies, the role of anticoagulant therapy and antiplatelet therapy on the development of arterial ischemic events in patients with VTE. This will help to find out how to efficiently prevent arterial events in a VTE-population.

Strengths and limitations

To the best of our knowledge, this is the first meta-analysis on risk factors of arterial ischemic events in patients with VTE. It was conducted with a strong methodology and strong statistical analyses were performed providing a clear summary of the existing knowledge. However, our systematic review and meta-analysis have some limitations. First, our overall estimates displayed significant heterogeneity for some risk factors, despite the use of appropriate techniques with random-effects model meta-analysis; so, conclusions have to be taken with caution. Second, there was a small number of studies included in the meta-analysis of each identified risk factor, which could hamper the assessment of publication bias and source of heterogeneity with reliability; therefore, the pooled HR assessment for each factor may be imprecise. Third, even if very similar in the majority of studies, the diagnosis criteria for VTE were not exactly the same in all included studies; therefore, the risk of bias related to

misdiagnosis of VTE, especially in retrospective studies could not be totally ruled out. Finally, only 55% of included studies have a low risk of bias in their methodological quality, yielding once again the necessity to take conclusions with caution.

Conclusions

Risk factors of arterial events in patients with VTE include some classic cardiovascular risk factors well recognized in the general population and other risk factors that are related to VTE. However, if several of these factors need confirmation by further prospective studies in order to have clinical implications, some such as cancer and the unprovoked character of VTE should already be taken into consideration in the prevention of arterial events in these populations. Further studies, ideally prospective cohorts, are also required to assess, the role of treatments and mainly anticoagulant therapy for the prevention of arterial events in VTE patients.

List of Abbreviations:

AMI: acute myocardial infarction

DVT: deep venous thrombosis

MACE: major adverse cardiovascular event

MALE: major adverse limb event

PE: pulmonary embolism

VTE: venous thromboembolism

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C. Article de revue 3 : décès cardiovasculaire après MVTE

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I. RESUME

Rationnel : De nombreuses études issues de la littérature récente ont montré que les maladies cardiovasculaires chez les patients atteints de maladie veineuse thromboembolique (MVTE) sont plus fréquentes que dans la population générale sans MVTE. Cependant, les données résumant l'impact des maladies cardiovasculaires sur la mortalité des patients atteints de MVTE sont manquantes. Dans cette revue systématique avec méta-analyse, nous avons cherché à déterminer la fréquence et l'incidence des décès cardiovasculaires chez les patients atteints de MVTE.

Méthodologie : Les bases de données MEDLINE et EMBASE ont été explorées pour rechercher des articles publiés entre le 1er janvier 2000 au 28 février 2021. Les études éligibles étaient des études de cohorte prospectives observationnelles incluant des patients atteints de MVTE et rapportant toutes les causes de décès. Les décès d'origine cardiovasculaire étaient définis comme les décès résultant d'une embolie pulmonaire nouvelle ou récidivante, les décès dus à un infarctus aigu du myocarde, une mort subite, une insuffisance cardiaque, les décès dus à un accident vasculaire cérébral, une dissection aortique ou des décès dus à d'autres causes cardiovasculaires. Des modèles à effets aléatoires ont été utilisés en méta-analyse pour déterminer tous les paramètres d'intérêt avec leur intervalle de confiance (IC) à 95 %.

Résultats : Treize études observationnelles portant sur 22 251 patients ont été identifiées et incluses. L'âge moyen/médian variait entre 49 et 75 ans. La proportion d'hommes variait de 38,3 % à 53,2 %. La fréquence globale des décès d'origine cardiovasculaire chez les patients atteints de MVTE était de 3,9 % (IC à 95 % : 2,5 % à 5,6 %), tandis que la fréquence globale de la mortalité toutes causes était de 12,0 % (IC à 95 % : 9,1 % à 15,4 %). La proportion de décès cardiovasculaires parmi toutes les causes de décès chez les patients atteints de MVTE était de 35,2 % (IC à 95 % : 22,2 % à 49,3 %). Le taux d'incidence de décès d'origine cardiovasculaire était de 1,92 pour 100 patients-années (IC à 95 % : 0 à 4,1). La fréquence des décès cardiovasculaires chez les patients atteints de MVTE était significativement plus élevée que chez les patients sans MVTE (risque relatif : 3,85, IC à 95 % : 2,75 à 5,39).

Conclusion : Cette méta-analyse ayant inclus 13 études de cohorte prospectives récentes, montre que les décès cardiovasculaires chez les patients atteints de MVTE sont plus fréquents que dans la population générale sans MVTE.

Mots-clés : mortalité cardiovasculaire ; décès cardiovasculaire ; maladie thromboembolique veineuse, fréquence ; incidence ; méta-analyse.

II. ARTICLE COMPLET

Cardiovascular mortality after venous thromboembolism: a meta-analysis of prospective cohort studies

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Cardiovascular Mortality after Venous Thromboembolism: A Meta-Analysis of Prospective Cohort Studies

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Abstract

Background: Many studies from current literature showed that cardiovascular diseases in patients with venous thromboembolism (VTE) are more frequent than in the general population without VTE. However, data summarizing the impact of cardiovascular diseases on mortality of patients with VTE are lacking. In this systematic review and meta-analysis, we aimed to determine the frequency and incidence rate of cardiovascular death in patients with VTE.

Methods: MEDLINE and EMBASE were searched from January 1st 2000 to February 28th 2021. Eligible studies were observational prospective cohort studies including patients with VTE and reporting all causes of death. Cardiovascular death was defined as deaths that result from new or recurrent pulmonary embolism, death due to an acute myocardial infarction, sudden cardiac death or heart failure, death due to stroke, death due to cardiovascular procedures or hemorrhage, death due to ruptured aortic aneurysm or aortic dissection and death due to other cardiovascular causes. Random-effect models meta-analysis served to determine all pooled effect size of interest with their 95% confidence interval (CI).

Results: Thirteen observational studies enrolling 22,251 patients were identified and included. The mean/median age varied between 49 and 75 years. The proportion of men ranged from 38.3% to 53.2%. The overall pooled frequency of cardiovascular death in patients with VTE was 3.9% (95% CI: 2.5% to 5.6%), while the overall pooled frequency of all-cause mortality was 12.0 % (95% CI: 9.1% to 15.4%). The pooled proportion of cardiovascular death among all causes of deaths in patients with VTE was 35.2% (95% CI: 22.2% to 49.3%). The pooled incidence rate of cardiovascular death was 1.92 per 100 patient-years (95% CI: 0 to 4.1). The frequency of cardiovascular death in patients with VTE was significantly higher than in patients without VTE (risk ratio: 3.85, 95% CI: 2.75 to 5.39).

Conclusion: Based on this updated meta-analysis from 13 prospective cohort studies, cardiovascular death in patients with VTE is more frequent than in the general population without VTE.

Keywords: cardiovascular mortality; cardiovascular death; venous thromboembolism, frequency; incidence; meta-analysis.

Introduction

The overall annual incidence of venous thromboembolism (VTE), defined as deep vein thrombosis (DVT), pulmonary embolism (PE), or both is estimated to be between 1 and 2 per 1000 of the population in the United States and Europe [4,5]. VTE, therefore, represents an important public health concern. Moreover, VTE is the third leading cause of cardiovascular death trailing myocardial infarction and stroke [3].

Many studies from the recent literature highlighted an increased long-term risk of all cardiovascular diseases, including new episodes of VTE and arterial cardiovascular events in patients presenting with previous VTE than in the general population without VTE [6,13,64]. Cardiovascular diseases are known to be responsible for 31% of all deaths in the general population worldwide, which represents approximately 18 million deaths each year [18]. In patients with acute VTE, death is more frequent than nonfatal recurrent VTE and the causes of death vary widely [65]. Few cohort studies, some with retrospective and other with prospective collection of data, reported on the causes of death in patients with VTE [35,66–68]. Some studies reported a frequency of cardiovascular death in patients with VTE higher than the current frequency of cardiovascular death known in general population [27,66,69], but data summarizing the results of relevant published observational prospective cohort studies are lacking.

A meta-analysis published in 2018 that included seven prospective randomized trials reporting on the causes of death in patients with VTE anticoagulated with direct oral anticoagulants, and comparing dabigatran, rivaroxaban, apixaban, and edoxaban with the standard anticoagulant treatment of VTE, reported a frequency of all-cause mortality of 2.4% (718/29,844), with cancer as the most frequent cause of death (42%) [70]. The other causes of death were, VTE (20%), infections (13%), hemorrhage (6%), heart disease (4%), and stroke (2%). The overall proportion of cardiovascular death among all deaths was 34.7% (249/718) in this study [70].

These data highlighted the fact that frequency of cardiovascular death in patient with VTE may be at least equal to the frequency of cardiovascular death known in general population. However, there is a need to summarize data from prospective observational cohort studies to clarify this question. Hence, we conducted this systematic review and meta-analysis with the aim to explore the frequency and incidence of cardiovascular death in patients with VTE based on observational prospective cohort studies from current literature. The final goal was to see

whether the frequency of cardiovascular death is higher in patients with VTE than in general population without VTE.

Methods

Design

This is a systematic review and meta-analysis that was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [21]. The protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the following registration number: CRD42021244492.

Search strategy

We conducted a comprehensive search in the MEDLINE/PubMed and EMBASE databases to identify potentially eligible studies. We used a combination of the following medical subject headings (MeSH): ‘pulmonary embolism’, ‘venous thromboembolism’, ‘venous thrombosis’, ‘mortality’, and ‘death’; and complementary keywords (‘cardiovascular death’, ‘cardiovascular mortality’). Titles and abstracts of all identified articles from literature search were independently screened by two investigators, and the full texts of eligible articles were further evaluated for final inclusion (SN and TG). Disagreements, were resolved by discussion. For duplicate publications, only the most comprehensive report including the largest sample size was considered.

Selection criteria

All population-based prospective cohort studies published between January 1, 2000 and February 28, 2021 that included human adults with VTE and reported the causes of death in detail, were included. Only original research articles were considered. We excluded editorials, reviews, commentaries, studies lacking primary data or with incomplete methods description and studies published in a language other than English. **Supplementary file 1** shows the search strategy conducted in PubMed/MEDLINE, and **Figure 1** represents the summary of the study selection.

Definition of outcome

Our primary outcome of interest was cardiovascular death, a composite outcome defined as deaths that result from new (for patients with DVT) or recurrent pulmonary embolism (for patients with PE), deaths due to acute myocardial infarction, sudden cardiac deaths or heart failure, deaths due to ischemic or hemorrhagic stroke, deaths due to cardiovascular procedures

or hemorrhage, deaths due to ruptured aortic aneurysm or aortic dissection and deaths due to other cardiovascular causes (peripheral arterial disease) [71,72]. Secondary outcome was deaths related to recurrent VTE only.

Supplementary file 1. PubMed search strategy

	Search	Results
#1	"Venous Thrombosis" [Tiab] OR "Pulmonary Embolism" [Tiab] OR "deep venous thrombosis" [Tiab] OR "superficial venous thrombosis" [Tiab] OR ("Pulmonary Embolism"[Mesh]) OR "Venous Thromboembolism"[Mesh] OR "Venous Thrombosis"[Mesh]	118086
#2	"Mortality"[Mesh] OR "Death"[Mesh] OR "cardiovascular mortality"[Tiab] OR "cardiovascular death"[Tiab]	546370
#3	#1 AND #2	5376
#4	#3 Limited to <ul style="list-style-type: none"> - Observational / comparative studies - Original research articles - Humans, - English language - Period from January 1st 2000 and February 28th 2021 	1046

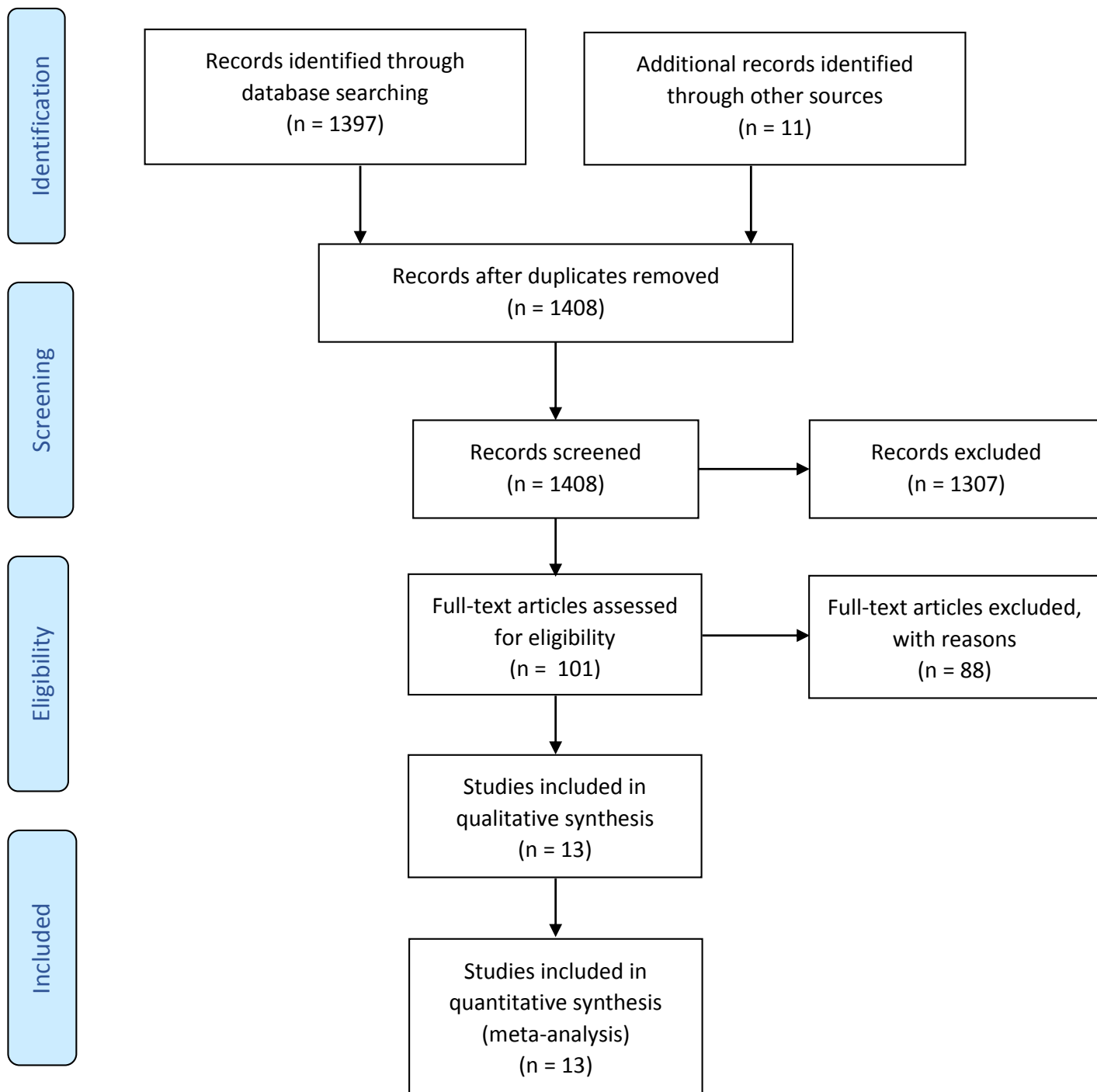


Figure 1: Flow chart of studies selection

Appraisal of the quality of included studies

Methodological quality and risk of bias of all included studies was evaluated using an adapted version of the Newcastle-Ottawa quality assessment scale (NOS) for evaluation of the quality of observational studies [22]. The NOS is formulated by a star allocation system, assigning a maximum of nine stars for the risk of bias in three areas: selection of study groups, comparability of groups and ascertainment of the outcome of interest. There is no validation study that provides a cut-off for interpretation of this score, despite the fact that many authors consider a score equal to or higher than 7 to define high quality studies (low risk of bias). Therefore, in our review, we considered a score from zero to three stars as high risk of bias, four to six stars as moderate risk of bias and seven to nine stars as low risk of bias, respectively. Details of stars allocation per category in each included study is presented in the **supplementary file 2**.

Data extraction and synthesis

We used a standardized data extraction sheet to collect information on first author names, year of publication, sample size (total, number of patients with VTE), type of VTE (PE, DVT or VTE for both), number and percentage of male, mean or median age, mean or median follow-up duration, number of deaths due to cardiovascular diseases as defined in the outcome definition section, number of deaths of any cause, number of deaths of unknown cause, follow-up in patient-year, when provided (if not, an approximation was calculated when possible from the overall follow-up period for closed cohorts, and the total number of participants, excluding those lost to follow-up). Data were extracted by one investigator (SN) and a second investigator (TG) double-checked extracted data for accuracy. Search results were compiled using the citation management software Zotero version 5.0.77.

Statistical analysis

Random effects models with inverse variance method were used to pool the effect sizes (frequency of cardiovascular death, and incidence rate of cardiovascular). Mantel-Haenszel method was used for meta-analysis of the risk ratio (RR) for comparison of frequency of cardiovascular death between patients with VTE and controls without VTE. All effect sizes of interest were reported with their 95% confidence intervals (CI) and the 95% prediction intervals for some. In studies with patients lost to follow-up, only the total number of patients at the end of follow-up was considered. Heterogeneity was assessed using the χ^2 test on Cochran's Q statistic and quantified by the I^2 value [55]. The I^2 statistic estimates the percentage

of total variation across studies due to true between-study differences rather than chance and varies between 0 and 100%, with values greater than 60-70% generally indicating the presence of substantial heterogeneity [56]. Egger's test and in few cases, Funnel plots were used to detect the presence of publication bias [52]. Forest plots were drawn to visualize the frequency of cardiovascular death in patients with VTE and extent of heterogeneity between studies. Data were analyzed using the “meta”, “dmetar”, and “metaphor” packages of the statistical software R, version 3.6.2. A p-value < 0.05 characterized statistically significant results.

Supplementary file 2: Assessment of methodological quality of included studies with the Newcastle-Ottawa quality assessment scale for cohort studies

Authors	Selection				Comparability	Outcome			Number of stars/Risk of Bias
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Chuang et al.	*	- no control group	*	*	- no control group	*	*	*	6 / Moderate
Çibietis et al.	*	- no control group	*	*	- no control group	*	*	- no statement	5 / Moderate
Monreal et al.	*	*	*	*	*	*	*	*	8 / Low
Brenner et al.	*	- no control group	*	*	- no control group	*	*	- no statement	5 / Moderate
Faller et al.	*	- no control group	*	*	- no control group	*	*	- no statement	5 / Moderate
Alonso-Martinez et al.	*	- no control group	*	*	- no control group	*	*	*	6 / Moderate
Castelli et al.	*	- no control group	*	*	- no control group	*	*	- no statement	5 / Moderate
Roach et al.	*	*	*	*	**	*	*	- no statement	8 / Low
Huerta et al.	*	*	*	*	**	*	*	- no statement	8 / Low
Prandoni et al.	*	*	*	*	**	*	*	*	9 / Low
Young et al.	*	- no control group	*	*	- no control group	*	*	*	6 / Moderate
Becattini et al.	*	- no control group	*	*	- no control group	*	*	- no statement	5 / Moderate
La Vecchia et al.	*	- no control group	*	*	- no control group	*	- no details on follow-up	- no statement	4 / Moderate

Thresholds for interpretation of the Newcastle-Ottawa scales used in our study. Good quality > Low risk of bias: 7-9 stars; Fair quality > Moderate risk of bias: 4-6 stars; Poor quality > High risk of bias: 0-3 stars.

Results

General characteristic of included studies

Our comprehensive search initially identified a total 1,408 observational cohort studies; of which 1,307 were excluded after screening of titles and abstracts. Full texts of the remaining 101 papers were thoroughly screened for eligibility, and 88 were excluded at this level (**Figure 1**). Finally, 13 studies enrolling 22,251 patients were found eligible and included in the meta-analysis [32,35–37,64,67–69,73–77]. They were published between 2003 and 2019. Number of participants with VTE varied from 48 to 5,717 per study. Mean or median age varied from 49 to 75 years, median or mean follow-up was reported for 7 studies and varied from 5 to 60 months, while the overall follow-up period was reported for 5 studies and varied from 1 to 12 months. **Table 1** gives the general characteristics of each included study. Of the studies included in systematic review, 4 (30.7%) had low [32,35,36,73], and 9 (69.3%) had moderate [37,64,67–69,74–77] risk of bias in their methodological quality. There was no study with high risk of bias.

Frequency and incidence of cardiovascular death

The overall pooled frequency of cardiovascular death in patients with VTE was 3.9% (13 studies, 22,251 patients, 95 % CI: 2.5 - 5.6; $I^2 = 96.4\%$, p-Egger: 0.043) (**Figure 2**), and the overall pooled frequency of all-cause mortality was 12.0 % (12 studies, 20,332 patients, 95% CI: 9.1 - 15.4; $I^2 = 97.5\%$, p-Egger: 0.1893) [32,35,37,64,67–69,73–77].

The pooled proportion of cardiovascular deaths among all causes of deaths in patients with VTE was 35.2% (12 studies, 1939 deaths, 95% CI: 22.2 - 49.3; $I^2 = 96.9\%$, p-Egger: 0.063) [32,35,37,64,67–69,73–77]. And the pooled proportion of deaths of unknown cause among all causes of deaths in patients with VTE was 9.9% (6 studies, 1,003 deaths, 95% CI: 6.1 - 14.4; $I^2 = 69.9\%$, p-Egger: 0.71)[35,67–69,73,76]. Some studies allowed us to calculate the frequency of death related to recurrent VTE only, and the pooled frequency was 0.9% (8 studies, 4,493 patients, 95 % CI: 0.2 - 1.7; $I^2 = 89.0\%$, p-Egger: 0.28)[27,37,64,67–69,73,77]. The pooled frequency of recurrent VTE-related deaths among all causes of deaths was 7.9% (8 studies, 805 deaths, 95% CI: 3.9 - 13.1; $I^2 = 72.9\%$, p-Egger: 0.84) [27,37,64,67–69,73,77].

Two studies reported frequency of cardiovascular death in patients with VTE and in controls without VTE [32,35]. The pooled frequency of cardiovascular death in controls was 0.3% (2 studies, 48,946 patients, 95% CI: 0.03 - 0.95; $I^2 = 97.0\%$) and was statically lower than the

pooled frequency of cardiovascular death in patients with VTE (pooled risk ratio: 3.85, 95% CI: 2.75 - 5.39; $I^2 = 0\%$, $p = 0.013$).

It was possible to calculate the incidence rate of cardiovascular death from an approximation of follow-up (in patient-year) in 4 studies[35,68,73,74]; thus, the pooled incidence rate of cardiovascular death was 1.92 per 100 patient-years (4 studies, 8,060 patient-years, 95% CI: 0.0 - 4.1; $I^2 = 90.7\%$). The funnel plot indicated the presence of an asymmetry attesting of a possible publication bias (**Figure 3**).

Sensitivity and subgroup analysis

In addition to these results, we calculated the frequency of cardiovascular death in patients with VTE categorizing studies according to the risk of bias (**Figure 4**). The pooled frequency of cardiovascular death in patients with VTE after meta-analysis including only studies with low risk of bias in their methodological quality was 2.0% (4 studies, 13,055 patients, 95% CI: 0.5 - 4.2, $I^2 = 98.3\%$)[32,35,36,73], while the pooled frequency of cardiovascular death in patients with VTE after meta-analysis including only studies with moderate risk of bias in their methodological quality was 5.4% (9 studies, 9,196 patients, 95% CI: 3.3 - 7.9, $I^2 = 98.2\%$)[37,64,67–69,74–77]. There was a statistically significant difference when comparing these two groups of studies (Q-test for between subgroup heterogeneity = 5.45, $p = 0.020$).

We also calculated the frequency of cardiovascular death in patients with VTE categorizing studies according to the type of VTE (**Figure 5**). The pooled frequency of cardiovascular death in studies including only patients with PE with or without DVT was 6.4% (6 studies, 2,216 patients, 95% CI: 2.9% to 11.2%)[37,67,68,74,76,77] and in studies with DVT only we found a pooled frequency of cardiovascular death of 2.1%, (2 studies, 2,038 patients, 95% CI: 0% to 7.2%)[64,73]. There was no statistically significant difference in the pooled frequency of cardiovascular death between these two groups of studies (Q-test for between subgroup heterogeneity = 2.21, $p = 0.14$).

Table 1: General characteristics of included studies and participants

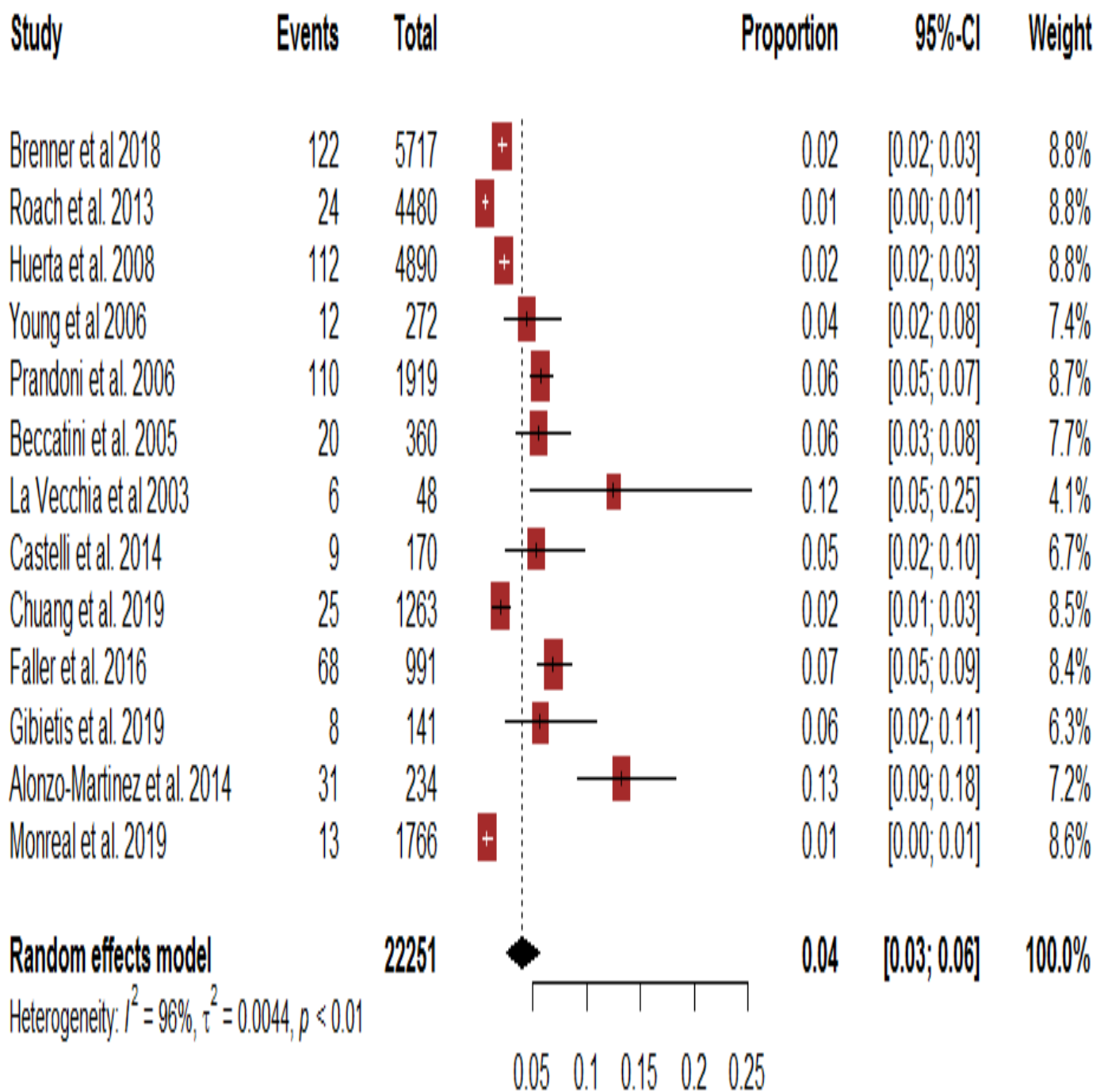
Authors, year	Number of patients with VTE	Men, n (%)	Mean/median age (years)	Follow-up	Type of VTE
Chuang, 2019	1263	745 (53.2%)	62.3	Overall follow-up: 12 months	PE (for all), with or without DVT
Gibietis, 2019	141	54 (38.3%)	66	Overall follow-up: 12 months	PE (for all), with or without DVT
Monreal, 2019	2056	1088 (52.9%)	59.8	Overall follow-up: 12 months	DVT
Brenner, 2018	5717	2961 (51.8%)	67	Median follow-up: 5 months	DVT or PE, all with cancer
Faller, 2016	991	528 (53.3%)	75	Median follow-up: 30 months	DVT or PE
Alonso-Martinez, 2014	234	114 (48.7%)	75	Median follow-up: 26 months	PE (for all), with or without DVT
Castelli, 2014	170	80 (47.1%)	70.2	Overall follow-up: 1 month	PE (for all) with or without DVT

- VTE: venous thromboembolism, PE: pulmonary embolism, - DVT: deep venous thrombosis.

Table 1 end:

Authors, year	Number of patients with VTE	Men, n (%)	Mean/median age (years)	Follow-up	Type of VTE
Roach, 2013	4480	2040 (45.5%)	49	Median/mean follow-up: 60 months	DVT or PE
Huerta, 2008	4890	-	-	Overall follow-up: 12 months	DVT or PE
Prandoni, 2006	1919	863 (44.9%)	62.5	Median follow-up: 49.5 months	DVT or PE
Young, 2006	316	140 (44.3%)	55	Mean follow-up: 34.8 months	DVT
Beccatini, 2005	360	160 (44.4%)	62.4	Median follow-up: 38 months	PE (for all) or DVT
La Vecchia, 2003	48	23 (47.8%)	64	Mean follow-up: not provided	PE (for all) or DVT

- VTE: venous thromboembolism, PE: pulmonary embolism, - DVT: deep venous thrombosis



- CI: confidence interval

Figure 2: Frequency of cardiovascular death

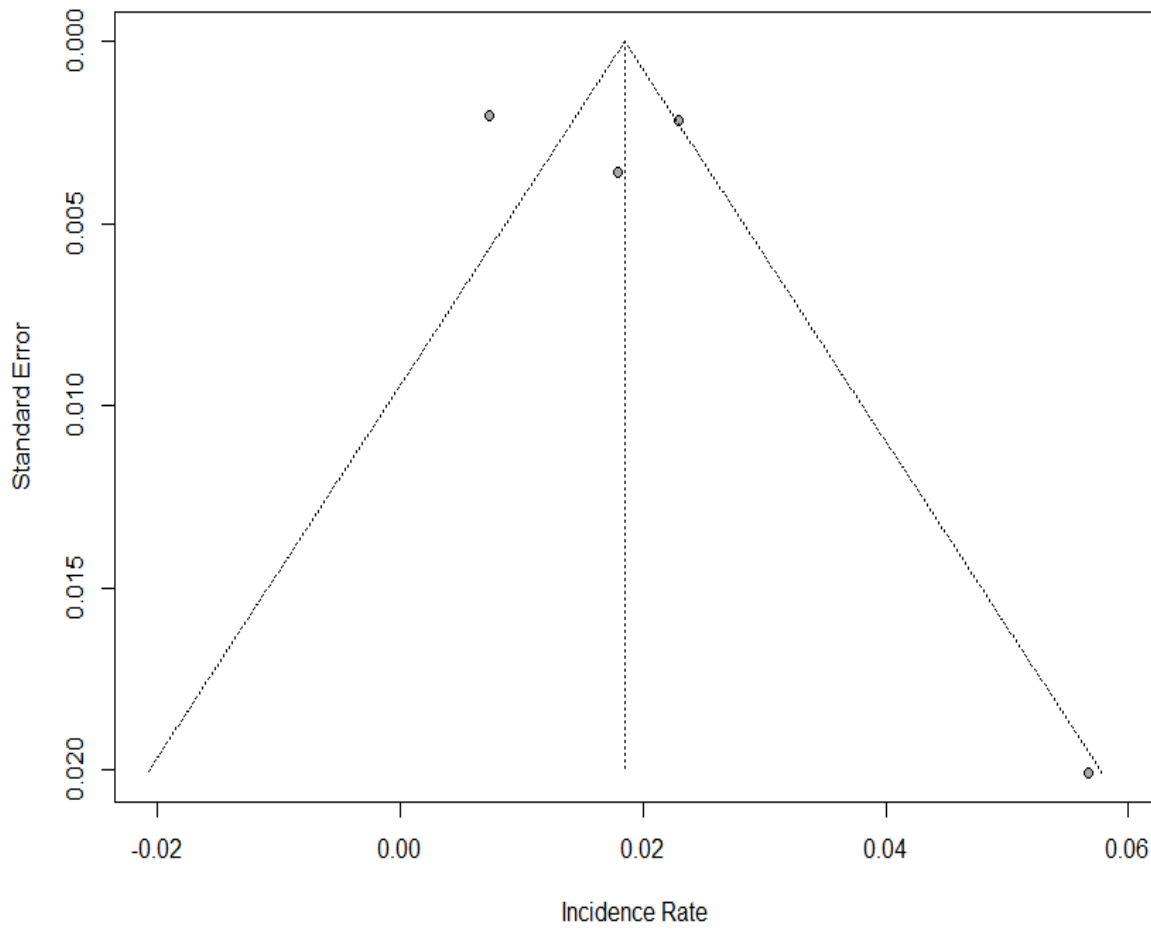
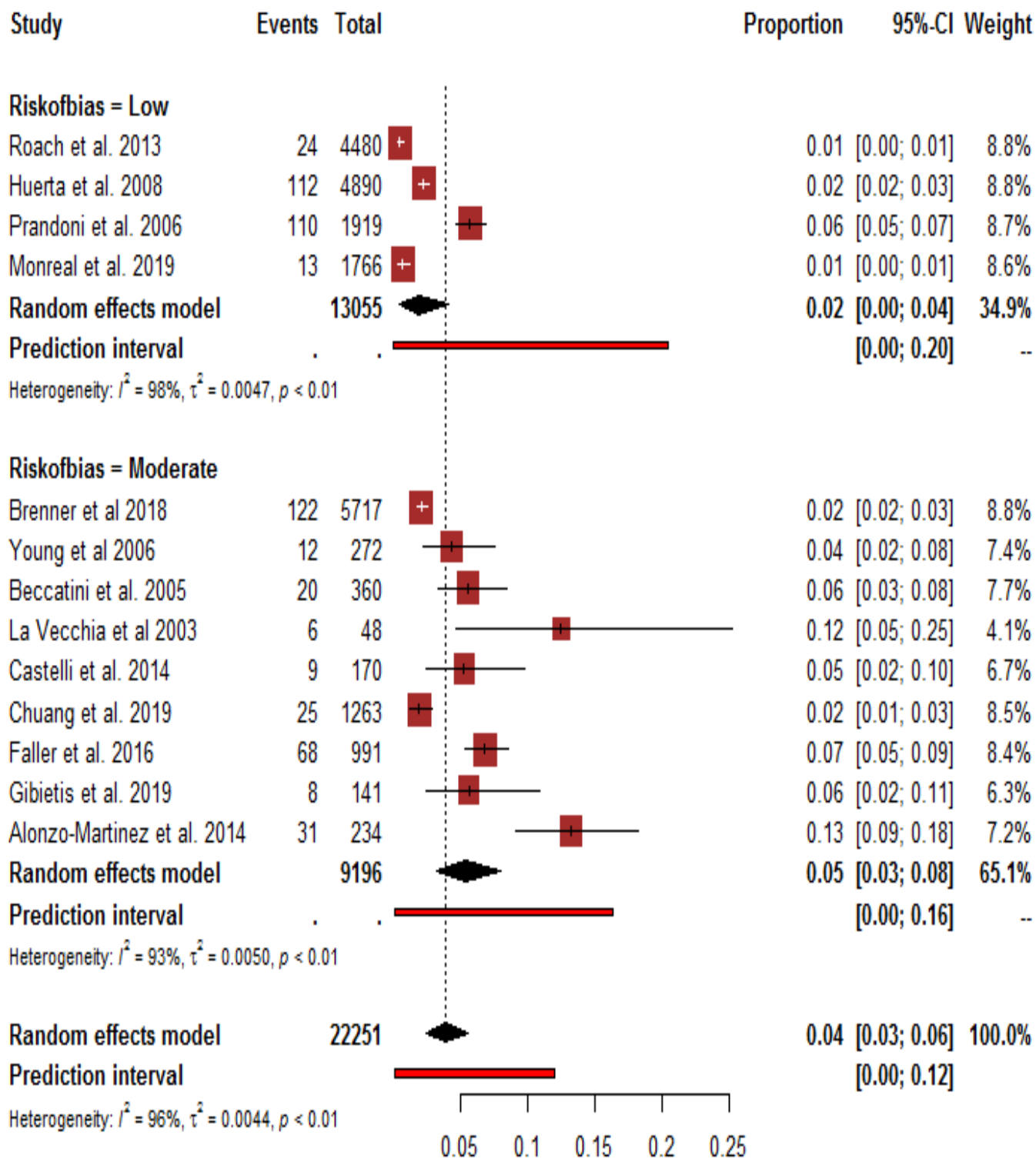


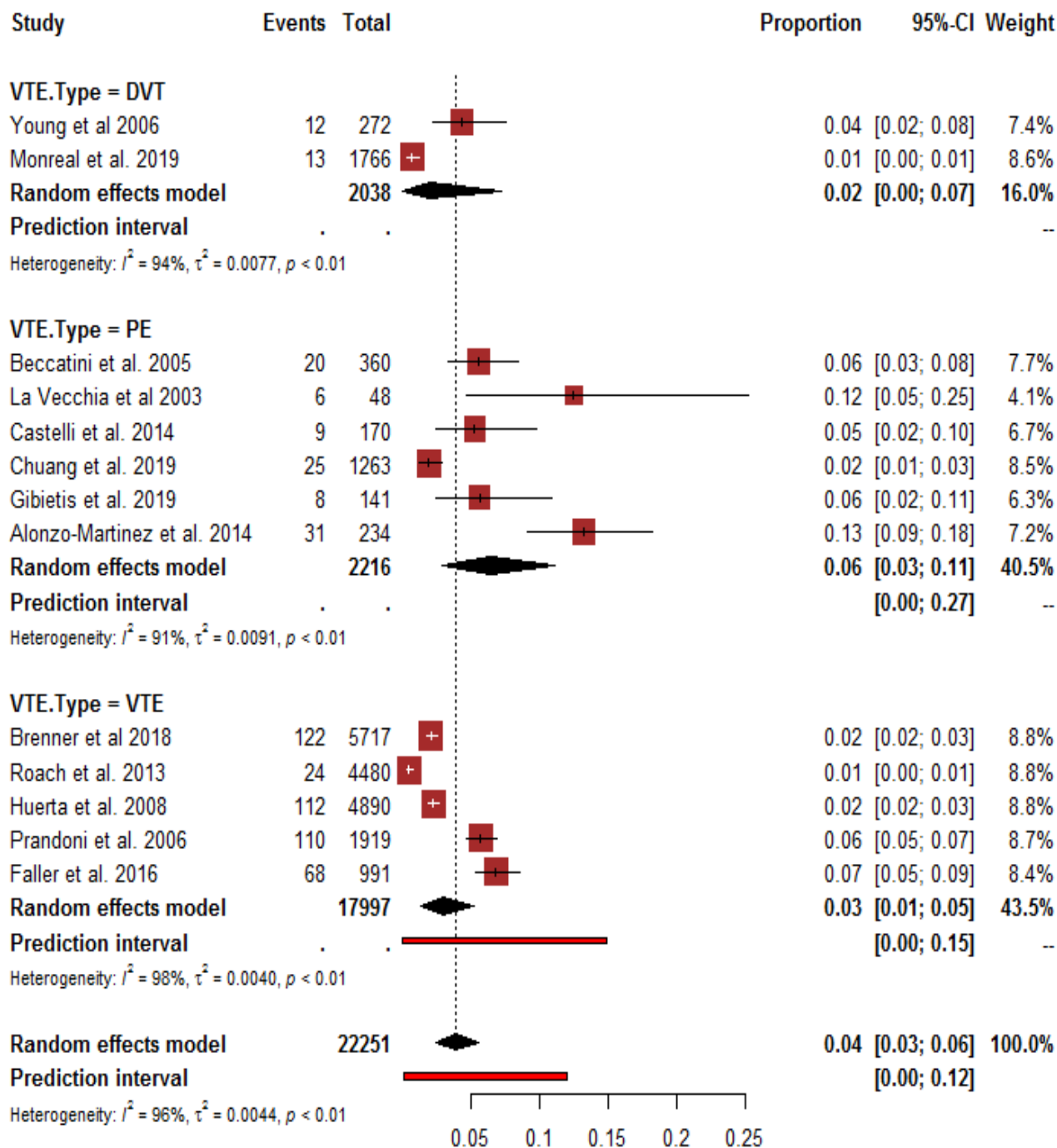
Figure 3: Funnel plot to assess publication bias in meta-analysis of cardiovascular death' incidence in patients with venous thromboembolism



Q-test for between subgroup heterogeneity = 5.45, p = 0.020.

- CI: confidence interval

Figure 4: Frequency of cardiovascular death in patients with venous thromboembolism with studies classified according to their risk of bias



Q-test for between subgroups (DVT, PE, VTE) heterogeneity = 3.29, $p = 0.19$

Q-test for between subgroups (DVT, PE) heterogeneity = 2.12, $p = 0.14$

- CI: confidence interval, - VTE: all venous thromboembolism, PE: pulmonary embolism (with or without DVT), - DVT: deep venous thrombosis only

Figure 5: Frequency of cardiovascular death in studies classified according to the type of venous thromboembolism

Discussion

We aimed to investigate the frequency and incidence of cardiovascular death in patients with VTE, compared to general population without VTE. The main findings of this systematic review and meta-analysis of observational prospective cohort studies, indicate that cardiovascular death is more frequent in patients with VTE than in the general population without VTE, as almost 4% of patients with VTE died of cardiovascular diseases.

Indeed, we found a pooled frequency of cardiovascular death of 3.9%, a pooled incidence of 1.92 per 100 patient-years and the pooled proportion of cardiovascular death among all causes of deaths was 35.2%, with 7.9% attributable to recurrent VTE. These results, that show a high frequency of cardiovascular death in patients with VTE, could be an under estimate given the high proportion of deaths of unknown cause, which represent about 10% of all causes of death in the selected studies. Regardless, the proportion of cardiovascular death among all causes of death in our review is consistent with the results of previous literature, including population-based studies and reviews [66,69,70]. For example, Gómez-Outes *et al*, found a proportion of cardiovascular death among all causes of death of 34.7% in their meta-analysis that included seven prospective randomized trials in patients with VTE on direct oral anticoagulants, and comparing different anticoagulant treatments [70]. However, the authors reported a pooled frequency of all causes of death of 2.4%, and a pooled frequency of cardiovascular death of 0.8%; which are lower than the 12.0% and 3.9 % found in our review [70]. These differences can be related to the design of studies, and the duration of follow-up in studies included in the two reviews. Indeed, Gómez-Outes *et al*, included only randomized trials in their meta-analysis, and the mean follow-up varied between 6 months and 18 months [70]. While our meta-analysis is based on observational studies only with a mean or median follow-up between 5 and 60 months. Additionally, mortality is likely higher in observational studies that include all kinds of patients than in randomized controlled trials which typically include younger and, in some cases, healthier patients. For example, the mean / median age in the studies included in our meta-analysis ranged from 49 to 75 years (with values < 60 years in only 3 studies)[32,64,73], while the mean age ranged from 55 to 58 years (all values < 60 years) in the studies included in the meta-analysis by Gómez-Outes *et al* [70].

We calculated the frequency of cardiovascular death in patients with VTE categorizing studies according to the type of VTE (PE with or without DVT, and DVT only). Although the frequency of cardiovascular death in studies including only patients with PE with or without

DVT of 6.4% appears to be higher than the results found in studies including patients with DVT only (2.1%), there was no statistically significant difference. These results, which may lead to conclude that cardiovascular deaths, and therefore cardiovascular disease, are not more frequent in patients with PE than in patients with DVT alone, are in opposition to the results of several studies [7,11], but they are consistent with results of a few previous population-based studies [32,42].

Only two studies included in our review reported data on cardiovascular death in patients with VTE and in controls without VTE, and the pooled frequency of cardiovascular death in controls was 0.3% [32,35]. The comparison of the frequency of cardiovascular death in patients with VTE and in controls led to a pooled risk ratio of 3.85, which is statistically significant. This finding supports the evidence that patients with VTE have not only an increased risk of cardiovascular diseases than the general population without VTE, but also an increased risk of cardiovascular death [15]. Moreover, according to our results, cardiovascular deaths are responsible for 35.2% of all deaths in patients with VTE, while they are known to be responsible for 31 % of all deaths in the general population [18].

There are several salient caveats regarding our findings. First, it is important to note that only a third of the 13 studies included in this review had low risk of bias in their methodological quality. Thus, we conducted a sensitivity analysis including only studies with low risk of bias in their methodological quality, and we found a pooled frequency of cardiovascular death of 2.0%, which was significantly lower than the 5.4% found while including only studies with moderate risk of bias. Second, the majority of our analyses displayed significant heterogeneity despite the use of appropriate technique with random-effects model meta-analysis. Finally, the Eggers' test indicates the presence of publication bias for the estimation of the main outcome, even if it was not the case for the estimation of proportion of cardiovascular death among all causes of death.

Notwithstanding these limitations, which imply the need to interpret our results with caution, to the best of our knowledge, this is the first meta-analysis of observational prospective cohort studies focusing on cardiovascular death in patients with VTE, with comparison to the general population. Moreover, this study, which synthesizes the results of relevant articles from current literature, provided evidence that cardiovascular death is more frequent in patients with VTE than in general population without VTE. These finding should have clinical implications

for prevention and treatment of cardiovascular diseases including recurrent VTE and arterial diseases in patients with VTE.

Conclusion

Based on this updated meta-analysis from 13 prospective cohort studies, cardiovascular death in patients with VTE is more common than in the general population, without VTE. Further studies, ideally prospective cohorts, are warranted to determine the risk factors of cardiovascular death in patients with VTE. However, more attention should already be paid to the prevention and management of cardiovascular diseases in patients with VTE.

List of Abbreviations:

DVT: deep venous thrombosis

PE: pulmonary embolism

VTE: venous thromboembolism

Declarations

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Author's contributions: Conception, designing of the protocol: SN, FC, LB. Literature search, studies selection, data extraction: SN, TG. Writing of the first draft: SN. Data management, data synthesis and analysis: SN. Critical revision: All authors. Final revision and approval of the final version: SN, TG, AD, CH. Guarantor of the review: SN.

D. Synthèse de la revue de littérature

Au décours de cette revue de littérature, nous pouvons tirer les conclusions suivantes :

- Les évènements cardiovasculaires artériels sont bien plus fréquents dans la population des patients ayant fait une MVTE que dans la population générale de sujets indemnes de MVTE.
- Ces évènements cardiovasculaires artériels sont plus fréquents chez les patients ayant fait une MVTE non provoquée que chez les patients ayant fait une MVTE provoquée.
- Les décès cardiovasculaires sont également bien plus fréquents dans cette population de patients atteints de MVTE que dans la population générale.
- Les facteurs de risques de des évènements artériels survenant après une MVTE incluraient certains facteurs de risque classiques connus en population générale et des facteurs propres aux patients atteints de MVTE.

Nous pouvons également faire les remarques suivantes :

- Parmi les études ayant explorés les facteurs de risque des complications artérielles chez les patients atteints de MVTE, il existe très peu d'étude de cohorte prospective à grande taille d'échantillon.
- La plupart de ces études ont ignoré le rôle compétitif potentiel attribuable aux décès non liés aux évènement cardiovasculaires étant survenus chez certains patients.
- Il est difficile au vu de la littérature actuelle de comparer clairement le risque d'évènement artériel chez les patients ayant fait une MVTE non provoquée aux patients ayant fait une MVTE provoquée par un facteur transitoire, étant donné que dans la majorité des études, le groupe des sujets avec MVTE provoquée incluait à la fois les sujets avec facteurs transitoire et les sujets avec cancer.
- Les facteurs de risque de décès cardiovasculaires restent inconnus dans cette population de sujets atteints de MVTE.
- Le rôle potentiel du traitement anticoagulant introduit pour la prise en charge de la MVTE sur le risque de survenu de complications artérielles ou de décès cardiovasculaires reste non exploré.

Nous avons donc par notre travail, dont les résultats sont présentés dans la suite de ce document, essayé d'apporter des éléments de réponse à ces questions.

Chapitre 3 :

METHODOLOGIE

1) Type d'étude

Il s'agit d'une étude de cohorte prospective. En effet, les patients inclus dans cette étude sont issus de la cohorte EDITH, qui était initialement une étude cas-témoins prospective multicentrique en milieu hospitalier et communautaire, ayant pour principal but d'évaluer les interactions entre les facteurs de risque génétiques et environnementaux de la MVTE dans l'ouest de la France. Seuls les cas de la cohorte EDITH, définis comme étant des patients atteints de MVTE confirmée, ont été considérés dans le cadre de ce travail.

2) Lieux de l'étude

La cohorte EDITH était initialement uni-centrique basée au Centre Hospitalier Régional et Universitaire de Brest (CHRU de Brest). Mais elle est devenue multicentrique à la suite de plusieurs amendements faisant évoluer les objectifs de l'étude initiale. Ainsi en Avril 2020, période où la cohorte EDITH a été rebaptisé « Breizh Cohort », elle comporte comme centres de recrutement en plus du CHRU de Brest avec son centre annexe (hôpital de Carhaix), le Centre Hospitalier de Quimper, le Centre Hospitalier de Morlaix, et l'Hôpital des Armées de Brest.

3) Durée de l'étude

L'étude EDITH est une cohorte ouverte dont les participants sont progressivement inclus depuis presque 30 ans. Dans le cadre de ce travail, nous nous sommes intéressés aux patients qui ont été inclus entre Avril 1992 (début des inclusion) et Décembre 2019. Elle n'a donc pas de durée de réalisation définie dans le temps.

4) Echantillonnage

a) Population cible

La population cible retenu pour ce travail était constituée de sujets adultes atteints de MVTE et consultant, ou hospitalisé dans l'un des centres de recrutement : le CHRU de Brest, le Centre Hospitalier de Quimper, le Centre Hospitalier de Morlaix, et l'Hôpital des Armées de Brest.

b) Taille de l'échantillon

Le nombre de sujet requis pour l'étude EDITH avait été définis en fonction des objectifs initialement définis. Plusieurs amendements ont ensuite eu lieu amenant parfois à une révision

du nombre de sujet nécessaire. L'un des objectifs de notre travail était de déterminer les facteurs de risque des complications artérielles chez un grand nombre de patients atteints de MVTE, afin de pallier aux données manquantes issues des études à grande taille d'échantillon dans la littérature. Pour cette raison, nous avons inclus tous les patients de la cohorte répondant à nos critères de sélection sans calcul préalable d'un nombre de sujet nécessaire.

c) Type d'échantillonnage

Les patients inclus dans la cohorte EDITH ont été inclus par échantillonnage consécutif non exhaustif basé sur les critères de sélection. Ainsi tous les patients potentiellement éligibles consultant ou hospitalisés dans l'un des centres de recrutements pendant la période de recrutement étaient sollicités pour participer à l'étude. Ils recevaient à cet effet une notice d'information leur donnant tous les détails sur l'étude (**Annexe 1**). Ils n'étaient ensuite inclus qu'après signature de la fiche de consentement éclairé (**Annexe 2**).

d) Critères de sélection

Les critères de sélections présentés sont ceux définis dans le cadre de ce travail et diffèrent légèrement des critères de sélection de la cohorte EDITH tel que définis initialement.

