Age-specific recurrence risk among adults with first-episode unprovoked venous thromboembolism

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PREFACE

Research Approval – The systematic review and meta-analysis portion of the thesis used published literature and aggregate data, and therefore did not require ethics approval. The secondary analysis of REVERSE data used anonymized data collected in a prospective cohort study with data collection from 2001 to 2006, and therefore did not require Ethics approval. The study was coordinated at the Ottawa Hospital Research Institute.

Yan Xu led the conception of each component study, developed the analysis plan, participated in data interpretation, and prepared the initial draft of manuscripts.

Marc Carrier is the MSc thesis supervisor, who provided supervision, funding, and critical review of all steps of the research presented herein. He approves the submission of this thesis and attests to the candidate's contributions.

Grégoire Le Gal is the MSc thesis co-supervisor. He provided supervision and guidance on study design, data analysis, interpretation, and provided critical review to the drafted manuscripts.

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TABLE OF CONTENTS

ABSTRACT

Oral anticoagulants (OACs) are indicated in the first-line treatment of venous thromboembolism (VTE), which comprises of deep vein thrombosis (DVT) and pulmonary embolism (PE). While contemporary guidelines recommend extended-duration anticoagulation after the first diagnosis of unprovoked VTE, the benefits and harms associated with this approach remain unclear across age groups, especially among older adults. Crucially, contemporary estimates of VTE recurrence have not incorporated all-cause mortality as a competing event, the risk of which increases with age. Therefore, we evaluated and synthesized existing literature on of the risk of all-cause mortality by age following completion of limited-duration anticoagulation for a first episode of unprovoked VTE. In addition, we determined the risk of VTE recurrence after completion of limited-duration OAC therapy by age, with death as a competing outcome using data from a prospective cohort study.

CHAPTER 1: Background

1.1 VTE incidence and its related mortality are modified by age

Venous thromboembolism, comprising of deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third leading cause of cardiovascular mortality after myocardial infarction and stroke [1]. While PE-related mortality in North America has declined from 4.7 to 2.6 deaths per 100,000 population over the span of 20 years, this rate has plateaued since 2006 [2]. In fact, VTE accounts for more than 500,000 hospital admissions in the United States each year [3], and it is one of the leading preventable causes of hospital-acquired morbidity globally [4, 5]. The need to optimize the diagnosis and treatment of VTE, therefore, cannot be overstated.

Both the incidence and case fatality rates of VTE are linearly correlated with increasing age. While VTE is rare among children <15 years at a rate of <5 per 100,000 person-years, its incidence rises to 450-600 per 100,000 person-years (or ~0.5% per year) among those aged 80 and above [6, 7]. A population-based prospective study from Worcester, Massachusetts demonstrated an important rise in VTE incidence over age 60 [6], which has been replicated in several other cohorts [8]. Overall, the cumulative probability of being diagnosed with a VTE has been estimated to be 10.7% among males aged 50-80 in a longitudinal cohort from Malmö, Sweden [9]. In terms of VTE-related mortality and PE-related mortality in particular, each 1-year increase in age is associated with a 3% relative risk increase in all-cause mortality within 30 days of PE diagnosis [10].

Half of all VTEs are not attributable to a transient or persistent risk factor, thus classifying them as unprovoked [11]. Among individuals with unprovoked incident VTEs, recurrence rates are 16% at two years and 36% at 10 years after discontinuing anticoagulation [12]. While major guidelines recommend long-term anticoagulation in patients with unprovoked VTE owing to the high risk of thrombotic recurrence [13, 14], approximately 70% of females and 60% of males with unprovoked

VTE will not experience recurrence after completing a time-limited course of antithrombotic therapy [12]. Therefore, OAC treatment duration after a first episode of unprovoked VTE requires consideration of *net clinical benefit* by estimating event rates and case fatality rates of both recurrent VTE and major bleeding with long-term *vs.* limited-duration anticoagulation.

1.2 Impact of age on risk of recurrent VTE is heterogeneous

Despite the association between increasing age and the risk of incident VTE, the relationship between age and risk of *recurrent* VTE is conflicting among studies to date. For example, age ≥65 years was an independent predictor of recurrence among females with a first-episode of unprovoked VTE in the REVERSE study, a prospective, clinical decision-rule derivation study in which all participants stopped anticoagulation after 6 months of OAC treatment [15]. On the other hand, the same relationship has not been observed in a prospective cohort from Austria [16], while another study of 124 patients in Cleveland, Ohio who were prospectively followed for 6 to 8 years, reported *lower* rates of VTE recurrence with age ≥65 years [17].

The conflicting impact of age on recurrent VTE extends into existing risk prediction tools [18]. One tool (the HERDOO$_2$ model) incorporates age ≥65 along with body mass index, post-thrombotic syndrome, and on-treatment VIDAS D-dimer level as predictors of increased VTE recurrence in females; it has been prospectively validated to risk stratify females with incident unprovoked VTE after 6 months of OAC treatment [19]. A separate externally validated tool (DASH model) includes age *less than* 50 years as a predictor of increased VTE recurrence along with abnormal off-treatment D-dimer, sex and hormonal therapy [20, 21]. While patients with known presence of "high-risk" thrombophilia (antiphospholipid antibody syndrome, antithrombin deficiency; protein C or protein S deficiency; or compound heterozygous or homozygous factor V Leiden or prothrombin gene mutation) were excluded from the derivation cohort of the HERDOO$_2$

model, these patients were included in the derivation cohort of the DASH model. Because younger age at diagnosis is associated with a higher risk of an underlying strong thrombophilia [22], which in turn is linked to higher risk of VTE recurrence after anticoagulant cessation, thrombophilia status may be an effect modifier on the relationship between age and recurrent VTE that could explain the discordant findings between the $HERDOO_2$ and DASH models. Neither the derivation or validation analyses of these models included all-cause mortality as a competing event.

1.3 Competing risk of death is not