➤ Critères d'inclusion

Était inclus dans cette étude :

- Tout patient atteint de MVTE symptomatique (confirmée par des examens paracliniques dédiés) et vu en consultation ou en hospitalisation dans l'un des centres de recrutement,
- Tout patient répondant au critère ci-dessus et résidant dans la région définissant le bassin de recrutement du CHRU de Brest, de ses annexes et des autres centres de recrutement,
- Tout patient répondant aux critères ci-dessus et ayant signé la fiche de consentement éclairé pour participer à l'étude.

Les cas de MVTE symptomatique ont été confirmées comme suit :

- TVP des membres inférieurs : TVP diagnostiquée sur la base de l'incompressibilité des veines profondes à échographie de compression en mode B [78].

- EP : confirmée par : (i) une tomodensitométrie pulmonaire (angioscanner) positive montrant un défaut de remplissage (défaut endoluminal) par du produit de contraste ou une occlusion complète d'une artère pulmonaire segmentaire ou d'une artère proximale ; (ii) ou une angiographie pulmonaire montrant un défaut intraluminal ou un défaut endovasculaire d'au moins 2 mm de diamètre ; (iii) ou une scintigraphie de ventilation/perfusion pulmonaire indiquant une forte probabilité d'EP (selon les critères PIOPED); (iv) ou une l'association d'une forte probabilité clinique et d'une TVP proximale à l'échographie [79].

➤ **Critères d'exclusion**

Était exclus de cette étude, tout patient remplissant les critères d'inclusion mais répondant en plus à l'un ou plusieurs des critères suivants :

- Age de moins de 18 ans au moment de l'inclusion,
- MVTE de site atypique (tout autre site que l'EP et la TVP des membres inférieurs),
- Thrombose veineuse superficielle sans EP ni TVP des membres inférieurs associé,
- Absence de traitement anticoagulant introduit pour la MVTE,
- Perdus de vue : absence de nouvelle par tout moyen de suivi plus d'un an après inclusion, et ce jusqu'au 31 Décembre 2020.
- Retrait du consentement éclairé au cours du suivi.

5) Considérations éthiques

L'étude EDITH a été conduite selon les recommandations de la déclaration d'Helsinki [80].

En effet,

- Le protocole de recherche a été soumis au Comité de Protection des Personnes, et une clairance éthique, dont le dernier amendement remonte au 20 Novembre 2013 a été obtenue sous le numéro : **EDITH II/RB 05.003 (Annexe 3)** ;
- Les autorisations administratives pour mener cette étude ont été obtenues des autorités de tous les centres de recrutement ;
- Les potentiels participants à l'étude EDITH étaient entièrement informés sur les différents aspects de l'étude, et leur inclusion dans l'étude n'était faite qu'après signature de la fiche de consentement éclairé qui leur était présentée et expliquée au préalable (**Annexe 2**) ;

- Les prélèvements sanguins qui ont été effectués n'ont été utilisés que dans le cadre de cette étude, et les restes ont été détruits ;
- Nous assurons que l'anonymat des participants ainsi que la confidentialité des informations recueillies ont été effectives ;
- Nous certifions que cette étude n'a en aucun cas nui à l'intégrité physique, mentale et sociale des participants et qu'elle n'a pas affecté leur suivi ;
- Les résultats des examens réalisés dans le cadre de cette étude ont été remis aux participants qui devaient les acheminer chez leurs médecins respectifs.

6) Collecte des données

➤ Inclusion

Un questionnaire standardisé a été utilisé à l'inclusion (**Annexe 4**) pour la collecte de données, dont entre autres, les caractéristiques générales (sexe, âge, groupe sanguin si disponible, antécédents personnels de MVTE), caractéristiques de la MVTE (type, localisation, facteurs de risque de la MVTE), facteurs de risque cardiovasculaire (tabagisme, diabète, hypertension, dyslipidémie, obésité, antécédents d'athérosclérose symptomatique), comorbidités (insuffisance cardiaque chronique, insuffisance respiratoire chronique, fibrillation auriculaire), traitement concomitant au diagnostic de la MVTE (anticoagulant, anti-agrégant plaquettaire, statines, traitement anticoagulant), données biologiques disponibles (hémogramme, concentration de créatinine sanguine) et type de traitement initié pour la MTEV. Les résultats du bilan de thrombophilie disponibles (mutation du facteur V Leiden, mutation 20210A du gène de la prothrombine), lorsqu'ils ont été réalisés, étaient également été reportés.

➤ Suivi

Un questionnaire standardisé a également été utilisé pour la collecte des données de suivi (**Annexe 5**), avec notamment la survenue des récidives de MVTE, de complications hémorragiques, ainsi que la survenue ou non des événements cardiovasculaires, dont les infarctus du myocarde (IDM), les accidents vasculaires cérébraux (AVC), les artériopathies oblitérantes des membres inférieurs (AOMI). Les données sur les modifications du traitement anticoagulant initial étaient également collectées. La prise en charge de la MVTE (choix du type et de la durée du traitement anticoagulant) a été faite pour chaque patient, sur la base des

recommandations actualisées de bonnes pratiques cliniques au moment de l'inclusion. Il n'y avait pas de standardisation des pratiques cliniques entre les différents centres de recrutement.

Après l'inclusion, les patients étaient invités à revenir en consultations de suivi à 3, 6 et 12 mois. Les consultations de suivi ultérieures étaient programmées annuellement et pouvaient se faire lors d'une consultation physique au centre de recherche clinique du CHU de Brest, ou par appel téléphonique. Les participants qui ne se présentaient pas en consultation et ne donnaient pas de réponse aux appels téléphoniques recevaient une lettre par courrier postal.

7) Définitions des termes opérationnels

- MVTE non provoquée : toute MVTE survenant sans cancer ni aucun des facteurs provoquant majeur transitoire parmi : chirurgie avec anesthésie générale > 30 minutes, fracture de la jambe ou traumatisme de jambe avec plâtre, affection aiguë avec hospitalisation d'au moins trois jours, grossesse en cours ou accouchement récent, contraceptif à base d'œstrogène, traitement hormonal substitutif de la ménopause, ou traitement hormonal pour la procréation médicale assistée, tous au cours des trois derniers mois.

- MVTE associée au cancer : toute MVTE survenant chez un patient ayant un cancer en cours de traitement ou non, ou un antécédent personnel de cancer.

- MVTE provoquée : toute MVTE associé à au moins un facteur majeur transitoire parmi : chirurgie avec anesthésie générale > 30 minutes, fracture de la jambe ou traumatisme de jambe avec plâtre, affection aiguë avec hospitalisation d'au moins trois jours, grossesse en cours ou accouchement récent, contraceptif à base d'œstrogène, traitement hormonal substitutif de la ménopause, ou traitement hormonal pour la procréation médicale assistée, tous au cours des trois derniers mois.

- Facteurs de risque cardiovasculaires : l'usage du tabac a été classé comme jamais, ancien ou actuel ; le diabète, l'hypertension et la dyslipidémie étaient définis par la présence de ces affections parmi les antécédents connus des patients et rapportés dans leurs dossiers médicaux ; ou par la présence de médicaments spécifiques de ces affections respectives les traitements des patients à l'inclusion. La taille et le poids étaient autodéclarés, sauf pour les patients qui pouvaient être pesés. L'indice de masse corporelle (IMC) était ensuite calculée et l'obésité était définie pour des valeurs $\geq 30,0$ kg/m² [81]. L'antécédent d'athérosclérose symptomatique (antécédent cardiovasculaire personnel) était défini par la présence d'un infarctus du myocarde,

d'un accident vasculaire cérébral ou d'une AOMI symptomatique dans les antécédents connus des patients.

- La clairance de la créatinine était calculée par la formule de Cockcroft-Gault, quand possible en utilisant la valeur de créatininémie la plus proche de la date d'inclusion. L'insuffisance rénale était définie pour une clairance inférieure à 60 ml/min [82].

- La période de suivi était définie comme le temps entre la date d'inclusion et la dernière visite ou la date du décès.

- La période de survie était définie comme le temps entre l'inclusion et la date du décès ou la dernière visite (pour patients exclus-vivants).

- La durée du traitement était définie comme la durée entre le début du traitement anticoagulant et l'interruption de celui-ci. Pour les patients chez qui il y a eu arrêt temporaire du traitement anticoagulant, la durée considérée était la durée du traitement initial (entre début et première interruption) ; et pour les patients chez qui le traitement anticoagulant était toujours en cours au dernier suivi, la durée du traitement anticoagulant était la durée entre le début du traitement et la date de dernière visite.

- Perdus de vue : tout patient dont nous n'avons pas pu avoir de nouvelles plus d'un an après leur inclusion dans l'étude et ce jusqu'au 31 décembre 2020.

8) Critères de jugement

Les principaux critères de jugement utilisés dans notre travail étaient :

- Les **événements cardiovasculaires majeurs indésirables**, *Major Adverse cardiovascular Events (MACE)*, incluant : les syndromes coronariens aigus (SCA) non mortels, les accidents vasculaires cérébraux (AVC) non mortels (ischémiques et hémorragiques), ou tout décès cardiovasculaires. Nous avons également utilisé une définition de MACE incluant les décès tout cause au lieu des décès cardiovasculaires seulement, ce critère a été appelé MACE-2.

- Les **événements majeurs indésirables des membres non mortels**, *Major adverse Limbs Events (MALE)*, incluant : l'ischémie aiguë des membres, l'ischémie critique des membres, l'amputation non traumatique des membres ou toute procédure de revascularisation des membres.

Les critères de jugement secondaires étaient :

- Les **événements thrombotiques artériel, Arterial Thrombotic Tvent (ATE)**, incluant : les infarctus aigus du myocarde, ou les AVC ischémique, ou les ischémies aiguës des membres, ou les ischémies viscérales aiguës (digestive ou rénale).
- Le **décès cardiovasculaire, cardiovascular death (CVDT)**, incluant : les décès dus à une nouvelle EP (pour les patients atteints de TVP) ou à une EP récidivante (pour les patients déjà atteints d'EP), les décès dus à un infarctus aigu du myocarde ou à une insuffisance cardiaque, les morts subites d'origine, les décès dus à une arythmie fatale, les décès dus à une AVC ischémique ou hémorragique, les décès dus à une intervention cardiovasculaire ou à une hémorragie, les décès dus à une rupture d'anévrisme aortique ou à une dissection aortique, et les décès dus à d'autres causes cardiovasculaires [71,72].
- Les **décès** toute causes.

Un **SCA** était défini par la présence d'une douleur thoracique typique, associée à un diagnostic final validé d'infarctus du myocarde avec ou sans sus-décalage du segment ST, ou d'angor instable [83].

Une **ischémie du myocarde** était définie par la présence d'une douleur thoracique suspecte avec au moins deux des critères suivants : modifications de l'ECG évoquant ischémie myocardique iii) développement d'ondes Q pathologiques, iv) preuve imagérique d'une nouvelle altération de la fonction myocardique, ou d'une nouvelle anomalie localisée la paroi myocardique compatible avec une étiologie ischémique ; v) identification d'un thrombus coronaire par imagerie intrac coronaire.

Un **AVC** était défini par la présence d'un nouveau déficit neurologique focal, avec des signes ou des symptômes durant plus de 24 heures associés à des anomalies vasculaires compatibles sur la tomodensitométrie (TDM) ou l'imagerie par résonance magnétique (IRM) [84]. Lorsqu'une complication hémorragique survenait à la suite d'un AVC ischémique, l'AVC était considéré comme ischémique avec transformation hémorragique et non comme AVC hémorragique.

Une **ischémie aiguë de membre** était définie par la présence de signe ou symptômes évoquant une insuffisance vasculaire menaçante de membre confirmée par hémodynamique ou imagerie ayant conduit à une intervention de revascularisation en urgence [85].

Une **ischémie critique de membre**, ou ischémie menaçante, était définie par la présence d'une douleur de repos ou une perte de substance (ulcères ou gangrène) évoluant depuis au moins 14 jours, étayée par des critères hémodynamiques de pression basse à la cheville (< 50 mmHg) ou aux orteils (< 30 mmHg), ou de faibles valeurs de pression transcutanée en oxygène ($TcPO_2 < 30$ mmHg) [85,86].

Une **ischémie viscérale aiguë** était définie par la présence de signes ou symptômes cliniques évocateurs d'une ischémie rénale ou d'une ischémie digestive, associés à la confirmation par imagerie (échographie Doppler ou imagerie en coupe).

Tous les événements ont été prédéfinis et collectés de manière prospective via un formulaire de collecte (*Case Report Form*, CRF); afin de confirmer tous les événements artériels, les dossiers de tous les patients chez lesquels au moins un événement d'intérêt est survenu, ou chez lesquels un décès de toutes causes est survenu au cours du suivi ont été explorés pour adjudication par un comité indépendant sur la base des critères définis en accord avec les référents des spécialités concernées par ces affections. Il est important de noter que pour tous les critères combinés, seul le premier événement à survenir était pris en compte chez les participants qui en avaient plus d'un.

9) Analyses statistiques

Les résultats sont présentés sous forme de fréquence (pourcentage) pour les variables catégorielles et de moyenne \pm écart-type (SD) ou médiane (25e-75e centiles) pour les variables continues, le cas échéant. Les comparaisons de groupes ont été faites par le test du chi carré, le test t de Student ou des équivalents, le cas échéant. Nous avons utilisé l'estimateur d'Aalen-Johansen pour évaluer le risque cumulé d'événements cardiovasculaires au fil du temps, en considérant le décès non lié aux événements d'intérêts comme des événements compétitifs [87]. En dehors de nos analyses principales univariées et multivariées, les incidences d'événement d'intérêt, entre deux groupes ont été comparés à l'aide du test de Log-Rank, après avoir calculé

le risque cumulé selon la méthode de Kaplan-Meier. Sinon, pour les analyses principales, lorsqu'un risque compétitif était considéré, la comparaison entre les incidences cumulées de deux groupes était effectuée par de la méthode de l'échantillon K de Gray [88]. Pour déterminer les facteurs de risque de MACE et de MALE, ainsi que des critères de jugement secondaires, lorsque cela était nécessaire, et lorsqu'un risque compétitif était considéré, nous avons utilisé des modèles de Fine et Gray. Nous avons d'abord mené des analyses univariées pour étudier l'association entre les prédicteurs potentiels, et nous avons ensuite sélectionné les variables qui répondaient à des conditions ci-dessous pour les analyses multivariées.

Pour être incluse dans les modèles multivariées, chaque variable devait remplir les conditions suivantes : avoir une valeur $p < 0,15$ en analyse univariée et voir une fréquence d'au moins 3 % dans la population d'étude. Pour la majorité des analyses statistiques, les données biologiques avec des valeurs manquantes et éligibles à l'inclusion dans les modèles multivariées, devaient être enregistrés dans au moins 90 % de la population d'étude pour être incluses dans ces modèles multivariées. Pour les variables catégorielles ayant plus de deux modalités, elles étaient incluses dans l'analyse multivariée si au moins une modalité remplissait les conditions requises. Avant l'analyse multivariée, des corrélations ont été recherchées entre certaines variables d'intérêt, sur la base de la pertinence clinique, et seule la variable la plus prévalente avec le plus petit nombre de valeurs manquantes était incluse dans le modèle multivarié final. Pour certains critères de jugement, une sélection manuelle des variables par méthode pas à pas descendante était effectuée, si le modèle multivarié initial n'affichait aucun résultat statistiquement significatif. Pour toutes analyses, les Hazard Ratios (HR) étaient toujours reportés avec leurs intervalles de confiance (IC) à 95 %.

De façon générale, nos analyses étaient des analyses de cas complets, excluant toutes les données manquantes, et sans aucune imputation. Toutefois, pour certains critères de jugements, et lorsque cela était possible, en plus de nos analyses principales, nous avons réalisé des analyses de sensibilité après imputation multiple de la base de données. Pour les MACE, les MALE et les ATE, nous avons également réalisé des analyses de sous-groupes pour déterminer séparément les facteurs de risque de ces événements composites chez les patients atteints de MVTE non provoquée et chez les patients atteints de MVTE associée au cancer. Les données ont été compilées dans un fichier Excel (Microsoft Excel version 2016), et analysées à l'aide du logiciel statistique R, version 3.6.3. Tous les tests statistiques étaient bilatéraux et une valeur $p < 0,05$ a été définie pour caractériser les résultats statistiquement significatifs.

Chapitre 4 :

RESULTATS

Dans cette section, nous vous présentons nos résultats en reprenant les articles rédigés qui ont été publiés, ou acceptés pour publication dans des journaux scientifiques. Ainsi, de même que dans la section sur la revue de littérature, nous ferons à chaque fois une présentation des résumés en langue française, suivi de chaque article complet dans la version finale. Les références et les mises en forme sont donc adaptés pour adéquation à ce document mais les informations présentées sont exactement pareilles que dans les articles. Nous ferons à la fin une synthèse générale.

Cinq mille cinq cent soixante-dix-sept (5577) patients ont été inclus dans la cohorte EDITH entre le Avril 1992 et Décembre 2019. Toutefois, après exclusion des patients des hôpitaux de Quimper et de Morlaix, des patients avec MVTE de site inhabituel ou thrombose veineuse superficielle, des patients mineurs au moment de leur inclusions et des patients perdus de vus après inclusion, nous avons retenus 4940 patients pour nos analyses principales. Des détails sur le processus de sélection des patients finalement retenus sont présentés dans l'article principal (article de résultat 1).

Les résultats s'articulent donc autour des articles suivants :

- **Article 1 :** Facteurs de risque d'événements cardiovasculaires majeurs indésirables (MACE, *Major Adverse Cardiovascular Events*) et d'événements majeurs indésirables des membres (MALE, *Major Adverse Limbs Events*) après une MVTE.
- **Article 2 :** Facteurs de risque d'événements artériels thrombotiques (ATE, *Arterial Thrombotic Events*) après une MVTE non provoquée et après une MVTE associée au cancer.
- **Article 3 :** Facteurs de risque de décès cardiovasculaire (CVDT, *Cardiovascular Death*) après MVTE.
- **Article 4 :** Anticoagulation pour MVTE : impact sur le risque d'événements cardiovasculaires majeurs indésirables (MACE).

A. Article de résultats 1 : facteurs de risque des MACE et des MALE après MVTE

Cet article intitulé "*Risk Factors of Major Adverse Cardiovascular Events and Major Adverse Limb Events after Venous Thromboembolism : A Large Prospective Cohort Study*" a été accepté pour publication dans le journal "*Seminar in Thrombosis and Haemostasis*" en Février 2022 et est actuellement sous presse.

I. RESUME

Rationnel : Les événements cardiovasculaires artériels en général, les événements indésirables cardiovasculaires majeurs (MACE) et les événements indésirables majeurs des membres (MALE) en particulier, se sont avérés plus fréquents chez les patients atteints de maladie veineuse thromboembolique (MVTE) que dans la population générale. Cependant, leurs facteurs de risque de ces affections restent peu explorés à partir des grandes études de cohorte prospectives.

Méthodologie : Nous avons cherché à déterminer les facteurs de risque de MACE et de MALE après MVTE en général, ainsi qu'après MVTE non provoquée et MVTE associée au cancer. Nous avons analysé les données d'une étude de cohorte prospective multicentrique, incluant des patients atteints de MVTE confirmée, dans l'ouest de la France. Les MACE incluait les syndromes coronariens aigus non mortels, les accidents vasculaires cérébraux non mortels, et les décès cardiovasculaires ; et les MALE incluait, l'ischémie aiguë de membres, l'ischémie critique de membres, l'amputation non traumatique ou toute revascularisation de membres. Les modèles de Fine et Gray ont servi à déterminer les facteurs de risque de MACE et MALE.

Résultats : Cette étude a inclus 4940 patients (46,9% d'hommes) avec un âge moyen de 64,6 ans. 914 patients (18,5%) avaient un cancer et 1784 (36,1%) avaient au moins un facteur de risque transitoire de MVTE. Au cours d'un suivi médian de 64 mois, au moins un MACE est survenu chez 17,3 % des participants (2,35 pour 100 patients-années) et un MALE chez 1,7 % (0,27 pour 100 patients-années). En analyse multivariée, les facteurs de risque identifiés de MACE étaient l'âge de 50 à 65 ans (vs. < 50 ans, HR : 2,00, IC à 95 % : 1,38 - 2,91), l'âge > 65 ans (vs. < 50 ans, HR 4,85, IC à 95 % : 3,35 - 7,02), l'EP associée à la TVP (vs TVP isolée, HR : 1,25, IC à 95 % : 1,02 - 1,55), la MVTE non provoquée (vs. TEV associée à un facteur de risque transitoire, HR : 1,29, 95 % IC : 1,04 - 1,59), la consommation actuelle de tabac (vs. jamais, HR : 1,45, IC à 95 % : 1,07 - 1,98), l'hypertension artérielle (HR : 1,61, IC à 95 % : 1,30 - 1,98), l'antécédent d'athérosclérose symptomatique (HR : 1,52, IC à 95 % : 1,17 - 1,98), l'insuffisance cardiaque chronique (HR : 1,71, IC à 95 % : 1,21 à 2,42), la fibrillation auriculaire (HR : 1,55, IC à 95 % : 1,15 à 2,08) et l'insertion d'un filtre cave (HR : 1,46, IC à 95 % : 1,03 - 2,08). Les facteurs de risque identifiés de MALE en analyse multivariée étaient : l'âge de 50 à 65 ans (vs. < 50 ans, HR : 3,49, IC à 95 % : 1,26 - 9,65) et la fibrillation auriculaire (HR : 2,37, IC à 95 % : 1,15 - 4,89).

Conclusion : Cette grande étude de cohorte prospective montre que les facteurs de risque de MACE et de MALE chez les patients atteints de MVTE comprenaient certains facteurs de risque cardiovasculaire traditionnels connus et des comorbidités antérieures d'une part, et d'autre part, d'autres facteurs de risque liés aux caractéristiques de la MVTE.

Mots-clés : maladie veineuse thromboembolique, événement artériel, MACE, MALE, cohorte prospective.

II. ARTICLE COMPLET

Risk Factors of Major Adverse Cardiovascular Events and Major Adverse Limb Events after Venous Thromboembolism: A Large Prospective Cohort Study

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Abstract

Background: Arterial cardiovascular events in general, major adverse cardiovascular events (MACE) and major adverse limb events (MALE) particularly, have been shown to be more frequent in patients with venous thromboembolism (VTE) than in the general population. However, their risk factors remain little explored from large prospective cohort studies.

Methods: We aimed to determine the risk factors of MACE and MALE after all VTE, and also after unprovoked VTE and cancer associated VTE. We analyzed data from a multicenter prospective cohort study, including patients with confirmed VTE in west of France. MACE included acute coronary syndrome, stroke, or cardiovascular death; and MALE included acute limb ischemia, critical limb ischemia, non-traumatic amputation, or any limb revascularization. Fine and Gray competing risk models, considering death as competing events, served to determine risk factors of MACE and MALE.

Results: This study included 4940 patients (46.9% of men) with mean age of 64.6 years. 914 patients (18.5%) had cancer and 1784 (36.1%) had at least one transient risk factor of VTE. During a median follow-up of 64 months, MACE occurred in 17.3% of participants (2.35 per 100 patient-years) and MALE in 1.7% (0.27 per 100 patient-years). In multivariable analysis, the identified risk factors of MACE were, age of 50 to 65 years (vs. < 50 years, HR: 2.00, 95% CI: 1.38 - 2.91), age > 65 years (vs. < 50 years, HR 4.85, 95% CI: 3.35 - 7.02), PE associated with DVT (vs isolated DVT, HR: 1.25, 95% CI: 1.02 - 1.55) , unprovoked VTE (vs. transient risk factor associated VTE, HR: 1.29, 95% CI: 1.04 - 1.59), current tobacco use (vs. never, HR: 1.45, 95% CI: 1.07 - 1.98), hypertension (HR: 1.61, 95% CI: 1.30 - 1.98), past history of symptomatic atherosclerosis (HR: 1.52, 95% CI: 1.17 - 1.98), chronic heart failure (HR: 1.71, 95% CI: 1.21 - 2.42), atrial fibrillation (HR: 1.55, 95% CI: 1.15 - 2.08), and vena cava filter insertion (HR: 1.46, 95% CI: 1.03 - 2.08). The identified risk factors of MALE in multivariable analysis were: age of 50 to 65 years (vs. to age < 50 years, HR: 3.49, 95% CI: 1.26 - 9.65), and atrial fibrillation (HR: 2.37, 95% CI: 1.15 - 4.89).

Conclusion: This large prospective cohort study shows that risk factors of MACE and MALE in patients with VTE included some traditional known cardiovascular risk factors, and previous comorbidities on the one hand, and on the other hand, other risk factors that are related to characteristic of VTE.

Keywords: venous thromboembolism, arterial event, MACE, MALE, prospective cohort.

Introduction

Venous thromboembolism (VTE), that includes deep venous thrombosis (DVT), pulmonary embolism (PE), is a serious condition, as it represents the third most common cause of death from cardiovascular diseases in the general population, after heart attacks and stroke [3]. Moreover, VTE remains frequent in clinical situations, despite all the efforts made to fight against it in recent years. Its incidence is estimated to be around 0.1 to 0.2 per 100 person-years in Europe and United States [4,5].

The relationship between development of VTE and the increased risk of further arterial complications has been reported in several studies; and this, either considering arterial ischemic events only, or all arterial complications resumed as Major Adverse Cardiovascular Events (MACE) or Major Adverse Limbs Events (MALE) [6,7]. If the association between arterial events and increased risk of VTE complications has been widely consensual since many years, may be because arterial diseases usually lead to hospitalization, and therefore temporally immobility which is an established provoking factor of VTE, the association between VTE and increased risk of arterial complications has remained at the level of hypothesis for a while [8–10]. However, based on many recent studies and even some meta-analysis, the increased risk of arterial complications in VTE population compared to the general population is nowadays established [6,11–13]. This over risk of arterial complications in general, as well as that of MACE and MALE particularly, has been shown to be emphasized in patients with unprovoked VTE and in patients with malignancies associated VTE [14,15].

Several studies have explored the reasons of this over risk of arterial cardiovascular complications in patients with VTE, and led to the conclusion that venous and arterial thrombotic events may share some common risk factors [15,16]. If these findings supported by a recent meta-analysis highlighted the hypothesis that arterial and venous thrombosis may be the manifestation of the same disease, there are very few large prospective cohort studies that interested on this question [17]. Particularly the question of risk factors of MACE and MALE in overall VTE population, and in subgroups of patients with unprovoked VTE or cancer-associated VTE specifically remained very little explored. Moreover, the few prospective cohort studies available in current literature, that determined risk factors of arterial complications in patients with VTE ignored for the majority of them, the impact of death as competing events [16,17].

Based on the above, we therefore aimed to determine, from a large prospective cohort study, the risk factors of MACE and MALE after an acute episode of symptomatic VTE of all cause, and after unprovoked VTE as well as after cancer associated VTE.

Methods

Study design and setting

From April 1992 to December 2019, all consecutive patients seen at consultation or during hospitalization in Brest University Teaching Hospital, Brest Military Hospital, Morlaix Hospital and Quimper Hospital (the four main hospitals from Finistère district, France) for an acute symptomatic PE or DVT were approached for consideration to be enrolled in this prospective cohort study. The design has been previously described [89]. The Ethics Committee of Brest University Hospital approved the study protocol (CCP-Ouest 6-390). Written informed consent was obtained from all participants before inclusion.

Patients selection criteria

Potentially eligible and consenting patients aged 18 years or older were consecutively included if they had an objectively confirmed symptomatic VTE. Symptomatic DVT of lower limbs was diagnosed based on non-compression of deep vein using a real-time B mode compression ultrasonography (CUS) [78]. Symptomatic PE was confirmed based on: (i) a positive computed tomography pulmonary angiography showing a central filling defect outlined by contrast material or a complete occlusion in a segmental or more proximal pulmonary artery; (ii) or a pulmonary angiography with an intraluminal filling defect or a sharp cut-off in a vessel of at least 2 mm in diameter; (iii) or a ventilation perfusion lung scan indicating a high probability for PE((using Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria); (iiii) or a high clinical probability associated to a proximal DVT on CUS [79]. Patients with atypical site or superficial venous thrombosis, patients unable to read and sign the written informed consent form or those who refused to participate were not included in the study.

Data collection and follow-up

A standardized questionnaire was used at the inclusion for data collection on general characteristics (gender, age, blood group if available, personal past history of VTE), characteristic of VTE (type, location, VTE risk factors), cardiovascular risk factors (tobacco use, diabetes, hypertension, dyslipidemia, obesity, past history of symptomatic atherosclerosis), comorbid conditions (chronic heart failure, chronic respiratory failure, atrial fibrillation), concomitant treatment at VTE diagnosis (anticoagulant, antiplatelet agent, statins,

anticoagulant therapy), available biological data (full blood count, creatinine concentration), and type of treatment initiated for VTE. Results of factor V Leiden mutation, and prothrombin gene 20210A mutation check-up, when realized, were also further reported.

Unprovoked VTE was defined as VTE without cancer or major transient provoking factor including: surgery with general anesthesia >30 minutes, leg fracture or leg injury with plaster cast, acute illness with hospitalization for at least three days, ongoing pregnancy or delivery, ongoing estrogen contraceptive treatment, ongoing menopause substitutive hormonal therapy, or hormonal therapy for assisted reproduction, all within the past three months. Tobacco use was classified as never, former, or current; diabetes, hypertension and dyslipidemia were defined by the presence of these diseases among known medical conditions in participants' files, or by the presence of respective specific medications in patient's treatment at inclusion. Height and weight were self-reported except for patients who could be weighted. Body mass index (BMI) was then computerized and obesity was defined for values ≥ 30.0 kg/m² [81]. Creatinine plasma concentration routinely measured in some participants during hospitalization and before initiation of treatment were recorded. Estimated creatinine clearance was calculated using the Cockcroft-Gault formula with the measurement closer to the date of inclusion. Renal insufficiency was defined as a clearance below 60 mL/min [82]. Past history of symptomatic atherosclerosis was defined as a self-reported and file confirmation of past myocardial infarction, stroke, or symptomatic peripheral artery disease of lower limbs.

For all participants, the management of VTE (choice of type and duration of anticoagulant treatment) was done based on updated recommendations for good clinical practice, at the time of inclusion and on patient's clinical characteristic. There was no standardization of clinical practices among participants hospitals. After inclusion, patients were instructed to return for follow-up visits at 3, 6, and 12 months. Further follow-ups were scheduled annually and could be done during a physical consultation at the clinical research center of Brest Teaching Hospital, or by phone call. Participants who did not presented them self for consultation and did not respond to phone call, were sent a letter by postal mail. The follow-up period was defined as time between the inclusion date and the last contact visit or the date of death (when there were enough details on circumstances of death and cause of death was adjudicated); the survival period was defined as time between inclusion and the date of death or the last contact visit (for alive participants). For those who temporally stopped anticoagulant treatment, the duration considered was the duration of the initial anticoagulant therapy, and for patients who did not stopped anticoagulant treatment at the last follow-up, the

duration of anticoagulant treatment was the duration from the beginning of the treatment until the last follow-up.

Definition of outcomes

The main outcomes considered in our study were Major Adverse Cardiovascular Events (MACE) including non-fatal acute coronary syndrome, all non-fatal stroke, or cardiovascular death, and non-fatal Major Adverse Limbs Events (MALE), including acute limb ischemia, acute critical limb ischemia, non-traumatic limb amputation, or any limb revascularization procedure. Secondary outcome was all-causes death. Of note, only the first arterial complication to occurred was considered in participant who had more than one. All cardiovascular events were predefined and prospectively collected via the case report form of the cohort; in order to confirm all arterial events, files of all patients in whom at least one arterial event of interest or in whom death of all cause occurred during follow-up were checked for adjudication by an independent clinical event committee.

Acute coronary syndrome was defined as the presence of typical ischemic chest pain and a final validated diagnosis of ST elevation or non-ST elevation myocardial infarction, or unstable angina [83]. Stroke was defined by the presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting more than 24 hours associated to compatible vascular abnormalities on computerized tomography (CT) or Magnetic Resonance Imaging (MRI) [84]. Cardiovascular death was defined as death due to new PE (for patients with DVT) or recurrent pulmonary embolism (for patients with PE), death due to an acute myocardial infarction or heart failure, sudden cardiac death, death due to fatal arrhythmia, death due to ischemic or hemorrhagic stroke, death due to cardiovascular procedures or hemorrhage, death due to ruptured aortic aneurysm or aortic dissection and death due to other cardiovascular causes [71,72]. Non cardiovascular deaths included death due to cancer or other cause different from cardiovascular and cancer, and did not included death of unknown or missed causes. Thus, to avoid an underestimation of the rate of MACE, all analyses concerning this outcome did not include patients who died of unknown/missed cause.

Acute limb ischemia was defined by a limb-threatening vascular insufficiency confirmed by hemodynamic or imaging and leads to an acute vascular intervention; while critical limb ischemia was defined as rest pain or tissue loss (ulcers or gangrene) for at least 14 days, supported by hemodynamic criteria of low ankle (< 50 mmHg) or toe (< 30 mmHg) pressures, or low transcutaneous oxygen values ($TcPO_2 < 30$ mmHg) [85,86].

Statistical analyses

Participants for whom, we did not succeed in getting news more than one year after their inclusion in the studies and before December 31, 2020, were considered lost to follow-up and excluded from our final analysis. Results are presented as frequency (percentage) for categorical variables, and mean \pm standard deviation (SD) or median (25th-75th percentiles) for continuous variables where applicable. Groups' comparisons used the Chi-square test, the Student *t*-test or equivalents where appropriate. We used the Aalen–Johansen estimator to evaluate the cumulative risk of cardiovascular events over time, considering death as competing events [87]. Apart from our main univariable and multivariable analyses, the rates of outcome events in two groups were compared using the log-rank test, after calculating the cumulative hazard according to the Kaplan–Meier life-table method. Otherwise, comparison between cumulative incidences of two groups was done using Gray's K-sample method [88]. To determine risk factors of MACE, and MALE, we used sub-distribution hazards models, also known as Fine-Gray models, taking into consideration deaths competing risk events. We first conducted univariable analyses to study the association between potential predictors and to select variables for the multivariable analyses.

To be included in multivariable models, each variable had to meet the following conditions: p-value < 0.15 in univariable analysis, and frequency of at least 3% in the study population. Biological data with missing values had to be recorded in more than 90% the study population to be included in multivariable models. For categorical variables with more than two levels, they were included in multivariable analysis if at least one level meted the required conditions. Prior to the multivariable analysis, correlations were searched between some variables of interest, based on clinical relevance, and only the most prevalent variable with the lower number of missing values was included in the final multivariable model. Backward manual selection of variables was conducted for some analyses, if the initial multivariable model displayed no statistically significant result. Hazard ratios (HR) were always reported with the 95% confidence interval (CI).

In addition to our main analyses, we conducted subgroup analyses to determine risk factors of MACE and MALE in patients with unprovoked VTE and in patients with cancer associated VTE separately. All our analysis (univariable and multivariable) were complete-cases analysis, excluding all missing data, and without any imputation. Data were compiled in an Excel file (Microsoft Excel version 2016), and analyzed using the statistical software R, version 3.6.3. All tests were two-sided and a p-value < 0.05 was used to characterize statistically significant results.

Results

Characteristic of the study population

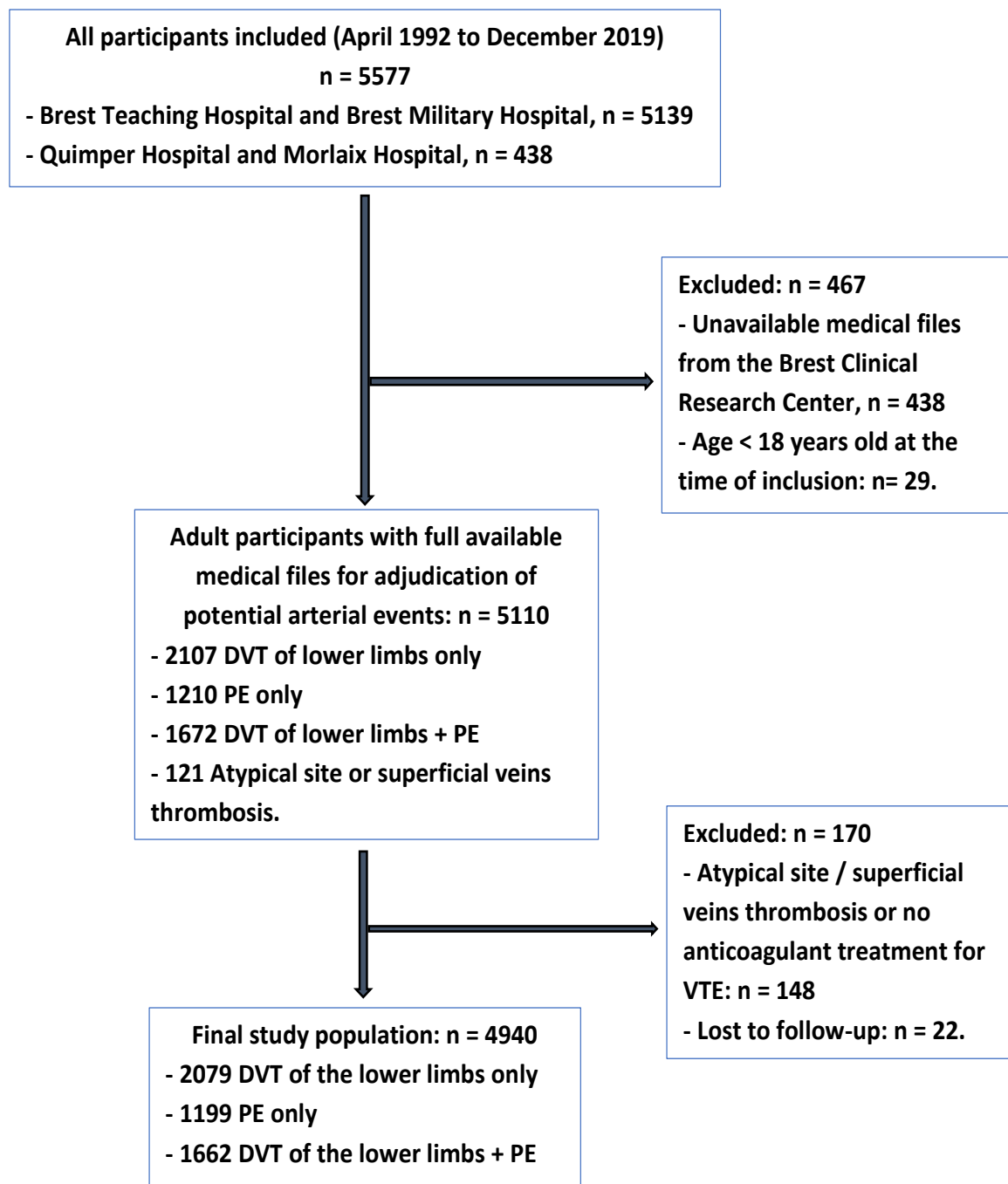
A total of 4940 patients with VTE (2316 men, 46.9%) were finally included in this study, after excluding those with atypical site or superficial venous thrombosis, those lost to follow-up, and patients who did not receive anticoagulant treatment for the index VTE (**Figure 1**). At least one transient provoking factor of VTE was identified in 1784 patients (36.1%), 914 patients had cancer associated VTE (18.5%), and 2242 patients had unprovoked VTE (45.4%). The median follow-up (IQR) was 64 months (34.0 - 113.0) in the overall study population; 80.5 months (52.0 - 137.0) in patients with transient provoking factors of VTE, 30 months (5.0 - 63.8) in patients with cancer and 68 months (42.0 - 110.0) in patients with unprovoked VTE. The majority of patients symptomatic PE (33.6% with associated DVT and 24.6% without associated DVT), and 42.1% had isolated DVT. The mean age at the diagnosis of VTE was 61.58 years in the overall study population, and 2434 patients (49.3%) were older than 65 years.

The most frequent known cardiovascular risk factor was hypertension (32.2%), and past history of symptomatic atherosclerosis was reported in 14.2% of participants. Vitamin K antagonist (VKA) was the most frequent anticoagulant agent used for VTE treatment (61.4%), direct oral anticoagulant therapy (DOAC) was used in 443 patients (9.0%). The median duration of anticoagulant therapy (IQR) was 6 months (3.0 - 41.0) and the majority of the study population (35.4%) was treated for more than 12 months; 2.5% of participants were diagnosed with VTE while already being on anticoagulant therapy, and 14.1% were on ongoing antiplatelet therapy at the time of VTE diagnosis. Characteristic of the study population stratified by provoking factors of VTE are presented in **Table 1**.

Incidence of MACE and MALE in the study population

During the median follow-up of 64 months (34.0 - 113.0), MACE occurred in 701 participants (17.3%), and MALE occurred in 83 participants (1.7%). The median time (IQR) from the diagnosis of VTE to arterial events was 31.0 months (7.0 - 72.0) for MACE, and 50.0 months (24.0 - 92.5) for MALE. While comparing the risk of arterial events in participants without considering death as competing events, the risk of MACE and MALE were significantly higher in participants with cancer and in participants with unprovoked VTE compared to participants with transient provoking factors of VTE. Results from the Aalen–Johansen estimation of cumulative incidence of MACE and MALE over time are respectively shown on **Figure 2** and on **Figure 3**. The cumulative risks of MACE and MALE stratified by

type of VTE regarding to the provoking factor are presented on **Figure 4**, with p-values of the Log-rank Test.



- VTE: venous thromboembolism, DVT: deep venous thrombosis, PE: pulmonary embolism.

Figure 1: Flow chart of participants.

Table 1: Characteristics of the study population stratified by provoking factors of VTE

	Overall (N = 4940)	Transient risk factor, N = 1784	Cancer, N = 914	No risk factor (unprovoked), N = 2242	p-values
General characteristics					
Gender (male)	2316 (46.9)	642 (36.0)	513 (56.1)	1161 (51.8)	<0.001
Mean age at VTE diagnosis (years) ± SD	61.58 ± 18.61	53.80 ± 20.31	69.31 ± 11.88	64.63 ± 17.21	<0.001
Age categories					<0.001
- < 50 years, n (%)	1338 (27.1)	789 (44.2)	56 (6.1)	493 (22.0)	
- 50 to 65 years, n (%)	1168 (23.6)	374 (21.0)	266 (29.1)	528 (23.6)	
- > 65 years, n (%)	2434 (49.3)	621 (34.8)	592 (64.8)	1221 (54.5)	
Personal past history of VTE, n (%)	1088/4912 (22.1)	299/1779 (16.8)	197/907 (21.7)	592/2226 (26.6)	<0.001
Blood group					0.001
- O group, n (%)	1155/3573 (32.3)	418/1398 (29.9)	261/684 (38.2)	476/1491 (31.9)	
- Non-O group, n (%)	2418/3573 (67.7)	980/1398 (70.1)	423/684 (61.8)	1015/1491 (68.1)	
Median follow-up, months	64.0 (34.0 - 113.0)	80.5 (52.0 - 137.0)	30.0 (5.0 - 63.8)	68.0 (42.0 - 110.0)	<0.001
Mean follow-up, years	6.3	7.7	3.3	6.4	<0.001
Characteristics of VTE					
Type of VTE					<0.001
- DVT only, n (%)	2079 (42.1)	889 (49.8)	342 (37.4)	848 (37.8)	
- PE only, n (%)	1199 (24.3)	402 (22.5)	222 (24.3)	575 (25.6)	
- DVT and PE, n (%)	1662 (33.6)	493 (27.6)	350 (38.3)	819 (36.5)	
Location of DVT (only)					<0.001
- Distal DVT, n (%)	743/2078 (35.8)	390/889 (43.9)	90/342 (26.3)	263/847 (31.1)	
- Proximal DVT, n (%)	1335/2078 (64.2)	499/889 (56.1)	252/342 (73.7)	584/847 (68.9)	
Type of VTE according to provoking factors					<0.001
- Transient factors associated VTE, n (%)	1784 (36.1)	1784 (100.0)	0 (0.0)	0 (0.0)	
- Cancer associated VTE, n (%)	914 (18.5)	0 (0.0)	914 (100.0)	0 (0.0)	
- Unprovoked VTE, n (%)	2242 (45.4)	0 (0.0)	0 (0.0)	2242 (100.0)	
Provoking risk factors of VTE					
Cancer characteristics					
Metastatic cancer at VTE diagnosis, n (%)	231/669 (34.5)	/	231/669 (34.5)	/	/
Active cancer at VTE diagnosis, n (%)	721/913 (79.0)	/	721/913 (79.0)	/	/
Ongoing chemotherapy, n (%)	356/766 (46.5)	/	356/766 (46.5)	/	/
Ongoing radiotherapy, n (%)	267/772 (34.6)	/	267/772 (34.6)	/	/
Transient provoking risk factors					
Surgery with general anesthesia >30 minutes within past 3 months, n (%)	624 (12.6)	472 (26.5)	152 (16.6)	0 (0.0)	<0.001
Leg injury associated with reduced mobility for at least three days, within past 3 months, n (%)	157 (3.2)	155 (8.7)	2 (0.2)	0 (0.0)	<0.001

Acute illness with hospitalization for at least three days, within past 3 months, n (%)	1056/4865 (21.7)	767/1779 (43.1)	289/895 (32.3)	0/2191 (0.0)	<0.001
Ongoing pregnancy, n (%)	70/2624 (2.7)	69/1142 (6.0)	1/401 (0.2)	0/1081 (0.0)	<0.001
Post-partum period within past 3 months, n (%)	59/2618 (2.3)	58/1138 (5.1)	1/399 (0.3)	0/1081 (0.0)	<0.001
Ongoing Estrogen contraceptive treatment, n (%)	386/2583 (14.9)	381/1133 (33.6)	5/397 (1.3)	0/1053 (0.0)	<0.001
Ongoing menopause substitutive hormonal therapy, n (%)	116/2618 (4.4)	105/1140 (9.2)	11/399 (2.8)	0/1079 (0.0)	<0.001
Ongoing hormonal therapy for assisted reproduction, n (%)	15/2156 (0.7)	5/994 (0.5)	10/337 (3.0)	0/825 (0.0)	<0.001
Classic cardiovascular risk factors*, n (%)					
Tobacco use, n (%)					<0.001
- Never, n (%)	2108/4089 (51.6)	836/1572 (53.2)	337/748 (45.1)	935/1769 (52.9)	
- Past, n (%)	1287/4089 (31.5)	417/1572 (26.5)	353/748 (47.2)	517/1769 (29.2)	
- Current, n (%)	694/4089 (17.0)	319/1572 (20.3)	58/748 (7.8)	317/1769 (17.9)	
Diabetes, n (%)	222 (4.5)	69 (3.9)	57 (6.2)	96 (4.3)	0.016
Hypertension, n (%)	1590 (32.2)	498 (27.9)	362 (39.6)	730 (32.6)	<0.001
Dyslipidemia, n (%)	754 (15.3)	216 (12.1)	161 (17.6)	377 (16.8)	<0.001
Obesity, n (%)	870/4347 (20.0)	323/1630 (19.8)	139/800 (17.4)	408/1917 (21.3)	0.066
Past history of symptomatic atherosclerosis, n (%)	701 (14.2)	224 (12.6)	156 (17.1)	321 (14.3)	0.006
Biological characteristics at VTE diagnosis					
Anemia, n (%)	1065/2938 (36.2)	358/922 (38.8)	366/659 (55.5)	341/1357 (25.1)	<0.001
Platelet count < 150 / μ L, n (%)	318/2883 (11.0)	70/904 (7.7)	122/644 (18.9)	126/1335 (9.4)	<0.001
Creatinine clearance (mL/min)					<0.001
- \geq 60	1331/1932 (68.9)	475/626 (75.9)	305/481 (63.4)	551/825 (66.8)	
- < 60	601/1932 (31.1)	151/626 (24.1)	176/481 (36.6)	274/825 (33.2)	
Heterozygous Factor V Leiden	576/4466 (12.9)	221/1665 (13.3)	68/785 (8.7)	287/2016 (14.2)	<0.001
Heterozygous G20210A prothrombin gene variant	273/4460 (6.1)	112/1662 (6.7)	31/784 (4.0)	130/2014 (6.5)	0.019
Homozygous Factor V Leiden, n (%)	24/4466 (0.5)	9/1665 (0.5)	3/785 (0.4)	12/2016 (0.6)	0.786
Homozygous G20210A prothrombin gene variant, n (%)	4/4460 (0.1)	1/1662 (0.1)	2/784 (0.3)	1/2014 (0.0)	0.233
Heterozygous Factor V Leiden and Heterozygous G20210A prothrombin gene variant, n (%)	30/4460 (0.7)	12/1662 (0.7)	1/784 (0.1)	17/2014 (0.8)	0.109
Others comorbidities at the diagnosis of VTE					
Chronic heart failure, n (%)	301 (6.1)	82 (4.6)	56 (6.1)	163 (7.3)	0.002
Chronic respiratory failure, n (%)	259 (5.2)	82 (4.6)	43 (4.7)	134 (6.0)	0.107
Atrial fibrillation, n (%)	218/4124 (5.3)	74/1564 (4.7)	56/774 (7.2)	88/1786 (4.9)	0.026
Treatment of VTE					
Type of anticoagulant treatment*					<0.001
- Vitamin K antagonists only, n (%)	3033 (61.4)	1114 (62.4)	398 (43.5)	1521 (67.8)	
- Direct oral anticoagulants only, n (%)	443 (9.0)	169 (9.5)	46 (5.0)	228 (10.2)	

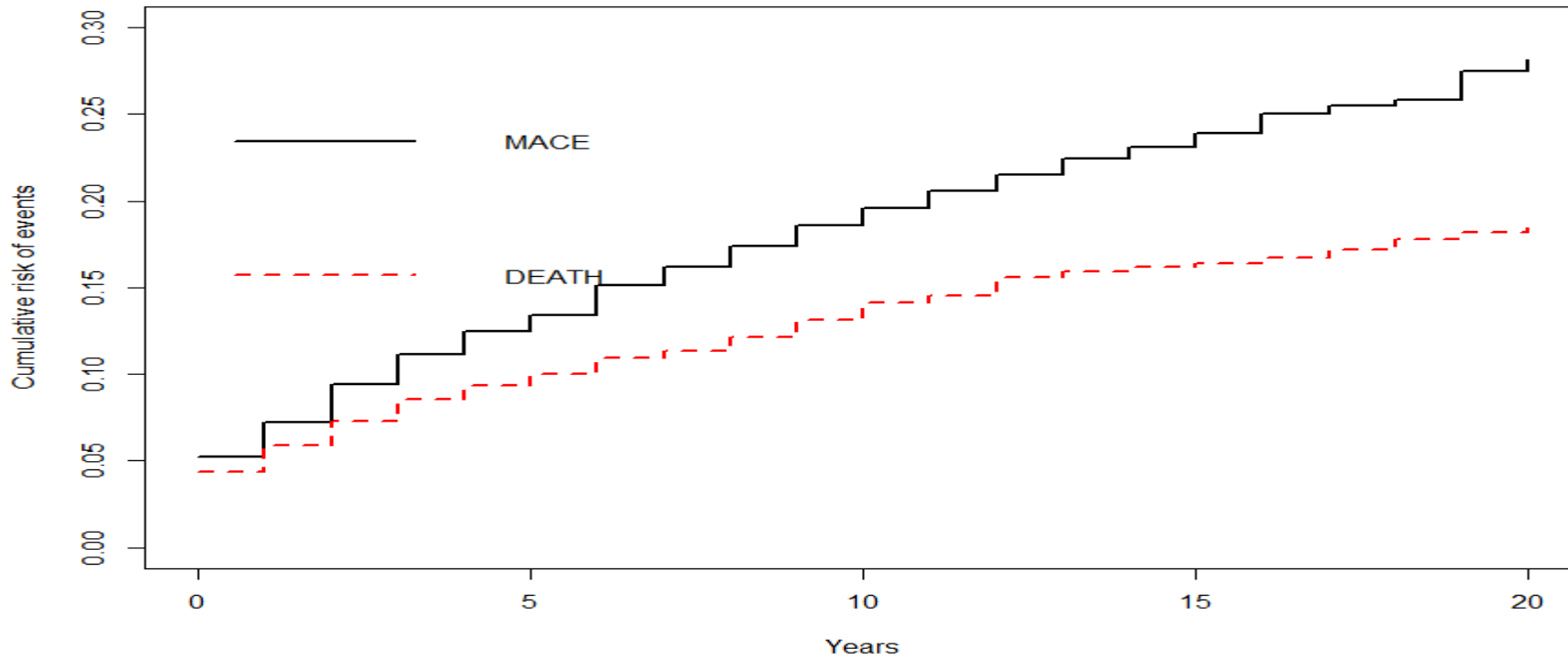
- Low-molecular-weight heparin only, n (%)	576 (11.7)	176 (9.9)	290 (31.7)	110 (4.9)	
- Others**	888 (18.0)	325 (18.2)	180 (19.7)	383 (17.1)	
Duration of anticoagulant therapy					<0.001
Median, months	6.0 (3.0 - 41.0)	6.0 (3.0 - 26.0)	6.0 (1.0 - 29.0)	6.0 (3.0 - 60.0)	
- 0 to 3] months	1492/4656 (32.0)	592/1709 (34.6)	327/852 (38.4)	573/2095 (27.4)	
- 3 to 12] months	1518/4656 (32.6)	613/1709 (35.9)	223/852 (26.2)	682/2095 (32.6)	
- Over 12 months	1646/4656 (35.4)	504/1709 (29.5)	302/852 (35.4)	840/2095 (40.1)	
Thrombolytic therapy, n (%)	38/4136 (0.9)	11/1570 (0.7)	6/773 (0.8)	21/1793 (1.2)	0.325
Vena cava filter, n (%)	208/4664 (4.5)	71/1731 (4.1)	56/862 (6.5)	81/2071 (3.9)	0.006
Concomitant treatment at the time of VTE diagnosis					
Anticoagulant therapy, n (%)	101/4090 (2.5)	29/1553 (1.9)	43/775 (5.5)	29/1762 (1.6)	<0.001
Antiplatelet therapy, n (%)	580/4125 (14.1)	189/1564 (12.1)	135/777 (17.4)	256/1784 (14.3)	0.002
Statins therapy, n (%)	450/4127 (10.9)	139/1566 (8.9)	105/776 (13.5)	206/1785 (11.5)	0.002

DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, SD: standard deviation

*Type of anticoagulant treatment after acute phase of VTE.

Others**: any other injectable treatment or multiple treatment (injectable treatment relayed by any oral treatment or conversely).

For variables presented as count (percentages), no denominator is shown when there is no missing data.

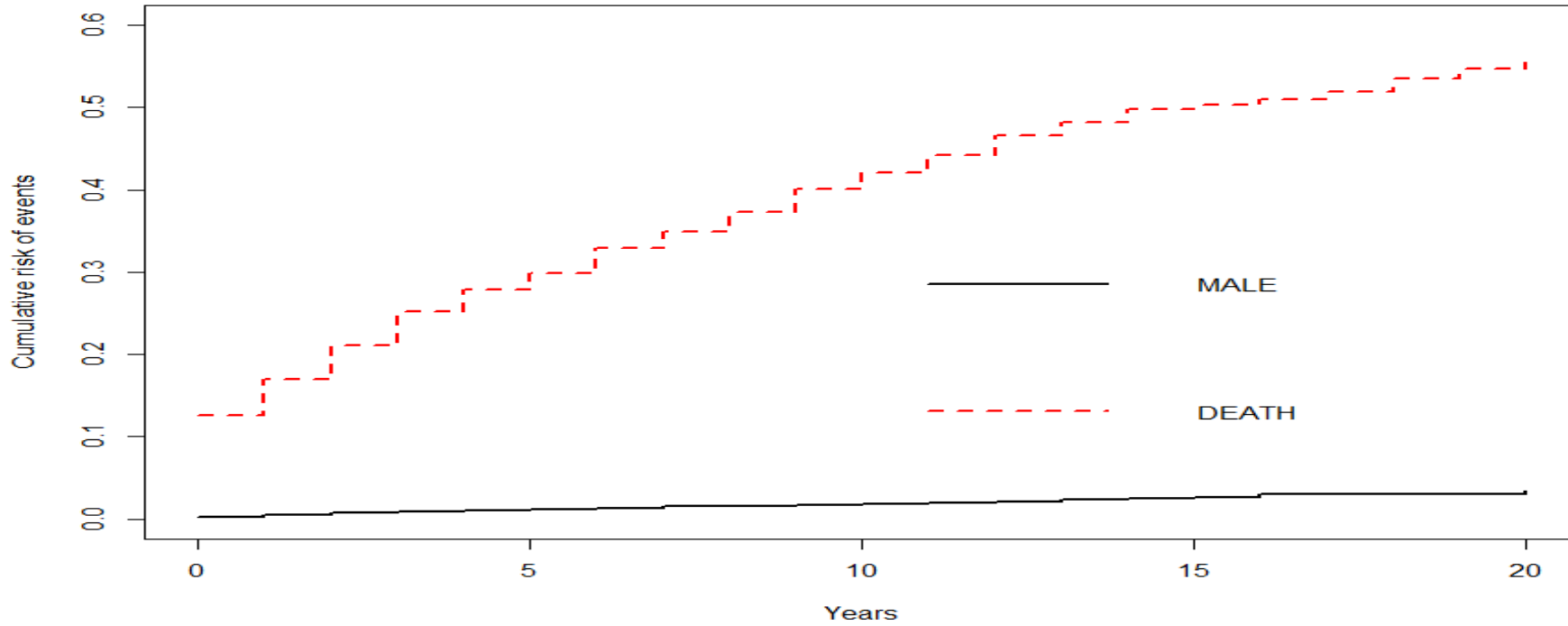


Number at Risk				
4061	2678	956	375	83

- MACE: major adverse cardiovascular event

Note: Death presented are death in patients who did not have MACE.

Figure 2: Aalen–Johansen estimation of cumulative incidence of MACE over time after venous thromboembolism diagnosis.

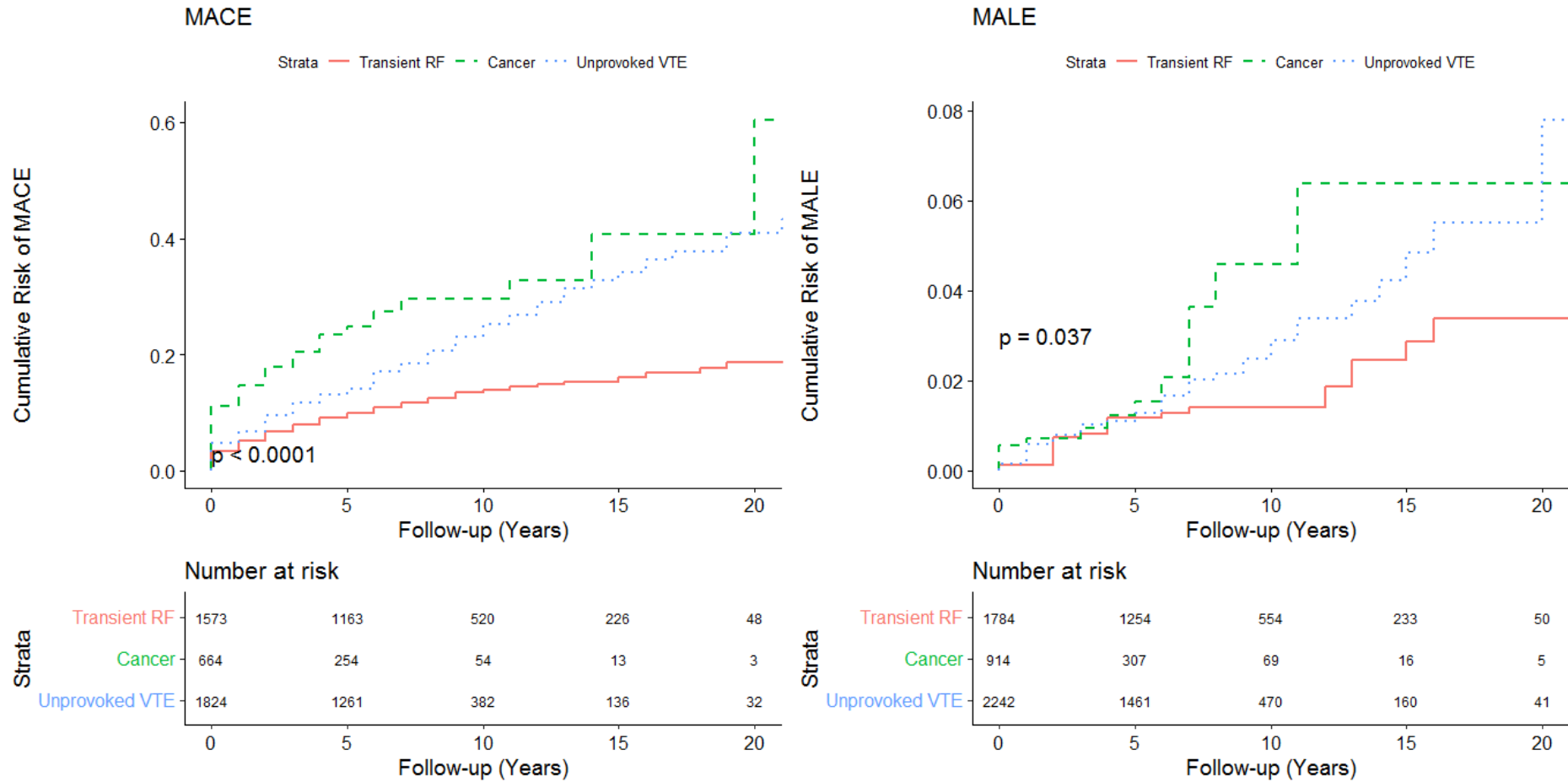


Number at Risk				
4940	3022	1093	409	96

- MALE: major adverse limb event

Note: Death presented are death in patients who did not have MALE.

Figure 3: Aalen–Johansen estimation of cumulative incidence of MALE over time after venous thromboembolism diagnosis.



- MACE: major adverse cardiovascular event, MALE: major adverse limb event, VTE: venous thromboembolism, RF: risk factor

Figure 4: Cumulative risks of MACE and MALE stratified by type of VTE regarding to the provoking factors.

The annual incidence rate of MACE in the overall study population was 2.35 per 100 patient-years, 1.55 per 100 patient-years in patients with transient provoking factors of VTE, 5.18 per 100 patient-years in patients with cancers, and 2.40 per 100 patient-years in patients with unprovoked VTE. The most frequent component of MACE was cardiovascular death, which occurred in 395/701 participants (56.3); non-fatal acute coronary syndrome occurred in 103/701 patients (14.7), and non-fatal stroke in 203/701 patients (29.0).

The annual incidence of MALE in the overall study population was 0.27 per 100 patient-years, 0.19 per 100 patient-years in patients with transient risk factors, 0.47 per 100 patient-years in patients with cancer and 0.30 per 100 patient-years in patients with unprovoked VTE. The most frequent component of MALE was acute limb ischemia, which occurred in 34/83 participants (41.0%).

The mortality rate was 6.20 per 100 patient-years in the overall study population, as 1920 participants died during follow-up (38.9%); the median survival in the overall study population was 14 years. Cardiovascular deaths represented 22.2% of all deaths (426 participants) and was the most frequent cause of death among known causes (44.0%). The distribution of MACE and MALE, as well as causes of death stratified by provoking factors of VTE, are given in details in **Table 2**. The Kaplan-Meier survival curves of the three groups of patients are presented on **Figure 5**.

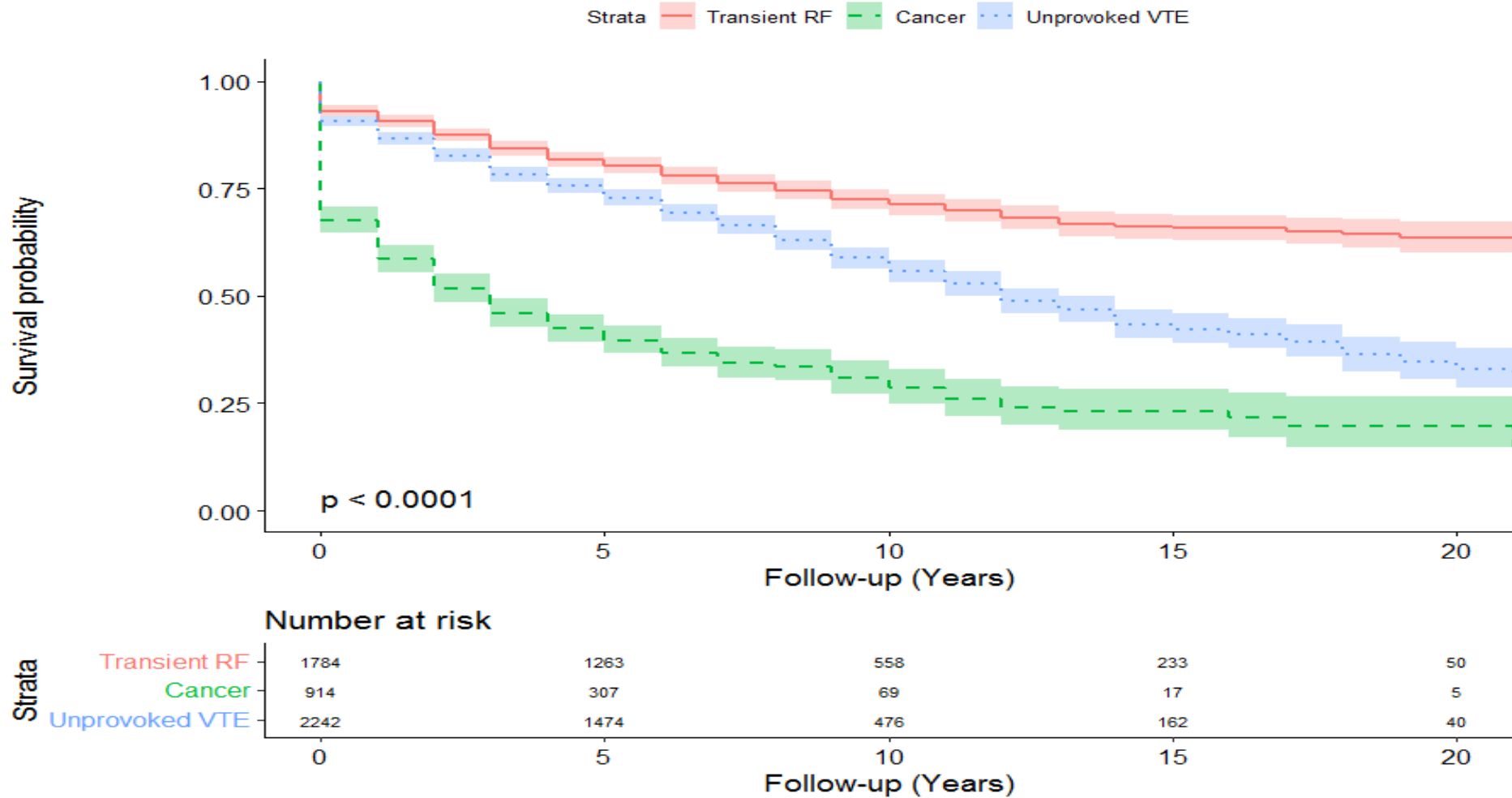
Table 2: Rates of cardiovascular events and causes of death stratified by provoking factor of VTE

	Overall, N = 4940	Transient risk factor, N = 1784	Cancer, N = 914	No risk factor (unprovoked), N = 2242	P-values
Cardiovascular events					
MACE, n (%)	701/4061 (17.3)	192/1573 (12.2)	147/664 (22.1)	362/1824 (19.8)	<0.001
Incidence of MACE per 100 patient-years (95% CI)	2.35 (2.18 - 2.53)	1.55 (1.33 - 1.80)	5.18 (4.39 - 6.06)	2.40 (2.17 - 2.65)	<0.001
Mean time from VTE to MACE, years	3.5	3.4	1.9	4.3	<0.001
Median time from VTE to MACE, months	31.0 (7.0 - 72.0)	33.0 (9.8 - 66.5)	12.0 (1.0 - 39.0)	38.0 (14.3 - 84.8)	<0.001
Type of MACE					0.043
- Non-fatal acute coronary syndrome, n (%)	103/701 (14.7)	37/192 (19.3)	12/147 (8.2)	54/362 (14.9)	
- Non-fatal stroke, n (%)	203/701 (29.0)	58/192 (30.2)	41/147 (27.9)	104/362 (28.7)	
- Cardiovascular death, n (%)	395/701 (56.3)	97/192 (50.5)	94/147 (63.9)	204/362 (56.4)	

MALE in overall follow-up, n (%)	83 (1.7)	26 (1.5)	14 (1.5)	43 (1.9)	0.490
Incidence of MALE (per 100 patient-years)	0.27 (0.21 - 0.33)	0.19 (0.13 - 0.38)	0.47 (0.26 - 0.79)	0.30 (0.22 - 0.41)	0.037
Mean time from VTE to MALE, years	5.2	5.3	3.7	5.6	0.450
Median time from VTE to MALE, months	50.0 (24.0 - 92.5)	42.0 (33.0 - 82.5)	47.0 (3.5 - 83.0)	66.0 (22.0 - 106.5)	0.451
Type of MALE					0.906
- Acute limb ischemia, n (%)	34/83 (41.0)	10/26 (38.5)	6/14 (42.9)	18/43 (41.9)	
- Critical limb ischemia, n (%)	9/83 (10.8)	2/26 (7.7)	2/14 (14.3)	5/43 (11.6)	
- Percutaneous revascularization, n (%)	18/83 (21.7)	7/26 (26.9)	1/14 (7.1)	10/43 (23.3)	
- Bypass ³ revascularization, n (%)	9/83 (10.8)	3/26 (11.5)	2/14 (14.3)	4/43 (9.3)	
- Limb amputation, n (%)	13/83 (15.7)	4/26 (15.4)	3/14 (21.4)	6/43 (14.0)	
Causes of deaths					
All-causes death, n (%)	1920 (38.9)	466 (26.1)	579 (63.3)	875 (39.0)	<0.001
Mortality rate (per 100 patient-years)	6.20 (5.93 - 6.47)	3.41 (3.11 - 3.73)	19.48 (18.07 - 20.95)	6.10 (5.71 - 6.50)	<0.001
Median survival, years	14 (13 - 16)	Not reached	3 (2 - 3)	12 (12 - 14)	<0.001
Specific causes of Death					<0.001
- Cardiovascular, n (%)	426/1920 (22.2)	112/466 (24.0)	97/579 (16.8)	217/875 (24.8)	
- Cancer, n (%)	252/1920 (13.1)	30/466 (6.4)	161/579 (27.8)	61/875 (7.0)	
- Non cardiovascular / non cancer, n (%)	290/1920 (15.1)	97/466 (20.8)	56/579 (9.7)	137/875 (15.7)	
- Unknown/unobserved, n (%)	952/1920 (49.6)	227/466 (48.7)	265/579 (45.8)	460/875 (52.6)	

VTE: venous thromboembolism, MACE: major adverse cardiovascular events, MALE: major adverse limbs event

For variables presented as count (percentages), no denominator is shown when there is no missing data.



- VTE: venous thromboembolism, RF: risk factor

Figure 5: Kaplan-Meier survival curves of participants stratified by type of VTE regarding to the provoking factors.

Risk factors of MACE in the study population

The results of univariable and multivariable analyses carried out to determine risk factors of MACE in the overall study population are presented in **Table 3**. After adjustment for all elected variables and considering death as competing events, the following factors were significantly associated with increased risk of MACE in multivariable analysis: age of 50 to 65 years (vs. age < 50 years, HR: 2.00, 95% CI: 1.38 - 2.91, $p < 0.001$), age > 65 years (vs. age < 50 years, HR 4.85, 95% CI: 3.35 - 7.02, $p < 0.001$), PE associated with DVT (vs isolated DVT, HR: 1.25, 95% CI: 1.02 - 1.55, $p = 0.035$), unprovoked VTE (vs. transient risk factor associated VTE, HR: 1.29, 95% CI: 1.04 - 1.59, $p = 0.019$), current tobacco use (vs. no tobacco use, HR: 1.45, 95% CI: 1.07 - 1.98, $p = 0.017$), hypertension (HR: 1.61, 95% CI: 1.30 - 1.98, $p < 0.001$), past history of symptomatic atherosclerosis (HR: 1.52, 95% CI: 1.17 - 1.98, $p = 0.002$), chronic heart failure (HR: 1.71, 95% CI: 1.21 - 2.42, $p = 0.002$), atrial fibrillation (HR: 1.55, 95% CI: 1.15 - 2.08, $p < 0.001$), and a vena cava filter insertion (HR: 1.46, 95% CI: 1.03 - 2.08, $p = 0.036$). Cancer-associated VTE was associated with significantly increased risk of MACE, as compared to transient provoking factors in univariable analysis, however, in multivariable analysis this association became non statistically significant (HR: 1.21; 95% CI: 0.92 - 1.59, $p = 0.180$). Regarding the influence of anticoagulation modalities, patients treated with DOAC had a reduced risk of MACE by almost 50% as compared to patients treated with VKA (adjusted HR: 0.53, 95% CI: 0.33 - 0.85, $p = 0.008$), and the risk of MACE was significantly lower in patients treated for 3 to 12 months and in patients treated for over 12 months, as compared to patients treated for 0 to 3 months in univariable and multivariable analyses (**Table 3**).

Risk factors of MALE in the study population

The identified risk factors of MALE in multivariable analysis after adjustment for confounding variables were: age of 50 to 65 years (vs. age < 50 years, HR: 3.49, 95% CI: 1.26 - 9.65, $p = 0.016$) and atrial fibrillation (HR: 2.37, 95% CI: 1.15 - 4.89, $p = 0.020$).

If the risk of MALE appeared to be higher in patients with cancer and in patients with unprovoked VTE, as compared to patients with transient provoking factors, while using a simple Log-rank Test (**Figure 4**), there was no statistically significant relationship between risk of MALE and type of VTE according to provoking factors of VTE, while considering death as competing events, as in all our main analyses (HRs for MALE were 1.34, 95% CI: 0.69 - 2.56, $p = 0.380$; and 1.43, 95% CI: 0.87 - 2.33, $p = 0.150$ in cancer patients and patients with unprovoked VTE, respectively). The results of univariable and multivariable analyses conducted to determine risk factors of MALE in the overall study population are presented in

Table 4. There was no statistically significant relationship between type of anticoagulant treatment, as well as duration of anticoagulant treatment and the risk of MALE (**Table 4**).

Table 3: Risk factors of acute MACE, univariable and multivariable analyses

	Univariable analysis		Multivariable analysis	
	Unadjusted HR (95% CI)	p-Value	Adjusted HR (95% CI)	p-Value
General characteristics				
Gender (male)	1.13 (0.97 - 1.30)	0.110	1.03 (0.84 - 1.25)	0.780
Age				
- < 50 years	-	ref	-	ref
- 50 to 65 years	2.58 (1.92 - 3.48)	< 0.001	2.00 (1.38 - 2.91)	< 0.001
- > 65 years	7.25 (5.65 - 9.30)	< 0.001	4.85 (3.35 - 7.02)	< 0.001
Personal past history of VTE	1.25 (1.06 - 1.48)	0.007	1.02 (0.83 - 1.25)	0.880
Blood group				
- O group	-	ref		
- Non-O group	0.77 (0.64 - 0.93)	0.005		
Characteristics of VTE				
Type of VTE				
- DVT only	-	ref	-	ref
- PE only	1.14 (0.94 - 1.40)	0.900	0.99 (0.77 - 1.26)	0.940
- DVT and PE	1.73 (1.47 - 2.05)	< 0.001	1.25 (1.02 - 1.55)	0.035
Location of DVT (only)				
- Distal DVT	-	ref		
- Proximal DVT	1.21 (0.93 - 1.59)	0.150		
Type of VTE according to provoking factors				
- Transient factors associated VTE	-	ref	-	ref
- Cancer associated VTE	2.23 (1.80 - 2.76)	< 0.001	1.21 (0.92 - 1.59)	0.180
- Unprovoked VTE	1.79 (1.50 - 2.13)	< 0.001	1.29 (1.04 - 1.59)	0.019
Others classic cardiovascular risk factors				
Tobacco use				
- Never,	-	ref	-	ref
- Past	1.32 (1.10 - 1.57)	0.002	1.15 (0.93 - 1.42)	0.210
- Current	0.64 (0.49 - 0.83)	< 0.001	1.45 (1.07 - 1.98)	0.017
Diabetes	1.57 (1.17 - 2.12)	0.002	0.91 (0.64 - 1.28)	0.590
Hypertension	2.32 (2.01 - 2.69)	< 0.001	1.61 (1.30 - 1.98)	< 0.001
Dyslipidemia	1.31 (1.09 - 1.57)	0.004	0.77 (0.57 - 1.05)	0.094
Obesity	0.93 (0.76 - 1.13)	0.440		
Past history of symptomatic atherosclerosis	2.88 (2.44 - 3.41)	< 0.001	1.52 (1.17 - 1.98)	0.002
Biological characteristics at VTE diagnosis				
Anemia	1.35 (1.11 - 1.64)	0.002		
Platelet count < 150 / μ L	1.31 (0.99 - 1.73)	0.062		
Creatinine clearance (mL/min)				
- \geq 60	-	ref		
- < 60	2.35 (1.85 - 2.99)	< 0.001		
Minor thrombophilia				
Heterozygous Factor V Leiden	0.67 (0.52 - 0.86)	0.001	0.78 (0.58 - 1.05)	0.110
Heterozygous G20210A prothrombin gene variant	0.98 (0.72 - 1.33)	0.890		
Homozygous Factor V Leiden	0.45 (0.11 - 1.79)	0.260		
Homozygous G20210A prothrombin gene variant	-	-		

Heterozygous Factor V Leiden and Heterozygous G20210A prothrombin gene variant	0.96 (0.42 - 2.19)	0.920		
Others comorbidities at the diagnosis of VTE				
Chronic heart failure	4.10 (3.27 - 5.14)	< 0.001	1.71 (1.21 - 2.42)	0.002
Chronic respiratory failure	2.73 (2.09 - 3.55)	< 0.001	1.31 (0.89 - 1.91)	0.170
Atrial fibrillation	3.33 (2.57 - 4.30)	< 0.001	1.55 (1.15 - 2.08)	<0.001
Treatment of VTE				
Type of anticoagulant treatment*				
- Vitamin K antagonists only	-	ref	-	ref
- Direct oral anticoagulants only	0.39 (0.25 - 0.60)	< 0.001	0.53 (0.33 - 0.85)	0.008
- Low-molecular-weight heparin only	1.29 (1.03 - 1.61)	0.028	1.09 (0.82 - 1.46)	0.550
- Others**	1.09 (0.89 - 1.31)	0.400	0.91 (0.72 - 1.14)	0.430
Duration of anticoagulant therapy				
- 0 to 3] months	-	ref	-	ref
- 3 to 12] months	0.70 (0.59 - 0.84)	< 0.001	0.70 (0.55 - 0.88)	<0.001
- Over 12 months	0.77 (0.65 - 0.93)	0.005	0.58 (0.46 - 0.74)	<0.001
Thrombolytic therapy	1.19 (0.57 - 2.45)	0.650		
Vena cava filter	2.26 (1.71 - 3.00)	< 0.001	1.46 (1.03 - 2.08)	0.036
Concomitant treatment at VTE diagnosis				
Curative anticoagulant therapy	2.80 (1.89 - 4.15)	< 0.001		
Antiplatelet therapy	2.52 (2.08 - 3.04)	< 0.001	1.11 (0.86 - 1.44)	0.440
Statins therapy	1.45 (1.14 - 1.83)	0.002	1.08 (0.74 - 1.57)	0.690

DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, HR: hazard ratio, CI: confidence interval. *Type of anticoagulant treatment after acute phase of VTE. Others**: any other injectable treatment or multiple treatment (injectable treatment relayed by any oral treatment or conversely)

Table 4: Risk factors of acute MALE, univariable and multivariable analyses

	Univariable analysis		Multivariable analysis	
	Unadjusted HR (95% CI)	p-Value	Adjusted HR (95% CI)	p-Value
General characteristics				
Gender (male)	2.00 (1.29 - 3.12)	0.002	1.27 (0.77 - 2.09)	0.340
Age				
- < 50 years	-	ref	-	ref
- 50 to 65 years	3.57 (1.65 - 7.71)	0.001	3.49 (1.26 - 9.65)	0.016
- > 65 years	3.65 (1.80 - 7.41)	< 0.001	2.52 (0.85 - 7.44)	0.093
Personal past history of VTE	0.90 (0.53 - 1.53)	0.690		
Blood group				
- O group	-	ref		
- Non-O group	0.48 (0.29 - 0.79)	0.004		
Characteristics of VTE				
Type of VTE				
- DVT only	-	ref		
- PE only	0.65 (0.34 - 1.27)	0.210		
- DVT and PE	1.40 (0.88 - 2.23)	0.150		
Location of DVT (only)				
- Distal DVT	-	ref		

- Proximal DVT	1.16 (0.56 - 2.36)	0.690		
Type of VTE according to provoking factors				
- Transient factors associated VTE, n (%)	-	ref		
- Cancer associated VTE, n (%)	1.34 (0.69 - 2.56)	0.380		
- Unprovoked VTE, n (%)	1.43 (0.87 - 2.33)	0.150		
Others classic cardiovascular risk factors				
Tobacco use				
- Never	-	ref	-	ref
- Past	2.21 (1.31 - 3.72)	0.002	1.63 (0.99 - 2.67)	0.054
- Current	1.03 (0.48 - 2.20)	0.950	1.78 (0.84 - 3.79)	0.130
Diabetes	2.78 (1.40 - 5.50)	0.003	1.49 (0.69 - 3.21)	0.310
Hypertension	1.98 (1.30 - 3.02)	0.001	1.25 (0.70 - 2.23)	0.450
Dyslipidemia	1.24 (0.71 - 2.17)	0.450		
Obesity	1.11 (0.64 - 1.93)	0.710		
Past history of symptomatic atherosclerosis	3.48 (2.22 - 5.46)	< 0.001	1.51 (0.68 - 3.33)	0.310
Biological characteristics at VTE diagnosis				
Anemia	0.77 (0.41 - 1.43)	0.400		
Platelet count < 150 / μ L	1.68 (0.79 - 3.58)	0.180		
Creatinine clearance (mL/min)				
- \geq 60	-	ref		
- < 60	1.64 (0.84 - 3.20)	0.150		
Heterozygous Factor V Leiden	0.32 (0.12 - 0.88)	0.026	0.35 (0.11 - 1.08)	0.068
Heterozygous G20210A prothrombin gene variant	0.99 (0.40 - 2.45)	0.990		
Homozygous Factor V Leiden	1.65 (0.22 - 12.30)	0.620		
Homozygous G20210A prothrombin gene variant	-	-		
Heterozygous Factor V Leiden and Heterozygous G20210A prothrombin gene variant	-	-		
Others comorbidities at the diagnosis of VTE				
Chronic heart failure	0.64 (0.20 - 2.05)	0.460		
Chronic respiratory failure	1.83 (0.84 - 3.96)	0.130	0.44 (0.11 - 1.86)	0.270
Atrial fibrillation	3.84 (2.02 - 7.30)	< 0.001	2.37 (1.15 - 4.89)	0.020
Treatment of VTE				
Type of anticoagulant treatment*				
- Vitamin K antagonists only	-	ref	-	ref
- Direct oral anticoagulants only	0.19 (0.03 - 1.41)	0.100	0.27 (0.04 - 2.11)	0.210
- Low-molecular-weight heparin only	0.86 (0.39 - 1.89)	0.720	0.81 (0.36 - 1.78)	0.590
- Others**	1.34 (0.79 - 2.26)	0.280	1.30 (0.72 - 2.33)	0.370
Duration of anticoagulant therapy				
- 0 to 3] months	-	ref		
- 3 to 12] months	0.97 (0.55 - 1.72)	0.920		
- Over 12 months	1.29 (0.75 - 2.24)	0.350		
Thrombolytic therapy				
Vena cava filter	0.52 (0.13 - 2.12)	0.370		
Concomitant treatment at VTE diagnosis				
Curative anticoagulant therapy	1.40 (0.34 - 5.78)	0.640		
Antiplatelet therapy	4.05 (2.47 - 6.64)	< 0.001	1.81 (0.89 - 3.94)	0.130
Statins therapy	1.59 (0.81 - 3.10)	0.180		

DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, HR: hazard ratio, CI: confidence interval. *Type of anticoagulant treatment after acute phase of VTE. Others**: any other injectable treatment or multiple treatment (injectable treatment relayed by any oral treatment or conversely)

Subgroups analyses.

In patients with unprovoked VTE, after adjustment for other confounding variables in multivariable analysis, the risk factors of MACE were: age > 65 years (vs. age < 50 years, HR: 3.81, 95% CI: 2.26 - 6.40, $p < 0.001$), PE associated with DVT (vs. isolated DVT, HR: 1.43, 95% CI: 1.03 - 1.96, $p = 0.031$), hypertension (HR: 1.39, 95% CI: 1.02 - 1.89, $p = 0.039$), past history of symptomatic atherosclerosis (HR: 1.69, 95% CI: 1.09 - 2.62, $p = 0.019$), and the placement of a vena cava filter (HR: 2.15, 95% CI: 1.30 - 3.55, $p = 0.027$) (**supplementary table 1**). The risk of MACE in this subgroup of patients was significantly lower in those treated with DOAC, as compared to patients treated with VKA (adjusted HR: 0.50, 95% CI: 0.25 - 0.96, $p = 0.039$); however, there was no significant relationship between the risk of MACE and duration of anticoagulant treatment. The only identified risk factor of MALE in patients with unprovoked VTE in multivariable analysis was ongoing antiplatelet treatment at diagnosis of VTE (HR: 3.74, 95% CI: 1.79 - 7.80, $p < 0.001$) (**supplementary table 2**).

In patients with cancer associated VTE, after adjustment for others confounders in multivariable analysis, the risk factors of MACE were: hypertension (HR: 1.85, 95% CI: 1.29 - 2.66, $p < 0.001$) and atrial fibrillation (HR: 1.96, 95% CI: 1.11 - 3.47, $p = 0.021$) (**Supplementary table 3**). The risk of MACE was reduced for patients with Heterozygous Factor V Leiden mutation (HR: 0.27, 95% CI: 0.08 - 0.84, $p = 0.025$) and for patients with dyslipidemia (HR: 0.57, 95% CI: 0.34 - 0.92, $p = 0.023$). There was also a relationship between duration of anticoagulant treatment and risk of MACE in patients with cancer, as adjusted HR for patients treated for 3 to 12 months (compared to patients treated for 0 to 3 months) was 0.47 (95% CI: 0.31 - 0.74, $p = 0.001$), and the adjusted HR for patients treated for over 12 months (compared to patients treated for 0 to 3 months) was 0.41 (95% CI: 0.25 - 0.64, $p < 0.001$). However, there was no significant relationship between risk of MACE and type of anticoagulant treatment in this subgroup of patients (**Supplementary table 3**). The identified risk factors of MALE in patients with cancer associated VTE in multivariable analysis were: male gender (HR: 9.88, 95% CI: 1.30 - 74.80, $p = 0.027$), PE associated with DVT (vs. isolated DVT, HR: 5.10, 95% CI: 1.14 - 22.80, $p = 0.033$), and atrial fibrillation (HR: 4.18, 95% CI: 1.14 - 15.40, $p = 0.031$) (**supplementary table 4**). There was no statistically significant relationship between risk of MALE and anticoagulant therapy (duration or type) neither in patients with unprovoked VTE nor in patients with cancer associated VTE.

Supplementary table 1: Risk factors of MACE in patients with unprovoked VTE

	Univariable analysis		Multivariable analysis	
	Unadjusted HR (95% CI)	p-Value	Adjusted HR (95% CI)	p-Value
General characteristics				
Gender (male)	0.70 (0.57 - 0.86)	< 0.001	0.87 (0.64 - 1.16)	0.330
Age				
- < 50 years	-	ref	-	ref
- 50 to 65 years	1.85 (1.22 - 2.80)	0.003	1.69 (0.99 - 2.89)	0.530
- > 65 years	5.31 (3.78 - 7.47)	< 0.001	3.81 (2.26 - 6.40)	< 0.001
Personal past history of VTE	1.06 (0.85 - 1.32)	0.620		
Blood group				
- O group	-	ref		
- Non-O group	0.83 (0.63 - 1.09)	0.180		
Characteristics of VTE				
Type of VTE				
- DVT only	-	ref	-	ref
- PE only	1.44 (1.08 - 1.90)	0.012	1.28 (0.89 - 1.83)	0.170
- DVT and PE	2.01 (1.58 - 2.56)	< 0.001	1.43 (1.03 - 1.96)	0.031
Location of DVT (only)				
- Distal DVT	-	ref		
- Proximal DVT	1.10 (0.72 - 1.71)	0.650		
Others classic cardiovascular risk factors				
Tobacco use				
- Never,	-	ref	-	ref
- Past	0.95 (0.73 - 1.25)	0.760	1.02 (0.72 - 1.42)	0.330
- Current	0.60 (0.42 - 0.86)	0.006	1.46 (0.93 - 2.28)	0.099
Diabetes	1.51 (0.98 - 2.33)	0.062	1.03 (0.56 - 1.58)	0.830
Hypertension	1.89 (1.54 - 2.32)	< 0.001	1.39 (1.02 - 1.89)	0.039
Dyslipidemia	1.11 (0.86 - 1.44)	0.410		
Obesity	0.95 (0.73 - 1.24)	0.700		
Past history of symptomatic atherosclerosis	2.49 (1.94 - 3.20)	< 0.001	1.69 (1.09 - 2.62)	0.019
Biological characteristics at VTE diagnosis				
Anemia	1.45 (1.08 - 1.95)	0.012		
Platelet count < 150 / μ L	1.11 (0.72 - 1.72)	0.630		
Creatinine clearance (mL/min)				
- \geq 60	-	ref		
- < 60	2.75 (1.93 - 3.91)	< 0.001		
Minor thrombophilia				
Heterozygous Factor V Leiden	0.78 (0.57 - 1.06)	0.120	1.02 (0.67 - 1.53)	0.920
Heterozygous G20210A prothrombin gene variant	0.89 (0.59 - 1.35)	0.590		
Homozygous Factor V Leiden	0.94 (0.24 - 3.71)	0.930		
Homozygous G20210A prothrombin gene variant	-	-		
Heterozygous Factor V Leiden and Heterozygous G20210A prothrombin gene variant	1.37 (0.61 - 3.10)	0.450		
Others comorbidities at the diagnosis of VTE				
Chronic heart failure	3.84 (2.83 - 5.20)	< 0.001	1.58 (0.88 - 2.82)	0.130
Chronic respiratory failure	2.59 (1.77 - 3.79)	< 0.001	1.62 (0.93 - 2.80)	0.086
Atrial fibrillation	2.76 (1.86 - 4.08)	< 0.001	1.39 (0.87 - 2.23)	0.160
Treatment of VTE				
Type of anticoagulant treatment*				
- Vitamin K antagonists only	-	ref	-	ref

- Direct oral anticoagulants only	0.37 (0.20 - 0.68)	0.001	0.50 (0.25 - 0.96)	0.039
- Low-molecular-weight heparin only	1.15 (0.70 - 1.86)	0.580	1.09 (0.57 - 2.06)	0.800
- Others**	1.14 (0.88 - 1.48)	0.330	0.91 (0.65 - 1.27)	0.590
Duration of anticoagulant therapy				
- 0 to 3] months	-	ref	-	ref
- 3 to 12] months	0.80 (0.62 - 1.06)	0.120	0.78 (0.52 - 1.17)	0.230
- Over 12 months	0.82 (0.63 - 1.07)	0.150	0.68 (0.46 - 1.02)	0.061
Thrombolytic therapy	1.50 (0.63 - 3.58)	0.360		
Vena cava filter	2.50 (1.65 - 3.78)	< 0.001	2.15 (1.30 - 3.55)	0.027
Concomitant treatment at VTE diagnosis				
Curative anticoagulant therapy	2.20 (1.00 - 4.86)	0.050		
Antiplatelet therapy	2.20 (1.58 - 2.79)	< 0.001	1.09 (0.73 - 1.64)	0.670
Statins therapy	1.30 (0.92 - 1.83)	0.140	0.85 (0.57 - 1.26)	0.420

DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, HR: hazard ratio, CI: confidence interval. *Type of anticoagulant treatment after acute phase of VTE. Others**: any other injectable treatment or multiple treatment (injectable treatment relayed by any oral treatment or conversely)

Supplementary table 2: Risk factors of MALE in patients with unprovoked VTE

	Univariable analysis		Multivariable analysis	
	Unadjusted HR (95% CI)	p-Value	Adjusted HR (95% CI)	p-Value
General characteristics				
Gender (male)	1.16 (0.64 - 2.12)	0.620		
Age				
- < 50 years	-	ref	-	ref
- 50 to 65 years	2.55 (0.79 - 8.27)	0.120	2.27 (0.55 - 9.36)	0.260
- > 65 years	3.19 (1.12 - 9.12)	0.030	1.95 (0.48 - 7.86)	0.350
Personal past history of VTE	0.78 (0.38 - 1.57)	0.480		
Blood group				
- O group	-	ref		
- Non-O group	0.72 (0.36 - 1.46)	0.360		
Characteristics of VTE				
Type of VTE				
- DVT only	-	ref		
- PE only	0.61 (0.25 - 1.49)	0.280		
- DVT and PE	1.15 (0.60 - 2.22)	0.660		
Location of DVT (only)				
- Distal DVT	-	ref		
- Proximal DVT	1.43 (0.47 - 4.33)	0.530		
Others classic cardiovascular risk factors				
Tobacco use				
- Never	-	ref	-	ref
- Past	1.72 (0.83 - 3.56)	0.140	1.51 (0.71 - 3.21)	0.280
- Current	0.54 (0.15 - 1.90)	0.340	0.96 (0.253 - 3.71)	0.960
Diabetes	3.04 (1.21 - 7.62)	0.018	2.29 (0.84 - 6.17)	0.100
Hypertension	1.10 (0.59 - 2.04)	0.770		
Dyslipidemia	1.09 (0.50 - 2.35)	0.830		
Obesity	1.44 (0.69 - 2.99)	0.330		
Past history of symptomatic atherosclerosis	2.65 (1.38 - 5.09)	0.003	1.28 (0.41 - 3.93)	0.670
Biological characteristics at VTE diagnosis				

Anemia	1.20 (0.49 - 2.89)	0.680		
Platelet count < 150 / μ L	1.88 (0.64 - 5.54)	0.250		
Creatinine clearance (mL/min)				
- \geq 60	-	ref		
- < 60	1.60 (0.62 - 4.08)	0.330		
Heterozygous Factor V Leiden	0.42 (0.13 - 1.34)	0.140	0.46 (0.11 - 1.85)	0.280
Heterozygous G20210A prothrombin gene variant	0.34 (0.04 - 2.48)	0.290		
Homozygous Factor V Leiden	-	-		
Homozygous G20210A prothrombin gene variant	-	-		
Heterozygous Factor V Leiden and Heterozygous G20210A prothrombin gene variant	-	-		
Others comorbidities at the diagnosis of VTE				
Chronic heart failure	0.32 (0.04 - 2.32)	0.260		
Chronic respiratory failure	1.69 (0.60 - 4.68)	0.320	0.25 (0.03 - 1.81)	0.170
Atrial fibrillation	3.58 (1.41 - 9.11)	0.007	2.14 (0.67 - 6.82)	0.200
Treatment of VTE				
Type of anticoagulant treatment*				
- Vitamin K antagonists only	-	-		
- Direct oral anticoagulants only	-	-		
- Low-molecular-weight heparin only	-	-		
- Others**	-	-		
Duration of anticoagulant therapy				
- 0 to 3] months	-	ref		
- 3 to 12] months	0.98 (0.42 - 2.27)	0.970		
- Over 12 months	1.35 (0.61 - 2.95)	0.460		
Thrombolytic therapy	-	-		
Vena cava filter	1.09 (0.26 - 4.51)	0.910		
Concomitant treatment at VTE diagnosis				
Curative anticoagulant therapy	-	-		
Antiplatelet therapy	4.19 (2.08 - 8.44)	< 0.001	3.74 (1.79 - 7.80)	< 0.001
Statins therapy	1.47 (0.57 - 3.81)	0.420		

DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, HR: hazard ratio, CI: confidence interval. *Type of anticoagulant treatment after acute phase of VTE. Others**: any other injectable treatment or multiple treatment (injectable treatment relayed by any oral treatment or conversely)

Supplementary table 3: Risk factors of MACE in patients with cancer associated VTE

	Univariable analysis		Multivariable analysis	
	Unadjusted HR (95% CI)	p-Value	Adjusted HR (95% CI)	p-Value
General characteristics				
Gender (male)	1.26 (0.92 - 1.73)	0.160		
Age				
- < 50 years	-	ref		
- 50 to 65 years	1.25 (0.56 - 2.78)	0.580		
- > 65 years	1.71 (0.80 - 3.66)	0.170		
Personal past history of VTE	0.77 (0.51 - 1.16)	0.210		
Blood group				
- O group	-	ref		
- Non-O group	0.76 (0.53 - 1.09)	0.130		
Characteristics of VTE				

Type of VTE				
- DVT only	-	ref		
- PE only	0.79 (0.51 - 1.21)	0.280		
- DVT and PE	1.07 (0.75 - 1.51)	0.720		
Location of DVT (only)				
- Distal DVT	-	ref		
- Proximal DVT	0.83 (0.48 - 1.43)	0.500		
Others classic cardiovascular risk factors				
Tobacco use				
- Never,	-	ref	-	ref
- Past	1.47 (1.03 - 2.11)	0.034	1.30 (0.86 - 1.95)	0.200
- Current	1.05 (0.53 - 2.12)	0.880	0.91 (0.39 - 2.13)	0.840
Diabetes	0.67 (0.32 - 1.40)	0.280		
Hypertension	1.38 (1.01 - 1.88)	0.043	1.85 (1.29 - 2.66)	<0.001
Dyslipidemia	0.61 (0.38 - 0.96)	0.033	0.57 (0.34 - 0.92)	0.023
Obesity	0.75 (0.47 - 1.19)	0.220		
Past history of symptomatic atherosclerosis	1.59 (1.10 - 2.31)	0.014	1.19 (0.69 - 2.04)	0.530
Biological characteristics at VTE diagnosis				
Anemia	1.32 (0.89 - 1.93)	0.160		
Platelet count < 150 / μ L	1.34 (0.86 - 2.08)	0.190		
Creatinine clearance (mL/min)				
- \geq 60	-	ref		
- < 60	1.57 (1.02 - 2.43)	0.041		
Minor thrombophilia				
Heterozygous Factor V Leiden	0.36 (0.15 - 0.85)	0.020	0.27 (0.08 - 0.84)	0.025
Heterozygous G20210A prothrombin gene variant	1.42 (0.69 - 2.89)	0.330		
Homozygous Factor V Leiden	-	-		
Homozygous G20210A prothrombin gene variant	-	-		
Heterozygous Factor V Leiden and Heterozygous G20210A prothrombin gene variant	-	-		
Others comorbidities at the diagnosis of VTE				
Chronic heart failure	1.74 (0.88 - 3.44)	0.110	1.04 (0.40 - 2.69)	0.930
Chronic respiratory failure	1.98 (1.13 - 3.45)	0.017	1.48 (0.75 - 2.92)	0.260
Atrial fibrillation	2.19 (1.27 - 3.79)	0.004	1.96 (1.11 - 3.47)	0.021
Treatment of VTE				
Type of anticoagulant treatment*				
- Vitamin K antagonists only	-	ref	-	ref
- Direct oral anticoagulants only	0.25 (0.06 - 0.99)	0.050	0.17 (0.02 - 1.32)	0.099
- Low-molecular-weight heparin only	1.05 (0.74 - 1.49)	0.800	0.81 (0.51 - 1.25)	0.340
- Others**	1.00 (0.66 - 1.51)	0.990	0.98 (0.59 - 1.61)	0.940
Duration of anticoagulant therapy				
- 0 to 3] months	-	ref	-	ref
- 3 to 12] months	0.47 (0.32 - 0.71)	< 0.001	0.47 (0.31 - 0.74)	0.001
- Over 12 months	0.41 (0.29 - 0.59)	< 0.001	0.41 (0.27 - 0.61)	< 0.001
Thrombolytic therapy	0.87 (0.16 - 4.73)	0.880		
Vena cava filter	1.82 (1.09 - 3.04)	0.022	1.48 (0.74 - 2.93)	0.260
Concomitant treatment at VTE diagnosis				
Curative anticoagulant therapy	1.33 (0.67 - 2.63)	0.410		
Antiplatelet therapy	1.52 (1.03 - 2.26)	0.037	1.54 (0.98 - 2.39)	0.580
Statins therapy	0.72 (0.43 - 1.24)	0.240		

DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, HR: hazard ratio, CI: confidence interval. *Type of anticoagulant treatment after acute phase of VTE. Others**: any other injectable treatment or multiple treatment (injectable treatment relayed by any oral treatment or conversely)

Supplementary table 4: Risk factors of MALE in patients with cancer associated VTE

	Univariable analysis		Multivariable analysis	
	Unadjusted HR (95% CI)	p-Value	Adjusted HR (95% CI)	p-Value
General characteristics				
Gender (male)	11.20 (1.49 - 83.90)	0.019	9.88 (1.30 - 74.80)	0.027
Age				
- < 50 years	-	ref		
- 50 to 65 years	0.67 (0.07 - 5.93)	0.720		
- > 65 years	1.07 (0.15 - 7.56)	0.940		
Personal past history of VTE	0.57 (0.12 - 2.58)	0.470		
Blood group				
- O group	-	ref		
- Non-O group	0.29 (0.07 - 1.17)	0.082		
Characteristics of VTE				
Type of VTE				
- DVT only	-	ref	-	ref
- PE only	0.79 (0.07 - 8.71)	0.850	0.80 (0.07 - 8.80)	0.860
- DVT and PE	5.20 (1.17 - 23.15)	0.030	5.10 (1.14 - 22.80)	0.033
Location of DVT (only)				
- Distal DVT	-	ref		
- Proximal DVT	0.33 (0.02 - 5.72)	0.450		
Others classic cardiovascular risk factors				
Tobacco use				
- Never	-	ref	-	ref
- Past	3.81 (0.81 - 17.9)	0.090	2.26 (0.52 - 9.85)	0.280
- Current	2.96 (0.26 - 32.6)	0.370	3.74 (0.31 - 45.20)	0.300
Diabetes	2.61 (0.60 - 11.4)	0.200		
Hypertension	2.04 (0.71 - 5.85)	0.180		
Dyslipidemia	0.73 (0.17 - 3.23)	0.680		
Obesity	1.46 (0.40 - 5.26)	0.570		
Past history of symptomatic atherosclerosis	5.00 (1.77 - 14.10)	0.002	2.44 (0.60 - 9.85)	0.210
Biological characteristics at VTE diagnosis				
Anemia	0.59 (0.18 - 1.88)	0.370		
Platelet count < 150 / μ L	1.36 (0.38 - 4.82)	0.640		
Creatinine clearance (mL/min)				
- \geq 60	-	ref		
- < 60	2.02 (0.57 - 7.15)	0.280		
Heterozygous Factor V Leiden	-	-	0.46 (0.15 - 1.41)	0.170
Heterozygous G20210A prothrombin gene variant	-	-		
Homozygous Factor V Leiden	-	-		
Homozygous G20210A prothrombin gene variant	-	-		
Heterozygous Factor V Leiden and Heterozygous G20210A prothrombin gene variant	-	-		
Others comorbidities at the diagnosis of VTE				
Chronic heart failure	2.88 (0.64 - 12.9)	0.170		
Chronic respiratory failure	4.02 (0.90 - 17.9)	0.068	1.54 (0.24 - 9.92)	0.650
Atrial fibrillation	4.97 (1.33 - 18.5)	0.017	4.18 (1.14 - 15.40)	0.031
Treatment of VTE				
Type of anticoagulant treatment*				
- Vitamin K antagonists only	-	-		
- Direct oral anticoagulants only	-	-		

- Low-molecular-weight heparin only	-	-		
- Others**	-	-		
Duration of anticoagulant therapy				
- 0 to 3] months	-	ref		
- 3 to 12] months	1.12 (0.28 - 4.38)	0.870		
- Over 12 months	1.32 (0.38 - 4.58)	0.660		
Thrombolytic therapy	-	-		
Vena cava filter	-	-		
Concomitant treatment at VTE diagnosis				
Curative anticoagulant therapy	1.92 (0.24 - 15.10)	0.540		
Antiplatelet therapy	2.76 (0.81 - 9.34)	0.100	1.20 (0.26 - 5.39)	0.810
Statins therapy	1.41 (0.30 - 6.46)	0.660		

DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, HR: hazard ratio, CI: confidence interval. *Type of anticoagulant treatment after acute phase of VTE. Others**: any other injectable treatment or multiple treatment (injectable treatment relayed by any oral treatment or conversely)

Discussion

The main findings from this large prospective cohort study on the risk factors of MACE and MALE in patients with VTE are the following: 1) consistent with other studies, the incidence of MACE and MALE was high in patients with VTE; 2) risk factors of MACE and MALE in patients with VTE included some traditional known major cardiovascular risk factors and comorbid conditions on the one hand, and other risk factors that are related to characteristic of VTE on the other hand; 3) the distribution of arterial cardiovascular complications among patients with VTE as well as risk factors of these complications were different depending on whether the VTE was associated with cancer or was considered to be unprovoked; 4) the anticoagulant therapy, both in terms of type of treatment and in terms of duration of treatment, may have influenced the risk of arterial cardiovascular complications after VTE.

Incidence of MACE and MALE

There are few studies that interested on the risk of MACE and MALE in VTE population, but in regard to the published ones in the current literature, the incidence of MACE and MALE in our study was similar to that previously reported in unselected patients with VTE, and in patients with unprovoked VTE or cancer associated VTE particularly [12,14,15]. For example, in a large retrospective cohort study by Chang *et al* in 2017, including 2154 patients with unprovoked VTE, MACE was reported in 24.3% of participants during an overall follow-up period of 10 years [15]. This proportion is slightly higher than the 19.8% found in patients with unprovoked VTE in our study. However, it is important to mention that even if MACE in our study included acute coronary syndrome, stroke and cardiovascular death, while in Chang

et al study', MACE included only acute coronary syndrome and stroke, our study is a prospective cohort where cardiovascular events were all blindly adjudicated events; in the study of Chang *et al*, cardiovascular events were retrospectively collected with MACE and MALE definitions' based on international classification of diseases (ICD) [15].

Risk factors of MACE and MALE

If several studies explored the risk factors of arterial cardiovascular events in general in the VTE population, with various definitions of composite arterial outcomes, only few studies focused on the risk factors of MACE and / or MALE in this population [14,15,26,40]. When adjusted on antithrombotic treatment characteristics, the risk factors of MACE / MALE identified in our study can be classified in three groups: (i) some traditional known major cardiovascular risk factors; (ii) comorbidities; and (iii) others risk factors that are related to characteristic of VTE. For risk factors of MACE, the first group included older age, current tobacco use (vs never used tobacco), hypertension, and past history of symptomatic atherosclerosis; the second group included chronic heart failure and atrial fibrillation; and the third group included unprovoked VTE (vs transient risk factors associated VTE) and PE associated with DVT (vs isolated DVT). For MALE, just two of these three groups were identified, the first group including older age and the second group including atrial fibrillation. If some of these risk factors of MACE and MALE in VTE population (especially from the group of major known cardiovascular risk factors as previous symptomatic atherosclerosis, older age, and hypertension) have been previously reported, our results are strengthened by the prospective design of the study, as majority of previous studies were retrospective cohort studies, and by the statistical models used that took into consideration the competing risk of death to MACE and MALE in contrast with previous studies [15,40].

The other risk factors from group 3 (characteristic of VTE as unprovoked VTE and PE associated with DVT) have also been previously reported as independent predictors of arterial cardiovascular events in a few studies, however, the limitations mention above were almost always present in these studies [11,40]. If relationships between the risk factors from group 2 (comorbidities as chronic heart failure and atrial fibrillation) and an increased risk of VTE or arterial events has been previously described in the general population, our study appears be the first to identify these factors as independent predictors of arterial events in patients with VTE [90–92]. Focusing on the risk factors of MACE/MALE related to the characteristics of unselected VTE, cancer-associated VTE and unprovoked VTE have been widely described as predictors of arterial events in the VTE population. However, in the majority of cases,

unprovoked VTE was compared to provoked VTE which included VTE related to transient provoking factors or cancer [11,14,29,40]. This had led to some confusion in the literature, for example, some authors reported contradictory results, with a higher risk of arterial events in patients with provoked VTE compared to those with unprovoked [14]. Considering VTE population in three groups (transient provoking factor related VTE, cancer-related VTE, and unprovoked VTE), we observed that patients with unprovoked VTE and cancer associated VTE may have a higher risk of arterial events than other patients in the VTE population. This was suggested in univariable analysis in our study considering death as competing events or not, even if only unprovoked VTE remained an independent predictor of MACE in multivariable analysis.

The particularities of patients with unprovoked or cancer-related VTE

The incidence of MACE in our study was 1.55 per 100 patient-years in patients with transient provoking factors of VTE as compared to 5.18 per 100 patient-years in patients with cancer-associated VTE, and 2.40 per 100 patient-years in those with unprovoked VTE. While the incidence of MALE was 0.19 per 100 patient-years in patients with transient risk factors as compared to 0.47 per 100 patient-years in patients with cancer related VTE and 0.30 per 100 patient-years in those with unprovoked VTE. Based on these results, we performed subgroup analyses to identified risk factors of MACE and MALE in patients with unprovoked VTE and in patients with cancer associated VTE separately. From these analyses, we can conclude as previously reported for some arterial cardiovascular events, that the risk factors of MACE and MALE differ between patients with cancer related VTE and those with unprovoked VTE [14,15,45]. Indeed, in patients with unprovoked VTE, the identified risk factors of MACE in multivariable analysis were: older age, PE associated with DVT (vs. isolated DVT), hypertension, past history of symptomatic atherosclerosis, and the placement of a vena cava filter; and the only identified risk factor of MALE in multivariable analysis was ongoing antiplatelet treatment at diagnosis of VTE. While in patients with cancer-associated VTE, the risk factors of MACE in multivariable analysis included hypertension and atrial fibrillation; and the identified risk factors of MALE in multivariable analysis were: male gender, PE associated with DVT (vs. isolated DVT), and atrial fibrillation. These findings have the potential to have clinical implications in the prevention of MACE and MALE in patients with VTE.

The influence of anticoagulant treatment

In the overall study population, we found that patients treated with DOAC had a reduced risk of MACE by almost 50% as compared to patients treated with VKA in multivariable

analysis and the risk of MACE was significantly lower in patients treated for longer duration. These results were not influenced by associated antiplatelet treatment nor statins use. In subgroup analyses, the risk of MACE in patients with unprovoked VTE, was significantly lower in patients treated with DOAC, as compared to patients treated with VKA; and this risk was significantly reduced with longer duration of anticoagulant treatment in patients with cancer-related VTE. These findings which had not been previously reported, may have important clinical implication for the determination of the optimal duration of anticoagulant treatment, particularly after an unprovoked VTE episode. While the parameters usually considered for anticoagulation duration after VTE are mainly based on risk factors of recurrent VTE after stopping treatment and on the risk factors of bleeding under anticoagulation, our findings highlight the need to consider associated risk factors of arterial complications in order to decide if anticoagulation should be prolonged or not after the usual initial 3 to 6 months duration, particularly in the setting of a first unprovoked VTE where the evidence for indefinite anticoagulation remains moderate [26,93,94]. However, further randomized clinical trials are needed in order to confirm this assumption.

Limitations and strength

The lack of sufficient biologicals data, to allow exploration of the role of biological characteristic as major thrombophilia on the risk of MACE and MALE is one of the major limitations of our study. The other flaws that deserve to be noticed are: first, related to the fact that our cohort event if prospective, was an open cohort with inclusion period of more than 20 years, therefore, the heterogeneity of follow-up duration and the change in treatment protocols of VTE, and prevention of arterial events, over years could have affect the number of our primary outcomes. Second, the incidence of cardiovascular death, therefore MACE could have been underestimated, due to the high proportion of death of unknown/missed causes. Third, there could be a surveillance bias and selective diagnosis of MACE and MALE, related to the fact that patients with cancer-associated or with unprovoked VTE were more likely to have a longer duration of follow-up and to continue anticoagulant treatment for longer period. Fourth, we only considered only baseline known cardiovascular risk factors present at the diagnosis of VTE; thus, we could have missed some of these conditions developed later in patients with long follow-up periods, and therefore omitted to control some potential confusion bias. Finally, we did not gather sufficient information on whether antiplatelet therapy was discontinued after VTE diagnosis or on the dose and type of antiplatelets or statins to included them in our analyses.

However, despite all these limitations, our study is one of the first large prospective cohort study with an important number of patients allowing to explore the risk factors of adjudicated MACE and MALE occurring after VTE. Moreover, we used rigorous and robust statistical methods, without neglecting the impact of death as competing events to MACE and MALE. Therefore, our results may have clinical implications for a better prevention of major arterial complications that occurred in some patients after VTE.

Conclusions

In this large prospective cohort study, we found that the risk factors of MACE and MALE in patients with VTE included some traditional known cardiovascular risk factors and comorbid conditions on the one hand, and other risk factors that are related to characteristics of VTE on the other hand. We also found that the distribution of arterial cardiovascular complications among patients with VTE usually at high risk of recurrence, as well as risk factors of these complications are different depending on if the VTE was associated with cancer or was considered to be unprovoked. This study also highlighted the potential role of anticoagulant therapy, particularly in terms of duration of treatment, on the risk of arterial cardiovascular events in patients with VTE.

List of Abbreviations:

CI: Confidence Interval

CUS: Compression Ultrasonography

DOAC: Direct Oral Anticoagulant

DVT: Deep Venous Thrombosis

HR: Hazard Ratio

IQR: Interquartile Range

LMWH: Low Molecule Weight Heparin

MACE: Major Adverse Cardiovascular Event

MALE: Major Adverse Limb Event

PE: Pulmonary Embolism

SD: Standard Deviation

VKA: Vitamin K Antagonist

VTE: Venous Thromboembolism

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Brest University Teaching Hospital (CCP-Ouest 6-390) with a last amendment approved on November 20, 2013 under reference number: EDITH II/RB 05.003. All participants signed a consent form.

Patient and Public Involvement: Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research

Availability of data and materials: The data that support the findings of this study are available from SRN or FC, upon reasonable request.

Competing interests: FC reported having received research grant support from Pfizer and fees for board memberships or symposia from Bayer and Astra Zeneca and having received travel support from Bayer, Daiichi Sankyo, Leo Pharma, InterMune, and Actelion. All other authors declare that they have no competing interests related to this study.

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Author’s contributions

Conception and design: SRN, FC, LB, RD, CDM, KL, ELM; acquisition of data: EP; Data analysis: SRN; Analysis and interpretation of data: SRN, FC, LB; Manuscript drafting: SRN; Manuscript revision: All authors; Approved the final version of the manuscript: All authors; Obtaining funding: FC. Administrative technical, and material support: FC, CT, RD, KL, RLM, ELM. Study supervision: FC; Full access to all the data of the study: FC, SRN; responsibility for all aspect of the study, reliability and freedom from bias of the data presented: All authors.

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B. Article de résultats 2 : facteurs de risque des ATE après MVTE non provoquée / liée au cancer

Cet article intitulé "*Risk factors of arterial thrombotic events after unprovoked venous thromboembolism, and after cancer associated venous thromboembolism: A prospective cohort study*" a été acceptée en Avril 2022 dans le journal "*Thrombosis Research*", et récemment publié. Référence : Noumegni et al. *Thrombosis Research*, 2022 Apr 29;214:93-105.

I. RESUME

Rationnel : La maladie veineuse thromboembolique (MVTE) non provoquée et la MTEV associée au cancer représentent la grande majorité des MTEV. L'association entre les événements thrombotiques ou ischémiques artériels (ATE) et la MTEV, en particulier lorsqu'ils sont d'origine inconnue, ou lorsqu'ils sont associés à un cancer a été établie dans la littérature. Toutefois, les facteurs de risque de ces événements artériels thrombotiques après MVTE restent inconnus.

Méthodologie : En utilisant des modèles de régression à risques spécifiques à la cause, avec le décès comme événement compétitif, la présente étude a déterminé les facteurs de risque d'ATE chez 2242 patients atteints de MVTE non provoquée et chez 914 patients atteints de MVTE associée au cancer, recrutés dans une cohorte prospective observationnelle multicentrique de patients atteints de MVTE confirmée dans ouest de la France ; ce qui faisait un total de 3156 participants. Les ATE comprenait au moins un des suivants : infarctus aigu du myocarde, accident vasculaire cérébral ischémique, ischémie aiguë de membre, ischémie aiguë du tractus digestif ou ischémie rénale aiguë.

Résultats : Au cours d'un suivi médian de 68 mois, 174 patients atteints de MVTE non provoquée ont développé une ATE (7,8%, incidence : 1,26 pour 100 patients-années) et 875 (39%) sont décédés. Parmi les patients atteints de MVTE associée au cancer, au cours d'un suivi médian de 30 mois, 57 ont développé une ATE (6,2 %, incidence : 1,98 pour 100 patients-années) et 579 (63 %) sont décédés. Après ajustement aux potentiels cofacteurs, les facteurs de risque identifiés d'ATE chez les patients atteints de MVTE non provoquée étaient l'âge > 65 ans (vs. < 50 ans, HR 2,59, IC à 95 % : 1,56 - 4,29), l'antécédent d'athérosclérose symptomatique (HR 2,11, IC à 95 % : 1,40 - 3,19) et un traitement par de l'héparine de bas poids moléculaire (vs. Traitement par antivitamine K, HR : 2,26, IC à 95 % : 1,13 - 4,52). Chez les patients atteints de MTE associée au cancer, les facteurs de risque identifiés d'ATE en analyse multivariée étaient : l'antécédent d'athérosclérose symptomatique (HR : 3,13, IC à 95 % : 1,72 - 5,67) et le traitement anticoagulant en cours au moment du diagnostic de MVTE (HR : 2,77, IC à 95 % : 1,07 - 7,22).

Conclusion : Le risque d'ATE après MVTE non provoquée et après MVTE associée à un cancer est déterminé par certains facteurs de risque cardiovasculaire classiques et est influencé par le traitement anticoagulant introduit pour la MVTE, ainsi que par la présence ou l'absence d'une anticoagulation en

cours au moment du diagnostic de MVTE. Ces résultats doivent être pris en compte pour une meilleure prévention des complications thrombotiques artérielles après une MVTE non provoquée ou associée au cancer.

Mots-clés : maladie thromboembolique veineuse non provoquée, cancer, événement thrombotique artériel, événements ischémiques artériels, étude de cohorte prospective.

II. ARTICLE COMPLET

Risk factors of arterial thrombotic events after unprovoked venous thromboembolism, and after cancer associated venous thromboembolism: A prospective cohort study

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Abstract

Background: Unprovoked venous thromboembolism (VTE) and VTE associated with malignancy represent the great majority of VTE. The association between arterial thrombotic or ischemic events (ATE) and VTE, particularly when they are of unknown origin, or when they are associated to cancer has been established. However, risk factors of arterial events in these populations remain unclear.

Methods: Using cause-specific hazard regression models with death as competing event, the current study determined risk factors of ATE in 2242 patients with unprovoked VTE and in 914 patients with cancer associated VTE recruited into a multi-center observational prospective cohort of patients with confirmed VTE in west of France; which made a total of 3156 participants. ATE included at least one of the following: acute myocardial infarction, acute ischemic stroke, acute limb ischemia, acute digestive tract ischemia or acute renal ischemia.

Results: During a median follow-up of 68 months, 174 patients with unprovoked VTE developed ATE (7.8%, incidence: 1.26 per 100 patient-years) and 875 (39%) died. Among patients with cancer associated VTE, during a median follow-up of 30 months, 57 developed ATE (6.2%, incidence: 1.98 per 100 patient-years), and 579 (63%) died. After adjustment for all cofounders, the identified risk factors of ATE in patients with unprovoked VTE were age > 65 years (vs. age < 50 years, HR 2.59, 95% CI: 1.56 - 4.29), past history of symptomatic atherosclerosis (HR 2.11, 95% CI: 1.40 - 3.19), and treatment with low molecule weight heparin (vs. treatment with vitamin K antagonists, HR: 2.26, 95% CI: 1.13 - 4.52). In patients with cancer associated VTE, the identified risk factors of ATE in multivariable analysis were: past history of symptomatic atherosclerosis (HR: 3.13, 95% CI: 1.72 - 5.67), and ongoing anticoagulant treatment at the diagnosis of VTE (HR: 2.77, 95% CI: 1.07 - 7.22).

Conclusion: The risk of ATE after unprovoked VTE and after cancer associated VTE, is determined by some classic cardiovascular risk factors and is influenced by anticoagulant treatment introduced for VTE, as well as the presence or absence of an ongoing anticoagulation at the diagnosis of VTE. These results should be considered for a better prevention of arterial thrombotic complications after unprovoked or cancer associated VTE.

Keywords: unprovoked venous thromboembolism, cancer, arterial thrombotic event, arterial ischemic events, prospective cohort study.

Introduction

Venous thromboembolism (VTE) of unknown origin, also known as unprovoked or idiopathic VTE, and VTE associated with malignancy represent the great majority of VTE [95]. Indeed, based on the current literature, in approximately 20 - 30% of patients with new cases of VTE, there is an underlying malignancy, whereas up to 25 - 50 % of incidents VTE are considered to be unprovoked, without a readily identifiable provoking factor [1,96,97]. Moreover, in patients with an apparently unprovoked VTE, 4 to 12% have an occult cancer which are usually diagnosed in the following months, during the treatment of VTE [98]. The association between increased risk of arterial thrombotic or ischemic events (ATE) and VTE, particularly when they are of unknown origin, or when they are associated to a malignancy has been established [12,13,28,40,42,45].

In fact, a meta-analysis conducted in 2010 by Becattini *et al* reported a pooled incidence rate ratio of 1.86 (95% confidence interval, CI: 1.19 to 2.89), while comparing the incidence of arterial cardiovascular events (including ischemic stroke and myocardial infarction) in patients with unprovoked VTE and in patients with provoked VTE [13]. A more recent meta-analysis conducted by Noumegni *et al* in 2021 reported a pooled incidence rate ratio of 1.32 (95 % CI: 1.08 - 1.61), comparing the incidence of all arterial events in patients with VTE and in controls without VTE; and a pooled incidence rate ratio of 2.26 (95% CI: 1.45 - 3.49), comparing the incidence of all arterial events in patients with unprovoked VTE and in patients with provoked VTE. While the comparison of the incidence of acute coronary syndrome and the incidence of stroke/transient ischemic attack between these two later groups of patients led to respective pooled incidence rate ratio of 2.07 (95% CI: 1.04 - 4.09) and 1.85 (95% CI: 1.60 - 2.14) [12]. As in the general population, patients with cancer associated VTE have also been shown to have significant increased risk of arterial thrombotic complications than other VTE patients, and cancer has even been reported as an independent risk factor of ATE in patients with VTE by several population-base study and by a recent meta-analysis [14,17,37,42].

Based on the above, we can notice that patients with unprovoked VTE and patients with cancer associated VTE should be considered as patients at high risk of arterial thrombosis as well as it is widely recognized that they are at high risk of VTE recurrence [99]. Several studies tried to determine the risk factors of some arterial thrombotic or ischemic complications in patients with VTE, sometime, considering cancer or unprovoked character of VTE as a potential predictor [14,37,42]. However, data on the risk factors of ATE after unprovoked VTE, and after cancer associated VTE, are still lacking. We therefore aimed to determine from a large prospective cohort study, the risk factors of ATE after unprovoked VTE and after cancer

associated VTE. We hypothesized that after unprovoked VTE or cancer associated VTE, the risk factors of ATE may include some specific risk factors, not known in the overall VTE population and in the general population.

Methods

Study design

This is a prospective cohort study, which participants are from a large multicenter hospital-based observational case-control and prospective cohort. The setting has been previously described [89,100]. The Ethics Committee of Brest University Hospital approved the study protocol (CCP-Ouest 6-390). Administrative approvals were also obtained from authorities of the Brest University Teaching Hospital and all others participants hospitals. Between April 1992 and December 2019, patients were informed about the different aspects of the study and were included only after providing a signed informed consent form.

Specific study population

This study was limited to patients with unprovoked VTE, and patients with cancer associated VTE. Unprovoked VTE was defined as VTE without cancer or major transient provoking factor including: surgery with general anesthesia >30 minutes, leg fracture or leg injury with plaster cast, acute illness with hospitalization for at least three days, ongoing pregnancy or delivery, ongoing estrogen contraceptive treatment, ongoing menopause substitutive hormonal therapy, or hormonal therapy for assisted reproduction, all within the past three months. Cancer associated VTE was defined as any VTE diagnosed in a participant with known past or ongoing cancer. All participants had an objective diagnosis of VTE (DVT of lower limb or PE). Symptomatic DVT of lower limbs was diagnosed based on non-compression of deep vein using a real-time B mode compression ultrasonography (CUS) [78]. Symptomatic PE was confirmed based on: (i) a positive computed tomography pulmonary angiography showing a central filling defect outlined by contrast material or a complete occlusion in a segmental or more proximal pulmonary artery; (ii) or a pulmonary angiography with an intraluminal filling defect or a sharp cut-off in a vessel of at least 2 mm in diameter; (iii) or a ventilation perfusion lung scan indicating a high probability for PE((using Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria); (iiii) or a high clinical probability associated to a proximal DVT on CUS [79].

Data collection

A standardized questionnaire was used at the inclusion for data collection on general characteristics (gender, age, blood group when available, personal past history of VTE), characteristics of VTE (type, location, provoking factor when present), classic cardiovascular risk factors (tobacco use, diabetes, hypertension, dyslipidemia, obesity, past history of symptomatic atherosclerosis), comorbid conditions (chronic heart failure, chronic respiratory failure, atrial fibrillation), concomitant treatment at VTE diagnosis (antiplatelet, statins, anticoagulant therapy), available biological data (full blood count, creatinine concentration), and type of treatment initiated for VTE. Results of factor V Leiden mutation, and prothrombin gene 20210A mutation check-up, were also further reported when available.

Past history of symptomatic atherosclerosis was defined as a self-reported and file confirmation of history of either myocardial infarction, stroke, or symptomatic peripheral artery disease of lower limbs. Tobacco use was classified as never, former, or current; diabetes, hypertension and dyslipidemia were defined by the presence of these diseases among known medical conditions in participants' files at inclusion, or by the presence of respective specific medications in patient's treatment. Height and weight were self-reported except for patients who could be weighted. Body mass index (BMI) was then calculated and obesity was defined for values ≥ 30.0 kg/m² [81]. Creatinine clearance was calculated using the Cockcroft-Gault formula with the measurement closer to the date of inclusion [82].

Management of VTE and follow-up

The management of VTE was done for all participants, and in all recruiting centers according to updated recommendations for good clinical practices, however, there was no standardization of treatment protocols among different centers. After inclusion, patients were instructed to return for follow-up visits at 3, 6, and 12 months. Further follow-ups were scheduled annually and could be done during a physical consultation at the clinical research center of Brest University Teaching Hospital, or by phone call. Participants who did not presented them self for consultation and did not respond to phone call, were sent a letter by postal mail. Participants for whom, we did not succeed in getting news more than one year after their inclusion in the study and until December 31, 2020, were consider lost to follow-up and not included in our final analysis. For patients who did not stopped anticoagulant treatment at the last follow-up, the duration of anticoagulant treatment considered in this study, was the duration from the beginning of the treatment until the last follow-up date. For those who temporally stopped anticoagulant treatment, the duration considered was the duration of the

initial anticoagulant therapy. The follow-up period was defined as time between the inclusion date and the last contact visit date, or the date of death.

Definition of clinical endpoints

The primary endpoint of our study was composite symptomatic arterial thrombotic event (ATE) including at least one of the following: acute myocardial infarction (AMI), or ischemic stroke, or acute limb ischemia, or acute digestive tract ischemia, or acute renal ischemia. Only the first event to occurred was considered, and all cases of ATE were adjudicated by an independent adjudication committee. Secondary endpoint was all causes death.

For adjudication purposes, AMI was defined by the presence of suspicious chest pain with at least two among of the following criteria: i) A rise of cardiac troponin (cTn) values with at least one value above the 99th percentile upper reference limit (URL); ii) New ischemic ECG changes iii) Development of pathological Q waves, iv) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; v) Identification of a coronary thrombus by intracoronary imaging. Ischemic stroke was defined by a new focal neurologic deficit, with signs or symptoms lasting more than 24 hours associated with compatible vascular ischemic abnormalities on computerized tomography or Magnetic Resonance Imaging. When hemorrhagic complication occurred as a consequence of ischemic stroke, the stroke was considered to be ischemic with hemorrhagic transformation and not hemorrhagic stroke.

Acute limb ischemia was defined by a limb-threatening vascular insufficiency confirmed by limb hemodynamics or imaging, that led to an acute vascular intervention [85]. Acute digestive tract ischemia and acute renal ischemia were defined by the presence of suspicious clinical signs or symptoms associated to imaging confirmation. In our study, cardiovascular death was defined as death due to new or recurrent PE, death due to an acute AMI, death due to heart failure, sudden cardiac death, death due to fatal arrhythmia, death due to ischemic or hemorrhagic stroke, death due to cardiovascular procedures or hemorrhage, death due to ruptured aortic aneurysm or aortic dissection and death due to other cardiovascular causes [71,72]. Non cardiovascular deaths were all death due to others causes, and did not included death of unknown or missed causes (unobserved deaths).

Statistical analysis

Data were analyzed using the statistical software R, version 3.6.3. Results are presented as frequency (percentage) for categorical variables, and mean \pm standard deviation (SD) or median (25th-75th percentiles) for continuous variables when necessary. Groups' comparisons

used the Chi-square test for categorical variables, and the Student *t*-test or equivalents for continue variables. We used the Aalen–Johansen estimator to evaluate the cumulative risk of ATE over time, considering death as competing events [87]. Apart from our main univariate and multivariate analyses, the rates of ATE in two groups were compared using the log-rank test, after calculating the cumulative hazard according to the Kaplan–Meier life-table method. Otherwise, comparison between cumulative incidences of ATE between two groups was done using Gray’s K-sample method [88]. To determine risk factors of ATE, we first conducted univariable analyses using cause-specific hazard regression models with death as competing event, for each independent variable. Prior to the multivariable analyses, we also search for correlations between some variables of interest, based on clinical relevance.

We further conducted multivariable analyses for the primary outcome, including in multivariable models, all variables with a *p*-value < 0.15 in univariable analysis and frequency of at least 3%. Eligible biological variables with missing values were included in the initial multivariable models only if they were recorded in more than 90% the study population. For categorical variables with more than two levels, they were included in multivariable analysis if at least one level meted the required conditions. To consider the potential impact of anticoagulant therapy on the risk of ATE, we analyzed treatment in participants who received only one family of anticoagulant after acute phase of VTE. Each initial multivariable model was reduced to a most parsimonious model using a manual backward selection method based on *p*-values, which was progressively reported as well as hazard ratio (HR). All analyses to determine risk factors of ATE were conducted in patients with unprovoked VTE and in patients with cancer associated VTE separately, and were complete-cases analysis excluding missing data. HR were reported with their 95% confidence interval (CI), and for all analyses, we used two-sided tests, with *p*-values < 0.05 characterizing statistically significant results.

Results

Baseline characteristics of participants

Of the 3156 participants finally included in this study, 2242 (71%) had unprovoked VTE and 914 (29%) had cancer associated VTE.

Among participants with unprovoked VTE, 1081 (48.2%) were women and the mean age was 64.63 ± 17.21 years, with 54.5% of participants being aged more than 65 years old. DVT and PE were concomitantly present in 819 participants (36.6%), while 37.8% of participants had isolated DVT and 25.6% of participants had isolated PE. The median follow-up was 68 months (interquartile range, IQR: 42.0 - 110.0) and the median survival was 12 years

(IQR: 12 - 14). Hypertension was the most frequent cardiovascular risk factors (32.6% of participants). The great majority of patients who received only one family anticoagulant after acute phase of VTE were treated with vitamin K antagonists (VKA) (81.8%), the median duration of anticoagulant therapy was 6 months (IQR: 3.0 - 60.0) and 40.1% of participants were treated for more than 12 months. Characteristics of the participants with unprovoked VTE stratified by ages categories are presented in **Table 1**.

Among participants with cancer associated VTE, 401 (43.9%) were women and the mean age was 69.31 ± 11.88 years, with 64.8% of participants being aged more than 65 years old. DVT and PE were concomitantly present in 350 participants (38.3%), while 37.4% of participants had DVT only and 24.3% of participants had isolated PE. The median follow-up was 30 months (IQR: 5.0 - 63.8) and the median survival was 3 years (IQR: 2 - 3). Hypertension was the most frequent cardiovascular risk factors (39.6% of participants). The great majority of patients who received only one family anticoagulant after acute phase of VTE were treated with VKA (54.2%), the median duration of anticoagulant therapy was 6 months (IQR: 1.0 - 29.0) and 35.4% of participants were treated for more than 12 months. The characteristics of participants with cancer associated VTE stratified by ages categories are presented in **Table 2**.

Table 1: Characteristic of the participants with unprovoked VTE stratified by ages categories.

	Overall (n = 2242)	Age: < 50 years N = 493	Age: 50 to 65 years N = 528	Age: > 65 years N = 1221
General characteristics and type of VTE				
Gender (female)	1081 (48.2)	140 (28.4)	171 (32.4)	770 (63.1)
Mean age at VTE diagnosis (years) ± SD	64.63 ± 17.21	38.93 ± 7.79	58.05 ± 4.66	77.85 ± 7.02
Age categories				
- < 50 years, n (%)	493 (22.0)	493 (100.0)	0 (0.0)	0 (0.0)
- 50 to 65 years, n (%)	528 (23.6)	0 (0.0)	528 (100.0)	0 (0.0)
- > 65 years, n (%)	1221 (54.5)	0 (0.0)	0 (0.0)	1221 (100.0)
Personal past history of VTE, n (%)	592/2226 (26.6)	105/488 (21.5)	158/526 (30.0)	329/1212 (27.1)
Blood group				
- O group, n (%)	476/1491 (31.9)	94/363 (25.9)	114/413 (27.6)	268/715 (37.5)
- Non-O group, n (%)	1015/1491 (68.1)	269/363 (74.1)	299/413 (72.4)	447/715 (62.5)
Type of VTE				
- DVT only, n (%)	848 (37.8)	246 (49.9)	225 (42.6)	377 (30.9)
- PE only, n (%)	575 (25.6)	132 (26.8)	126 (23.9)	317 (26.0)
- DVT and PE, n (%)	819 (36.6)	115 (23.3)	177 (33.5)	527 (43.2)
Others classic cardiovascular risk factors, n (%)				
Tobacco use, n (%)				
- Never, n (%)	935/1769 (52.9)	153/436 (35.1)	195/459 (42.5)	587/874 (67.2)

- Past, n (%)	517/1769 (29.2)	92/436 (21.1)	171/459 (37.3)	254/874 (29.1)
- Current, n (%)	317/1769 (17.9)	191/436 (43.8)	93/459 (20.3)	33/874 (3.8)
Diabetes, n (%)	96 (4.3)	7 (1.4)	23 (4.4)	66 (5.4)
Hypertension, n (%)	730 (32.6)	31 (6.3)	143 (27.1)	556 (45.5)
Dyslipidemia, n (%)	377 (16.8)	14 (2.8)	100 (18.9)	263 (21.5)
Obesity, n (%)	408/1917 (21.3)	96/455 (21.1)	115/476 (24.2)	197/986 (20.0)
Past history of symptomatic atherosclerosis, n (%)	321 (14.3)	16 (3.2)	56 (10.6)	249 (20.4)
Biological characteristics at VTE diagnosis				
Anemia, n (%)	341/1357 (25.1)	50/268 (18.7)	58/301 (19.3)	233/788 (29.6)
Platelet count < 150 / μ L, n (%)	126/1335 (9.4)	19/265 (7.2)	26/297 (8.8)	81/773 (10.5)
Creatinine clearance (mL/min)				
- \geq 60	551/825 (66.8)	168/170 (98.8)	176/195 (90.3)	207/460 (45.0)
- < 60	274/825 (33.2)	2/170 (1.2)	19/195 (9.7)	253/460 (55.0)
Heterozygous Factor V Leiden	287/2016 (14.2)	93/457 (20.4)	96/497 (19.3)	98/1062 (9.2)
Heterozygous G20210A prothrombin gene variant	130/2014 (6.5)	33/457 (7.2)	34/497 (6.8)	63/1060 (5.9)
Homozygous Factor V Leiden, n (%)	12/2016 (0.6)	4/457 (0.9)	4/497 (0.8)	4/1062 (0.4)
Homozygous G20210A prothrombin gene variant, n (%)	1/2014 (0.0)	0/457 (0.0)	0/497 (0.0)	1/1060 (0.1)
Heterozygous Factor V Leiden and Heterozygous G20210A prothrombin gene variant, n (%)	17/2014 (0.8)	5/457 (1.1)	6 (1.2)	6/1060 (0.6)
Others comorbidities at the diagnosis of VTE				
Chronic heart failure, n (%)	163 (7.3)	3 (0.6)	9 (1.7)	151 (12.4)
Chronic respiratory failure, n (%)	134 (6.0)	5 (1.0)	26 (4.9)	103 (8.4)
Atrial fibrillation, n (%)	88/1786 (4.9)	1/419 (0.2)	6/457 (1.3)	81/910 (8.9)
Treatment of VTE				
Type of anticoagulant treatment*				
- Vitamin K antagonists only, n (%)	1521 (67.8)	297 (60.2)	333 (63.1)	891 (73.0)
- Direct oral anticoagulants only, n (%)	228 (10.2)	91 (18.5)	73 (13.8)	64 (5.2)
- Low-molecular-weight heparin only, n (%)	110 (4.9)	37 (7.5)	29 (5.5)	44 (3.6)
- Multiple treatment, n (%)	383 (17.1)	68 (13.8)	93 (17.6)	222 (18.2)
Duration of anticoagulant therapy				
Median, months	6.0 (3.0 - 60.0)	6.0 (3.0 - 39.0)	6.0 (3.0 - 60.0)	7.0 (4.0 - 59.0)
- 0 to 3] months	573/2095 (27.4)	155/476 (32.6)	143/516 (27.7)	275/1103 (24.9)
- 3 to 12] months	682/2095 (32.6)	165/476 (34.7)	155/516 (30.0)	362/1103 (32.8)
- Over 12 months	840/2095 (40.1)	156/476 (32.8)	218/516 (42.2)	466/1103 (42.2)
Discontinuation of anticoagulant therapy during follow-up				
- No	989 (44.1)	160 (32.5)	218 (41.3)	611 (50.0)
- Temporary discontinuation	440 (19.6)	118 (23.9)	114 (21.6)	208 (17.0)
- Permanent discontinuation	813 (36.3)	215 (43.6)	196 (37.1)	402 (32.9)
Thrombolytic therapy, n (%)	21/1793 (1.2)	1/421 (0.2)	8/455 (1.8)	12/917 (1.3)
Concomitant treatment at the time of VTE diagnosis				
Curative anticoagulant therapy, n (%)	29/1762 (1.6)	9/416 (2.2)	4/451 (0.9)	16/895 (1.8)
Antiplatelet therapy, n (%)	256/1784 (14.3)	7/421 (1.7)	43/454 (9.5)	206/909 (22.7)
Statins therapy, n (%)	206/1785 (11.5)	7/421 (1.7)	57/455 (12.5)	142/909 (15.6)

DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, SD: standard deviation

For variables presented as count (percentages), no denominator is shown when there is no missing data.

*Type of anticoagulant treatment after acute phase of VTE.

Table 2: Characteristic of the participants with cancer associated VTE stratified by ages categories.

	Overall (n = 914)	Age: < 50 years N = 56	Age: 50 to 65 years N = 266	Age: > 65 years N = 592
General characteristics and type of VTE				
Gender (female)	401 (43.9)	24 (42.9)	103 (38.7)	274 (46.3)
Mean age at VTE diagnosis (years) ± SD	69.31 ± 11.88	42.57 ± 6.04	59.38 ± 4.24	76.30 ± 6.73
Age categories				
- < 50 years, n (%)	56 (6.1)	56 (100.0)	0 (0.0)	0 (0.0)
- 50 to 65 years, n (%)	266 (29.1)	0 (0.0)	266 (100.0)	0 (0.0)
- > 65 years, n (%)	592 (64.8)	0 (0.0)	0 (0.0)	592 (100.0)
Personal past history of VTE, n (%)	197/907 (21.7)	11 (19.6)	52/264 (19.7)	134/587 (22.8)
Blood group				
- O group, n (%)	261/684 (38.2)	18/50 (36.0)	81/220 (36.8)	162/414 (39.1)
- Non-O group, n (%)	423/684 (61.8)	32/50 (64.0)	139/220 (63.2)	252/414 (60.9)
Type of VTE				
- DVT only, n (%)	342 (37.4)	22 (39.3)	103 (38.7)	217 (36.7)
- PE only, n (%)	222 (24.3)	12 (21.4)	68 (25.6)	142 (24.0)
- DVT and PE, n (%)	350 (38.3)	22 (39.3)	95 (35.7)	233 (39.4)
Cancer characteristics				
Metastatic cancer at VTE diagnosis, n (%)	231/669 (34.5)	20/43 (46.5)	83/205 (40.5)	128/421 (30.4)
Active cancer at VTE diagnosis, n (%)	721 (78.9)	48 (85.7)	227 (85.7)	446 (75.3)
Location of primary cancer				
- Broncho-pulmonary, n (%)	91 (10.0)	7 (12.5)	41 (15.4)	43 (7.3)
- Urogenital tract, n (%)	259 (28.3)	7 (12.5)	59 (22.2)	193 (32.6)
- Breast, n (%)	129 (14.1)	6 (10.7)	29 (10.9)	94 (15.9)
- Ovarian, n (%)	21 (2.3)	0 (0.0)	8 (3.0)	13 (2.2)
- Digestive tract, n (%)	109 (11.9)	5 (8.9)	34 (12.8)	70 (11.8)
- Stomach, n (%)	21 (2.3)	2 (3.6)	6 (2.3)	13 (2.2)
- Pancreas, n (%)	40 (4.4)	3 (5.4)	17 (6.4)	20 (3.4)
- Liver, n (%)	7 (0.8)	0 (0.0)	2 (0.8)	5 (0.8)
- Otho-rhino-laryngeal area, n (%)	24 (2.6)	2 (3.6)	13 (4.9)	9 (1.5)
- Hematologic, n (%)	125 (13.7)	14 (25.0)	31 (11.7)	80 (13.5)
- Cerebral cancer, n (%)	11 (1.2)	0 (0.0)	7 (2.6)	4 (0.7)
- Cutaneous, n (%)	22 (2.4)	1 (1.8)	6 (2.3)	15 (2.5)
- Unknown, n (%)	55 (6.0)	9 (16.1)	13 (4.9)	33 (5.6)
Others classic cardiovascular risk factors, n (%)				
Tobacco use, n (%)				
- Never, n (%)	337/748 (45.1)	19/46 (41.3)	71/225 (31.6)	247/477 (51.8)
- Past, n (%)	353/748 (47.2)	14/46 (30.4)	120/225 (53.3)	219/477 (45.9)
- Current, n (%)	58/748 (7.8)	13/46 (28.3)	34/225 (15.1)	11/477 (2.3)
Diabetes, n (%)	57 (6.2)	2 (3.6)	13 (4.9)	42 (7.1)
Hypertension, n (%)	362 (39.6)	7 (12.5)	82 (30.8)	273 (46.1)
Dyslipidemia, n (%)	161 (17.6)	3 (5.4)	44 (16.5)	114 (19.3)

Obesity, n (%)	139/800 (17.4)	6/49 (12.2)	47/243 (19.3)	86/508 (16.9)
Past history of symptomatic atherosclerosis, n (%)	156 (17.1)	4 (7.1)	25 (9.4)	127 (21.5)
Biological characteristics at VTE diagnosis				
Anemia, n (%)	366/659 (55.5)	20/38 (52.6)	107/189 (56.6)	239/432 (55.3)
Platelet count < 150 / μ L, n (%)	122/644 (18.9)	7/38 (18.4)	42/184 (22.8)	73/422 (17.3)
Creatinine clearance (mL/min)				
- \geq 60	305/481 (63.4)	28/30 (93.3)	118/139 (84.9)	159/312 (51.0)
- < 60	176/481 (36.6)	2/30 (6.7)	21/139 (15.1)	153/312 (49.0)
Heterozygous Factor V Leiden	68/785 (8.7)	5/47 (10.6)	22/223 (9.9)	41/515 (8.0)
Heterozygous G20210A prothrombin gene variant	31/784 (4.0)	1/9 (2.1)	12/223 (5.4)	18/514 (3.5)
Homozygous Factor V Leiden, n (%)	3/785 (0.4)	0/9 (0.0)	2/223 (0.9)	1/515 (0.2)
Homozygous G20210A prothrombin gene variant, n (%)	2/784 (0.3)	0/9 (0.0)	1/223 (0.4)	1/514 (0.2)
Heterozygous Factor V Leiden and Heterozygous G20210A prothrombin gene variant, n (%)	1/784 (0.1)	0/9 (0.0)	1/223 (0.4)	0/514 (0.0)
Others comorbidities at the diagnosis of VTE				
Chronic heart failure, n (%)	56 (6.1)	2 (3.6)	12 (4.5)	42 (7.1)
Chronic respiratory failure, n (%)	43 (4.7)	3 (5.4)	10 (3.8)	30 (5.1)
Atrial fibrillation, n (%)	56/774 (7.2)	0/45 (0.0)	4/231 (1.7)	52/498 (10.4)
Treatment of VTE				
Type anticoagulant treatment*				
- Vitamin K antagonists only, n (%)	398 (43.5)	16 (28.6)	91 (34.2)	291 (49.2)
- Direct oral anticoagulants only, n (%)	46 (5.0)	4 (7.1)	15 (5.6)	27 (4.6)
- Low-molecular-weight heparin only, n (%)	290 (31.7)	22 (39.3)	115 (43.2)	153 (25.8)
- Multiple treatment, n (%)	180 (19.7)	14 (25.0)	45 (16.9)	121 (20.4)
Duration of anticoagulant therapy				
Median, months	6.0 (1.0 - 29.0)	6.0 (0.8 - 26.5)	4.5 (1.0 - 14.0)	6.0 (2.0 - 36.0)
- 0 to 3] months	327/852 (38.4)	21/52 (40.4)	115/248 (46.4)	191/552 (34.6)
- 3 to 12] months	223/852 (26.2)	13/52 (25.0)	63/248 (25.4)	147/552 (26.6)
- Over 12 months	302/852 (35.4)	18/52 (34.6)	70/248 (28.2)	214/552 (38.8)
Discontinuation of anticoagulant therapy during follow-up				
- No	557 (60.9)	32 (57.1)	146 (54.9)	379 (64.0)
- Temporary discontinuation	100 (10.9)	6 (10.7)	29 (10.9)	65 (11.0)
- Permanent discontinuation	257 (28.1)	18 (32.1)	91 (34.2)	148 (25.0)
Thrombolytic therapy, n (%)	6/773 (0.8)	1/45 (2.2)	4/230 (1.7)	1/498 (0.2)
Concomitant treatment at the time of VTE diagnosis				
Curative anticoagulant therapy, n (%)	43/775 (5.5)	5/45 (11.1)	12/231 (5.2)	26/499 (5.2)
Antiplatelet therapy, n (%)	135/777 (17.4)	2/45 (4.4)	21/230 (9.1)	112/502 (22.3)
Statins therapy, n (%)	105/776 (13.5)	2/45 (4.4)	34/230 (14.8)	69/501 (13.8)

DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, SD: standard deviation

For variables presented as count (percentages), no denominator is shown when there is no missing data.

*Type of anticoagulant treatment after acute phase of VTE.

Arterial thrombotic events (ATE) and deaths in the study population

Rates of ATE, deaths and causes of deaths in patients with unprovoked VTE and in patients with cancer associated VTE are respectively presented in **Table 3** and **Table 4**.

Among patients with unprovoked VTE, during the mean follow-up of 6.4 years, 174 had at least one ATE (7.8%), for an incidence of 1.26 per 100 patient-years. Ischemic stroke that occurred in 110/174 participants (63.2%), was the most frequent ATE, followed by acute AMI (40/174, 23.0%). The mean time from the diagnosis of VTE to the occurrence of ATE was 4.7 years. 66 ATE occurred in the 989 participants who did not stopped anticoagulant therapy during follow-up (6.7%), while 108 ATE occurred in the 1253 participants who had a permanent or temporary discontinuation of anticoagulant therapy during follow-up (8.6%). Of all patients with unprovoked VTE, 875 (39%) died during follow-up and cardiovascular diseases were the most frequent causes of death among the known causes, representing 24.8% of all deaths.

Among patients with cancer associated VTE, during the mean follow-up of 3.3 years, 57 had at least one ATE (6.2%), for an incidence of 1.98 per 100 patient-years. The mean time from the diagnosis of VTE to the occurrence of ATE was 3.2 years. Ischemic stroke that occurred in 43 of these 57 participants (75.4%), was the most frequent ATE, followed by acute AMI (8/57, 14.0%). Of the 557 participants who did not stopped anticoagulant therapy during follow-up, 27 (4.8%) had at least one ATE, while 30 ATE occurred in the 357 participants who had a permanent or temporary discontinuation of anticoagulant therapy during follow-up (8.4%). Of all patients with cancer associated VTE, 579 (63%) died during follow-up and cancer was the most frequent causes of deaths among the known causes, representing 27.8% of all deaths.

The curves of the cumulative risk of ATE and deaths in patients with unprovoked VTE compared to patients with cancer associated VTE are presented on **Figure 1**. The curves of the cumulative risk of ATE stratified by age categories in patients with unprovoked VTE and in patients with cancer are presented separately on **Figure 2**; and **Figure 3** give the survivals probability curves stratified by ages categories in patients with unprovoked VTE and in patients with cancer separately. Note that the p-values presented on these figures are those of Log-rank test without competing events.

Table 3: Rates of arterial thrombotic events and causes of death stratified by age categories in patients with unprovoked VTE

	Overall N = 2242	Age: < 50 years N = 493	Age: 50 to 65 years N = 528	Age: > 65 years N = 1221
Median follow-up, months	68.0 (42.0 - 110.0)	95.0 (49.0 - 155.0)	70.0 (60.0 - 108.2)	62.0 (30.0 - 99.0)
Mean follow-up, years	6.4	8.6	6.8	5.4
ATE in overall follow-up, n (%)	174 (7.8)	25 (5.1)	32 (6.1)	117 (9.6)
Incidence of ATE (per 100 patient-years)	1.26 (1.08 - 1.46)	0.60 (0.39 - 0.89)	0.93 (0.63 - 1.31)	1.88 (1.56 - 2.25)
Mean time to ATE (years)	4.7	7.4	4.7	4.1
Median time to ATE (months)	46.0 (23.0 - 83.8)	80.0 (22.0 - 142.0)	54.5 (17.0 - 85.5)	40.0 (24.0 - 78.0)
Type of ATE				
- Acute myocardial infarction, n (%)	40/174 (23.0)	7/25 (28.0)	7/32 (21.9)	26/117 (22.2)
- Ischemic stroke, n (%)	110/174 (63.2)	13/25 (52.0)	22/32 (68.8)	75/117 (64.1)
- Acute limb ischemia, n (%)	16/174 (9.2)	3/25 (12.0)	2/32 (6.2)	11/117 (9.4)
- Acute visceral ischemia, n (%)	8/174 (4.6)	2/25 (8.0)	1/32 (3.1)	5/117 (4.3)
All ATE in patients who did not stopped anticoagulant therapy, n (%)	66/989 (6.7)	6/160 (3.8)	13/218 (6.0)	47/611 (7.7)
All ATE in patients who stopped anticoagulant therapy, n (%)	108/1253 (8.6)	19/333 (5.7)	19/310 (6.1)	70/610 (11.5)
- ATE during anticoagulant therapy in patients who stopped anticoagulant treatment, n (%)	10/1253 (0.8)	3/333 (0.9)	1/310 (0.3)	6/610 (1.0)
- ATE after anticoagulant therapy in patients who stopped anticoagulant treatment, without reintroduction, n (%)	54/784 (6.9)	12/211 (5.7)	9/192 (4.7)	33/381 (8.7)
- ATE after anticoagulant therapy in patients who stopped anticoagulant treatment, with reintroduction, n (%)	44/437 (10.1)	4/117 (3.4)	9/114 (7.9)	31/206 (15.0)
Causes of deaths				
All-causes death, n (%)	875 (39.0)	56 (11.4)	115 (21.8)	704 (57.7)
Median survival, years	12 (12 - 14)	NA	20 (17 - NA)	8 (7 - 8)
Specific causes of Death				
- Cardiovascular, n (%)	217/875 (24.8)	9/56 (16.1)	28/115 (24.3)	180/704 (25.6)
- Cancer, n (%)	61/875 (7.0)	7/56 (12.5)	14/115 (12.2)	40/704 (5.7)
- Non cardiovascular / non cancer, n (%)	137/875 (15.7)	10/56 (17.9)	17/115 (14.8)	110/704 (15.6)
- Unknown, n (%)	460/875 (52.6)	30/56 (53.6)	56/115 (48.7)	374/704 (53.1)

ATE: arterial thrombotic event, VTE: venous thromboembolism

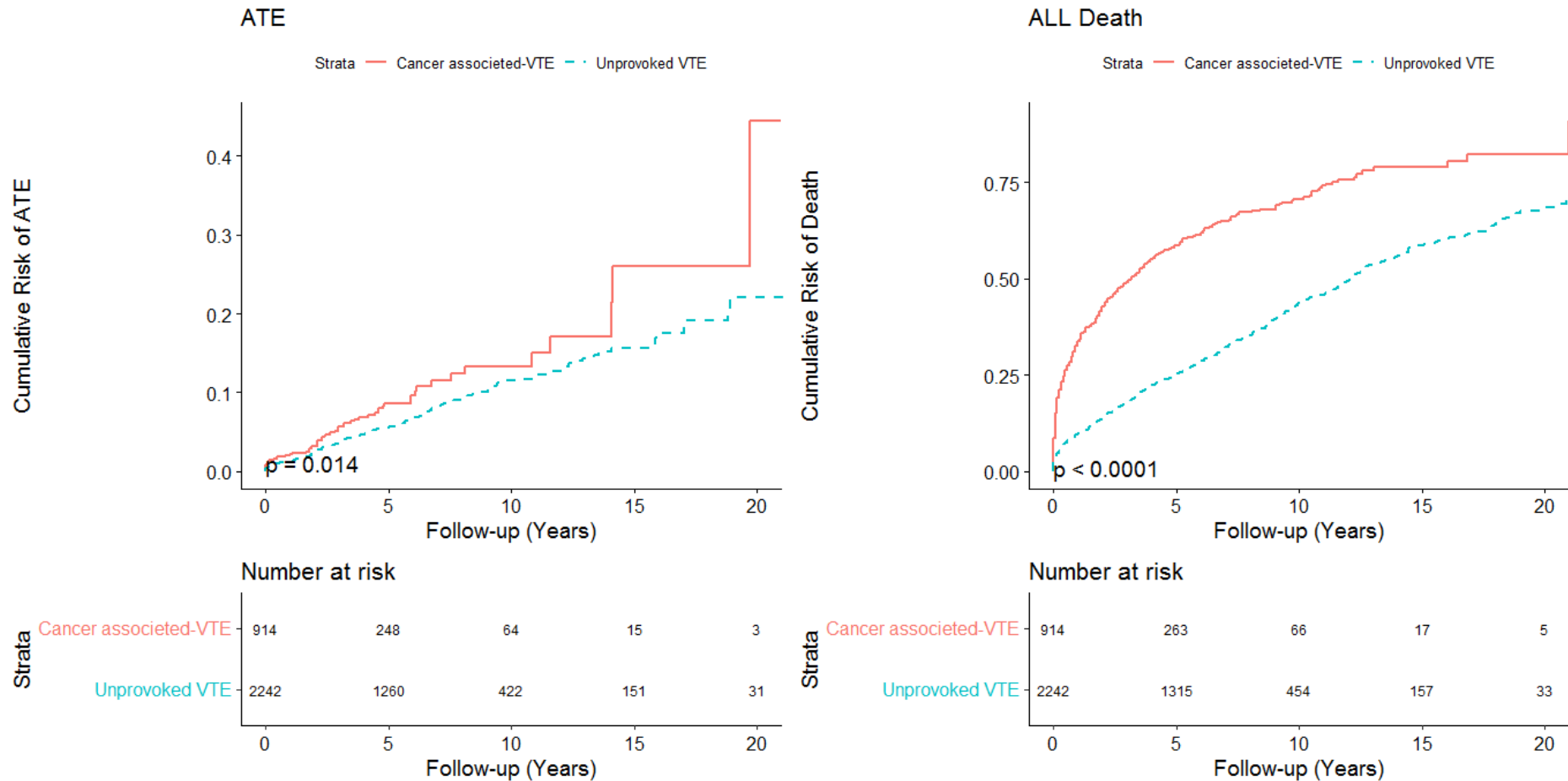
For variables presented as count (percentages), no denominator is shown when there is no missing data.

Table 4: Rates of atherothrombotic events and causes of death stratified by age categories in patients with cancer associated VTE

	Overall N = 914	Age: < 50 years N = 56	Age: 50 to 65 years N = 266	Age: > 65 years N = 592
Median follow-up, months	30.0 (5.0 - 63.8)	33.0 (8.8 - 92.0)	27.0 (5.0 - 62.0)	61.0 (5.0 - 63.0)
Mean follow-up, years	3.3	4.7	3.2	3.1
ATE in overall follow-up, n (%)	57 (6.2)	2 (3.6)	13 (4.9)	42 (7.1)
Incidence of ATE (per 100 patient-years)	1.98 (1.50 - 2.56)	0.75 (0.09 - 2.69)	1.59 (0.85 - 2.69)	2.35 (1.69 - 3.16)
Mean time to ATE (years)	3.2	1.5	4.8	2.9
Median time to ATE (months)	29.0 (6.0 - 56.0)	22.5 (17.8 - 27.3)	30.0 (2.0 - 51.0)	28.5 (7.0 - 57.5)
Type of ATE				
- Acute myocardial infarction, n (%)	8/57 (14.0)	0/2 (0.0)	3/13 (23.1)	5/42 (11.9)
- Ischemic stroke, n (%)	43/57 (75.4)	2/2 (100.0)	8/13 (61.5)	33/42 (78.6)
- Acute limb ischemia, n (%)	5/57 (8.8)	0/0 (0.0)	2/13 (15.4)	3/42 (7.1)
- Acute visceral ischemia, n (%)	1/57 (1.8)	0/0 (0.0)	0/13 (0.0)	1/42 (2.4)
All ATE in patients who did not stopped anticoagulant therapy, n (%)	27/557 (4.8)	2/32 (6.3)	7/146 (4.8)	18/379 (4.7)
All ATE in patients who stopped anticoagulant therapy, n (%)	30/357 (8.4)	0/24 (0.0)	6/120 (5.0)	24/213 (11.3)
- ATE during anticoagulant therapy in patients who stopped anticoagulant treatment, n (%)	6/357 (1.7)	0/24 (0.0)	2/120 (1.7)	4/213 (1.9)
- ATE after anticoagulant therapy in patients who stopped anticoagulant treatment, without reintroduction, n (%)	13/240 (5.4)	0/17 (0.0)	2/84 (2.4)	11/139 (7.9)
- ATE after anticoagulant therapy in patients who stopped anticoagulant treatment, with reintroduction, n (%)	11/97 (11.3)	0/6 (0.0)	2/29 (6.9)	9/62 (14.5)
Causes of deaths				
All-causes death, n (%)	579 (63.3)	31 (55.4)	155 (58.3)	393 (66.4)
Median survival, years	3 (2 - 3)	7 (2 - NA)	3 (2 - 4)	3 (2 - 3)
Specific causes of Death				
- Cardiovascular, n (%)	97/579 (16.8)	6/31 (19.4)	23/155 (14.8)	68/393 (17.3)
- Cancer, n (%)	161/579 (27.8)	9/31 (29.0)	55/155 (35.5)	97/393 (24.7)
- Non cardiovascular / non cancer, n (%)	56/579 (9.7)	4/31 (12.9)	14/155 (9.0)	38/393 (9.7)
- Unknown, n (%)	265/579 (45.8)	12/31 (38.7)	63/155 (40.6)	190/393 (48.3)

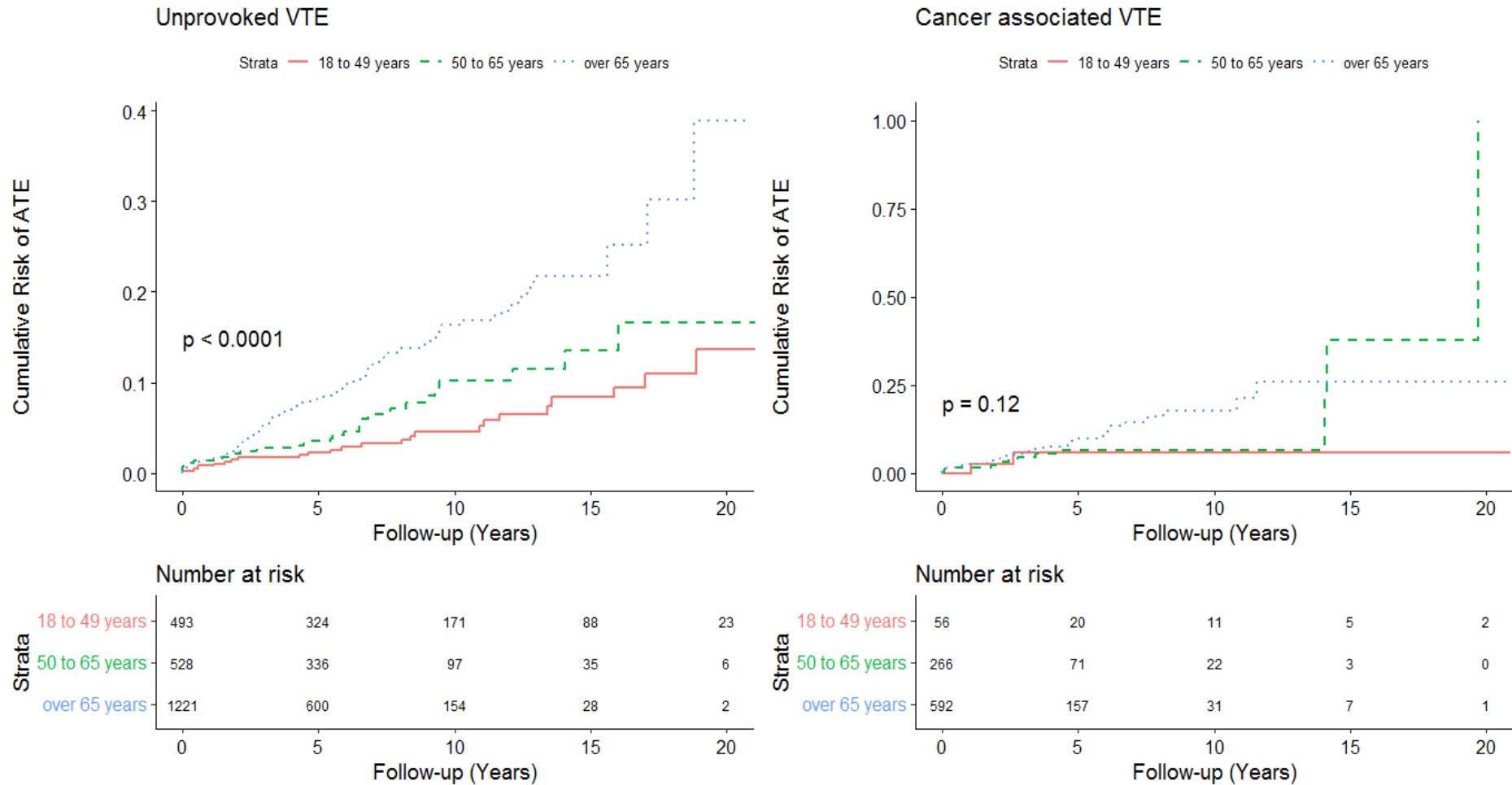
ATE: arterial thrombotic event, VTE: venous thromboembolism

For variables presented as count (percentages), no denominator is shown when there is no missing data.



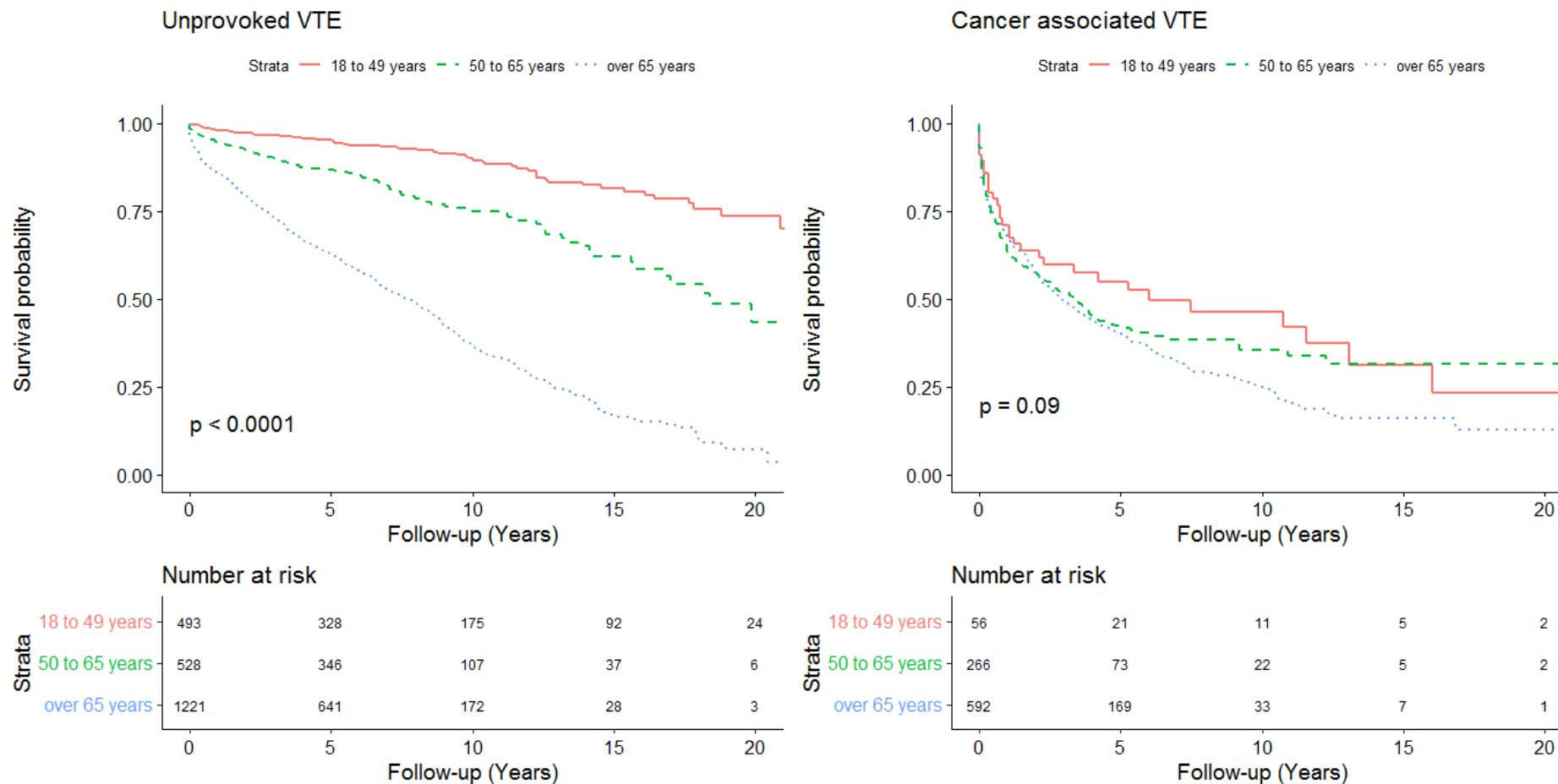
- ATE: arterial thrombotic event, VTE: venous thromboembolism

Figure 1: Cumulative risk of ATE and deaths in patients with unprovoked VTE compared to patients with cancer associated VTE.



- ATE: arterial thrombotic event, VTE: venous thromboembolism

Figure 2: Cumulative risks of ATE stratified by age categories in patients with unprovoked VTE and in patients with cancer associated VTE.



- VTE: venous thromboembolism

Figure 3: survivals probability curves stratified by ages categories in patients with unprovoked VTE and in patients with cancer.

Risk factors of ATE in patients with unprovoked VTE

The results of univariable and multivariable analyses conducted to determine risk factors of ATE in the participants with unprovoked VTE are presented in **Table 5**.

After adjustment for eligible cofounders in multivariable analysis, the only factors that remained significantly associated with high risk of ATE were: age > 65 years (compared to age < 50 years, HR 2.59, 95% CI: 1.56 - 4.29, $p < 0.001$), past history of symptomatic atherosclerosis (HR 2.11, 95% CI: 1.40 - 3.19, $p < 0.001$), and treatment with low molecule weight heparin (LMWH) (compared to treatment with VKA, HR: 2.26, 95% CI: 1.13 - 4.52, $p = 0.020$).

Risk factors of ATE in patients with cancer associated VTE

The results of univariable and multivariable analyses conducted to determine risk factors of ATE in the participants with cancer associated VTE are presented in **Table 6**.

In multivariable analysis, after adjustment for eligible cofounders, the identified risk factors of ATE were: past history of symptomatic atherosclerosis (HR: 3.13, 95% CI: 1.72 - 5.67, $p < 0.001$), and ongoing anticoagulant treatment at the diagnosis of VTE (HR: 2.77, 95% CI: 1.07 - 7.22, $p = 0.036$). There was no significant relationship between anticoagulant therapy and risk of ATE in patients with cancer associated VTE, neither in univariable analyses nor in multivariable analyses.

Table 5: Risk factors of ATE in the participants with unprovoked VTE

	Univariable analysis		Multivariable analysis	
	Unadjusted HR (95%CI)	p	Adjusted HR (95% CI)	p
General characteristics and type of VTE				
Gender (female)	1.26 (0.93 - 1.70)	0.124	1.09 (0.76 - 1.55)	0.640
Age categories				
- < 50 years	-	ref	-	ref
- 50 to 65 years	1.56 (0.92 - 2.66)	0.095	1.35 (0.75 - 2.45)	0.319
- > 65 years	3.11 (1.99 - 4.85)	< 0.001	2.59 (1.56 - 4.29)	< 0.001
Personal past history of VTE	1.09 (0.79 - 1.52)	0.570		
Blood group				
- O group	-	ref		
- Non-O group	0.76 (0.52 - 1.09)	0.139		
Type of VTE				
- DVT only	-	ref	-	ref
- PE only	1.42 (0.96 - 2.09)	0.074	1.33 (0.84 - 2.09)	0.222
- DVT and PE	1.45 (1.02 - 2.05)	0.039	1.42 (0.95 - 2.13)	0.086
Others classic cardiovascular risk factors, n (%)				
Tobacco use				
- Never	-	ref	-	ref
- Past	0.85 (0.57 - 1.26)	0.430	0.86 (0.50 - 1.48)	0.593
- Current	0.53 (0.32 - 0.91)	0.021	0.96 (0.47 - 1.95)	0.927
Diabetes	2.22 (1.26 - 3.91)	0.006	1.68 (0.87 - 3.28)	0.123
Hypertension	1.99 (1.46 - 2.70)	< 0.001	1.14 (0.71 - 1.84)	0.577
Dyslipidemia	1.35 (0.94 - 1.96)	0.109	0.98 (0.61 - 1.58)	0.945
Obesity	1.08 (0.74 - 1.58)	0.684		
Past history of symptomatic atherosclerosis	2.62 (1.85 - 3.72)	< 0.001	2.11 (1.40 - 3.19)	< 0.001
Biological characteristics at VTE diagnosis				
Anemia, n (%)	1.45 (0.94 - 2.24)	0.092		
Platelet count < 150 / μ L	1.89 (1.09 - 3.29)	0.023		
Creatinine clearance (mL/min)				
- \geq 60	-	ref		
- < 60	2.53 (1.56 - 4.14)	< 0.001		
Heterozygous Factor V Leiden	0.66 (0.41 - 1.07)	0.088	0.87 (0.59 - 1.26)	0.456
Heterozygous G20210A prothrombin gene variant	0.59 (0.28 - 1.28)	0.183		
Homozygous Factor V Leiden	-	-		
Homozygous G20210A prothrombin gene variant	-	-		
Heterozygous Factor V Leiden and Heterozygous G20210A prothrombin gene variant	0.55 (0.08 - 3.92)	0.549		
Others comorbidities at the diagnosis of VTE				
Chronic heart failure	2.26 (1.37 - 3.74)	0.001	1.40 (0.79 - 2.48)	0.242
Chronic respiratory failure	0.90 (0.40 - 2.05)	0.809		
Atrial fibrillation	2.59 (1.43 - 4.69)	0.002	1.46 (0.69 - 3.04)	0.314
Treatment of VTE				
Type of anticoagulant treatment*				
- Vitamin K antagonists only	-	ref	-	ref
- Direct oral anticoagulants only	0.65 (0.30 - 1.43)	0.288	0.79 (0.36 - 1.73)	0.568
- Low-molecular-weight heparin only	1.79 (0.90 - 3.57)	0.093	2.26 (1.13 - 4.52)	0.020
Duration of anticoagulant treatment				

- 0 to 3] months	-	ref		
- 3 to 12] months	0.91 (0.60 - 1.38)	0.676		
- Over 12 months	1.02 (0.69 - 1.52)	0.896		
Thrombolytic therapy	1.99 (0.63 - 6.24)	0.240		
Discontinuation of anticoagulant therapy during follow-up				
- No	-	ref		
- Temporary discontinuation	1.08 (0.74 - 1.58)	0.677		
- Permanent discontinuation	0.94 (0.66 - 1.33)	0.738		
Concomitant treatment at the time of VTE diagnosis				
Curative anticoagulant therapy	2.19 (0.69 - 6.89)	0.181		
Antiplatelet therapy	2.54 (1.72 - 3.76)	< 0.001	1.39 (0.77 - 2.54)	0.269
Statins therapy	1.30 (0.79 - 2.14)	0.298		

ATE: arterial thrombotic event, DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, HR: hazard ratio, CI: confidence interval. *Type of anticoagulant treatment after acute phase of VTE.

Table 6: Risk factors of ATE in participants with cancer associated VTE

	Univariable analysis		Multivariable analysis	
	Unadjusted HR (95%CI)	p	Adjusted HR (95% CI)	p
General characteristics and type of VTE				
Gender (female)	0.69 (0.40 - 1.19)	0.180		
Age categories				
- < 50 years	-	ref	-	ref
- 50 to 65 years	2.16 (0.48 - 9.82)	0.316	1.81 (0.22 - 15.08)	0.585
- > 65 years	3.25 (0.76 - 13.88)	0.111	2.60 (0.31 - 21.53)	0.375
Personal past history of VTE	0.65 (0.32 - 1.27)	0.201		
Blood group				
- O group	-	ref		
- Non-O group	0.82 (0.44 - 1.51)	0.521		
Type of VTE				
- DVT only	-	ref		
- PE only	0.72 (0.34 - 1.53)	0.391		
- DVT and PE	1.12 (0.63 - 1.99)	0.696		
Cancer characteristics				
Metastatic cancer at VTE diagnosis	1.29 (0.61 - 2.71)	0.507		
Active cancer at VTE diagnosis	0.90 (0.51 - 1.59)	0.726		
Location of primary cancer				
- Broncho-pulmonary	0.34 (0.05 - 2.48)	0.287		
- Urogenital tract	0.86 (0.48 - 1.52)	0.613		
- Breast	0.97 (0.48 - 1.93)	0.938		
- Ovarian	0.72 (0.09 - 5.39)	0.750		
- Digestive tract*	1.96 (0.99 - 3.91)	0.055	1.75 (0.84 - 3.60)	0.133
- Stomach	0.89 (0.12 - 6.46)	0.911		
- Pancreas	1.97 (0.47 - 8.23)	0.353		
- Liver	8.26 (1.10 - 61.89)	0.039		
- Otho-rhino-laryngeal area	0.63 (0.09 - 4.53)	0.643		
- Hematologic	1.13 (0.55 - 2.29)	0.747		
- Cerebral cancer	-	0.996		
- Cutaneous	0.51 (0.07 - 3.69)	0.505		
- Unknown	0.75 (0.23 - 2.42)	0.626		

Others classic cardiovascular risk factors, n (%)				
Tobacco use				
- Never	-	ref	-	ref
- Past	1.54 (0.83 - 2.84)	0.167	1.49 (0.80 - 2.78)	0.203
- Current	2.09 (0.82 - 5.25)	0.119	2.09 (0.82 - 5.33)	0.119
Diabetes	1.09 (0.34 - 3.53)	0.874		
Hypertension	2.05 (1.19 - 3.52)	0.008	1.52 (0.83 - 2.76)	0.168
Dyslipidemia	1.16 (0.61 - 2.21)	0.642		
Obesity	0.57 (0.24 - 1.35)	0.201		
Past history of symptomatic atherosclerosis	3.05 (1.75 - 5.32)	< 0.001	3.13 (1.72 - 5.67)	< 0.001
Biological characteristics at VTE diagnosis				
Anemia	1.93 (1.04 - 3.57)	0.0374		
Platelet count < 150 / μ L	1.89 (1.09 - 3.29)	0.023		
Creatinine clearance (mL/min)				
- \geq 60	-	ref		
- < 60	2.23 (1.12 - 4.43)	0.022		
Heterozygous Factor V Leiden	0.65 (0.23 - 1.83)	0.417		
Heterozygous G20210A prothrombin gene variant	0.68 (0.16 - 2.85)	0.595		
Homozygous Factor V Leiden	-	-		
Homozygous G20210A prothrombin gene variant	-	-		
Heterozygous Factor V Leiden and Heterozygous G20210A prothrombin gene variant	-	-		
Others comorbidities at the diagnosis of VTE				
Chronic heart failure	-	-		
Chronic respiratory failure	1.39 (0.43 - 4.45)	0.583		
Atrial fibrillation	1.56 (0.56 - 4.34)	0.399		
Treatment of VTE				
Type of anticoagulant treatment*				
- Vitamin K antagonists only	-	ref	-	ref
- Direct oral anticoagulants only	0.40 (0.05 - 3.00)	0.376	0.36 (0.05 - 2.79)	0.332
- Low-molecular-weight heparin only	1.65 (0.87 - 3.14)	0.128	1.18 (0.57 - 2.38)	0.652
Duration of anticoagulant treatment				
- 0 to 3] months	-	ref		
- 3 to 12] months	0.94 (0.48 - 1.85)	0.877		
- Over 12 months	0.73 (0.37 - 1.40)	0.343		
Thrombolytic therapy	-	-		
Discontinuation of anticoagulant therapy during follow-up				
- No	-	ref		
- Temporary discontinuation	1.58 (0.81 - 3.05)	0.176		
- Permanent discontinuation	0.91 (0.49 - 1.69)	0.759		
Concomitant treatment at the time of VTE diagnosis				
Curative anticoagulant therapy	3.68 (1.43 - 9.46)	0.006	2.77 (1.07 - 7.22)	0.036
Antiplatelet therapy	2.30 (1.25 - 4.24)	0.007	1.34 (0.57 - 3.15)	0.509
Statins therapy	1.45 (0.70 - 2.99)	0.316		

ATE: arterial thrombotic event, DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, HR: hazard ratio, CI: confidence interval. *Type of anticoagulant treatment after acute phase of VTE.

Discussion

In this study which aimed to determine the risk factors of ATE after unprovoked VTE and after cancer associated VTE, we found and that the risk of ATE in these specific populations, is determined by some classic cardiovascular risk factors and is influenced by anticoagulant treatment introduced for VTE, as well as the presence or absence of an ongoing anticoagulation at the diagnosis of VTE. Our results also confirmed as previously show that the risk of ATE after unprovoked VTE and after cancer associated VTE is high.

Incidence of ATE after unprovoked VTE and after cancer associated VTE

As previously reported in the literature, the risk of ATE after unprovoked VTE and after cancer associated VTE was high in our study population [27,40,45]. Indeed, among patients with unprovoked VTE, 7.8% had at least one ATE during the median follow-up of 68 months, for an incidence of 1.26 per 100 patient-years. Ischemic stroke that represent 63.2% of cases, was the most frequent ATE, followed by acute AMI (23.0% of cases). The frequency and incidence of ATE in patients with unprovoked VTE, found in our study is similar to the frequency of arterial events of 10.4% and incidence of 1.27 per 100 patient-years found in a recent meta-analysis of 8 cohort studies [12,32].

Among patients with cancer associated VTE, during the median follow-up of 30 months, 6.2% of them had at least one ATE, for an incidence of 1.98 per 100 patient-years. Ischemic stroke represents 75.4% of cases, followed by acute AMI (14.0% of cases). These numbers are considerably higher than those found by Brenner *et al* who reported a frequency of 1.1% of arterial ischemic events in 5717 patients with active cancer and VTE, with 66% of cases being ischemic stroke and 23% being AMI [27]. However, it is important to note that even if their study was a multicenter prospective cohort study as ours, the median follow-up duration was only 5 months compared to 30 months in our study. Moreover, their definition of composite outcome of ATE was more restrictive than ours, including only AMI, ischemic stroke and lower limb amputation [27]. These results also highlighted as previously reported, the fact that subsequent arterial thrombotic complications occurred early after VTE, and our data bring more precisions, as they show that ATE occurred more early after the diagnosis of VTE in patients with cancer associated VTE than in patients with unprovoked VTE [6,27]. Indeed, the mean time from the diagnosis of VTE to ATE occurrence was 3.3 years in patients with cancer associated VTE, and 4.7 years in patients with unprovoked VTE. This should have clinical implications while dealing with the prevention of ATE in these patients at high risk of arterial thrombotic complications.

Risk factors of ATE in patients with unprovoked VTE

In our study population, the identified risk factors of ATE in patients with unprovoked VTE after adjustment for other potential cofounders, included older age (age > 65 years vs. age < 50 years), past history of symptomatic atherosclerosis and treatment with LMWH (vs. VKA). We can notice that these risk factors include some classic cardiovascular risk factors as older age and past history of atherosclerosis, which are common risk factors of arterial cardiovascular events in the general population and have also been reported in the general VTE population by few studies [16,20]. However, the association between treatment with LMWH (vs. VKA) and increased risk of ATE, in patients with unprovoked VTE has never been reported. A tendency was also found in our result of a reduced risk of ATE in patients treated with DOAC compared to patients treated with VKA, either in univariable (HR: 0.65) or in multivariable analysis (HR: 0.79), despite non-statistically significant results. If few studies, of retrospective design explored the risk factors of some composite outcomes including arterial complications, in patients with unprovoked VTE, very few studies previously explored the risk factors of arterial thrombotic complications alone in patients with unprovoked VTE considering the competing risk of deaths [15,45].

Risk factors of ATE in patients with cancer associated VTE

In multivariable analysis, the identified risk factors of ATE in patients with cancer associated VTE were: past history of symptomatic atherosclerosis and ongoing anticoagulant treatment at the diagnosis of VTE. These risk factors also include past history of atherosclerosis which is a major known cardiovascular risk factor, and finally the only risk factor which came out both in patients with unprovoked VTE and in patients with cancer associated VTE in our study. The role of ongoing anticoagulant treatment at the diagnosis of VTE as an independent risk factor of ATE in patients with cancer related VTE has never been reported previously. If this seems difficult to explain, we think that patients who developed venous thrombosis with an ongoing anticoagulant treatment may generally be at high risk of all type of thrombosis, as are patients who developed recurrent VTE under treatment [101]. It could have been interesting to explore the biological thrombotic profile of these patients; unfortunately, we did not have sufficient biological data in our study to deeply explore the role of biological parameters, as anti-phospholipid antibodies, on the risk of ATE. The only type of primary cancer that was associated with increased risk of ATE in univariable analysis was liver cancer with an HR of 8.26 (95% CI: 1.10 - 61.89), however, its frequency of only 0.8% did not allow us to adjust it for other cofounders in multivariable analysis. Even if, it is not among the known most

prothrombotic malignancies, liver cancer has already been shown to be associated with a hypercoagulability state which could lead to an increased risk of venous and arterial thrombosis [102,103]. As previously said, if several studies reported cancer as an independent risk factor of arterial complications in patients with VTE, none explored the risk factors of ATE in patients with cancer associated VTE [14,37,42].

Global clinical implications, strengths and limitations

Our results confirm the high risk of arterial thrombotic complications in patients with unprovoked VTE and in patients with cancer associated VTE. Most important, using rigorous and robust statistical methods, we determined the risk factors of these complications in this population of patients generally at high risk of all type of thrombosis. To the best of our knowledge, this is the first large prospective study to explore the risk factors of ATE in patients with unprovoked VTE and in patients with cancer associated VTE, considering the competing risk of deaths. Moreover, all VTE cases were objectively confirmed and all ATE were adjudicated by independent committee. Our finding should therefore, have direct clinical implications for the prevention of ATE in patients with unprovoked or cancer associated VTE, and could be the basis for the further development of predictive scores.

To consider the potential role of anticoagulant therapy introduced for VTE on the risk of ATE in patients with unprovoked or cancer associated VTE, we used type and duration of anticoagulant treatment in our analyses as potential predictors of ATE. Although we don't have a clear explanation to the significant association between treatment with LMWH (vs VKA) and the risk of ATE after unprovoked VTE, as previously mentioned, we think that the association between ongoing anticoagulation at the diagnosis of VTE and the risk of ATE after cancer-related VTE, may be due to the fact the patients concerned may have a high baseline prothrombotic profile because of known or unknown thrombophilia, or other prothrombotic cardiovascular diseases as atrial fibrillation or patent foramen oval. However, we did not collect enough data to efficiently explore the impact of these factors on the risk of ATE [30,92,104]. Nevertheless, the orientation given by our result raises the question whether the prevention of ATE after unprovoked VTE and after cancer associated VTE should not take into consideration the family of anticoagulant treatment introduced for the treatment of VTE, added to others usually implemented measures. These results highlighted the necessity to deeply explore the role of anticoagulation used for VTE on the risk of subsequent arterial complications, through further randomized clinical trials.

Added to the screening for thrombophilia or others factors as patent foramen oval of which we did not have enough data to explore their role on the risk of ATE in our study population, our study has other limitations. First, we could have underestimated the incidence of arterial thrombotic complications, as all events considered in our study were hard events, not including other acute coronary syndrome nor transient ischemic attack. Second, our study was an open cohort with inclusion period of more than 2 decades, therefore, the change in treatment protocols of VTE over years and follow-up duration could have affected the number of ATE finally reported. Third, participants were not treated with a standardized protocol, therefore, treatment could have varied with local practices and physician experience, and induce some bias in our study. Fourth, we considered only baseline comorbid conditions present at the inclusion; thus, we could have ignored some conditions developed later during follow-up, and therefore omitted to control some potential confusion bias. Finally, we did not record enough information on whether antiplatelet therapy was discontinued after VTE diagnosis or on the dose and type of antiplatelets or statins to included them in our analyses.

Conclusions

In conclusion, our results from this large prospective cohort study show as previously described, that the risk of ATE after unprovoked VTE and after cancer associated VTE is high, and that this risk is determined by some classic cardiovascular risk factors and is influenced by anticoagulant treatment introduced for VTE, as well as the presence or absence of an ongoing anticoagulation at the diagnosis of VTE. These results may help to better prevent further arterial cardiovascular complications in patients who developed unprovoked VTE or cancer associated VTE.

List of Abbreviations:

AMI: Acute Myocardial Infarction

ATE: Arterial Thrombotic Event

CI: Confidence Interval

CUS: Compression Ultrasonography

DOA: Direct Oral Anticoagulant

DVT: Deep Venous Thrombosis

HR: Hazard Ratio

IQR: Interquartile Range

LMWH: Low Molecule Weight Heparin

PE: Pulmonary Embolism

SD: Standard Deviation

VKA: Vitamin K antagonists

VTE: Venous Thromboembolism

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Brest University Teaching Hospital (CCP-Ouest 6-390) with a last amendment approved on November 20, 2013 (ref number: EDITH II/RB 05.003). All participants signed a consent form. Administrative approvals were also obtained from authorities of the Brest University Teaching Hospital.

Competing interests: FC reports having received research grant support from Pfizer and fees for board memberships or symposia from Bayer and Astra Zeneca and having received travel support from Bayer, Daiichi Sankyo, Leo Pharma, InterMune, and Actelion. All other authors declare that they have no competing interests related to this study.

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Author’s contributions

Conception and design: SRN, FC, LB, RD; acquisition of data: EP; Data analysis: SRN; Analysis and interpretation of data: SRN, FC, LB; Manuscript drafting: SRN; Manuscript revision: All authors; Approved the final version of the manuscript: All authors; Obtaining funding: FC. Administrative technical, and material support: FC, CT, RD. Study supervision: FC; Full access to all the data of the study: FC, SRN; responsibility for all aspect of the study, reliability and freedom from bias of the data presented: All authors.

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C. Article de résultats 3 : facteurs de risque de décès cardiovasculaire après MVTE

Cet article intitulé "*Risk factors of cardiovascular death after venous thromboembolism: Results from a prospective cohort study*" a été accepté pour publication dans le journal "Thrombosis and Haemostasis" en Mars 2022 et est actuellement sous presse.

I. RESUME

Rationnel : Les décès cardiovasculaires (CVDT) sont plus fréquents chez les patients atteints de maladie veineuse thromboembolique (MTEV) que dans la population générale, cependant, les facteurs de risque associés à ce risque élevé de CVDT chez les patients atteints de MVTE ne sont pas décrits.

Méthodologie : Pour déterminer les facteurs de risque de CVDT chez les patients atteints de MVTE à partir d'une étude de cohorte prospective multicentrique, des modèles de risque de sous-distribution de Fine et Gray ont été utilisés.

Résultats : Sur les 3988 patients inclus, 426 (10,7%) sont décédés de CVDT au cours d'un suivi médian de 5 ans. Les facteurs de risque de CVDT après analyses multivariées étaient : l'âge de 50-65 ans (vs. < 50 ans, HR : 3,22, IC à 95 % : 1,67 - 6,62), l'âge > 65 ans (vs. < 50 ans, HR : 7,60, IC à 95 % : 3,73 - 15,52), la MVTE associée au cancer (vs. MVTE associé à un facteur transitoire, HR : 1,73, IC à 95 % : 1,15 - 2,61), la MVTE non provoquée (vs MVTE associé à un facteur transitoire, HR : 1,42, IC à 95 % : 1,02 - 2,00), le tabagisme ancien (vs jamais fumé, HR : 1,43, IC à 95 % : 1,06 - 1,94), le tabagisme actuel (vs jamais fumé, HR : 1,87, IC à 95 % : 1,15 - 3,01), l'hypertension (HR : 2,11, IC à 95 % : 1,51 - 2,96), l'insuffisance cardiaque chronique (HR : 2,28, IC à 95 % : 1,37 - 3,79), l'insuffisance respiratoire chronique (HR : 1,72, IC à 95 % : 1,02 - 2,89) et la fibrillation auriculaire (RR : 1,67, IC à 95 % : 1,06 - 2,60). Le risque de CVDT était significativement réduit chez les patients traités par des anticoagulants oraux direct (vs antivitamine K) et chez les patients traités plus de 3 mois.

Conclusion : Les facteurs de risque de CVDT après MVTE comprennent certains des facteurs de risque cardiovasculaires traditionnels et d'autres facteurs de risque liés aux caractéristiques de la MVTE et aux comorbidités des patients.

Mots-clés : maladie veineuse thromboembolique, décès cardiovasculaire, mortalité cardiovasculaire, facteur de risque, prédicteur, cohorte prospective.

II. ARTICLE COMPLET

Risk factors of cardiovascular death after venous thromboembolism: Results from a prospective cohort study

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Abstract

Background: Cardiovascular deaths (CVDT) are more frequent in patients with venous thromboembolism (VTE) than in the general population, however, risk factors associated with this increased risk of CVDT in patients with VTE are undescribed.

Methods: To determine the risk factors of CVDT in patients with VTE from a multicenter prospective cohort study, Fine and Gray sub-distribution hazard models, were conducted.

Results: Of the 3988 included patients, 426 (10.7%) died of CVDT during a median follow-up 5 years. The risk factors of CVDT after multivariate analyses were: age of 50-65 years (vs. < 50 years, HR: 3.22, 95% CI: 1.67 - 6.62), age > 65 years (vs. < 50 years, HR: 7.60, 95% CI: 3.73 - 15.52), cancer-associated VTE (vs. transient risk factor-related VTE, HR: 1.73, 95% CI: 1.15 - 2.61), unprovoked-VTE (vs. transient risk factor-related VTE, HR: 1.42, 95% CI: 1.02 - 2.00), past tobacco (vs. never, HR: 1.43, 95% CI: 1.06 - 1.94), current tobacco (vs. never, HR: 1.87, 95% CI: 1.15 - 3.01), hypertension (HR: 2.11, 95% CI: 1.51 - 2.96), chronic heart failure (HR: 2.28, 95% CI: 1.37 - 3.79), chronic respiratory failure (HR: 1.72, 95% CI: 1.02 - 2.89), and atrial fibrillation (HR: 1.67, 95% CI: 1.06 - 2.60). The risk of CVDT was significantly reduced with direct oral anticoagulant (vs. vitamin-K antagonists) and with longer duration of treatment (>3 months).

Conclusions: Risk factors of CVDT after VTE include some traditional cardiovascular risk factors and others risk factors that are related to characteristics of VTE, and patients' comorbidities.

Keywords: venous thromboembolism, cardiovascular death, cardiovascular mortality, risk factor, predictor, prospective cohort.

Introduction

Many efforts are being doing worldwide to fight against cardiovascular diseases, however, they remain a major public health concern, as they are responsible of 32% of all death, taking an estimated 18 million lives each year [57,105]. Arterial cardiovascular events which represent 85% of all cardiovascular death (CVDT), have be shown to be more frequent in patients with venous thromboembolism (VTE) than in the general population [12,105]. Moreover, if VTE represents the third leading cause of CVDT, after heart attack and stroke in the general population, it has also been shown that patients who developed VTE, are at high risk of CVDT than the general population [3].

Indeed, several studies and even few meta-analyses reported a proportion of CVDT among all deaths higher than the 32% known in the general population [27,37,66,70,106]. In the most recent meta-analysis by Noumegni *et al* that included 13 cohort studies, and aimed to explore the frequency and incidence of CVDT in patients with VTE compared to the general population, the authors found a pooled proportion of CVDT among all causes of deaths of 35.2% in patients with VTE [106]. Moreover, the authors were able to compared frequency of CVDT in patients with VTE and in controls without VTE in two studies and they found a pooled risk ratio of 3.85, which was statistically significant [32,35,106].

In the goal to reduce the incidence of arterial cardiovascular events and the incidence of recurrent VTE, which are the most frequent causes of cardiovascular deaths in patients with VTE, several studies explored the risk factors of these events in patients with VTE [14,15,40,41,107,108]. Despite the fact that the great majority of these studies did not consider the impact of non-cardiovascular death as potential competing events to their outcome of interest, they allowed to do a considerable progress in the prevention of all cardiovascular events after VTE [14,15,40,41,107,108]. However, data are lacking on the risk factors of CVDT after VTE. Determining these risk factors is all the more important given that not all recurrent VTE nor all arterial cardiovascular events that occur after VTE will be fatal.

We therefore aimed to determine the risk factors of CVDT from a large population of patients diagnosed with VTE and followed prospectively. The final goal being to identify modifiable factors that could be acted on in daily clinical practice to efficiently prevent CVDT after VTE.

Methods

Study design and population

The design and setting of the prospective cohort from which the data of this study came, have been previously described [100]. Briefly, it was a multicenter hospital-based observational prospective cohort study that started inclusion since 1992, evaluating the interactions between genetic and environmental factors of venous disease thromboembolism in the west of France [100]. The last inclusions considered in this study were done in December 2019.

Patients included in this study were eligible and consenting adults with an objective diagnosis of VTE. Symptomatic DVT of lower limbs was diagnosed based on non-compression of deep vein using a real-time B mode compression ultrasonography (CUS) [78]. Symptomatic PE was confirmed based on: (i) a positive computed tomography pulmonary angiography showing a central filling defect outlined by contrast material or a complete occlusion in a segmental or more proximal pulmonary artery; (ii) or a pulmonary angiography with an intraluminal filling defect or a sharp cut-off in a vessel of at least 2 mm in diameter; (iii) or a ventilation perfusion lung scan indicating a high probability for PE (using Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria); (iiii) or a high clinical probability associated to a proximal DVT on CUS [79]. Patients with atypical site or superficial venous thrombosis, patients unable to read and sign the written informed consent form or those who refused to participate were not included in the study.

Data collection and follow-up

Detailed information about general characteristics of participants, characteristic of VTE, comorbidities (chronic heart failure, chronic respiratory failure, atrial fibrillation), risk factors for thrombosis, and ongoing treatment at the diagnosis of VTE (anticoagulant treatment, antiplatelet, statins) were collected by validated questionnaire and by reviewing medical records at baseline. Cardiovascular risk factors namely tobacco use, hypertension, diabetes mellitus, dyslipidemia, and past history of symptomatic atherosclerosis, were also recorded at inclusion, as well as some available biological data (full blood count, creatinine concentration). Results of factor V Leiden mutation, and prothrombin gene 20210A mutation check-up, when realized, were also further reported.

Unprovoked VTE was defined as VTE without cancer or major transient provoking factor including: surgery with general anesthesia for more than 30 minutes, leg fracture or leg injury with plaster cast, acute illness with hospitalization for at least three days, ongoing

pregnancy or delivery, ongoing estrogen contraceptive treatment, ongoing menopause substitutive hormonal therapy, or hormonal therapy for assisted reproduction, all within the past three months. Height and weight were self-reported except for patients who could be weighted. Body mass index (BMI) was then computerized and overweight was defined for values ≥ 25 kg/m², obesity for values ≥ 30.0 kg/m² [81]. Estimated creatinine clearance was calculated using the Cockcroft-Gault formula with the measurement closer to the date of inclusion. Renal insufficiency was defined as a clearance below 60 mL/min [82]. Past history of symptomatic atherosclerosis was defined as a self-reported and file confirmation history of either myocardial infarction, stroke, or symptomatic peripheral artery disease of lower limbs.

After inclusion, patients were instructed to return for follow-up visits at 3, 6, and 12 months. Further follow-ups were scheduled annually and could be done during a physical consultation or by phone call. Participants who did not present themselves for consultation and did not respond to phone call, were sent a letter by postal mail. Participants for whom, we did not succeed in getting news more than one year after their inclusion in the study and before December 31, 2020, were considered lost to follow-up and not included in the final analyses. The follow-up period was defined as years between the inclusion date and the date of last contact visit or death. For patients in whom anticoagulation was not discontinued at the last follow-up, the duration of anticoagulant treatment was the duration from the beginning of the treatment until the last follow-up. For those, in whom there was a temporary discontinuation of anticoagulation, the duration considered was the duration of the initial anticoagulant therapy.

Outcomes

The primary outcomes considered in our study was CVDT, defined as deaths due to new PE (for patients with DVT), deaths due to subsequent complications of initial non-fatal PE or recurrent PE (for patients with PE), deaths due to an acute myocardial infarction, sudden cardiac deaths or heart failure, deaths due to fatal arrhythmia, deaths due to ischemic or hemorrhagic stroke, deaths due to cardiovascular procedures or hemorrhage, deaths due to ruptured aortic aneurysm or aortic dissection and deaths due to other cardiovascular causes [71,72]. All causes of death were adjudicated by an independent mortality adjudication committee, and non-cardiovascular deaths included all other causes of death.

Statistical analysis

Data were analyzed using the statistical software R, version 3.6.2. and a p-value < 0.05 was used to characterize all statistically significant results. In descriptive analyses, results are

presented as mean \pm standard deviation (SD) or median (25th-75th percentiles) where applicable, for continuous variables, and frequency (percentage) for categorical variables. Groups' comparisons used the Student *t*-test or equivalents and the Chi-square test where appropriate. We used the Aalen–Johansen estimator to evaluate the cumulative risk of CVDT over time, considering non-cardiovascular death as competing events [87]. Apart from our main univariable and multivariable analyses, the rates of outcome events in two groups were compared using the log-rank test, after calculating the cumulative hazard according to the Kaplan–Meier life-table method. Otherwise, comparison between cumulative incidences of outcomes among two groups was done using Gray's K-sample method [88].

Univariable and multivariable Fine and Gray sub-distribution hazard models, considering non cardiovascular deaths as competing events, were used to determine risk factors of CVDT. After univariable analyses, only variable with *p* value < 0.15 and frequency of 3% or above, were included in multivariable models. Biological variables with missing values were included in multivariable analysis only if they satisfied these conditions and had less than 25% of missing values in the study population. Categorical variables with more than 2 levels were included in multivariable analysis if one or more levels satisfied the required conditions. All univariable and multivariable models used were complete-cases models excluding all missing data.

Results

Characteristic of the study population

A total of 3988 subjects met the inclusions criteria for this study, 1859 (46.6%) were men. The flow chart of the study population is presented on Figure 1. The mean age at inclusion was 58.72 ± 18.64 years in the study population, and 32.0% were aged less than 50 years old. 1782 patients (44.7%) had unprovoked VTE, 649 had cancer associated VTE (16.3%), and 1557 had VTE related to a transient risk factor (39.0%). 21.8% of participants had past history of VTE, and 11.5% had past history of symptomatic atherosclerosis. The median follow-up in the overall study population was 5 years (interquartile range: 4.0 - 10.0). 1290 participants (32.3%) had DVT and PE, while 1008 had isolated PE (25.3%), and 1690 had isolated DVT (42.4%).

Hypertension, dyslipidemia, and diabetes, were respectively present in 32.0%, 16.2%, and 4.4% of participants. Direct oral anticoagulant (DOAC) only and vitamin K antagonists (VKA) only were respectively used in 10.6% and in 58.5% of participants, and the median duration of anticoagulant therapy was 6 months. 12.2% of participants were on antiplatelet therapy and

2.0% were already on anticoagulant therapy at the diagnosis of VTE. Characteristics of the study population stratified gender are presented in **Table 1**.

Table 1: Characteristics of the study population stratified by gender

	Overall (n = 3988)	Men (n = 1859)	Women (n = 2129)
General characteristics			
Mean age at VTE diagnosis (years) ± SD	58.72 ± 18.64	58.39 ± 16.16	59.00 ± 20.56
Age categories			
- < 50 years, n (%)	1275 (32.0)	556 (29.9)	719 (33.8)
- 50 to 65 years, n (%)	1020 (25.6)	614 (33.0)	406 (19.1)
- > 65 years, n (%)	1693 (42.5)	689 (37.1)	1004 (47.2)
Personal past history of VTE, n (%)	868/3974 (21.8)	384/1851 (20.7)	484/2123 (22.8)
Blood group			
- O group, n (%)	932/3014 (30.9)	443/1400 (31.6)	489/1614 (30.3)
- Non-O group, n (%)	2082/3014 (69.1)	957/1400 (68.4)	1125/1614 (69.7)
Median follow-up, years	5.0 (4.0 - 10.0)	6.0 (4.0 - 10.0)	5.0 (3.0 - 9.0)
Mean follow-up, years	6.9 ± 5.2	7.3 ± 5.3	6.5 ± 5.1
Characteristics of VTE			
Type of VTE			
- DVT only, n (%)	1690 (42.4)	754 (40.6)	936 (44.0)
- PE only, n (%)	1008 (25.3)	456 (24.5)	552 (25.9)
- DVT and PE, n (%)	1290 (32.3)	649 (34.9)	641 (30.1)
Type of VTE according to provoking factors			
- Transient factors associated VTE, n (%)	1557 (39.0)	542 (29.2)	1015 (47.7)
- Cancer associated VTE, n (%)	649 (16.3)	360 (19.4)	289 (13.6)
- Unprovoked VTE, n (%)	1782 (44.7)	957 (51.5)	825 (38.8)
Provoking risk factors of VTE			
Cancer characteristics			
Metastatic cancer at VTE diagnosis, n (%)	164/529 (31.0)	93/289 (32.2)	71/240 (29.6)
Active cancer at VTE diagnosis, n (%)	485/649 (74.8)	281/359 (78.3)	204/289 (70.6)
Transient provoking risk factors			
Surgery within past 3 months, n (%)	518 (13.0)	254 (13.7)	264 (12.4)
Leg injury associated with reduced mobility for at least three days, within past 15 days, n (%)	142 (3.6)	71 (3.8)	71 (3.3)
Acute illness confined to bed in hospital for at least three days, within past 3 months, n (%)	810/3963 (20.4)	399/1849 (21.6)	411/2114 (19.4)
Ongoing pregnancy, n (%)	69/2129 (3.2)	/	69 (3.2)
Post-partum period within past 3 months, n (%)	59/2124 (2.8)	/	59/2124 (2.8)
Estrogen contraceptive treatment, n (%)	384/2088 (18.4)	/	384/2088 (18.4)
Menopause substitutive hormonal therapy, n (%)	110/2124 (5.2)	/	110/2124 (5.2)
Hormonal therapy for assisted reproduction, n (%)	13/1873 (0.7)	2/2 (100.0)	11/1871 (0.6)
Classic cardiovascular risk factors*, n (%)			
Tobacco use, n (%)			
- Never, n (%)	1852/3572 (51.8)	569/1658 (34.3)	1283/1914 (67.0)
- Past, n (%)	1083/3572 (30.3)	762/1658 (46.0)	321/1914 (16.8)
- Current, n (%)	637/3572 (17.8)	327/1658 (19.7)	310/1914 (16.2)

Diabetes, n (%)	177 (4.4)	105 (5.6)	72 (3.4)
Hypertension, n (%)	1276 (32.0)	561 (30.2)	715 (33.6)
Dyslipidemia, n (%)	648 (16.2)	309 (16.6)	339 (15.9)
Obesity/overweight, n (%)	2115/3681 (57.5)	1068/1722 (62.0)	1047/1959 (53.4)
Past history of symptomatic atherosclerosis, n (%)	458 (11.5)	264 (14.2)	194 (9.1)
Biological characteristics at VTE diagnosis			
Anemia, n (%)	739/2281 (32.4)	328/1089 (30.1)	411/1192 (34.5)
Platelet count < 150 / μ L, n (%)	230/2240 (10.3)	140/1072 (13.1)	90/1168 (7.7)
Creatinine clearance < 60 mL/min	455/1667 (27.3)	148/805 (18.4)	307/862 (35.6)
Heterozygous Factor V Leiden	511/3736 (13.7)	261/1746 (14.9)	250/1990 (12.6)
Heterozygous G20210A prothrombin gene variant	239/3734 (6.4)	107/1746 (6.1)	132/1988 (6.6)
Homozygous Factor V Leiden, n (%)	20/3736 (0.5)	8/1746 (0.5)	12/1990 (0.6)
Homozygous G20210A prothrombin gene variant, n (%)	4/3734 (0.1)	3/1746 (0.2)	1/1988 (0.1)
Heterozygous Factor V Leiden and Heterozygous G20210A prothrombin gene variant, n (%)	28/3734 (0.7)	15/1746 (0.9)	13/1988 (0.7)
Others comorbidities at the diagnosis of VTE			
Chronic heart failure, n (%)	144 (3.6)	61 (3.3)	83 (3.9)
Chronic respiratory failure, n (%)	158 (4.0)	100 (5.4)	58 (2.7)
Atrial fibrillation, n (%)	141/3574 (3.9)	75/1669 (4.5)	66/1905 (3.5)
Treatment of VTE			
Type of anticoagulant treatment*			
- Vitamin K antagonists only, n (%)	2331 (58.5)	1034 (55.6)	1297 (60.9)
- Direct oral anticoagulants only, n (%)	422 (10.6)	228 (12.3)	194 (9.1)
- Low-molecular-weight heparin only, n (%)	487 (12.2)	243 (13.1)	244 (11.5)
- Others**	748 (18.8)	354 (19.0)	394 (18.5)
Duration of anticoagulant therapy			
Median, months	6.0 (3.0 - 50.0)	6.0 (3.0 - 47.3)	6.0 (3.0 - 52.5)
- 0 to 3] months	1210/3872 (31.2)	584/1812 (32.2)	626/2060 (30.4)
- 3 to 12] months	1305/3872 (33.7)	595/1812 (32.8)	710/2060 (34.5)
- Over 12 months	1357/3872 (35.0)	633/1812 (34.9)	724/2060 (35.1)
Thrombolytic therapy, n (%)	36/3587 (1.0)	12/1681 (0.7)	24/1906 (1.3)
Vena cava filter, n (%)	150/3893 (3.9)	85/1819 (4.7)	65/2074 (3.1)
Concomitant treatment at the time of VTE diagnosis			
Curative anticoagulant therapy, n (%)	71/3553 (2.0)	40/1661 (2.4)	31/1892 (1.6)
Antiplatelet therapy, n (%)	435/3577 (12.2)	241/1675 (14.4)	194/1902 (10.2)
Statins therapy, n (%)	381/3579 (10.6)	193/1676 (11.5)	188/1903 (9.9)

DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, SD: standard deviation

*Type of anticoagulant treatment after acute phase of VTE. Others**: any other anticoagulant agent, or multiple treatment (injectable or oral treatment relayed by another oral or injectable treatment).

For variables presented as count (percentages), no denominator is shown when there is no missing data.

Rates of CVDT in the study population

CVDT occurred in 426 participants during follow-up (10.7%), and the mean time from the diagnosis of VTE to CVDT was 3.3 years (**Table 2**). The incidence of CVDT was 1.54 per 100 patient-years in the study population, 1.63 per 100 patient-years in men, and 1.48 per 100 patient-years in women. Deaths due to VTE was the most frequent component of CVDT (42.5%), followed by heart failure (18.1%) and stroke (13.8%). The Aalen-Johansen estimation

of cumulative incidence of cardiovascular and non-cardiovascular deaths in the overall study population, and stratified by gender are presented on **Figure 2**.

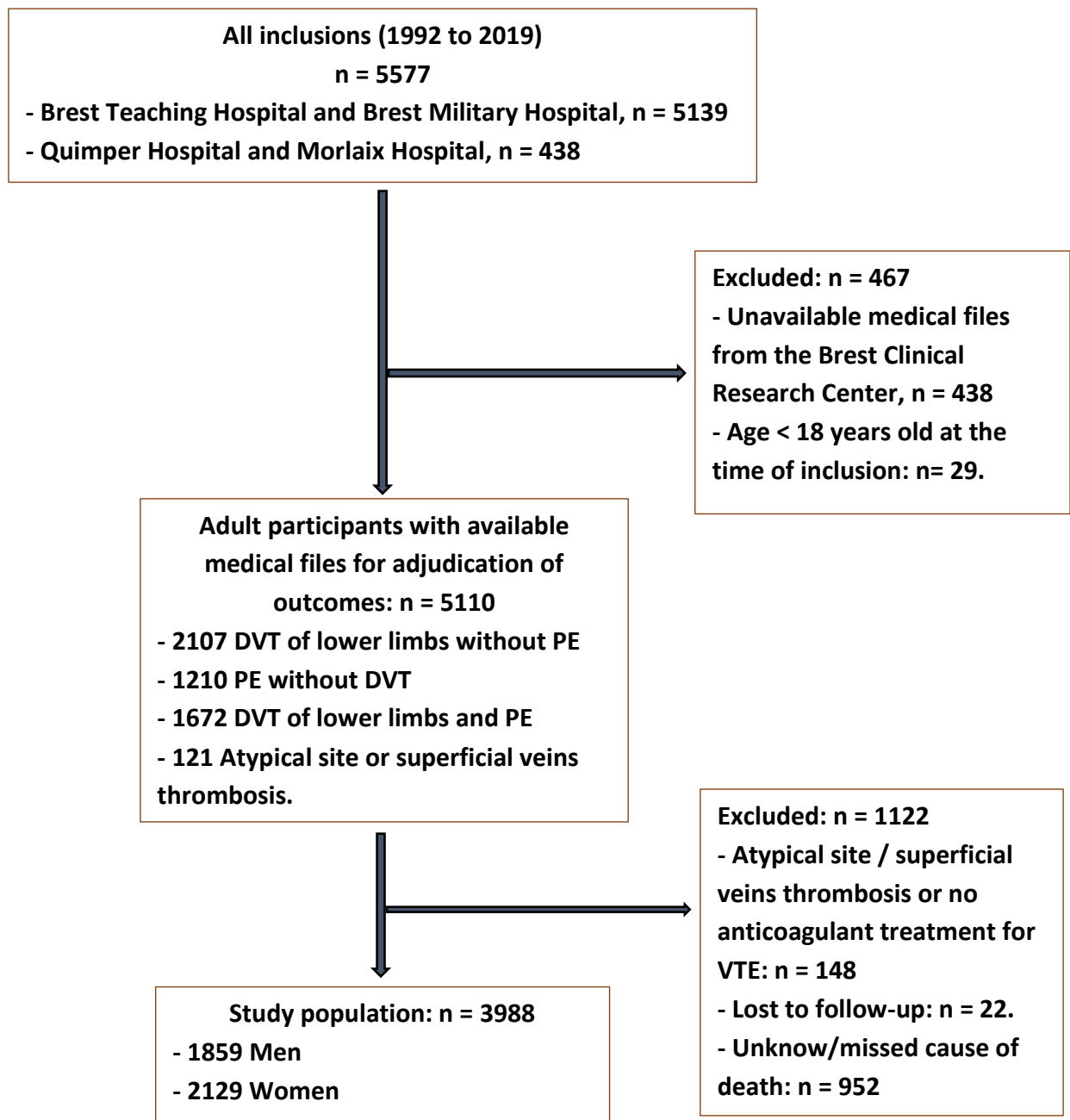
The global mortality rate in the overall study population was 3.51 per 100 patient-years, 4.04 per 100 patient-years in men, and 3.09 per 100 patient-years in women, as 968 (24.3%) of participants died during follow-up (489 men and 479 women). However, the survival probability did not fall under 50% neither in the overall study population, nor in different gender categories (**Figure 3**). Among other causes of death, cancer was reported for 252 participants (26.0% of all deaths). Rates of all-causes deaths and CVDT as well as specific causes of deaths, are given in **Table 2**, globally and stratified by gender.

Table 2: Rates of all death and cardiovascular deaths stratified by gender

	Overall (n = 3988)	Men (n = 1859)	Women (n = 2129)
All death, n (%)	968 (24.3)	489 (26.3)	479 (22.5)
Incidence of all death per 100 patient-years (95% CI)	3.51 (3.29 - 3.73)	4.04 (3.69 - 4.41)	3.09 (2.82 - 3.37)
Median survival, years	Not reached	Not reached	Not reached
Causes of Death			
- Cardiovascular, n (%)	426/968 (44.0)	197/489 (40.3)	229/479 (47.8)
- Cancer, n (%)	252/968 (26.0)	149/489 (30.5)	103/479 (21.5)
- Non cardiovascular / non cancer, n (%)	290/968 (30.0)	143/489 (29.2)	147/479 (30.7)
CVDT in all population, n (%)	426 (10.7)	197 (10.6)	229 (10.8)
Incidence of CVDT per 100 patient-years (95% CI)	1.54 (1.40 - 1.69)	1.63 (1.41 - 1.87)	1.48 (1.29 - 1.68)
Mean time from VTE to CVDT, years	3.3 ± 4.0	3.4 ± 4.3	3.1 ± 3.7
Median time from VTE to CVDT, years	2.0 (0.0 - 5.0)	1.0 (0.0 - 6.0)	2.0 (0.0 - 5.0)
Details of CVDT			
- VTE, n (%)	181/426 (42.5)	78/197 (39.6)	103/147 (45.0)
- Myocardial infarction, n (%)	20/426 (4.7)	11/197 (5.6)	9/147 (3.9)
- Stroke, n (%)	59/426 (13.8)	21/197 (10.7)	38/147 (16.6)
- Sudden death/cardiac arrest, n (%)	24/426 (5.6)	16/197 (8.1)	8/147 (3.5)
- Heart failure, n (%)	77/426 (18.1)	36/197 (18.3)	41/147 (17.9)
- Hemorrhagic complication apart from hemorrhagic stroke, n (%)	38/426 (8.9)	23/197 (11.7)	15/147 (6.6)
- Complications of cardiac or vascular intervention, n (%)	11/426 (2.6)	7/197 (3.6)	4/147 (1.7)
- Arrhythmia or conduction disorders, n (%)	9/426 (2.1)	2/197 (1.0)	7/147 (3.1)
- Visceral infarction (digestif tract/renal), n (%)	6/426 (1.4)	3/197 (1.5)	3/147 (1.3)
- Aortic dissection, n (%)	1/426 (0.2)	0/197 (0.0)	1/147 (0.4)

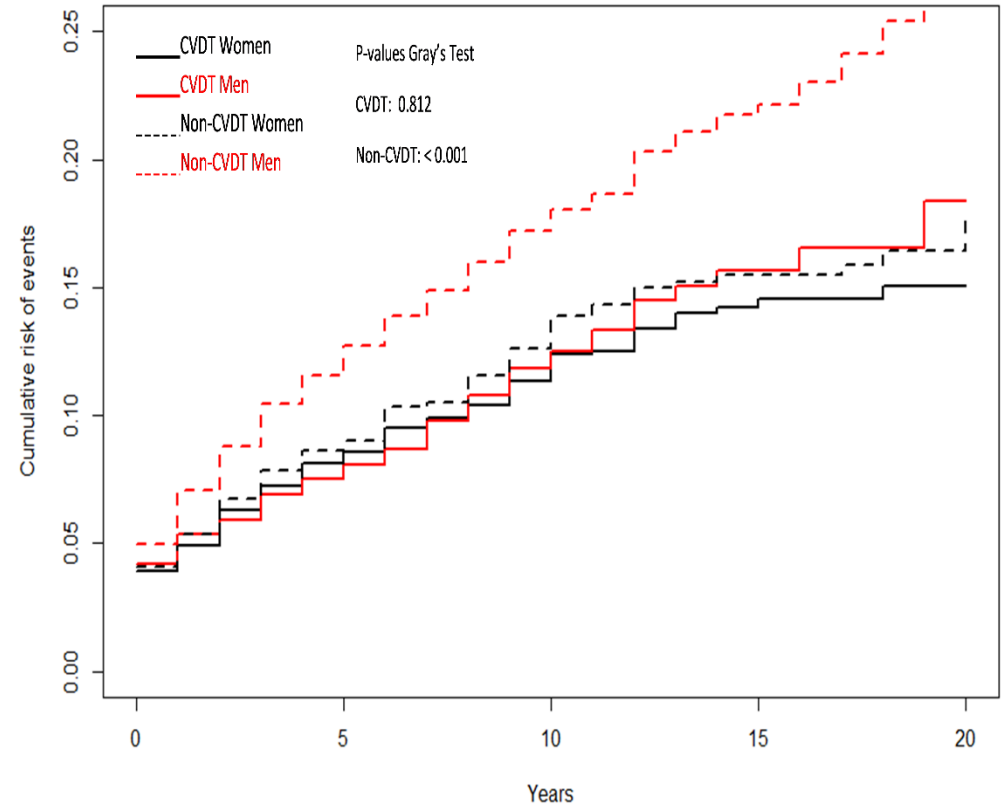
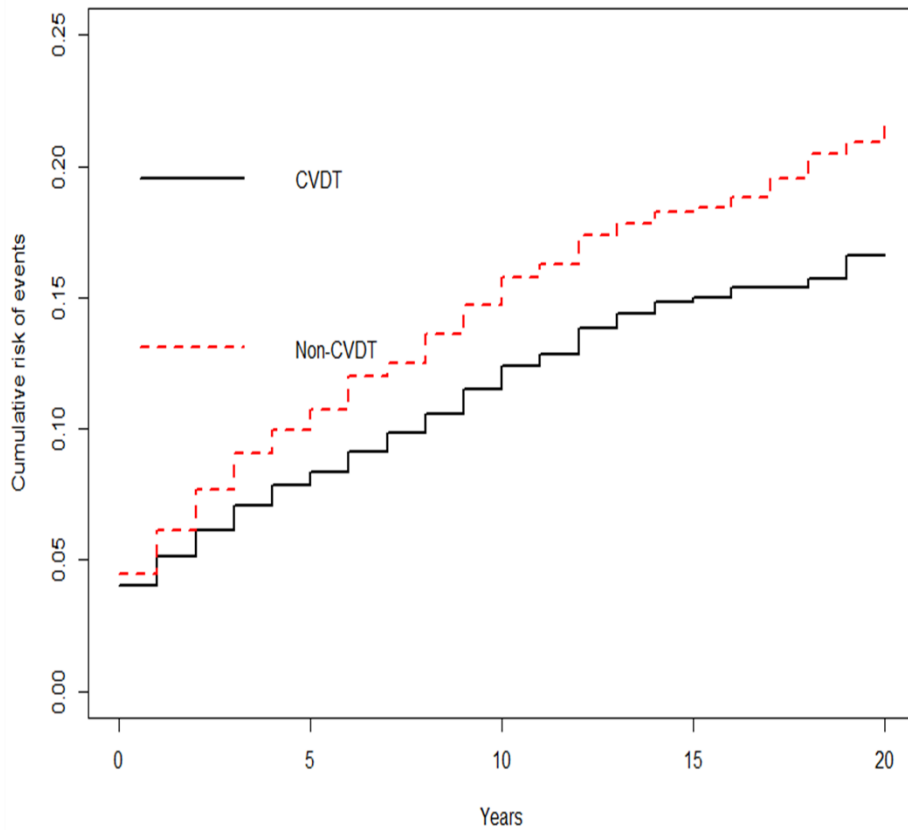
CVDT: cardiovascular death, VTE: venous thromboembolism, CI: confidence interval

For variables presented as count (percentages), no denominator is shown when there is no missing data.



DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism

Figure 1: Flow chart of the study population



Number at Risk	0	5	10	15	20
	3988	2764	1011	394	91

Number at Risk	0	5	10	15	20
Women	2129	1522	596	233	49
Men	1859	1242	415	161	42

- CVDT: cardiovascular death, Non-CVDT: non-cardiovascular death

Figure 2: Aalen–Johansen estimation of cumulative incidence of cardiovascular and non-cardiovascular deaths.

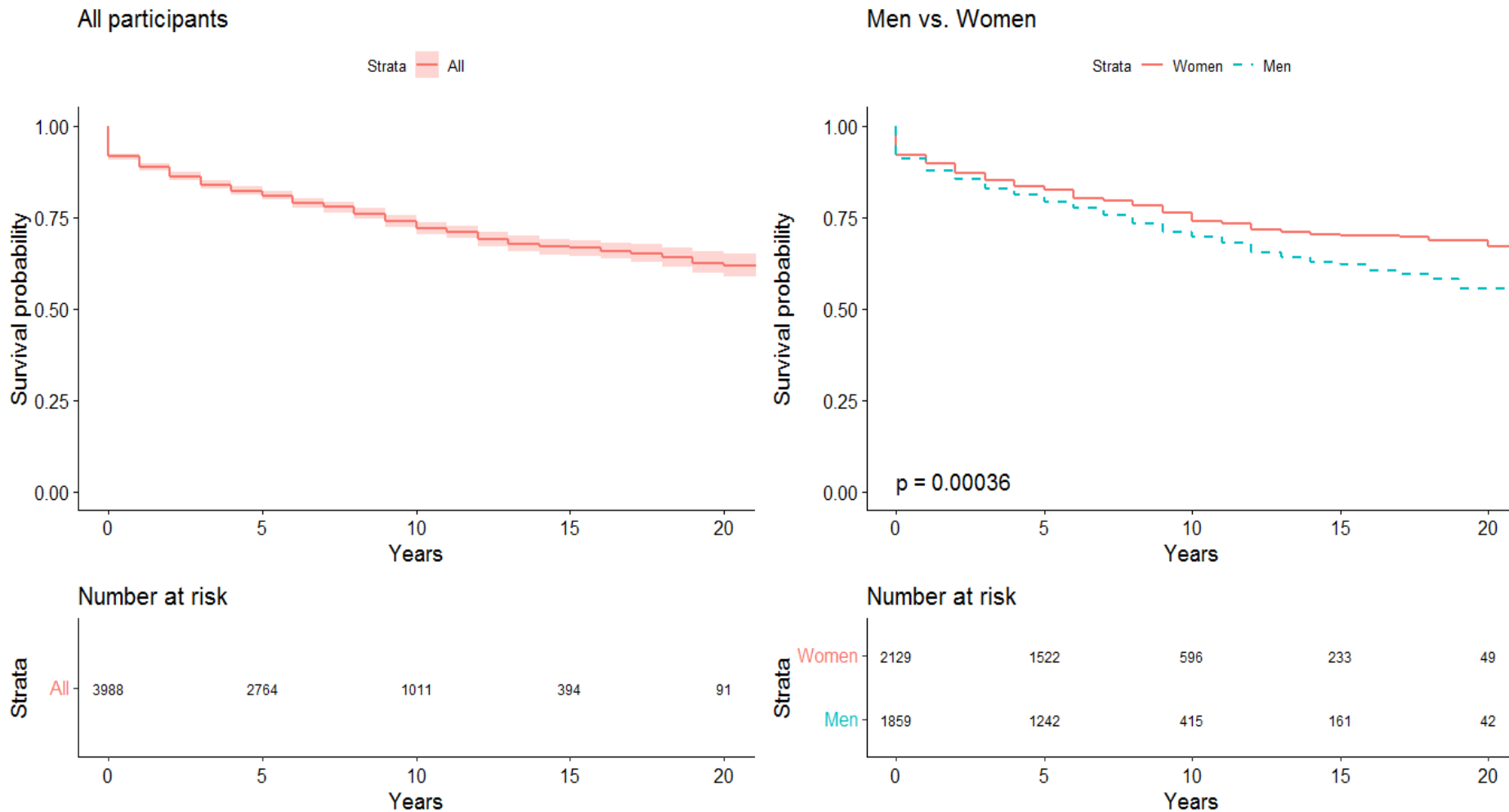


Figure 3: The Kaplan-Meier curves of survival probability in the overall study population, and stratified by gender.

Risk factors of CVDT in the study population

In univariable analysis, the identified factors associated to increased risk of CVDT in the study population were: age of 50 to 65 years (compared to age < 50 years, $p < 0.001$), age > 65 years (compared to age < 50 years, $p < 0.001$), PE associated to DVT (compared to DVT only, $p < 0.001$), cancer associated VTE (compared to transient risk factor related VTE, $p < 0.001$), unprovoked VTE (compared to transient risk factor related VTE, $p < 0.001$), past tobacco use (compared to no tobacco use, $p = 0.002$), hypertension ($p < 0.001$), past history of symptomatic atherosclerosis ($p < 0.044$), creatinine clearance < 60 mL/min ($p < 0.001$), chronic heart failure ($p < 0.001$), chronic respiratory failure ($p < 0.001$), atrial fibrillation ($p < 0.001$), treatment with low molecule weight heparin (LMWH) (compared to treatment with VKA, $p = 0.012$), vena cava filter ($p < 0.001$), ongoing antiplatelet treatment at the diagnosis of VTE ($p < 0.001$), and ongoing anticoagulant treatment at the diagnosis of VTE ($p < 0.001$) (**Table 3**).

In multivariable analysis, after adjustment for all eligible potential cofactors, the risk factors of CVDT identified in the study population were: age of 50 to 65 years (compared to age < 50 years, HR: 3.22, 95% CI: 1.67 - 6.62, $p < 0.001$), age > 65 years (compared to age < 50 years, HR: 7.60, 95% CI: 3.73 - 15.52, $p < 0.001$), cancer associated VTE (compared to transient risk factor related VTE, HR: 1.73, 95% CI: 1.15 - 2.61, $p = 0.009$), unprovoked VTE (compared to transient risk factor related VTE, HR: 1.42, 95% CI: 1.02 - 2.00, $p = 0.043$), past tobacco use (compared to no tobacco use, HR: 1.43, 95% CI: 1.06 - 1.94, $p = 0.020$), current tobacco use (compared to no tobacco use, HR: 1.87, 95% CI: 1.15 - 3.01, $p = 0.011$), hypertension (HR: 2.11, 95% CI: 1.51 - 2.96, $p < 0.001$), chronic heart failure (HR: 2.28, 95% CI: 1.37 - 3.79, $p = 0.002$), chronic respiratory failure (HR: 1.72, 95% CI: 1.02 - 2.89, $p = 0.042$), and atrial fibrillation (HR: 1.67, 95% CI: 1.06 - 2.60, $p = 0.026$).

Of note, in univariable and multivariable analysis, the risk of CVDT was significantly reduced for patients treated with DOAC (compared to patients treated with VKA, adjusted HR: 0.17, 95% CI: 0.05 - 0.54, $p = 0.003$), and for patients treated for longer duration (3 to 12 months, adjusted HR: 0.43, 95% CI: 0.29 - 0.61, $p < 0.001$; and over 12 months, adjusted HR: 0.33, 95% CI: 0.23 - 0.47, $p < 0.001$) as compared to patients treated for 0 to 3 months. It was also the case for patients with heterozygote factor V Leiden mutation (adjusted HR: 0.48, 95% CI: 0.26 - 0.88, $p = 0.017$). The results of univariable and multivariable analyses to determine risk factors of CVDT in the overall study population are presented in **Table 3**.

Table 3: risk factors of cardiovascular death, univariable and multivariable analyses

	Univariable analysis		Multivariable analysis	
	Unadjusted HR (95% CI)	p-Value	Adjusted HR (95% CI)	p-Value
General characteristics				
Gender (male)	1.02 (0.85 - 1.24)	0.800		
Age				
- < 50 years	-	ref	-	ref
- 50 to 65 years	4.30 (2.66 - 6.96)	< 0.001	3.22 (1.67 - 6.62)	< 0.001
- > 65 years	13.90 (9.07 - 21.42)	< 0.001	7.60 (3.73 - 15.52)	< 0.001
Personal past history of VTE	1.19 (0.96 - 1.48)	0.110	1.04 (0.74 - 1.43)	0.830
Blood group				
- O group	-	ref	-	ref
- Non-O group	0.75 (0.59 - 0.97)	0.027	0.99 (0.73 - 1.33)	0.950
Characteristics of VTE				
Type of VTE				
- Isolated DVT	-	ref	-	ref
- Isolated PE	1.19 (0.91 - 1.56)	0.190	0.89 (0.59 - 1.35)	0.580
- DVT and PE	2.04 (1.65 - 2.53)	< 0.001	1.38 (0.98 - 1.94)	0.068
Location of DVT (only)				
- Distal DVT	-	ref		
- Proximal DVT	0.91 (0.65 - 1.27)	0.570		
Type of VTE according to provoking factors				
- Transient factors associated VTE	-	ref	-	ref
- Cancer associated VTE	2.50 (1.91 - 3.27)	< 0.001	1.73 (1.15 - 2.61)	0.009
- Unprovoked VTE	1.84 (1.46 - 2.30)	< 0.001	1.42 (1.02 - 2.00)	0.043
Others classic cardiovascular risk factors				
Tobacco use				
- Never	-	ref	-	ref
- Past	1.44 (1.15 - 1.80)	0.002	1.43 (1.06 - 1.94)	0.020
- Current	0.55 (0.38 - 0.79)	0.001	1.87 (1.15 - 3.01)	0.011
Diabetes	1.39 (0.93 - 2.09)	0.110	0.87 (0.51 - 1.49)	0.630
Hypertension	2.65 (2.20 - 3.21)	< 0.001	2.11 (1.51 - 2.96)	< 0.001
Dyslipidemia	1.17 (0.91 - 1.49)	0.220		
Obesity/overweight	0.99 (0.81 - 1.22)	0.940		
Past history of symptomatic atherosclerosis	2.61 (2.10 - 3.25)	< 0.001	1.28 (0.84 - 1.92)	0.250
Biological characteristics at VTE diagnosis				
Anemia	1.23 (0.96 - 1.59)	0.110		
Platelet count < 150 / μ L	0.86 (0.55 - 1.32)	0.480		
Creatinine clearance (mL/min)				
- \geq 60	-	ref		
- < 60	2.53 (1.85 - 3.48)	< 0.001		
Minor thrombophilia				
Heterozygous Factor V Leiden	0.57 (0.40 - 0.81)	0.002	0.48 (0.26 - 0.88)	0.017
Heterozygous G20210A prothrombin gene variant	0.89 (0.58 - 1.36)	0.590		
Homozygous Factor V Leiden	-	-		
Homozygous G20210A prothrombin gene variant	-	-		
Heterozygous Factor V Leiden and Heterozygous G20210A prothrombin gene variant	0.99 (0.32 - 3.09)	0.990		
Others comorbidities at the diagnosis of VTE				
Chronic heart failure	5.42 (4.20 - 6.99)	< 0.001	2.28 (1.37 - 3.79)	0.002
Chronic respiratory failure	3.45 (2.54 - 4.68)	< 0.001	1.72 (1.02 - 2.89)	0.042
Atrial fibrillation	3.64 (2.66 - 4.99)	< 0.001	1.67 (1.06 - 2.60)	0.026

Treatment of VTE				
Type of anticoagulant treatment*				
- Vitamin K antagonists only	-	ref	-	ref
- Direct oral anticoagulants only	0.20 (0.09 - 0.43)	< 0.001	0.17 (0.05 - 0.54)	0.003
- Low-molecular-weight heparin only	1.40 (1.07 - 1.84)	0.012	0.79 (0.52 - 1.22)	0.290
- Others**	1.03 (0.81 - 1.32)	0.800	0.70 (0.49 - 1.02)	0.065
Duration of anticoagulant treatment				
- 0 to 3] months	-	ref	-	ref
- 3 to 12] months	0.52 (0.41 - 0.65)	< 0.001	0.43 (0.29 - 0.61)	< 0.001
- Over 12 months	0.50 (0.39 - 0.64)	< 0.001	0.33 (0.23 - 0.47)	< 0.001
Thrombolytic therapy	0.81 (0.27 - 2.43)	0.710		
Vena cava filter	2.55 (1.81 - 3.58)	< 0.001	1.35 (0.95 - 2.52)	0.082
Concomitant treatment at VTE diagnosis				
Curative anticoagulant therapy	2.89 (1.78 - 4.71)	< 0.001		
Antiplatelet therapy	2.33 (1.83 - 2.98)	< 0.001	0.81 (0.54 - 1.21)	0.300
Statins therapy	1.15 (0.83 - 1.60)	0.410		

DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, HR: hazard ratio, CI: confidence interval.

*Type of anticoagulant treatment after acute phase of VTE.

Others**: any other anticoagulant agent, or multiple treatment (injectable or oral treatment relayed by another oral or injectable treatment).

Discussion

We aimed to determine the risk factors of CVDT that occurred after VTE. The main findings of this large prospective and observational cohort study, indicate that risk factors of CVDT after VTE include some traditional major known cardiovascular risk factors and others risk factors that are related to characteristics of VTE, and patients' comorbidities. Our results also show that the risk of CVDT after VTE may also depend on the type and duration of anticoagulant treatment used for VTE.

Incidence of CVDT

The frequency and incidence of CVDT in our study population was high. In fact, 10.7% of participants included in our study died of a fatal a cardiovascular disease, given an incidence of CVDT of 1.54 per 100 patient-years in our study population. Moreover, CVDT represent 44% of all death in our study. These numbers are globally similar to those previously reported by some population-based study and those found in a recent meta-analysis [35,68,73,74,106]. Indeed, the authors reported an overall pooled frequency of CVDT of 3.9 % (13 studies, 22,251 patients), a pooled incidence of CVDT of 1.92 per 100 patient-year (4 studies), and a pooled proportion of CVDT among all-causes deaths was 35.2% (12 studies) [106]. If the frequency of CVDT found in our study seems to be higher than the frequency reported by the authors in this met-analysis, it is important to note that we excluded from our study, patients with unknown

cause of death, while for some studies included in their meta-analysis, the authors reported pooled proportion of deaths of unknown cause of 9.9% among all causes of deaths in patients with VTE (6 studies) [106]. So, the real frequency of CVDT could have been underestimated.

In the above meta-analysis, the authors reported a pooled frequency of recurrent VTE-related deaths among all causes of deaths of 8% (8 studies), while in our study, almost 43% of CVDT were due to VTE (recurrent VTE, with PE in clinical presentation, or subsequent complications of initially non-fatal PE), which represent 18.7% of all deaths (181/968). These difference can be explained on the one hand by the almost 10% frequency of death of unknown cause reported by the authors, and on the other hand, by the fact that, they only considered death related to recurrent VTE, differently to our study, were deaths due to further complications of initially non-fatal PE were classified as death related to VTE, as well as death due to recurrent VTE [106]. By the way, another meta-analysis published in 2018, reporting on the causes of death in patients with VTE anticoagulated with direct oral anticoagulants found a frequency of VTE related death among all death of 20% [70].

Risk factors of CVDT

The identified risk factors for and increased risk of CVDT after VTE in our study can be classified into three groups. The first group include some traditional known major cardiovascular risk factors (older age, past or current tobacco use, and hypertension), the second group include risk factors related to characteristics of VTE (unprovoked VTE, and cancer associated VTE), and the third group include risk factors related to comorbid conditions of patients present at the diagnosis of VTE (chronic heart failure, chronic respiratory failure and atrial fibrillation). Several studies explored the risk factors of some cardiovascular diseases and the risk factors of overall mortality in patients who developed VTE, however, to the best of our knowledge, there is no previous data on the risk factors of deaths due to cardiovascular diseases that occurred after VTE [2,14,32,68,69,73]. This could make the discussion of our results a bit complex, nevertheless, we can notice that some risk factors of CVDT identified in our study as older age, hypertension, unprovoked VTE, cancer associated VTE, and chronic lung disease, have been previously described as risk factors of subsequent arterial cardiovascular diseases after VTE in at least two observational studies [11,14–16,42].

Among other risk factors, smoking has also been reported as predictor of major cardiovascular events including CVDT, in women with VTE in one study [11]. While atrial fibrillation, and chronic heart failure which are known risk factors of cardiovascular disease and death in the general population, have been shown to have a relationship with incident VTE

[90–92,109,110]. Therefore, to efficiently deal with the prevention of CVDT after VTE, physicians should pay a particular attention for an early identification and management of these conditions. Despite the fact that, this was not the primary aim of our study, we also explored the role of anticoagulant treatment in our study on the risk of CVDT, and we found in univariable and multivariable analyses that the risk of CVDT was significantly reduced for patients treated with DOAC (vs. VKA, 83% of risk reduction in multivariable analysis), and for patients treated for longer duration (3 to 12 months vs. 0 to 3 months, 57% of risk reduction in multivariable analysis; > 12 months vs. 0 to 3 months, 77% of risk reduction in multivariable analysis). Even if these results need to be confirmed by further studies, mainly randomized controlled trials, they may already be taken into consideration for a better prevention of CVDT after VTE.

Strengths and limitations

There are several salient caveats regarding our findings. Firstly, it is important to note that our study was an open cohort with inclusion period extended on many years, thus, the changes in treatment protocols of VTE over years, could have affected the follow-up duration of some participants, and therefore, the number of CVDT finally reported. Secondly, the treatment protocols were not standardized among all centers, therefore, treatment could have varied with local practices and experiences of physicians, and thus induced some bias. Thirdly, only baseline comorbid conditions of patients present at the inclusion were considered in our analyses; thus, we could have ignored some conditions that occurred later during follow-up, and therefore omitted to explore some potential predictors of CVDT. Finally, due to insufficient data, we could not explore the role of some biological parameters as biological thrombophilia on the risk of CVDT in our study population. Notwithstanding these limitations, which should be kept in mind while interpreting our results, to the best of our knowledge, this is the first study, and the first large prospective cohort to explore the risk factors of deaths due to cardiovascular diseases that occurred after VTE. Moreover, this study, which used rigorous statistical methods, provided strong results that should have direct clinical implications for a better prevention of CVDT after VTE. It also allowed us to highlight a possible significant relation between type and duration of anticoagulant treatment introduced for VTE and the risk of subsequent CVDT; henceforth this should be explored in further studies, ideally randomized controlled trials and considered in routine clinical practice if confirmed.

Conclusions

Results from this large prospective cohort study, showed that risk factors of CVDT after VTE include traditional major cardiovascular risk factors (older age, tobacco use, and hypertension) and others risk factors that are related to characteristics of VTE (unprovoked VTE, and cancer associated VTE), and patients' comorbidities (chronic heart failure, chronic respiratory failure and atrial fibrillation). This study also showed that the risk of CVDT after VTE may also depend on the type and duration of anticoagulant treatment, with a reduction of risk for patients treated with DOAC and for patients treated for longer duration. Our findings may have potential clinical implications, as the identification and control of these identified predictors in routine clinical practice could contribute for a better prevention of cardiovascular mortality after VTE.

What is Known on this Topic?

- CVDT are more frequent patients with VTE than in general population
- Risk factors of CVDT in patients with VTE unknown

What Does this Paper Add?

- Identification from a large prospective cohort study of risk factors of CVDT in patients with VTE, which include some classic cardiovascular risk factors and other risk factors that are related to characteristics of VTE and to patients' comorbidities.
- Identification of possible role of anticoagulation for VTE on the risk of CVDT (to be confirmed by randomized controlled trial).

List of Abbreviations:

CI: Confidence Interval

CUS: Compression Ultrasonography

CVDT: Cardiovascular Death

DOAC: Direct Oral Anticoagulants

DVT: Deep Venous Thrombosis

HR: Hazard Ratio

LMWH: Low Molecule Weight Heparin

PE: Pulmonary Embolism

SD: Standard Deviation

VKA: Vitamin K Antagonists

VTE: Venous Thromboembolism

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Brest University Teaching Hospital (CCP-Ouest 6-390) with a last amendment approved on November 20, 2013 under reference number: EDITH II/RB 05.003. Administrative approvals were also obtained from authorities of the Brest University Teaching Hospital and all other recruiting centers. All participants signed a consent form.

Availability of data and materials: The data that support the findings of this study are available from SRN or FC, upon reasonable request.

Competing interests: FC reports having received research grant support from Pfizer and fees for board memberships or symposia from Bayer and Astra Zeneca and having received travel support from Bayer, Daiichi Sankyo, Leo Pharma, InterMune, and Actelion. All other authors declare that they have no competing interests related to this study.

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Author’s contributions

Conception and design: SRN, FC, LB, RD; acquisition of data: EP; Data analysis: SRN; Analysis and interpretation of data: SRN, FC, LB; Manuscript drafting: SRN; Manuscript revision: All authors; Approved the final version of the manuscript: All authors; Obtaining funding: FC. Administrative technical, and material support: FC, CT, RD. Study supervision: FC; Full access to all the data of the study: FC, SRN; responsibility for all aspect of the study, reliability and freedom from bias of the data presented: All authors.

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D. Article de résultats 4 : Impact du traitement anticoagulant sur le risque de MACE après MVTE

Cet article intitulé "*Anticoagulation for Venous Thromboembolism: impact on the Risk of Major Adverse Cardiovascular Events*" a été accepté en Mai 2022 dans le journal *CHEST*, et est en instance de publication.

I. RESUME

Rationnel : Il a été récemment établi que les patients qui ont développé une maladie veineuse thromboembolique (MVTE) courent un risque plus important d'événements cardiovasculaires indésirables majeurs (MACE) que la population générale. Cependant, on ne sait pas si l'anticoagulation utilisée pour la MVTE influence le risque de MACE.

Méthodologie : Nous avons inclus des patients d'une large cohorte prospective, qui n'ont reçu qu'une seule famille de traitement anticoagulant après la phase aiguë de MTEV, parmi lesquels l'antivitamine K (AVK) et les anticoagulants oraux directs (AOD). Les MACE incluait, les syndromes coronariens aigus non mortel, les accident vasculaire cérébraux non mortel, et les décès toutes causes. Le critère de jugement secondaire, les MACE-2, incluait les décès cardiovasculaires en lieu et place des décès toutes causes. Les modèles proportionnels de Cox et les modèles de Fine et Gray ont servi à étudier la relation entre les caractéristiques de l'anticoagulation et le risque d'évènement d'intérêt.

Résultats : Au total, 3790 patients (47,2 % d'hommes, âge moyen : 60,48 ans) ont été inclus. 1228 patients (32,4%) ont été traités pendant 0 à 3 mois (médiane : 6 mois). Comparativement à ces patients, ceux traités pendant 3 à 12 mois (HR : 0,64, IC à 95 % : 0,54 - 0,76), ou plus de 12 mois (HR : 0,47, IC à 95 % : 0,39 - 0,56) avaient un risque significativement réduit de MACE après ajustement pour les facteurs de confusion potentiels. Les résultats étaient similaires pour les MACE-2 (HR-3-12 mois : 0,61, IC à 95 % : 0,47 - 0,79 ; HR-12 mois : 0,52, IC à 95 % : 0,39 - 0,68). Après ajustement en analyse multivariée, il y avait un risque réduit de MACE (HR : 0,53, IC à 95 % : 0,39 - 0,71) et de MACE-2 (HR : 0,48, IC à 95 % : 0,29 - 0,77) chez les patients traités par AOD (vs. AVK).

Conclusion : Le traitement de la MTEV pendant plus de 3 mois est associé à une diminution de risque de MACE, tout comme le traitement par AOD versus AVK. Ces résultats, qui peuvent influencer le choix des stratégies d'anticoagulation pour la MVTE, doivent être confirmés par des essais cliniques randomisés.

Mots-clés : maladie veineuse thromboembolique, évènement cardiovasculaire majeur, traitement anticoagulant, cohorte prospective.

II. ARTICLE COMPLET

Anticoagulation for Venous Thromboembolism: impact on the Risk of Major Adverse Cardiovascular Events

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Abstract

Background: It was recently established that patients who developed venous thromboembolism (VTE) are at increased risk of major adverse cardiovascular events (MACE) than the general population. However, whether the anticoagulation used for VTE influences the risk of MACE remains undescribed.

Research question: Does the anticoagulant treatment for VTE impact the risk of subsequent MACE?

Study design and methods: We included patients from a large prospective cohort, who received only one family of anticoagulant treatment after the acute phase of VTE, among which, vitamin K antagonist (VKA), and direct oral anticoagulants (DOAC). MACE included non-fatal acute coronary syndrome, or non-fatal stroke, or all-cause death. The secondary outcome, MACE-2, included cardiovascular deaths instead of all-cause deaths. Cox proportional and Fine and Gray models served to study the relationship between anticoagulation characteristics and the risk of outcomes.

Results: A total of 3790 patients (47.2% of men, mean age: 60.48 years) were included. 1228 patients (32.4%) were treated for 0 to 3 months (median: 6 months). Compared to these patients, those treated for 3 to 12 (HR: 0.64, 95% CI: 0.54 - 0.76), or over 12 months (HR: 0.47, 95% CI: 0.39 - 0.56) had a significant reduced risk of MACE after adjustment for confounders. Findings were similar for MACE-2 (HR-3-12 months: 0.61, 95% CI: 0.47 - 0.79; HR-over 12 months: 0.52, 95% CI: 0.39 - 0.68). After adjustment for confounders, there was a reduced risk of MACE (HR: 0.53, 95% CI: 0.39 - 0.71) and MACE-2 (HR: 0.48, 95% CI: 0.29 - 0.77) in patients treated with DOAC (vs. VKA).

Interpretation: Treatment of VTE for more than 3 months is associated with a reduced risk of MACE, as is treatment with DOAC versus VKA. These findings, which may influence the choice of anticoagulation strategies for VTE, need confirmation by randomized clinical trials.

Keywords: Venous thromboembolism, major adverse cardiovascular events, anticoagulant therapy, prospective cohort.

Introduction

Heart attacks, stroke and venous thromboembolism (VTE), represent the three most frequent causes of death in the general population worldwide. Despite the effort done in recent years for the prevention and management of VTE, this vascular disease remains frequent in clinical practice [3–5]. If there has been for several years some controversies in the scientific community about the higher risk of cardiovascular complications after VTE, updated data from recent literature confirmed that all Major adverse cardiovascular events (MACE) are more frequent in patients who developed VTE than in the general population without VTE [12,106].

Regarding the management of VTE, the arrival of direct oral anticoagulants (DOAC) has been of great advance in the fight against this disorder [10]. According to recommendations of various learned societies, DOAC rejoined the group of the most frequently used anticoagulant agents in the treatment of VTE, with low molecule weight heparin (LMWH), and vitamin K antagonist (VKA) [61,63,98]. They are even recommended as first line therapy in several clinical situation [98]. However, it is important to note that type and duration of anticoagulant treatment for the management of VTE are mainly determined by the risk of recurrence based on provoking factors of VTE, and the risk of bleeding complications [10]. For example, patients with VTE provoked by transient risk factor should be treated for 3 months, patients with cancer-associated VTE, for at least 6 months, and patients with unprovoked VTE for indefinite duration in absence of high risk of bleeding complication [61–63].

If several observational studies and randomized clinical trials explored the impact of anticoagulant therapy in terms of duration as well as in terms of type or family of treatment, on the risk of recurrent VTE and on the risk of hemorrhagic complications, and supported for some of them the current recommendations, studies exploring the impact of anticoagulant therapy on the risks of MACE are lacking [62,93,111–113]. Of course, the prevention or treatment of arterial cardiovascular events is mainly based on antiplatelet therapy, instead of anticoagulant therapy as in VTE [54]. However, while considering the overall risk of cardiovascular complications after VTE, to know if the anticoagulation for VTE has an impact on the risk of subsequent MACE could influence the decision regarding the duration of treatment, and even the choice of the type of treatment particularly if anticoagulation is recommended for long duration.

Therefore, in this study, we examined the relationship between the duration and type of anticoagulant treatment and the risk of MACE that occurred after VTE.

Methods

Study design and setting

Patients included in this study are from a large prospective and multicentric cohort of patient with VTE in the west of France. Details on setting were previously described [89]. The study was approved by the Ethics Committee of Brest University Teaching Hospital (CCP-Ouest 6-390). All participants were informed about the different aspects of the study and were included between April 1992 and December 2019, only after providing a signed informed consent form.

Patients selection criteria

All potentially eligible patients aged 18 years old or over who was seen at consultation or during hospitalization in one of the four recruiting hospitals, were consecutively enrolled if they have a confirmed diagnosis of symptomatic VTE. Symptomatic DVT was confirmed by non-compression of deep vein of the lower limbs using a real-time B mode compression ultrasonography (CUS) [78]. Symptomatic PE was diagnosed by one of the following: (i) a positive computed tomography pulmonary angiography showing a central filling defect outlined by contrast material or a complete occlusion in a segmental or more proximal pulmonary artery; (ii) or a pulmonary angiography with an intraluminal filling defect or a sharp cut-off in a vessel of at least 2 mm in diameter; (iii) or a ventilation perfusion lung scan indicating a high probability for PE (using Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria); (iiii) or a high clinical probability associated to a proximal DVT on CUS [79]. Patients with atypical site or superficial veins thrombosis as well as patients unable to read and sign the informed consent form or those who refused to participate were not included. This study was limited to patients who received only one family of anticoagulant treatment after acute phase of VTE, among vitamin K antagonists (VKA), direct oral anticoagulants (DOAC) and low molecule weight heparin (LMWH).

Data collection and follow-up

Characteristics of selected patients were collected at inclusion using a standardized questionnaire. The collected characteristics presented in this study include general characteristics (gender and age), characteristics of VTE (DVT or PE and provoking factor of VTE), cardiovascular risk factors (tobacco use, diabetes, hypertension, dyslipidemia, obesity, and past history of symptomatic atherosclerosis), comorbidities (chronic heart failure and atrial fibrillation), concomitant treatment at VTE diagnosis (antiplatelet therapy, anticoagulant therapy or statins), and type of treatment initiated for VTE.

Unprovoked VTE was defined as VTE without cancer or major transient provoking factor including: surgery with general anesthesia >30 minutes, leg fracture or leg injury with plaster cast, acute illness with hospitalization for at least three days, ongoing pregnancy or delivery, ongoing estrogen contraceptive treatment, ongoing menopause substitutive hormonal therapy, or hormonal therapy for assisted reproduction, all within the past three months. Tobacco use was classified as never, former, or current; diabetes, hypertension and dyslipidemia were defined by the presence of these diseases among known medical conditions in participants' files, or by the presence of respective specific medications in patient's treatment at inclusion, and patients reporting having these diseases. Height and weight were self-reported except for patients who could be weighted. Body mass index (BMI) was then computerized and obesity was defined for values ≥ 30.0 kg/m² [81]. Past history of symptomatic atherosclerosis was defined as a self-reported and file confirmation of past myocardial infarction, stroke, or symptomatic peripheral artery disease of lower limbs.

The management of VTE (choice of type and duration of anticoagulant treatment) was done based on updated recommendations for good clinical practice, at the time of inclusion and on patient's clinical characteristics. There was no standardization of clinical practices among participants hospitals. After inclusion, patients were instructed to return for follow-up visits at 3, 6, and 12 months. Further follow-ups were scheduled annually and could be done during a physical consultation at the clinical research center of Brest University Teaching Hospital, or by phone call. Participants who did not presented themselves for consultation and did not respond to phone call, were sent a letter by postal mail. The follow-up period was defined as time between the inclusion date and the last contact visit or the date of death (when there were enough details on circumstances of death and cause of death was adjudicated). For patients who temporally stopped anticoagulant treatment (with or without physicians agreement'), the duration of anticoagulation was the time between the beginning and the first discontinuation, and for patients who did not stopped anticoagulant treatment at the last follow-up, the duration of anticoagulation was the duration from the beginning of the treatment until the last follow-up date.

Definition of outcomes

Our primary outcome was Major Adverse Cardiovascular Events (MACE), which included one of the following: all-cause death, non-fatal stroke, and non-fatal acute coronary syndrome. As in several previous studies, all-cause death was preferred to cardiovascular death, as the third component of MACE in our study because adjudication of unobserved deaths also

known as deaths of unknown causes has always been a challenge in clinical research [114,115]. Moreover, unobserved deaths has been often considered as deaths of cardiovascular origin unless a non-cardiovascular cause could be clearly proven [116]. We therefore considered MACE-2 made of non-fatal acute coronary syndrome, non-fatal stroke or cardiovascular death, as our secondary outcome. To avoid under-estimation of cardiovascular death and therefore MACE-2, all analysis concerning this outcome were done in a subgroup of study population excluding patients for whom the causes of death were unknown (unobserved deaths) and who did not have non-fatal acute coronary syndrome or non-fatal stroke during follow-up. All events of interest were predefined and prospectively collected via case report forms, and the files of all patients in whom at least one event of interest occurred during follow-up were checked for adjudication by an independent clinical adjudication committee.

Acute coronary syndrome was defined as the presence of typical ischemic chest pain and a final validated diagnosis of ST elevation or non-ST elevation myocardial infarction, or unstable angina [83]. Stroke was defined by the presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting more than 24 hours associated to compatible vascular abnormalities on computerized tomography (CT) or Magnetic Resonance Imaging (MRI) [84]. Cardiovascular death was defined as death resulting of one of the following causes: pulmonary embolism, myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedures, hemorrhage, ruptured aortic aneurysm, aortic dissection, or other cardiovascular causes [71].

Statistical analyses

The study population was stratified into three groups based on the duration of the anticoagulant therapy: one group made of patients treated for 0 to 3 months, one group made of patients treated for 3 to 12 months, and one group made of patients treated for more than 12 months. Results are presented as frequency (percentage) for categorical variables, and mean \pm standard deviation (SD) or median (25th-75th percentiles) for continuous variables where applicable. Groups' comparisons used the Chi-square test, the Student *t*-test or equivalents where appropriate. The cumulative hazard of MACE over time was calculating according to the Kaplan–Meier life-table method, and Aalen–Johansen estimator was used to calculate the cumulative risk of MACE-2 [87].

The rates of MACE in two groups were compared using the log-rank test, and the cumulative incidences of MACE-2 in two groups was compared using Gray's K-sample method, also known as Gray's test [88]. To study the relationship between anticoagulation

characteristics (type and duration) and the risk of MACE, we used univariable and multivariable cox proportional-hazard models. For the relation between these characteristics and the risk of MACE-2, we used univariable and multivariable sub-distribution hazards models, also known as Fine-Gray models, considering non-cardiovascular deaths as competing risk events. The multivariable models included for the two outcomes all characteristics of the study population that had a significant different distribution among the three groups of participants stratified by the categories of anticoagulant duration and was statistically associated to the outcome in univariable analysis.

All univariable and multivariable models were complete-cases models excluding missing data. However, in addition to our main analyses, we conducted sensitivity analysis for the main outcome (MACE) after multiple imputation of the database. Hazard ratios (HR) were always reported with the 95% confidence interval (CI). Data were compiled in an Excel file (Microsoft Excel version 2016), and analyzed using the statistical software R, version 3.6.3. All tests were two-sided and a p-value < 0.05 characterized statistically significant results. Patients for whom, we did not succeed in getting news during follow-up for more than one year after their inclusion in the studies and before December 31, 2020, were considered lost to follow-up and not included in the final analysis nor presented in the results.

Results

Participant characteristic's

A total of 3790 patients were included in this study (mean age: 60.48 ± 18.72 years), of which 1787 were men (47.2%). **The Supplementary figure 1** shows the flow chart of participants. The median duration of anticoagulant treatment was 6.0 months (interquartile range, IQR: 3.0-35.8). Of the study population, 1228 patients were treated for 0 to 3 months (32.4%), 1271 patients were treated for 3 to 12 months (33.5%), and 1291 patients were treated for over 12 months (34.1%). The median follow-up was 68.0 months in the overall study population (IQR: 36.0-119.0). Vitamin K antagonists (VKA) was the most frequent type of anticoagulant in the study population (2788 patients, 73.6%). **Table 1** gives the characteristics of the study population stratified by duration of anticoagulant treatment, and **Table 2** gives the characteristics of the study population stratified by type of anticoagulant treatment.

Table 1: Characteristics of the study population stratified by duration of anticoagulation

	Overall, N = 3790	Duration of treatment			p-values
		0 to 3] months N = 1228	3 to 12] months N = 1271	Over 12 months N = 1291	
General characteristics					
Gender (male)	1787 (47.2)	582 (47.4)	605 (47.6)	600 (46.5)	0.832
Mean age at VTE diagnosis (years) ± SD	60.48 ± 18.72	59.38 ± 19.09	58.28 ± 19.21	63.69 ± 17.42	<0.001
Age categories					<0.001
- < 50 years, n (%)	1111 (29.3)	402 (32.7)	422 (33.2)	287 (22.2)	
- 50 to 65 years, n (%)	911 (24.0)	308 (25.1)	288 (22.7)	315 (24.4)	
- > 65 years, n (%)	1768 (46.6)	518 (42.2)	561 (44.1)	689 (53.4)	
Personal history of VTE, n (%)	848/3779 (22.4)	212/1222 (17.3)	220/1269 (17.3)	416/1288 (32.3)	<0.001
Characteristics of VTE					
Type of VTE					<0.001
- DVT only, n (%)	1618 (42.7)	632 (51.5)	555 (43.7)	431 (33.4)	
- PE only, n (%)	917 (24.2)	237 (19.3)	306 (24.1)	374 (29.0)	
- DVT and PE, n (%)	1255 (33.1)	359 (29.2)	410 (32.3)	486 (37.6)	
Type of VTE according to provoking factors					<0.001
- Transient factors associated VTE, n (%)	1394 (36.8)	481 (39.2)	509 (40.0)	404 (31.3)	
- Cancer associated VTE, n (%)	677 (17.9)	265 (21.6)	187 (14.7)	225 (17.4)	
- Unprovoked VTE, n (%)	1719 (45.4)	482 (39.3)	575 (45.2)	662 (51.3)	
Classic cardiovascular risk factors					
Tobacco use, n (%)					0.012
- Never, n (%)	1659/3198 (51.9)	458/933 (49.1)	596/1126 (52.9)	605/1139 (53.1)	
- Past, n (%)	990/3198 (31.0)	295/933 (31.6)	325/1126 (28.9)	370/1139 (32.5)	
- Current, n (%)	549/3198 (17.2)	180/933 (19.3)	205/1126 (18.2)	164/1139 (14.4)	
Diabetes, n (%)	166 (4.4)	38 (3.1)	48 (3.8)	80 (6.2)	<0.001
Hypertension, n (%)	1179 (31.1)	299 (24.3)	367 (28.9)	513 (39.7)	<0.001
Dyslipidemia, n (%)	563 (14.9)	119 (9.7)	201 (15.8)	243 (18.8)	<0.001
Obesity, n (%)	675/3376 (20.0)	178/1041 (17.1)	214/1167 (18.3)	283/1168 (24.2)	<0.001
History of symptomatic atherosclerosis, n (%)	507 (13.4)	161 (13.1)	145 (11.4)	201 (15.6)	0.008
Other comorbidities at the diagnosis of VTE					
Chronic heart failure, n (%)	201 (5.3)	72 (5.9)	46 (3.6)	83 (6.4)	0.004
Atrial fibrillation, n (%)	160/3200 (5.0)	42/932 (4.5)	38/1131 (3.4)	80/1137 (7.0)	<0.001
Renal failure (creatinine clearance < 60 mL/min)	419/1430 (29.3)	111/415 (26.7)	126/413 (30.5)	182/602 (30.2)	0.397
Treatment of VTE					

Type of anticoagulant treatment					<0.001
- Vitamin K antagonists only, n (%)	2788 (73.6)	677 (55.1)	1069 (84.1)	1042 (80.7)	
- Direct oral anticoagulants only, n (%)	441 (11.6)	228 (18.6)	82 (6.5)	131 (10.1)	
- Low-molecular-weight heparin only, n (%)	561 (14.8)	323 (26.3)	120 (9.4)	118 (9.1)	
Permanent discontinuation of anticoagulant treatment during follow-up					<0.001
- No	2163 (57.1)	428 (34.9)	557 (43.8)	1178 (91.2)	
- Yes	1627 (42.9)	800 (65.1)	714 (56.2)	113 (8.8)	
Duration of anticoagulant therapy					
Median (interquartile range), months	6.0 (3.0 - 35.8)	1.0 (0.0 - 3.0)	6.0 (5.0 - 7.0)	61.0 (34.0 - 97.5)	<0.001
Duration categories					<0.001
- 0 to 3] months	1228 (32.4)	1228 (100.0)	0 (0.0)	0 (0.0)	
- 3 to 12] months	1271 (33.5)	0 (0.0)	1271 (100.0)	0 (0.0)	
- Over 12 months	1291 (34.1)	0 (0.0)	0 (0.0)	1291 (100.0)	
Ongoing treatment at the diagnosis of VTE					
Anticoagulant therapy, n (%)	84/3179 (2.6)	40/948 (4.2)	11/1105 (1.0)	33/1126 (2.9)	<0.001
Antiplatelet therapy, n (%)	418/3203 (13.1)	105/942 (11.1)	109/1127 (9.7)	204/1134 (18.0)	<0.001
Statins therapy, n (%)	327/3207 (10.2)	86/942 (9.1)	99/1131 (8.8)	142/1134 (12.5)	0.005

DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, SD: standard deviation

For variables presented as count (percentages), no denominator is shown when there is no missing data.

Table 2: Characteristics of the study population stratified by type of anticoagulant treatment

	Overall, N = 3790	Type of treatment			p-values
		VKA N = 2788	DOAC N = 441	LMWH N = 561	
General characteristics					
Gender (male)	1787 (47.2)	1262 (45.3)	241 (54.6)	284 (50.6)	<0.001
Mean age at VTE diagnosis (years) ± SD	60.48 ± 18.72	61.77 ± 18.73	52.85 ± 17.65	60.04 ± 18.10	<0.001
Age categories					<0.001
- < 50 years, n (%)	1111 (29.3)	752 (27.0)	203 (46.0)	156 (27.8)	
- 50 to 65 years, n (%)	911 (24.0)	627 (22.5)	120 (27.2)	164 (29.2)	
- > 65 years, n (%)	1768 (46.6)	1409 (50.5)	118 (26.8)	241 (43.0)	
Personal history of VTE, n (%)	848/3779 (22.4)	667/2778 (24.0)	77/440 (17.5)	104/561 (18.5)	0.001
Characteristics of VTE					
Type of VTE					<0.001
- DVT only, n (%)	1618 (42.7)	1233 (44.2)	175 (39.7)	210 (37.4)	
- PE only, n (%)	917 (24.2)	598 (21.4)	148 (33.6)	171 (30.5)	
- DVT and PE, n (%)	1255 (33.1)	957 (34.3)	118 (26.8)	180 (32.1)	
Type of VTE according to provoking factors					<0.001

- Transient factors associated VTE, n (%)	1394 (36.8)	1056 (37.9)	168 (38.1)	170 (30.3)	
- Cancer associated VTE, n (%)	677 (17.9)	349 (12.5)	46 (10.4)	282 (50.3)	
- Unprovoked VTE, n (%)	1719 (45.4)	1383 (49.6)	227 (51.5)	109 (19.4)	
Classic cardiovascular risk factors					
Tobacco use, n (%)					< 0.001
- Never, n (%)	1659/3198 (51.9)	1210/2214 (54.7)	220/438 (50.2)	229/546 (41.9)	
- Past, n (%)	990/3198 (31.0)	639/2214 (28.9)	123/438 (28.1)	228/546 (41.8)	
- Current, n (%)	549/3198 (17.2)	365/2214 (16.5)	95/438 (21.7)	89/546 (16.3)	
Diabetes, n (%)	166 (4.4)	117 (4.2)	12 (2.7)	37 (6.6)	0.008
Hypertension, n (%)	1179 (31.1)	858 (30.8)	119 (27.0)	202 (36.0)	0.007
Dyslipidemia, n (%)	563 (14.9)	418 (15.0)	67 (15.2)	78 (13.9)	0.785
Obesity, n (%)	675/3376 (20.0)	487/2396 (20.3)	102/434 (23.5)	86/546 (15.8)	0.008
History of symptomatic atherosclerosis, n (%)	507 (13.4)	412 (14.8)	31 (7.0)	64 (11.4)	<0.001
Other comorbidities at the diagnosis of VTE					
Chronic heart failure, n (%)	201 (5.3)	175 (6.3)	8 (1.8)	18 (3.2)	<0.001
Atrial fibrillation, n (%)	160/3200 (5.0)	115/2215 (5.2)	8/10 (1.9)	37/554 (6.7)	0.002
Renal insufficiency (creatinine clearance < 60 mL/min)	419/1430 (29.3)	306/812 (37.7)	32/256 (12.5)	81/362 (22.4)	<0.001
Treatment of VTE					
Type of anticoagulant treatment					<0.001
- Vitamin K antagonists only, n (%)	2788 (73.6)	2788 (100.0)	0 (0.0)	0 (0.0)	
- Direct oral anticoagulants only, n (%)	441 (11.6)	0 (0.0)	441 (100.0)	0 (0.0)	
- Low-molecular-weight heparin only, n (%)	561 (14.8)	0 (0.0)	0 (0.0)	561 (100.0)	
Permanent discontinuation of anticoagulant treatment during follow-up					<0.001
- No	2163 (57.1)	1632 (58.5)	211 (47.8)	320 (57.0)	
- Yes	1627 (42.9)	1156 (41.5)	230 (52.2)	241 (43.0)	
Duration of anticoagulant therapy					
Median (interquartile range), months	6.0 (3.0 - 35.8)	6.0 (4.0 - 57.0)	3.0 (0.0 - 24.0)	2.0 (0.0 - 9.0)	<0.001
Duration categories					<0.001
- 0 to 3] months	1228 (32.4)	677 (24.3)	228 (51.7)	323 (57.6)	
- 3 to 12] months	1271 (33.5)	1069 (38.3)	82 (18.6)	120 (21.4)	
- Over 12 months	1291 (34.1)	1042 (37.4)	131 (29.7)	118 (21.0)	
Ongoing treatment at the diagnosis of VTE					
Anticoagulant therapy, n (%)	84/3179 (2.6)	44/2186 (2.0)	4/435 (0.9)	36/558 (6.5)	<0.001
Antiplatelet therapy, n (%)	418/3203 (13.1)	311/2207 (14.1)	38/441 (8.6)	69/555 (12.4)	0.007
Statins therapy, n (%)	327/3207 (10.2)	222/2211 (10.0)	48/441 (10.9)	57/555 (10.3)	0.865

VKA: vitamin K antagonists, DOAC: direct oral anticoagulants, LMWH: low molecule weight heparin, DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, SD: standard deviation.

For variables presented as count (percentages), no denominator is shown when there is no missing data.

MACE in the study population

Of the overall study population, MACE occurred in 1520 patients during follow-up (40.1%), annual incidence: 6.30 per 100 patient-years (95% CI: 6.00-6.62). The median duration from the diagnosis of VTE to MACE was 30.0 months (IQR: 7.0-70.0). The mortality rate in the overall study population was 5.59 per 100 patient-years (95% CI: 5.31-5.89), and all-cause death was the most frequent component of MACE (1281/1520, 84.3%), followed by non-fatal stroke (164/1520, 10.8%). The **Table 3** gives the frequency and incidence of MACE in the study population with distribution according to anticoagulation duration.

MACE-2 in the study population

Cardiovascular deaths represented 23.2% of all deaths (324/1398) in the study population. Excluding patients who died of unobserved deaths without having had others components of MACE-2, cardiovascular deaths represented 43.4% of all death (324/746) and was the most frequent component of MACE-2 (300/539, 55.7%), which occurred in 16.8% of patients (539/3201), leading to an annual incidence of MACE-2 of 2.24 per 100 patient-years (95% CI: 2.06-2.44) (**Table 3**).

Table 3: MACE, and causes of death stratified by duration of anticoagulation

Overall study population	Overall N = 3790	0 to 3] months N = 1228	3 to 12] months N = 1271	Over 12 months N = 1291	<i>p-values</i>
Median follow-up, months	68.0 (36.0 - 119.0)	51.0 (9.0 - 97.3)	90.0 (60.0 - 146.0)	70.0 (49.0 - 108.0)	<0.001
Characteristics of MACE					
MACE, n (%)	1520 (40.1)	565 (46.0)	474 (37.3)	481 (37.3)	<0.001
Incidence of MACE per 100 patient-years (95% CI)	6.30 (6.00 - 6.62)	9.01 (8.32 - 9.76)	4.90 (4.48 - 5.35)	5.88 (5.38 - 6.41)	<0.001
Components of MACE					
- Non-fatal acute coronary syndrome, n (%)	75/1520 (4.9)	19/565 (3.4)	25/474 (5.3)	31/481 (6.4)	
- Non-fatal stroke, n (%)	164/1520 (10.8)	44/565 (7.8)	62/474 (13.1)	58/481 (12.1)	
- All-causes death, n (%)	1281/1520 (84.3)	502/565 (88.8)	387/474 (81.6)	392/481 (81.5)	
Characteristics of MACE-2					
MACE-2, n (%)	539/3201 (16.8)	188/997 (18.9)	181/1110 (16.3)	170/1094 (15.5)	0.108
Incidence of MAC-2 per 100 patient-years (95% CI)	2.24 (2.06 - 2.44)	3.01 (2.59 - 3.46)	1.88 (1.61 - 2.17)	2.08 (1.78 - 2.41)	<0.001
Components of MACE-2					
					<0.001

- Non-fatal acute coronary syndrome, n (%)	75/539 (13.9)	19/188 (10.1)	25/181 (13.8)	31/170 (18.2)	
- Non-fatal stroke, n (%)	164/539 (30.4)	44/188 (23.4)	62/181 (34.3)	58/170 (34.1)	
- Cardiovascular death, n (%)	300/539 (55.7)	125/188 (66.5)	94/181 (51.9)	81/170 (47.6)	
Characteristic of death					
Total deaths, n (%)	1398 (36.9)	540 (44.0)	422 (33.2)	436 (33.8)	<0.001
Mortality rate per 100 patient-years (95% CI)	5.59 (5.31 - 5.89)	8.37 (7.71 - 9.07)	4.19 (3.81 - 4.60)	5.14 (4.68 - 5.64)	<0.001
Median survival, years	17 (14 - 19)	12 (10 - 14)	Not reached (21 - Not reached)	14 (12 - Not reached)	<0.001
Causes of death					0.092
Known	- Cardiovascular, n (%)	324/1398 (23.2)	138/540 (25.6)	102/422 (24.2)	84/436 (19.3)
	- Cancer, n (%)	201/1398 (14.4)	79/540 (14.6)	62/422 (14.7)	60/436 (13.8)
	- Non cardiovascular / non cancer, n (%)	221/1398 (15.8)	78/540 (14.4)	77/422 (18.2)	66/436 (15.1)
Unknown, n (%)	652/1398 (46.6)	245/540 (45.4)	181/422 (42.9)	226/436 (51.8)	
Cardiovascular deaths among all deaths of known causes, n (%)	324/746 (43.4)	138/295 (46.8)	102/241 (42.3)	84/210 (40.0)	0.290
Component of cardiovascular deaths					0.007
- VTE, n (%)	135/324 (41.7)	74/138 (53.6)	33/102 (32.4)	28/84 (33.3)	
- Myocardial infarction, n (%)	14/324 (4.3)	5/138 (3.6)	5/102 (4.9)	4/84 (4.8)	
- Stroke, n (%)	45/324 (13.9)	17/138 (12.3)	16/102 (15.7)	12/84 (14.3)	
- Sudden death/cardiac arrest, n (%)	20/324 (6.2)	7/138 (5.1)	9/102 (8.8)	4/84 (4.8)	
- Heart failure, n (%)	59/324 (18.2)	12/138 (8.7)	22/102 (21.6)	25/84 (29.8)	
- Cardiovascular hemorrhagic complications apart from hemorrhagic stroke, n (%)	29/324 (9.0)	16/138 (11.6)	8/102 (7.8)	5/84 (6.0)	
- Complications of cardiac or vascular intervention, n (%)	9/324 (2.8)	4/138 (2.9)	2/102 (2.0)	3/84 (3.6)	
- Arrhythmia or conduction disorders, n (%)	7/324 (2.2)	1/138 (0.7)	3/102 (2.9)	3/84 (3.6)	
- Visceral infarction (digestif tract/renal), n (%)	5/324 (1.5)	1/138 (0.7)	4/102 (3.9)	0/84 (0.0)	
- Aortic dissection, n (%)	1/324 (0.3)	1/138 (0.7)	0/102 (0.0)	0/84 (0.0)	

MACE: major adverse cardiovascular event including non-fatal acute coronary syndrome, non-fatal stroke and all-cause death

MACE-2: major adverse cardiovascular events including non-fatal acute coronary syndrome, non-fatal stroke, and cardiovascular death

VTE: venous thromboembolism, CI: confidence interval.

For variables presented as count (percentages), no denominator is shown when there is no missing data.

Duration of anticoagulant therapy and the risk of MACE

Compared to patients treated for 0 to 3 months, the risk of MACE was significantly lower in patients treated for longer periods in univariable and multivariable analyses (**Table 4**). Indeed, the adjusted HR was 0.64 (95% CI: 0.54-0.76, $p < 0.001$) for patients treated for 3 to 12 months group, and 0.47 (95% CI: 0.39-0.56, $p < 0.001$) for patients treated for more than 12 months (**Table 4**). The **Figure 1** shows the curves of the cumulative risk of MACE comparing patients treated for 3 to 12 months and over 12 months to those treated for 0 to 3 months. We found similar results exploring the relationship between duration of anticoagulant treatment and the risk of MACE after multiple imputation (**Supplementary table 1**), and while adjusting for renal failure in patients for whom creatine clearance were available (HR 3-12 months vs. 0-3 months: 0.58, 95% CI: 0.46-0.75, $p < 0.001$; HR 3-12 months vs. 0-3 months: 0.44, 95% CI: 0.35-0.56, $p < 0.001$).

Type of anticoagulant therapy and the risk of MACE

Compared to patients treated only with VKA, patients treated with DOAC showed significant lower risk of MACE in univariable and multivariable analyses (adjusted HR: 0.53, 95% CI: 0.39-0.71, $p < 0.001$). While patients treated with LMWH had a significantly higher risk of MACE in univariable and multivariable analyses (adjusted HR: 1.46, 95% CI: 1.23-1.75, $p < 0.001$). Cumulative incidence of MACE stratified by type of anticoagulant treatment is presented on **Supplementary figure 2**.

Anticoagulant therapy and the risk of MACE-2

The risk of MACE-2 was also significantly lower in patients treated for longer periods in univariable and multivariable analysis (**Supplementary table 4**). The adjusted sHR was 0.61 (95% CI: 0.47-0.79, $p < 0.001$) for the 3 to 12 months group, and 0.52 (95% CI: 0.39-0.68, $p < 0.001$) for the over 12 months group, as compared to the 0 to 3 months group (**Supplementary table 4**). The curves of the cumulative risk of MACE-2 (Aalen-Johansen estimation) stratified by duration of anticoagulant treatment is presented on the **Figure 2**.

Compared to patients treated with VKA, patients treated with DOAC showed significant lower risk of MACE-2 in univariable and multivariable analyses (adjusted sHR: 0.48, 95% CI: 0.29-0.77, $p < 0.001$). While the comparison of the risk of MACE-2 between patients treated with LMWH and those treated with VKA gave non statistically significant results in multivariable analysis (adjusted sHR: 1.07, 95% CI: 0.80-1.43, $p = 0.63$).

The **Figure 3** shows forest plots of the adjusted HR from the multivariable analyses of the relationship between anticoagulant characteristics and the risk of MACE and MACE-2. The relationship between other characteristics of the study population and the risk of outcomes in univariable analyses are given in **Supplementary table 3** for MACE and **Supplementary table 4** for MACE-2.

Sensitivity analyses

After excluding the first 3 months of follow-ups subsequent to the diagnosis of VTE, 3674 patients were still at risk of MACE and 1415 had MACE during follow-up (38,5%). The risk of MACE remained significantly lower in patients treated for 3 to 12 months (adjusted HR: 0.76, 95% CI: 0.63-0.91, $p < 0.001$) and in patients treated for over 12 months (adjusted HR: 0.57, 95% CI: 0.47-0.68, $p < 0.001$), as compared to patients treated for 0 to 3 months (**Figure 4**).

After excluding the VTE-related death from MACE-2 and adjusted analyses for potential cofounders (footnote supplementary table 2), we found a significant relationship between anticoagulation duration and the risk of MACE-2 (HR 3-12 months vs. 0-3 months: 0.48, 95% CI: 0.31-0.74, $p < 0.001$; HR 3-12 months vs. 0-3 months: 0.35, 95% CI: 0.21-0.56, $p < 0.001$).

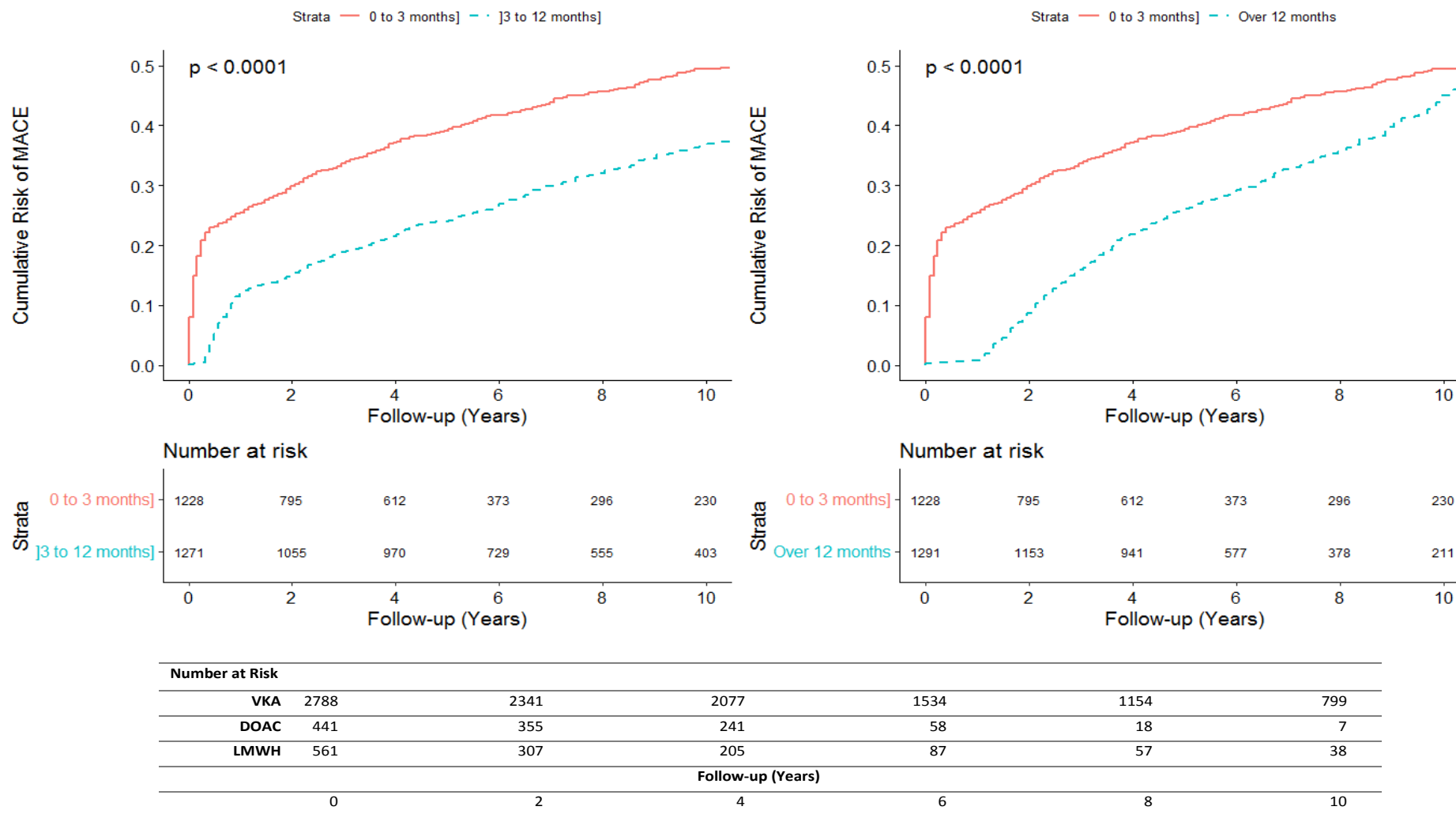
Table 4: Relationship between anticoagulant therapy and the risk of MACE

	Univariable analysis		Multivariable analysis*	
	Unadjusted HR (95% CI)	p-Value	Adjusted HR (95% CI)	p-Value
Type of anticoagulant treatment				
- Vitamin K antagonists only	-	ref	-	ref
- Direct oral anticoagulants only	0.41 (0.31 - 0.54)	< 0.001	0.53 (0.39 - 0.71)	< 0.001
- Low-molecular-weight heparin only	2.00 (1.75 - 2.28)	< 0.001	1.46 (1.23 - 1.75)	< 0.001
Duration of anticoagulant therapy				
- 0 to 3] months	-	ref	-	ref
- 3 to 12] months	0.61 (0.54 - 0.68)	< 0.001	0.64 (0.54 - 0.76)	< 0.001
- Over 12 months	0.66 (0.59 - 0.75)	< 0.001	0.47 (0.39 - 0.56)	< 0.001

MACE: major adverse cardiovascular event including non-fatal acute coronary syndrome, non-fatal stroke and all-causes death

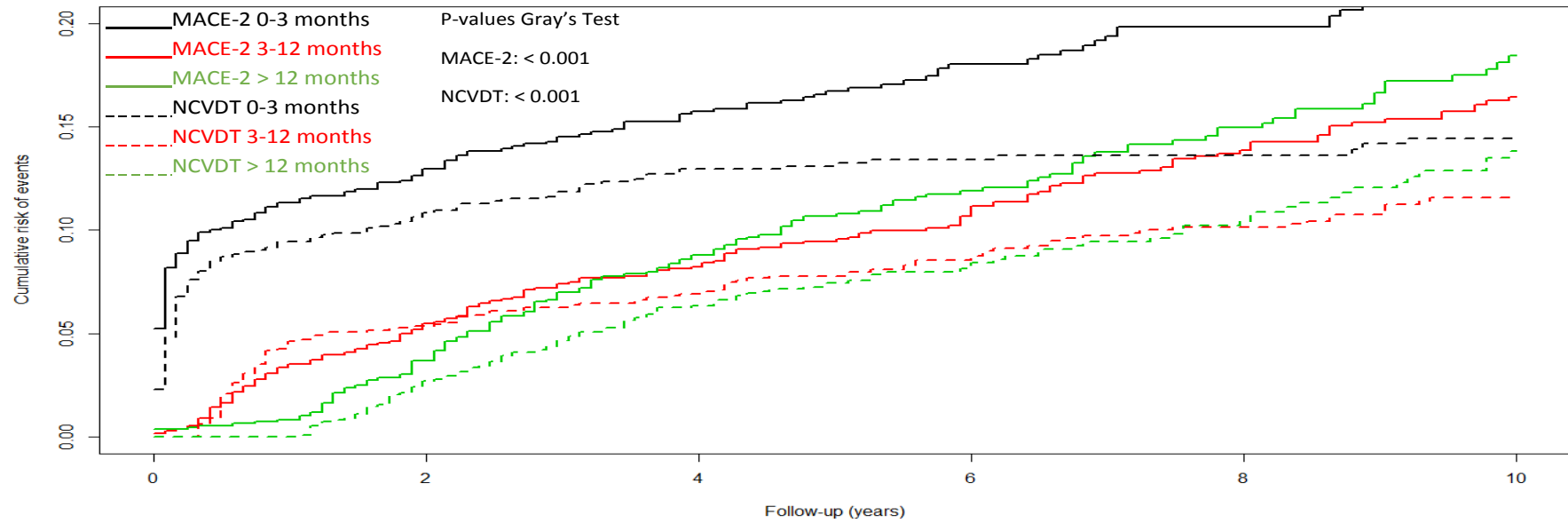
HR: hazard ratio, CI: confidence interval.

*Adjusted for age, personal history of VTE, type of VTE, provoking factor of VTE, tobacco use, diabetes, hypertension, dyslipidemia, obesity, history of symptomatic atherosclerosis, chronic heart failure, atrial fibrillation, ongoing anticoagulant treatment at the diagnosis of VTE, ongoing anti-platelet therapy and ongoing statin therapy at the diagnosis of VTE.



MACE: major adverse cardiovascular event including non-fatal acute coronary syndrome, non-fatal stroke and all-causes death. VKA: vitamin K antagonists, DOAC: direct oral anticoagulants, LMWH: low molecule weight heparin.

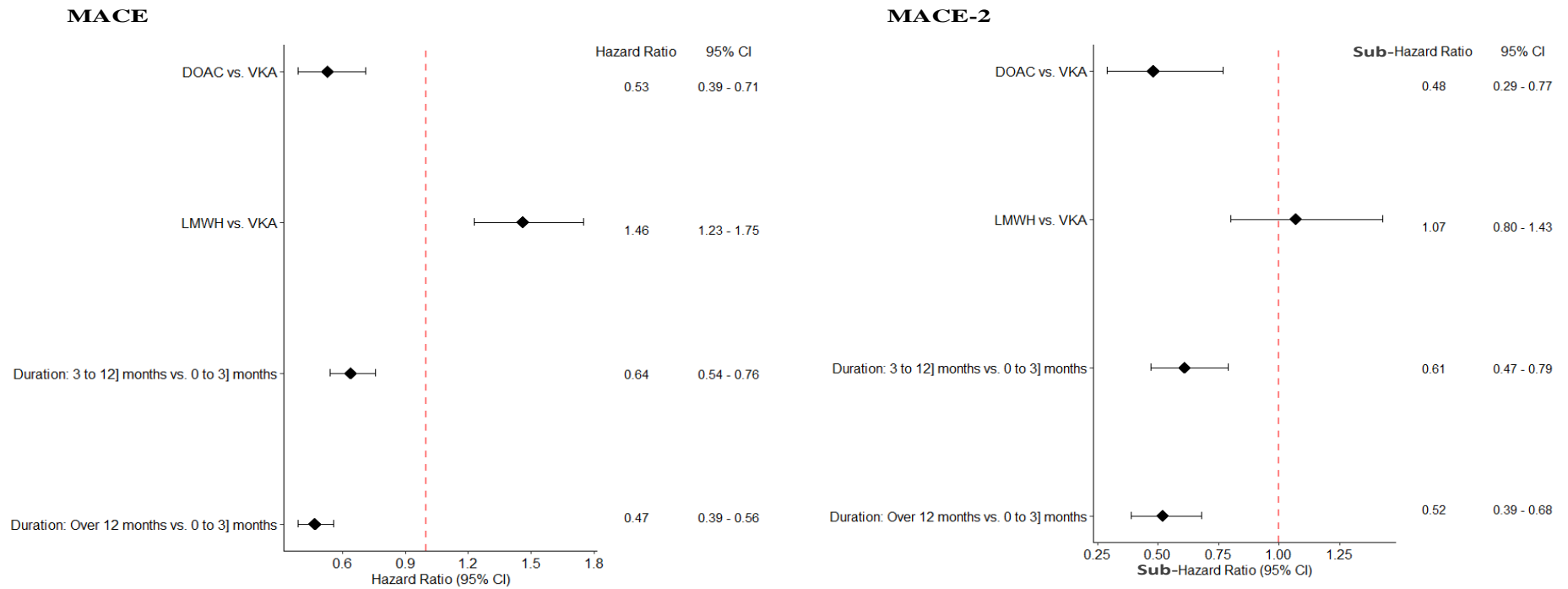
Figure 1: Cumulative incidence of MACE stratified by duration of treatment.



Number at Risk						
0-3 months	997	691	544	326	263	208
3-12 months	1110	966	912	684	523	380
> 12 months	1094	997	856	523	343	195
VKA	2300	2031	1874	1392	1055	738
DOAC	421	342	238	56	17	7
LMWH	480	281	200	85	57	38

MACE-2: major adverse cardiovascular events including non-fatal acute coronary syndrome, non-fatal stroke, and cardiovascular death
 NCVDT: non-cardiovascular deaths in patient who do not have non-fatal acute coronary syndrome or stroke.
 VKA: vitamin K antagonists, DOAC: direct oral anticoagulants, LMWH: low molecule weight heparin.

Figure 2: Cumulative incidence of MACE-2 and non-cardiovascular deaths stratified by duration of treatment.



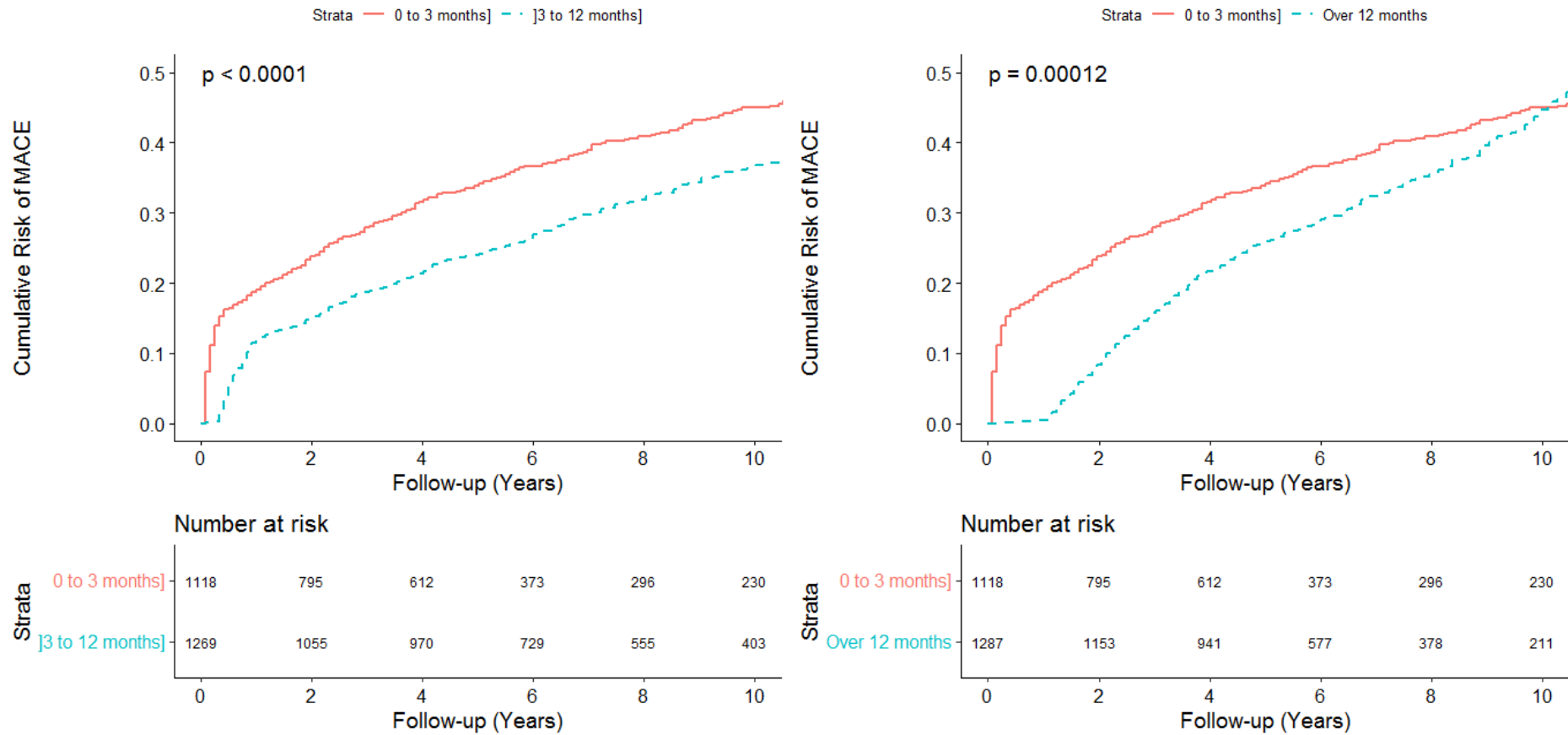
MACE: major adverse cardiovascular event including non-fatal acute coronary syndrome, non-fatal stroke and all-causes death

MACE-2: major adverse cardiovascular events including non-fatal acute coronary syndrome, non-fatal stroke, and cardiovascular death

VKA: vitamin K antagonists, DOAC: direct oral anticoagulants, LMWH: low molecule weight heparin, CI: confidence interval.

Multivariable models adjusted for age, personal history of VTE, type of VTE, provoking factor of VTE, tobacco use, diabetes, hypertension, dyslipidemia, obesity, history of symptomatic atherosclerosis, chronic heart failure, atrial fibrillation, ongoing anticoagulant treatment at the diagnosis of VTE, ongoing anti-platelet therapy and ongoing statin therapy at the diagnosis of VTE.

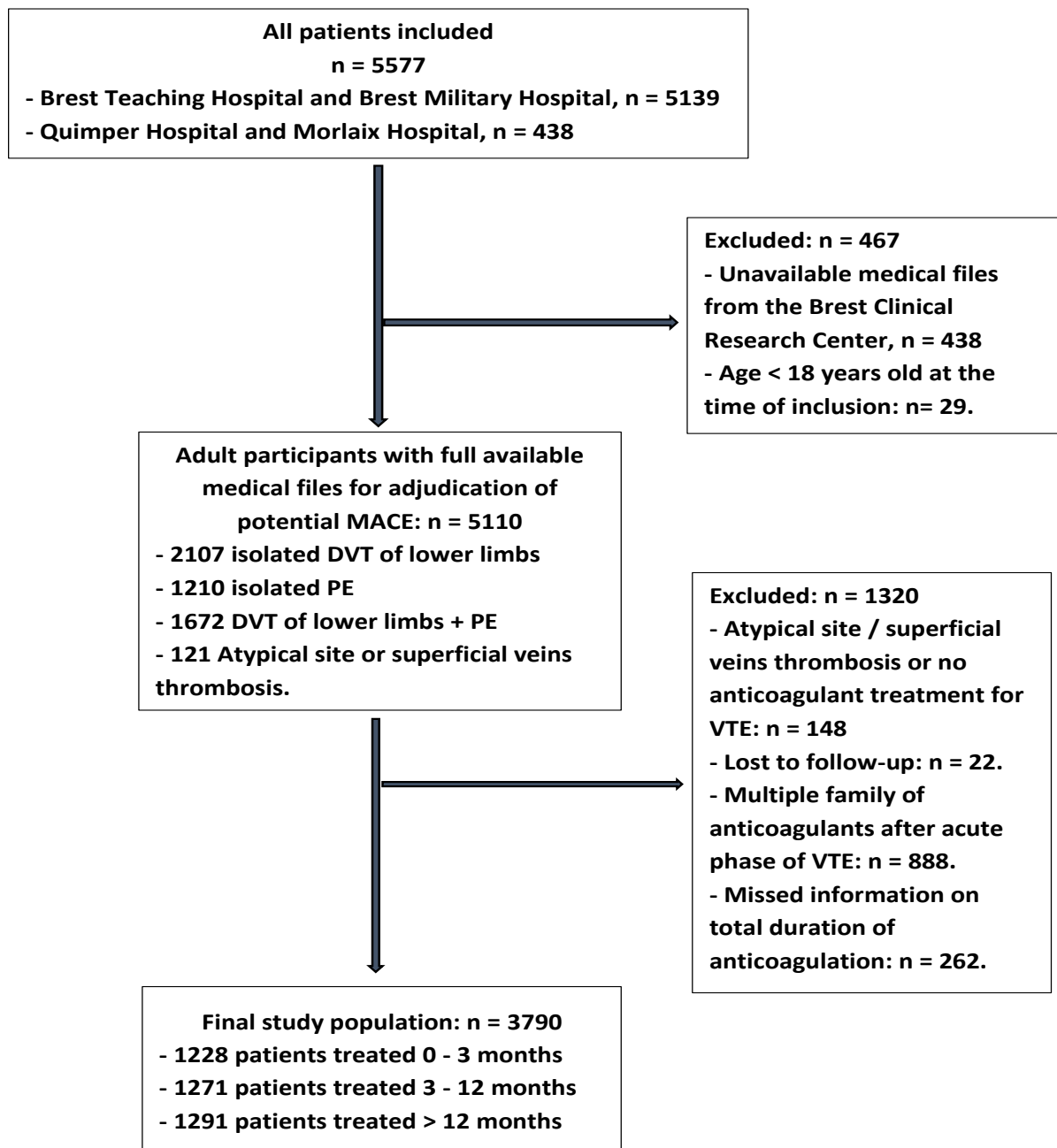
Figure 3: Anticoagulant characteristics and risk of MACE, adjusted hazard, and sub-hazard ratios.



MACE: major adverse cardiovascular event including non-fatal acute coronary syndrome, non-fatal stroke and all-causes death

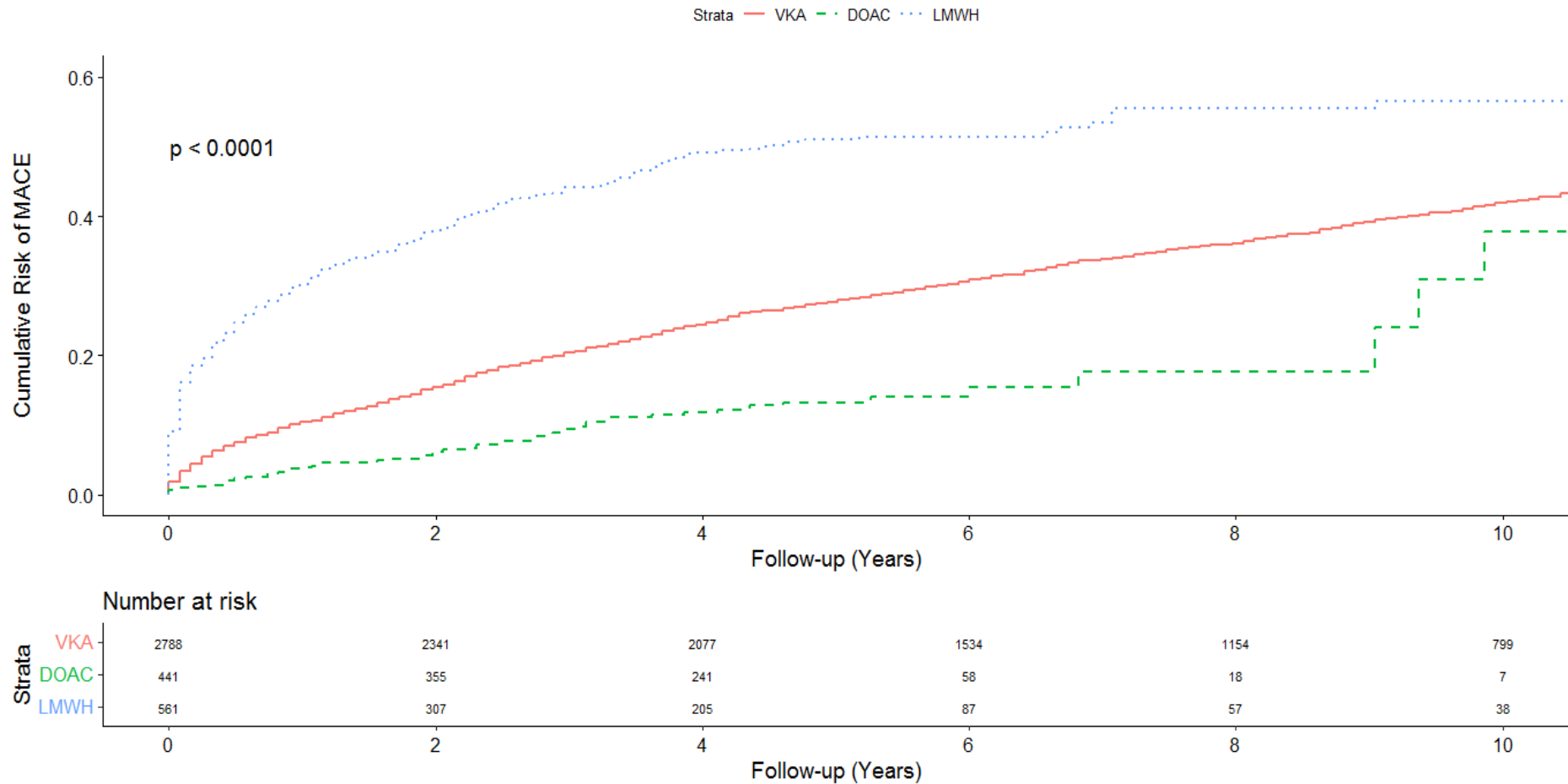
Note: time 0 on this graph correspond to 3 months after diagnosis of VTE

Figure 4: Cumulative incidence of MACE stratified by duration of treatment from 3 months after diagnosis of VTE.



DVT: deep venous thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, MACE: major adverse cardiovascular events

Supplementary figure 1: Flow chart of participants to the study.



VKA: vitamin K antagonists, DOAC: direct oral anticoagulants therapy, LMWH: low molecule weight heparin, MACE: major adverse cardiovascular events

Supplementary Figure 2: Cumulative incidence of MACE stratified by type of anticoagulant treatment.

Supplementary table 1: Relationship between anticoagulant therapy and the risk of MACE after multiple imputation

	Univariable analysis		Multivariable analysis*	
	Unadjusted HR (95% CI)	p-Value	Adjusted HR (95% CI)	p-Value
Type of anticoagulant treatment				
- Vitamin K antagonists only	-	ref	-	ref
- Direct oral anticoagulants only	0.41 (0.31 - 0.54)	< 0.001	0.49 (0.37 - 0.64)	< 0.001
- Low-molecular-weight heparin only	2.00 (1.75 - 2.28)	< 0.001	1.46 (1.25 - 1.69)	< 0.001
Duration of anticoagulant therapy				
- 0 to 3] months	-	ref	-	ref
- 3 to 12] months	0.61 (0.54 - 0.68)	< 0.001	0.60 (0.53 - 0.69)	< 0.001
- Over 12 months	0.66 (0.59 - 0.75)	< 0.001	0.47 (0.41 - 0.54)	< 0.001

MACE: major adverse cardiovascular event, HR: hazard ratio, CI: confidence interval.

*Adjusted for age, personal past history of VTE, type of VTE, provoking factor of VTE, tobacco use, diabetes, hypertension, dyslipidemia, obesity, past history of symptomatic atherosclerosis, chronic heart failure, atrial fibrillation, ongoing anticoagulant treatment at the diagnosis of VTE, ongoing anti-platelet therapy and ongoing statin therapy at the diagnosis of VTE.

Supplementary table 2: Relationship between anticoagulant therapy and the risk of MACE-2

	Univariable analysis		Multivariable analysis*	
	Unadjusted sHR (95% CI)	p-Value	Adjusted sHR (95% CI)	p-Value
Type of anticoagulant treatment				
- Vitamin K antagonists only	-	ref	-	ref
- Direct oral anticoagulants only	0.39 (0.26 - 0.61)	< 0.001	0.48 (0.29 - 0.77)	< 0.001
- Low-molecular-weight heparin only	1.31 (1.04 - 1.64)	0.011	1.07 (0.80 - 1.43)	0.630
Duration of anticoagulant therapy				
- 0 to 3] months	-	ref	-	ref
- 3 to 12] months	0.71 (0.58 - 0.87)	< 0.001	0.61 (0.47 - 0.79)	< 0.001
- Over 12 months	0.76 (0.62 - 0.93)	< 0.001	0.52 (0.39 - 0.68)	< 0.001

MACE-2: major adverse cardiovascular events including non-fatal acute coronary syndrome, non-fatal stroke, and cardiovascular death

sHR: sub-hazard ratio, CI: confidence interval.

*Adjusted for age, personal past history of VTE, type of VTE, provoking factor of VTE, tobacco use, diabetes, hypertension, dyslipidemia, past history of symptomatic atherosclerosis, chronic heart failure, atrial fibrillation, ongoing anticoagulant treatment at the diagnosis of VTE, ongoing statin therapy at the diagnosis of VTE, and ongoing anti-platelet therapy at the diagnosis of VTE.

Supplementary table 3: Relationship between characteristic of participants and the risk of MACE, univariable analysis

	Univariable analysis	
	Unadjusted HR (95% CI)	p-Value
General characteristics		
Gender (male)	1.22 (1.11 - 1.35)	< 0.001
Age		
- < 50 years	-	ref
- 50 to 65 years	4.05 (3.27 - 5.03)	< 0.001
- > 65 years	10.53 (8.69 - 12.76)	< 0.001
Personal past history of VTE	1.14 (1.02 - 1.29)	0.024
Characteristics of VTE		
Type of VTE		
- DVT only	-	ref
- PE only	1.05 (0.91 - 1.19)	0.524
- DVT and PE	1.46 (1.30 - 1.63)	< 0.001
Type of VTE according to provoking factors		
- Transient factors associated VTE	-	ref
- Cancer associated VTE	4.72 (4.10 - 5.42)	< 0.001
- Unprovoked VTE	1.74 (1.54 - 1.97)	< 0.001
Others classic cardiovascular risk factors		
Tobacco use		
- Never,	-	ref
- Past	1.54 (1.35 - 1.74)	< 0.001
- Current	0.66 (0.54 - 0.79)	< 0.001
Diabetes	1.86 (1.51 - 2.29)	< 0.001
Hypertension	2.20 (1.99 - 2.45)	< 0.001
Dyslipidemia	1.17 (1.01 - 1.34)	0.031
Obesity	0.88 (0.76 - 1.01)	0.068
Past history of symptomatic atherosclerosis	2.77 (2.46 - 3.13)	< 0.001
Others comorbidities at the diagnosis of VTE		
Chronic heart failure	3.73 (3.18 - 4.37)	< 0.001
Atrial fibrillation	3.68 (3.06 - 4.45)	< 0.001
Renal insufficiency (creatinine clearance < 60 mL/min)	2.68 (2.26 - 3.18)	< 0.001
Treatment of VTE		
Type of anticoagulant treatment		
- Vitamin K antagonists only	-	ref
- Direct oral anticoagulants only	0.41 (0.31 - 0.54)	< 0.001
- Low-molecular-weight heparin only	2.00 (1.75 - 2.28)	< 0.001
Duration of anticoagulant therapy		
- 0 to 3] months	-	ref
- 3 to 12] months	0.61 (0.54 - 0.68)	< 0.001
- Over 12 months	0.66 (0.59 - 0.75)	< 0.001
Ongoing treatment at the diagnosis of VTE		
Anticoagulant therapy	4.01 (3.11 - 5.19)	< 0.001
Antiplatelet therapy	2.60 (2.26 - 2.99)	< 0.001
Statins therapy	1.39 (1.16 - 1.67)	< 0.001

MACE: major adverse cardiovascular event including non-fatal acute coronary syndrome, non-fatal stroke and all-causes death

HR: hazard ratio, CI: confidence interval, DVT: deep venous thrombosis, MACE: major adverse cardiovascular event, PE: pulmonary embolism, VTE: venous thromboembolism, CI: confidence interval.

Supplementary table 4: Relationship between characteristic of participants and the risk of MACE-2, univariable analysis

	Univariable analysis	
	Unadjusted HR (95% CI)	p-Value
General characteristics		
Gender (male)	1.12 (0.95 - 1.32)	0.190
Age		
- < 50 years	-	ref
- 50 to 65 years	2.55 (1.83 - 3.55)	< 0.001
- > 65 years	7.53 (5.70 - 9.94)	< 0.001
Personal past history of VTE	1.28 (1.06 - 1.54)	0.010
Characteristics of VTE		
Type of VTE		
- DVT only	-	ref
- PE only	1.11 (0.88 - 1.40)	0.360
- DVT and PE	1.78 (1.47 - 2.15)	< 0.001
Type of VTE according to provoking factors		
- Transient factors associated VTE	-	ref
- Cancer associated VTE	2.18 (1.71 - 2.78)	< 0.001
- Unprovoked VTE	1.69 (1.39 - 2.05)	< 0.001
Others classic cardiovascular risk factors		
Tobacco use		
- Never,	-	ref
- Past	1.38 (1.13 - 1.69)	0.001
- Current	0.66 (0.48 - 0.89)	0.007
Diabetes	1.76 (1.27 - 2.45)	< 0.001
Hypertension	2.56 (2.17 - 3.02)	< 0.001
Dyslipidemia	1.41 (1.14 - 1.74)	0.001
Obesity	1.07 (0.86 - 1.32)	0.560
Past history of symptomatic atherosclerosis	2.89 (2.39 - 3.51)	< 0.001
Others comorbidities at the diagnosis of VTE		
Chronic heart failure	4.60 (3.56 - 5.95)	< 0.001
Atrial fibrillation	3.36 (2.51 - 4.50)	< 0.001
Renal insufficiency (creatinine clearance < 60 mL/min)	2.35 (1.76 - 3.15)	< 0.001
Treatment of VTE		
Type of anticoagulant treatment		
- Vitamin K antagonists only	-	ref
- Direct oral anticoagulants only	0.39 (0.26 - 0.61)	< 0.001
- Low-molecular-weight heparin only	1.31 (1.04 - 1.64)	0.022
Duration of anticoagulant therapy		
- 0 to 3] months	-	ref
- 3 to 12] months	0.71 (0.58 - 0.87)	< 0.001
- Over 12 months	0.76 (0.62 - 0.93)	0.008
Ongoing treatment at the diagnosis of VTE		
Anticoagulant therapy	3.10 (2.05 - 4.67)	< 0.001
Antiplatelet therapy	2.57 (2.06 - 3.19)	< 0.001
Statins therapy	1.56 (1.19 - 2.05)	0.001

MACE-2: major adverse cardiovascular events including non-fatal acute coronary syndrome, non-fatal stroke, and cardiovascular death

HR: hazard ratio, CI: confidence interval, DVT: deep venous thrombosis, CVDT: cardiovascular death, PE: pulmonary embolism, VTE: venous thromboembolism, CI: confidence interval.

Discussion

This prospective cohort study shows that there is a significant association between anticoagulation for VTE and risk of subsequent MACE. Indeed, after adjustment for all potential confounding variables, anticoagulant treatment for more than 3 months was associated with at least 36% reduction of the risk of MACE. While patients treated with DOAC had a 47% reduced risk of MACE as compared to patients treated with VKA.

As previously reported in the literature, our study found high rates of MACE in patients with VTE with an incidence of 6.30 per 100 patient-years [14,15]. MACE occurred in 40% of the study population, and this proportion seems higher than the 24% found in a study published in 2017 [15]. However, the authors included in their composite MACE outcome, all stroke and all acute coronary syndrome, while in our study MACE included non-fatal acute coronary syndrome, non-fatal stroke, and all-cause deaths [15]. Moreover, considering cardiovascular deaths instead of all-cause deaths, we had only a 16.8 % proportion of MACE (MAC-2) in our study population. It is also important to mention that in the above study, the authors reported 17.36% frequency of all-cause deaths in the VTE population [15].

Concerning the potential relationship between the duration of anticoagulant treatment introduced for VTE and the risk of subsequent MACE, our results highlighted a reduced risk of these complications in patients treated for longer duration. Indeed, comparing patients treated for 3 to 12 months or patients treated for more than 12 months to patients treated for 0 to 3 months, we found respective risk reduction of 36% and 53% for MACE, and similar results were observed, considering cardiovascular deaths as the third component of MACE, with a 39% risk reduction of MACE-2 in patients treated for 3 to 12 months and 48% risk reduction of MACE-2 in patients treated for over 12 months, as compared to patients treated for 0 to 3 months. Based on these findings which resulted from analyses that were adjusted on the risk factors of VTE, other cardiovascular risk factors, and on the type of treatment, we can notice that irrespectively of the type of VTE (provoked or unprovoked), treatment for more than 3 months significantly reduced the risk of MACE. If our results are confirmed by further studies, the prevention of MACE in patients with VTE, may be an argument to adjust the duration of anticoagulation in some patients usually treated for short period only to prevent VTE recurrence [61,98]. These findings addressing the impact of the duration of anticoagulant treatment for VTE on the risk of subsequent MACE, were not previously described. Nevertheless, they highlighted the potential necessity to consider the risk of these events as well as the risk of

recurrent VTE and the risk of bleeding complication for the decision of anticoagulation duration [61,98,117].

According to the impact of the type of anticoagulation on the risk of MACE, we found a significant reduction of the risk of MACE by 47% in patients treated with DOAC as compared to patients treated with VKA in multivariable analysis. While there was a significantly increased risk of MACE by 46% in patients treated with LMWH as compared to patients treated with VKA after adjustment for confounding variables. Considering cardiovascular deaths instead of all-cause deaths, as third component of MACE, and considering the competing risk of non-cardiovascular deaths, we had a confirmation of the reduction of the risk of MACE-2 by 52% in patients treated with DOAC as compared to patients treated with VKA in multivariable analysis, however, there was not statistically significant difference of the risk of MACE among patients treated with LMWH and patients treated with VKA in multivariable analysis. If several studies explored the impact of the type of treatment initiated for VTE on the risk of recurrent VTE and risk of bleeding complications, either comparing VKA to DOAC or VKA to LMW, we did not find data comparing these families of anticoagulant treatment regarding their effects on the risk of MACE that occurred after VTE [65,118,119]. It is important to note that in the context of an observational study as ours, no formal conclusion should be done regarding the comparison of the risk of MACE among different type of treatment groups, as patients features are very different across these groups and without randomization, their comparability cannot be assured. Even if our results and existing data may lead to a general preference for DOAC, particularly in patients treated for longer periods[65,113,119]; and especially knowing that VKA have been shown to promote vascular calcifications and increased risk of some arterial cardiovascular events in the general population [120,121].

Even if the best study design to study the impact of anticoagulant treatment on the risk of MACE that occurred after VTE would be randomized controlled trials, the findings from this study already provide preliminary answers to the fundamental question of the role of antithrombotic therapy on the risk of major cardiovascular complications in the VTE population, as desired by some previous studies [14,42]. Moreover, the large sample size of our study population, the prospective cohort design, the adjudicated outcomes, and the rigorous and robust statistical methods used are so many strengths that should be kept in mind while interpreting the results of this observational study. However there are some limitations which deserve to be mentioned. First, this is an open cohort study in which inclusion of participants were done during several years, therefore, the change in treatment and follow-up of VTE over

years could have affected the effective number of MACE recorded. Second, there could have been a surveillance bias and a selective diagnosis of some outcomes, due to the fact that participants with unprovoked VTE or cancer related VTE were more likely to have continued anticoagulant treatment for longer period, and have longer duration of follow-up, particularly for those included in recent years. Finally, even if our analyses were adjusted for ongoing antiplatelet therapy or statins at the time of VTE diagnosis, we did not collect sufficient information to efficiently explore the impact of these treatments and their potential interaction with anticoagulant treatment.

Interpretation

We found in this prospective cohort study, that the risk of MACE that occurred after VTE was significantly reduced in patients treated for longer duration. We also found a significant relationship between type of anticoagulant treatment and the risk of MACE, with a reduced risk in patients treated with DOAC as compared to those treated with VKA. These findings, may influence the choice of type and duration of anticoagulant treatment for VTE, however, they need confirmation by randomized controlled clinical trials.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Brest University Teaching Hospital (CCP-Ouest 6-390) with a last amendment approved on November 20, 2013 under reference number: EDITH II/RB 05.003. Administrative approvals were also obtained from authorities of all participants hospitals. All included patients signed a participant consent form.

Author's contributions

Conception and design: SRN, FC, LB, RD, ELM; acquisition of data: EP; Data analysis: SRN; Analysis and interpretation of data: SRN, FC, LB; Manuscript drafting: SRN; Manuscript revision: All authors; Approved the final version of the manuscript: All authors; Obtaining funding: FC. Administrative technical, and material support: FC, CT, RD. Study supervision: FC; Full access to all the data of the study: FC, SRN; responsibility for all aspect of the study, reliability and freedom from bias of the data presented: All authors.

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Chapitre 5 :

SYNTHESE

GENERALE

I. RESULTATS

Le l'objectif général de ce travail était de déterminer les facteurs de risque des affections cardiovasculaires artérielles chez les patients atteints de MVTE. Nous nous étions fixé un objectif principal et 3 objectifs secondaires. Les principaux résultats en fonction de ces objectifs peuvent se résumer comme suit :

➤ **Le premier objectif était de déterminer les facteurs de risques des MACE et des MALE survenant après MVTE.**

Après analyses multivariées 4940 patients inclus tous avec MVTE confirmée et EP et / ou TVP, les facteurs de risques identifiés de MACE (survenus chez 17.3% des patients) étaient : l'âge supérieur à 50 ans, l'EP associée à la TVP (vs TVP isolée), la MVTE non provoquée (vs. TEV associée à un facteur de risque transitoire), la consommation actuelle de tabac (vs jamais), l'hypertension, l'antécédent d'athérosclérose symptomatique, l'insuffisance cardiaque chronique, la fibrillation auriculaire et l'insertion d'un filtre dans la veine cave.

Les facteurs de risque de MALE (survenues chez 1.7% des patients) identifiés en analyse multivariée étaient : l'âge de 50 à 65 ans (vs. < 50 ans) et la fibrillation auriculaire.

➤ **Le deuxième objectif était de déterminer les facteurs de risques des ATE survenant après MVTE non provoquée et après MVTE associée au cancer.**

Dans une population de 2242 patients atteints de MVTE non provoquée et chez 914 patients atteints de MVTE associée au cancer, 174 patients atteints de MVTE non provoquée ont développé une ATE (7.8%) et 57 ont développé une ATE (6,2%) parmi les patients atteints de MVTE associée au cancer. Après analyses multivariées, les facteurs de risque identifiés d'ATE chez les patients atteints de MVTE non provoquée étaient l'âge > 65 ans (vs. < 50 ans), l'antécédent d'athérosclérose symptomatique et un traitement par de l'héparine de bas poids moléculaire (vs. Traitement par antivitamine K). Chez les patients atteints de MTE associée au cancer, les facteurs de risque identifiés d'ATE étaient : l'antécédent d'athérosclérose symptomatique et la présence d'un traitement anticoagulant au moment du diagnostic de MVTE.

➤ **Le troisième objectif était de déterminer les facteurs de risques des CVDT survenant après MVTE.**

Dans une population de 3988 patients incluant pour ceux qui sont décédés uniquement les décès de cause connus, 426 sont décédés de CVDT (10,7%). Les facteurs de risque de CVDT

après analyse multivariée étaient : âge de plus de 50 ans, la MVTE associée au cancer (vs. MVTE associé à un facteur transitoire), la MVTE non provoquée (vs MVTE associé à un facteur transitoire), le tabagisme ancien ou actuel (vs jamais fumé), l'hypertension, l'insuffisance cardiaque chronique, l'insuffisance respiratoire chronique et la fibrillation auriculaire. Le risque de CVDT était significativement réduit chez les patients traités par des anticoagulants oraux direct que chez ceux traités par antivitamine K et chez les patients traités plus de 3 mois que chez ceux traités pour une durée inférieure ou égale à 3 mois.

➤ **Le quatrième objectif était de déterminer l'impact du traitement anticoagulant de la MVTE sur le risque de MACE.**

Dans une population de 3790 patients qui n'ont reçu qu'une seule famille de traitement anticoagulant après la phase aiguë de la MTEV, parmi les AVK, les AOD et les HBPM. Les patients traités pendant plus de 3 mois avaient un risque de MACE significativement inférieur à ceux des patients traités de 0 à 3 mois ; et les patients traités par AOD avaient un risque significativement inférieur à celui des patients traités par AVK. Les résultats étaient presque similaires en prenant une définition des MACE incluant les décès cardiovasculaires en lieu et place des décès toute cause.

II. FORCES ET LIMITES

La bonne interprétation de ces résultats nécessite de prendre en compte principales forces et limites de notre travail, bien sûr nous les avons discutés spécifiquement à chaque objectif et plus en détails dans les articles concernés.

Concernant les limites, premièrement, nous n'avions pas assez de données biologiques pour explorer le rôle des anomalies biologiques tel que les thrombophilies majeures sur le risque de MACE, de MALE, d'ATE ou de CVDT. Deuxièmement, notre cohorte, bien que prospective, était une cohorte ouverte avec une période d'inclusion de plus de 20 ans, donc, l'hétérogénéité de la durée de suivi et le changement des protocoles de traitements de la MVTE au fil des années, auraient pu affecter le nombre final d'évènement artériels ou de décès d'origine cardiovasculaire. Troisièmement, l'incidence de certains évènements d'intérêt tel que les CVDT ou les MACE incluant les décès de cause cardiovasculaire, pourrait avoir été sous-estimée, en raison de la forte proportion de décès de causes inconnues.

Quatrièmement, il pourrait y avoir un biais de surveillance et un diagnostic sélectif des évènements artériels liés au fait que les patients atteints de MVTE associée à un cancer ou de MVTE non provoquée étaient plus susceptibles d'avoir une durée de suivi plus longue et de continuer le traitement anticoagulant pendant une période plus longue. Cinquièmement, nous n'avons pris en compte que les facteurs de risque cardiovasculaire connus à l'inclusion des patients, donc au moment du diagnostic de la MVTE. De ce fait, nous avons peut-être ignoré certains facteurs de risque modifiables qui se seraient développées au cours du suivi, surtout que ce dernier était assez long pour certains patients ; ainsi, nous avons peut-être omis de contrôler certains biais de confusion potentiels. Enfin, nous n'avons pas recueilli suffisamment d'informations sur l'arrêt du traitement antiplaquettaire après le diagnostic de MVTE ou sur la dose et le type d'antiplaquettaires ou de statines pour les inclure dans nos analyses.

Malgré ces toutes ces limites, notre étude est l'une des premières études de cohorte prospective de très grande taille d'échantillon ayant exploré les facteurs de risque de d'évènement artériels et de décès d'origine cardiovasculaire survenant après une MVTE. De plus tous les cas de MVTE ont été confirmés par des outils diagnostiques adéquats, et les évènements artériels ont été adjudiqués par un comité d'adjudication indépendant. Il est également à noter que nous avons utilisé des méthodes statistiques rigoureuses et robustes, en prenant en compte pour la plupart des analyses, le caractère compétitif potentiel des décès non liés aux causes cardiovasculaires en général, vis-à-vis des évènements artériels d'intérêt.

En fin notre étude est la première grande cohorte prospective dans laquelle l'impact potentiel du traitement anticoagulant introduit pour MVTE sur l'incidence des évènements artériels ultérieurs est exploré ; ceci permet tout de même d'avoir des signaux qui indiquent la nécessité d'effectuer des essais cliniques randomisés pour d'avantage étudier cette question capitale pour la prise en charge clinique des patients atteints de MVTE. Eut égard de ces points positifs, nos résultats peuvent avoir des implications cliniques pour une meilleure prévention des complications artérielles majeures survenant après MVTE.

Chapitre 6 :

CONCLUSIONS

Au terme de ce travail de recherche dont l'objectif principal était de déterminer les facteurs de risque des affections cardiovasculaires artérielles survenant après MVTE, nous pouvons formuler les conclusions suivantes :

- Les facteurs de risque de MACE et de MALE survenant après MVTE incluent certains facteurs de risque cardiovasculaire traditionnels et des comorbidités antérieures d'une part, et d'autre part, d'autres facteurs de risque liés aux caractéristiques de la MVTE.
- Le risque d'ATE après MVTE non provoquée et après MVTE associée au cancer est déterminé par certains facteurs de risque cardiovasculaire classiques et est influencé par le traitement anticoagulant introduit pour la MVTE, ainsi que par la présence ou l'absence d'une anticoagulation en cours au moment du diagnostic de MVTE.
- Les facteurs de risque de CVDT après MVTE comprennent certains facteurs de risque cardiovasculaires traditionnels et d'autres facteurs de risque liés aux caractéristiques de la MVTE d'une part, et des comorbidités des patients d'autre part.
- Le traitement de la MTEV pendant plus de 3 mois est associé à une diminution de risque de MACE, tout comme le traitement par AOD versus AVK. Ces résultats, qui peuvent influencer le choix des stratégies d'anticoagulation pour la MVTE, doivent être confirmés par des essais cliniques randomisés.

Chapitre 7 :

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ANNEXES

- *Annexe 1 : Notice d'information*

- *Annexe 2 : Formulaire de consentement éclairé*

- *Annexe 3 : Clairance éthique du comité de protection des personnes*

- *Annexe 4 : Formulaire de collecte d'informations à l'inclusion*

- *Annexe 5 : Formulaire de collecte d'informations durant le suivi*

1. NOTICE D'INFORMATION

PROGRAMME D'ETUDES DES DETERMINANTS ET INTERACTIONS DE LA THROMBOSE VEINEUSE –
EDITH II

FORMULAIRE D'INFORMATION

Promoteur : CHRU de Brest – 2 Avenue Foch - 29609 Brest Cedex
Investigateur principal : Professeur Mottier – CHRU de Brest – Hôpital de la Cavale Blanche – Centre d'Investigation Clinique, Avenue Tanguy Prigent- 29609 Brest Cedex

Madame, Monsieur,

La phlébite est due à la formation d'un caillot dans une veine. La fragmentation de ce caillot et sa migration vers le poumon se traduit par une embolie pulmonaire. La phlébite et l'embolie pulmonaire sont donc deux localisations de la même maladie et sont réunies sous le terme de maladie veineuse thromboembolique (MVTE). Les causes possibles sont appelées « facteurs de risque ». Leur présence accroît le risque de caillot mais ne suffit pas à l'engendrer. Les facteurs de risque sont multiples et c'est souvent l'association de plusieurs facteurs qui aboutit à la formation du caillot. L'évolution, la gravité, les risques de récurrence restent mal connus et plusieurs questions restent posées : chez les patients qui présentent une phlébite, quels sont ceux qui, au cours d'une récurrence, peuvent présenter une embolie pulmonaire et d'autre part, chez les patients qui ont présenté une phlébite ou une embolie pulmonaire, quels sont les facteurs de risque de récurrence ? La réponse à ces questions est fondamentale pour définir la durée du traitement.

L'objectif de cette cohorte est triple :

- identifier les facteurs pronostiques de la MVTE
- identifier, chez les patients qui ont présenté une phlébite et/ou une embolie pulmonaire, le mode de récurrence, c'est-à-dire sous la forme d'une phlébite seule ou d'une embolie pulmonaire ;
- identifier les facteurs de risque de récurrence d'une phlébite et/ou d'une embolie pulmonaire. Ces facteurs de risque peuvent être constitutionnels (d'origine génétique) ou acquis, liés à des facteurs d'environnement (médicaments, maladies acquises, voyages, etc).

Cette étude demande la participation de sujets qui ont une phlébite et/ou une embolie pulmonaire, comme vous.

Si vous acceptez de participer, un enquêteur vous interrogera pour connaître vos antécédents. Une prise de sang sera réalisée pour analyser les différentes anomalies qui peuvent modifier la coagulation du sang et rechercher des variations biologiques (acquises ou génétiques) qui peuvent prédisposer aux récurrences de la maladie veineuse thromboembolique. Du sang sera congelé et conservé pour pouvoir réaliser ultérieurement des dosages.

Si vous recevez actuellement un traitement anticoagulant, lors de votre consultation dans l'établissement après l'arrêt du traitement, un nouveau prélèvement veineux sera réalisé pour rechercher des anomalies de la coagulation qui ne peuvent pas être mesurées sous anticoagulant. La découverte d'anomalie de la coagulation pourra influencer votre traitement : durée du traitement anticoagulant et prescription de mesure de prévention pour éviter une phlébite.

Par ailleurs, si vous acceptez, vous recevrez une fois par an :

- Soit par courrier, un questionnaire que nous vous demandons de bien vouloir nous réadresser
- Soit par téléphone, nous vous demanderons de répondre à quelques questions. Cela vous prendra 15 Minutes.

Votre participation à cette étude est entièrement volontaire et bénévole. Vous êtes libre de refuser d'y participer ainsi que de mettre un terme à votre participation à l'étude à n'importe quel moment. Dans ce cas, vous devez informer le médecin hospitalier qui vous suit de votre décision. Le traitement informatique de vos données personnelles sera réalisé sauf opposition écrite de votre part.

Un traitement de vos données personnelles, données médicales recueillies y compris les prélèvements sanguins, tout questionnaire et les données relatives à vos habitudes de vie vous concernant, va être mis en œuvre pour permettre d'analyser les résultats de la recherche au regard de l'objectif de cette dernière.

Ces données seront identifiées par un numéro de code et vos initiales.

Le personnel impliqué dans l'étude est soumis au secret professionnel, tout comme votre médecin traitant.

Conformément aux dispositions de loi relative à l'informatique aux fichiers et aux libertés (loi du 6 janvier 1978 modifiée en 2004), vous disposez d'un droit d'accès et de rectification. Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette étude.

Vous pouvez également accéder directement ou par l'intermédiaire d'un médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L 1111-7 du Code de la Santé Publique.

Ces droits s'exercent auprès du médecin qui vous suit dans le cadre de cette étude.

La recherche a été approuvée le 22 Décembre 2004 par le Comité de Protection des Personnes de la recherche Biomédicale (CPPRB) et enregistrée par la DGS le 13 Janvier 2005. L'étude ci-dessus a été approuvée par le CPP Ouest 6 en date du 30 avril 2012 et déclarée à l'Afssaps. Une assurance spécifique a été souscrite par le promoteur de l'étude auprès de la SHAM

Paraphe patient

Paraphe Médecin

Version du 26 Mars 2012

2. FORMULAIRE DE CONSENTEMENT ECLAIRE

PROGRAMME D'ETUDES DES DETERMINANTS ET INTERACTIONS DE LA THROMBOSE VEINEUSE – EDITH II

FORMULAIRE DE CONSENTEMENT

Promoteur : CHRU de Brest – 2 Avenue Foch - 29609 Brest Cedex
 Investigateur principal : Professeur Mottier – CHRU de Brest – Hôpital de la Cavale Blanche – Centre d'Investigation Clinique, Avenue Tanguy Prigent- 29609 Brest Cedex

Je soussigné (e), Mme, Mr (*Rayer la mention inutile*) :

Nom : Prénom :

Date de naissance : Adresse :

..... déclare avoir pris connaissance du formulaire d'information et avoir bien compris le déroulement de l'étude observationnelle à laquelle j'accepte de participer. Il m'a été exposé que l'objectif de cette enquête constituée d'interrogatoire et de prise de sang, est de rechercher les différents facteurs de risque qui pourraient expliquer une récurrence d'une phlébite ou d'une embolie pulmonaire, en particulier toutes les anomalies génétiques susceptibles de favoriser les récurrences.

Il m'a été précisé que je suis libre d'accepter ou de refuser de participer à cette étude observationnelle, sans que cela ne modifie ma prise en charge médicale. Je pourrai, à tout moment, si je le désire, interrompre ma participation en le signalant au médecin chargé de cette étude, sans encourir la moindre responsabilité et sans aucun préjudice pour la qualité des soins qui me seront prodigués.

J'ai compris que les données collectées à l'occasion de la étude seront protégées dans le respect de la confidentialité. Elles pourront uniquement être consultées par les personnes soumises au secret professionnel appartenant à l'équipe du médecin investigateur.

J'accepte que les données enregistrées à l'occasion de cette étude puissent faire l'objet d'un traitement informatisé. J'ai bien noté que le droit d'accès prévu par la loi du 6 janvier 1978 modifiée en 2004 relative à l'informatique, aux fichiers et aux libertés s'exerce à tout moment auprès du médecin qui me suit dans le cadre de cette étude et qui connaît mon identité. Je pourrai exercer mon droit de rectification et d'opposition auprès de ce même médecin.

La recherche a été approuvée le 22 Décembre 2004 par le Comité de Protection des Personnes de la recherche Biomédicale (CPPRB) et enregistrée par la DGS le 13 Janvier 2005. L'étude ci-dessus a été approuvée par le CPP Ouest 6 en date du 30 Avril 2012 et déclarée à l'Afssaps.

J'accepte de participer à cette recherche dans les conditions précisées ci-dessus, avec la prise de sang qui servira à la constitution d'une plasmathèque et d'une DNathèque permettant d'approfondir les connaissances sur la recherche de facteurs génétiques de l'ensemble des pathologies vasculaires, artérielle et veineuse.

Lors de la consultation après l'arrêt du traitement anticoagulant, j'accepte de réaliser un nouveau prélèvement veineux pour la recherche d'anomalies au niveau de facteurs de la coagulation qui ne peuvent pas être dosé sous traitement anticoagulant.

J'accepte que vous preniez de mes nouvelles par téléphone ou par courrier une fois par an.

Fait à Brest, le

Nom et signature de l'Investigateur

Signature du patient

Un exemplaire pour le patient, un exemplaire pour le médecin.

Version du 26 Mars 2012

3. CLAIRANCE ETHIQUE DU COMITE DE PROTECTION DES PERSONNES

COMITE de PROTECTION des PERSONNES
Bâtiment II Bts - CHU MORVAN - 5 avenue Foch - 29609 BREST Cedex

Madame Mariannick LE BOT – Présidente du Comité
Docteur Yves GUEDES – Docteur Dominique CARLHANT – Madame Pascale PLANCHE
Secrétariat : Mme LE BRAS Alice – 02.98.22.31.11 & 02.98.22.36.21 - Fax : 02-98-22-31-09 - E. mail : copprb@chu-brest.fr

COPIE

Monsieur le Docteur Emmanuel OGER
Département de Médecine Interne & Pneumologie
CHU de LA CAVALE BLANCHE

Nos Réf.: 4.390

Objet : Avis du Comité
Etude EDITH II

Brest, le 4 janvier 2005

Cher Ami,

Le 16 novembre 2004, le Comité de Protection des Personnes de Brest a examiné le protocole intitulé :

«Programme d'études des déterminants et interactions de la Thrombose Veineuse.»

Et a émis un AVIS FAVORABLE sous réserve que certaines réponses soient apportées aux différentes questions posées en session.

Le 22 décembre 2004, le comité a reçu une version du protocole prenant en compte les modifications demandées, et apportant les réponses aux différentes questions soulevées.

L'avis favorable peut donc prendre effet à partir de cette date.

En vous souhaitant bonne réception,
Nous vous prions de recevoir nos salutations les meilleures.

Madame Mariannick LE BOT,
Présidente du Comité.

AVIS DU COMITE CONSULTATIF DE PROTECTION DES PERSONNES

38. Nom et adresse du Comité : C.C.P.P.R.B.
Hôpital Cavale Blanche
CHU de BREST
- 39: Avis favorable Avis défavorable
40. Date de l'avis : 22 décembre 2004
Amendement 1 : Avis favorable le 14 février 2005
Amendement 2 : Avis favorable le 11 Décembre 2007
Amendement 3 : Avis favorable le 7 juillet 2009
Amendement 4 : Avis favorable le 15 décembre 2009
Amendement 5 : Avis favorable le 23 mars 2010
Amendement 6 : Avis favorable le 14 Décembre 2010
Amendement 7 : Avis favorable le 12 avril 2011
Amendement 8 : Avis favorable le 30 avril 2012
Amendement 9 : Avis favorable le 30 avril 2012
Amendement 10-11-12 : Avis favorable le 25 septembre 2012
Amendement 13 : Avis favorable le 18 décembre 2012
Amendement 14 : Avis favorable le 19 mars 2013
Amendement 15 : Avis favorable le 14 mai 2013
Amendement 16 : Avis favorable le 11 juin 2013
Amendement 17 : Avis favorable le 9 juillet 2013
Amendement 18: Avis favorable le 19 novembre 2013



COMITE DE PROTECTION DES PERSONNES OUEST VI
Centre Hospitalier Universitaire Cavale Blanche – Boulevard Tanguy Prigent – 29609 BREST Cedex

Présidente
Dr. Dominique KOWALSKI
Vice-présidente
Mme Marie-Claire DUMAS
Secrétaire Général
Dr. Claire POULLAOUËC
Trésorier
Dr. Catherine BALCON

Madame LALLIER
CHRU Brest Morvan
Pôle Recherche

Brest, le 20 novembre 2013

Nos réf : CPP Ouest 6 – 390/ MS18
Vos réf : EDITH II/RB 05.003

Objet : Modification substantielle

Cher Confrère,

Le mardi 19 novembre 2013, le Comité de Protection des Personnes Ouest VI a examiné la modification substantielle n° 1 de l'étude intitulée :

Programme d'étude des déterminants et interactions de la Thrombose Veineuse. EDITH II

Le promoteur est le CHRU de Brest
Dont l'investigateur est le Docteur DAN PETESCH

Cette modification porte sur la demande de modification du document d'information destiné aux patients recrutés dans les centres de Morlaix, Quimper et HIA : collection pour DNathèque uniquement ; et modification du consentement

Après avoir reçu et étudié les documents suivants :

- La lettre d'information et de consentement au patient

Le Comité a émis à l'unanimité un avis favorable.

Ont participé aux délibérations

- | | |
|--------------------------|---|
| - Dr. Carlhant | Qualifiée en matière de recherche biomédicale |
| - Dr Gueret | Médecin |
| - Dr. Poullaouec | Qualifiée en raison de compétence en matière de biostatistique |
| - Mme L'Eilde-Balcon | Pharmacienne |
| - Mme Gloanec | Travailleur social |
| - Mme Vourc'h | Qualifiée en raison de compétence en matière juridique |
| - Mme Omnes, Mme Quentel | Représentantes des associations agréées de malades et d'usagers du système de santé |

Ont participé sans voix délibérative

- Mme Tigreat
Infirmière

Restant à votre disposition pour tout renseignement complémentaire, je vous prie de croire, Monsieur, à l'assurance de mes salutations les meilleures.

Dominique KOWALSKI CARLHANT
Présidente du CPP Ouest VI

**4. FORMULAIRE DE COLLECTE D'INFORMATIONS A
L'INCLUSION**

N° EDITH 11.|_|_|_|_|

N° EPI-GETBO III 90-_|_|_|_|_|

**ETUDE DES DETERMINANTS ET INTERACTIONS
DE LA THROMBOSE VEINEUSE**

EDITH

ET

EPI-GETBO III

CAHIER D'OBSERVATION

PROMOTEUR

CENTRE HOSPITALIER UNIVERSITAIRE DE BREST
29609 BREST CEDEX

COORDONNATEUR

DOMINIQUE MOTTIER
GROUPE D'ETUDE DE LA THROMBOSE DE BRETAGNE OCCIDENTALE
(G.E.T.B.O. - EA 3878)

DEPARTEMENT DE MEDECINE INTERNE ET PNEUMOLOGIE
HOPITAL DE LA CAVALE BLANCHE, 29609 BREST CEDEX

	signes évocateurs :	Douleur à la palpation	<input type="checkbox"/> Non	<input type="checkbox"/>
Oui				
		Oedème	<input type="checkbox"/> Non	<input type="checkbox"/>
Oui				
Suspicion d'embolie pulmonaire			<input type="checkbox"/> Non	<input type="checkbox"/>
Oui				
	Si oui, symptômes évocateurs :	Douleur thoracique	<input type="checkbox"/> Non	<input type="checkbox"/>
Oui				
		Dyspnée	<input type="checkbox"/> Non	<input type="checkbox"/>
Oui				
	signes évocateurs	Hémoptysie	<input type="checkbox"/> Non	<input type="checkbox"/>
Oui				
		Autres	<input type="checkbox"/> Non	<input type="checkbox"/>
Oui				

Examens complémentaires (résultats à joindre) :

Echo-Doppler veineux : oui non Date |__|__| |__|__|
|__|__|__|__|

Membre inf. Membre sup Examen fait par Dr.....

- | | |
|--|--|
| <input type="checkbox"/> Pas de thrombose profonde | <input type="checkbox"/> Thrombose distale |
| <input type="checkbox"/> Thrombose proximale | <input type="checkbox"/> Thrombose veineuse musculaire |
| <input type="checkbox"/> Thrombose veineuse sur cathéter | <input type="checkbox"/> Thrombose superficielle |

Où : CHRU Brest HIA CH Landerneau
 CH Cornouaille Clinique Cabinet d'angiologie
 Cabinet de radiologie CH Morlaix
 Autre :

Scintigraphie V/Q : oui non Date |__|__| |__|__|
|__|__|__|__|

normale faible intermédiaire forte

TomoScintigraphie : oui non Date |__|__| |__|__|
|__|__|__|__|

normale non évocateur évocateur

Angioscanner ou autres scanners : oui non Date |__|__| |__|__|
|__|__|__|

normal EP autre diagnostic

Examen fait par Dr

Où : CHRU Brest HIA CH Landerneau
 Clinique Cabinet d'angiologie Cabinet de radiologie
 Autre :

Echographie cardiaque diagnostique : oui non Date |__|__| |__|__|
|__|__|__|

(1^{ère} intention pour les EP grave)

signes indirects (dilatation du VD, septum paradoxal)
 signes directs (thrombus visualisé)

VALIDATION DU DIAGNOSTIC

TVP des membres inférieurs :

<input type="checkbox"/> Oui	<input type="checkbox"/> Non
<input type="checkbox"/> Distale	<input type="checkbox"/> Proximale
<input type="checkbox"/> Symptomatique	<input type="checkbox"/> Asymptomatique
<input type="checkbox"/> Documentée	<input type="checkbox"/> Non documentée
<input type="checkbox"/> Pas sur cathéter	<input type="checkbox"/> Sur cathéter

EP :

<input type="checkbox"/> Oui	<input type="checkbox"/> Non
<input type="checkbox"/> Symptomatique	<input type="checkbox"/> Asymptomatique
<input type="checkbox"/> Documentée	<input type="checkbox"/> Non documentée

Autre thrombose :

sup	<input type="checkbox"/> TV Musculaire	<input type="checkbox"/> TVP Membre
	<input type="checkbox"/> Système porte	<input type="checkbox"/> Jugulaire/ss
clavière	<input type="checkbox"/> Thrombophlébite cérébrale	<input type="checkbox"/> TV superficielle
	<input type="checkbox"/> Symptomatique	<input type="checkbox"/> Asymptomatique
	<input type="checkbox"/> Documentée	<input type="checkbox"/> Non documentée
	<input type="checkbox"/> Sur cathéter	<input type="checkbox"/> Pas sur cathéter

« Inpatient » ou « Outpatient » (Inpatient = cas nosocomial *i.e.* survenu à l'hôpital)

Diagnostic de MVTE sous traitement anticoagulant curatif ? Oui Non
Si OUI, bien conduit ? Oui Non

E. LE MOIGNE F. COUTURAUD A. DELLUC K. LACUT D. MOTTIER L. DE ST MARTIN

Traitement de la MVTE

Quel traitement anticoagulant a été initié pour la MVTE ?

- HNF ou HBPM ou Fondaparinux + AVK,
 HNF seule HBPM seule Fondaparinux seule
 Nouvel anticoagulant oral (NACO) Nom : Dose :
 AVK seul Pas de traitement anticoagulant TTAC à dose préventive

Pour quelle durée prévue ?

(nota : [= non inclus donc si 3 mois (exemple), alors créneau [3 mois ; 6 mois [et non [1 mois ; 3 mois [)

- < 1 mois [1 mois ; 3 mois [[3 mois ; 6 mois [
 [6 mois ; 1 an [≥ 1 an mais avec une date prévisible au long cours

Filtre cave ? Oui Non Si oui, date de pose : |_|_| |_|_| |_|_|_|_|

Thrombolyse Oui Non Si oui, date |_|_| |_|_| |_|_|_|_|

1. Contexte post-opératoire

Avez-vous subi une intervention chirurgicale il y a moins de 3 mois ? Non Oui

Si oui, date : |_|_| |_|_| |_|_|_|_|

Type d'intervention |_|_| (cf. cahier codage en début de classeur)

Prévention de la MVTE pour cet événement :

- Aucune prévention Contention seule

Traitement anticoagulant préventif, si oui : nom :, dose :

Date de début : |_|_| |_|_| |_|_|_|_| durée : jours,

Déjà sous traitement anticoagulant curatif

2. Immobilisation d'un membre inférieur

Avez-vous eu un traumatisme avec immobilisation (plâtre, strapping, déchirure musculaire...) d'un membre inférieur il y a moins d'1 mois ? Non Oui

6.1 Juste avant l'épisode actuel, vous étiez :

- Domicile Maison de retraite Convalescence/ moyen séjour
 Clinique psychiatrique Hospitalisé Autres :

6.2 Evaluation de l'autonomie (Cf cahier de codage en début de classeur)

Autonomie la dernière semaine avant l'événement |_|

6.3. Dans les trois mois précédents l'épisode pour les patients « out patient » (ou hospitalisation actuelle pour les patients « témoins » ou « cas in patient »)

- Avez-vous été hospitalisé(e) Non Oui

Motif : anémie cardiovasculaire gastro-intestinale

métabolique

neurologique rénale respiratoire

sepsis

autres,

Préciser pourquoi (pour chaque motif):.....

Si oui, dans un service de : Médecine Chirurgie (sans intervention chirurgicale)

Date d'admission : |_|_| |_|_| |_|_|_|_|_|_|

Date de sortie : |_|_| |_|_| |_|_|_|_|_|_|

Durant cette hospitalisation, prévention de la MVTE ?

Aucune prévention Contention seule

Traitement anticoagulant préventif, si oui : nom :, dose :

.....

Date de début : |_|_| |_|_| |_|_|_|_|_|_| durée : jours,

Déjà sous traitement anticoagulant curatif

- Avez-vous séjourné dans un centre de convalescence ou moyen séjour ? Non

Oui

Si oui, Date d'admission : |_|_| |_|_| |_|_|_|_|_|_|

Date de sortie : |_|_| |_|_| |_|_|_|_|_|_|

Durant cette hospitalisation, prévention de la MVTE ?

Aucune prévention Contention seule

Traitement anticoagulant préventif, si oui : nom :, dose :

.....

Date de début : |_|_|_| |_|_|_| |_|_|_|_|_|_| durée : jours,

Déjà sous traitement anticoagulant curatif

6.3. Dans les trois mois précédents cet épisode (suite),

- Avez-vous séjourné dans un service de psychiatrie ? Non

Oui

Si oui, Date d'admission : |_|_|_| |_|_|_| |_|_|_|_|_|_|

Date de sortie : |_|_|_| |_|_|_| |_|_|_|_|_|_|

Durant cette hospitalisation, prévention de la MVTE ?

Aucune prévention Contention seule

Traitement anticoagulant préventif, si oui : nom :
dose :

Date de début : |_|_|_| |_|_|_| |_|_|_|_|_|_| durée : jours,

Déjà sous traitement anticoagulant curatif

7. Voyage récent (datant de moins d'un mois, durée > 3 H) Non

Oui

(un aller-retour ou un trajet interrompu constituent deux voyages)

Date du voyage le plus significatif : |_|_|_| |_|_|_| |_|_|_|_|_|_| Durée du trajet : |_|_|_| heures

Mode de transport : Avion Train Automobile Bateau

Commentaire :

.....
.....
.....
.....
.....
.....
.....

8 Autres circonstances favorisantes < 1 mois, hors hospitalisation : uniquement pour les patients « out patient »)

Non Oui

Infection Affection rhumatologique

Autres, préciser.....

Date de début de la circonstance favorisante : |_|_|_| |_|_|_| |_|_|_|_|_|_|

9 Le patient présente t-il des troubles des fonctions supérieures (démence, troubles du comportement...)?

Non Oui

1. Antécédents cardiovasculaires

Avez-vous souffert :

- 1. d'une pathologie coronarienne** Non Oui
- Si oui, infarctus du myocarde Non Oui
- angioplastie coronaire Non Oui
- pontage aortocoronaire Non Oui
- année du 1^{er} évènement coronaire : |_|_|_|_|_|
- 2. d'insuffisance cardiaque** Non Oui
- Année de diagnostic |_|_|_|_|_|
- 3. d'insuffisance respiratoire chronique** Non Oui
- Année de diagnostic |_|_|_|_|_|
- 4. d'un accident vasculaire cérébral** Non Oui
- Si oui, ischémique (1) ou hémorragique (2) 1 2
- Année du dernier AVC: |_|_|_|_|_|
- 5 Accident ischémique transitoire** Non Oui
- Année du dernier AIT: |_|_|_|_|_|
- 6. d'une artériopathie oblitérante des membres inférieurs** Non Oui
- Si oui, claudication d'effort Non Oui
- pontage : Non Oui
- Si oui, année : |_|_|_|_|_|

Amputation : Non

Oui

Si oui, année : |_|_|_|_|

7. Une AC/FA (arythmie cardiaque par fibrillation auriculaire) Non

Oui

Année de diagnostic : |_|_|_|_|

Traitement anti-thrombotique Non

Oui

2. Antécédents thromboemboliques veineux

Avez-vous un antécédent personnel de MVTE ? Non

Oui

(TVP MI, EP, TV musculaire ou superficielle, membre sup., du système porte, jugulaire et/ou sous-clavière, thrombophlébite cérébrale). Ne pas mentionner les TV dues aux perfusions

Episodes	Localisation <i>(cf. cahier de codage en début de classeur)</i>	Documenté <i>(cf. cahier de codage)</i>	Année	Circonstances <i>(si non idiopathique, cf. cahier codage)</i>
1				
2				
3				

Taille de la famille :

Vous avez : |_|_| fils |_|_| filles |_|_| frères |_|_|
soeurs

Existe-t-il un antécédent familial de thrombose veineuse ? Non

Oui

chez |_|_| fils Age le plus jeune au moment de l'ETEV

|_|_|

chez |_|_| filles Age le plus jeune au moment de l'ETEV

|_|_|

chez |_|_| frères et sœurs Age le plus jeune au moment de l'ETEV

|_|_|

chez |_|_| parents (père/mère) Age le plus jeune au moment de l'ETEV |_|_|

DONNEES CLINIQUES

Score de Villalta

<u>SYMPTOMES SUBJECTIFS</u>	<u>COTATION DE 0 à 3</u>
Lourdeurs de jambes	
Douleurs des membres inférieurs	
Crampes	

Cotation de 0 à 3 :

0 : absent,

1 : léger,

2 = modéré

3 = sévère

→

Calcul

Prurit	
Paresthésies	
SIGNES OBJECTIFS	
Œdème pré tibial	
Induration cutanée (hypodermite scléreuse)	
Hyperpigmentation	
Nouvelles dilatations veineuses (cliniques)	
Rougeur (érythème, dermo-hypodermite)	
Douleur à la compression du mollet	
Ulcère veineux : <input type="checkbox"/> Absent <input type="checkbox"/> Présent	
Si ulcère veineux présent et score < 15 : alors score total sera = 15	
Si ulcère veineux présent et score ≥ 15 : on garde le score total du tableau	

Score d'Aujesky

Variables		
FC ≥ 100/mn	<input type="checkbox"/> Non	<input type="checkbox"/> Oui
PAS < 100 mmHg	<input type="checkbox"/> Non	<input type="checkbox"/> Oui
FR ≥ 30/mn	<input type="checkbox"/> Non	<input type="checkbox"/> Oui
T°C < 36°	<input type="checkbox"/> Non	<input type="checkbox"/> Oui
Perturbation de l'état de conscience (désorientation, léthargie, stupeur, coma)	<input type="checkbox"/> Non	<input type="checkbox"/> Oui
Saturation O ² < 90 % en <i>air ambiant</i>	<input type="checkbox"/> Non	<input type="checkbox"/> Oui

SCORE NYHA (Essoufflement)

<input type="checkbox"/>	Stade 1	Aucune dyspnée, capacité d'effort normale pour l'âge
<input type="checkbox"/>	Stade 2	Dyspnée nulle au repos mais apparaissant pour des activités normales pour l'âge
<input type="checkbox"/>	Stade 3	Dyspnée nulle au repos mais apparaissant pour des activités inférieures à la normale pour l'âge
<input type="checkbox"/>	Stade 4	Dyspnée au moindre effort et/ou au repos

Poids (kg) |__|__|__| Taille (cm) |__|__|__|

Groupe sanguin :

 A B AB O Ne sait pas Rhésus positif Rhésus négatif Ne sait pasCarte vue Non Oui

Tabagisme Non Ancien Actuel

Si oui, âge de début /_/_/

Combien de cigarettes par jour en moyenne /_/_/

Si arrêt, à quel âge? /_/_/

Histoire obstétricale

Combien avez-vous eu de grossesses ? /_/_/

Combien avez-vous eu d'enfants ? /_/_/

Avez-vous fait des fausses-couches ? Non

Oui

Si oui, combien ? /_/_/

Avez-vous eu une hystérectomie ? Non

Oui

1. Antiagrégants plaquettaires

Au moment du diagnostic de MVTE, preniez –vous un traitement par antiagrégant plaquettaire ?

 Non Oui Si oui : Monothérapie

Bithérapie

Si oui,

 Antécédent cardiovasculaire autres,

préciser :

(Vérifier antécédent page 9)

Traitement n°1 : nom :, dose :par jour

Début depuis < à 3 mois ≥ à 3 moisMaintenu associé au traitement anticoagulant Non Oui

Traitement n°2 : nom :, dose :par jour

Début depuis < à 3 mois ≥ à 3 moisMaintenu associé au traitement anticoagulant Non Oui**2. Statines**Au moment du diagnostic de MVTE, preniez –vous un traitement par statine ? Non

Oui

Si oui : nom du traitement : dose.....par jour

Début depuis < à 3 mois ≥ à 3 mois

3. Autres traitements dans les 3 mois précédents

Traitement au long cours, institué il y a plus 3 mois et toujours en cours :

Traitement au long cours, institué il y a moins de 3 mois et toujours en cours :

Traitement pris de façon transitoire au cours des 3 derniers mois (type antibiotique, AINS ou antalgique en cure courte...)

Variables mesurées le jour de l'admission (avant le début du traitement anticoagulant de préférence) ou dans les jours suivants par défaut.

TCA patient	_ _ secondes
TP (Temps de Quick)	_ _ _ exprimé en %
Fibrine (Fibrinogène)	_ , _ _ en g/L
D-dimères	_ _ _ _ en ng/mL (1 µg/mL = 1000 ng/mL)
Hémoglobine	_ _ , _ en g/dL
Globules blancs (leucocytes) mm ³)	_ _ _ _ _ par mm ³ (1 Giga/l = 1000 par mm ³)
Plaquettes mm ³)	_ _ _ _ _ _ par mm ³ (1 Giga/l = 1000 par mm ³)
CRP	_ _ _ , _ en mg/L
Créatinine	_ _ _ en µmol/L

Titre : Epidémiologie et facteurs de risque des complications artérielles chez les patients atteints de maladie veineuse thromboembolique

Mots clés : Maladie veineuse thromboembolique, complications artérielles, cohorte prospective

Résumé :

Des études récentes ont montré que les affections cardiovasculaires en général sont plus fréquentes chez les patients atteints de maladie thromboembolique veineuse (MTEV) que dans la population générale ; cependant, les facteurs de risque des affections cardiovasculaires chez ces patients restent très peu explorés, de même que l'impact potentiel sur ces affections du traitement anticoagulant de la MVTE. Une revue de littérature avec méta-analyses, nous a permis de confirmer le surrisque d'affections cardiovasculaires artérielles chez les patients atteints de MVTE par rapport à la population générale. Nous avons ensuite déterminé dans une cohorte prospective multicentrique de 4940 patients atteints de MVTE, en utilisant principalement des modèles de risque compétitifs, les facteurs de risques des événements cardiovasculaires majeurs indésirables et des

événements majeurs indésirables des membres après toute MVTE, les facteurs de risque d'événements artériels thrombotiques après MVTE non provoquée et après MVTE associée au cancer, les facteurs de risque des décès cardiovasculaires après toute MVTE, et l'impact du traitement anticoagulant initié pour MVTE sur le risque de survenue des événements cardiovasculaires majeurs indésirables. Nos résultats ont montré d'une part, que les facteurs de risque d'affections cardiovasculaires artérielles incluent certains facteurs de risque cardiovasculaires classiques, certaines comorbidités, et certaines caractéristiques de la MVTE ; et d'autre part que l'anticoagulation pour MVTE influence le risque d'affections cardiovasculaires majeures ultérieures même si ces résultats restent à être confirmés par des essais cliniques randomisés.

Title : Epidemiology and risk factors of arterial complications after venous thromboembolism

Keywords : Venous thromboembolism, arterial complications, prospective cohort

Abstract :

Recent studies have shown that arterial cardiovascular diseases are more common in patients with venous thromboembolic disease (VTE) than in the general population; however, risk factors of arterial cardiovascular diseases in these patients remain little explored, as well as the potential impact of anticoagulant therapy used for VTE on the risk of these diseases. A literature review with meta-analyses, allowed us to confirm that there is an increased risk of arterial cardiovascular events in patients with VTE, as compared to the general population. After what, we determined in a multicenter prospective cohort of 4940 patients with VTE, using mainly competing risk models, the risk factors of major adverse cardiovascular events and major adverse limbs events that occurred

after any VTE, the risk factors for arterial thrombotic events after unprovoked VTE and after cancer-associated VTE, the risk factors for cardiovascular death after any VTE, and the potential impact of anticoagulant treatment initiated for VTE on the risk of occurrence of major adverse cardiovascular events. Our main analyzes showed on the one hand, that the risk factors for arterial cardiovascular diseases include certain classic cardiovascular risk factors, some comorbidities, and some characteristics of VTE; and on the other hand, that anticoagulation for VTE influences the risk of subsequent major cardiovascular events even if these results remain to be confirmed by randomized clinical trials.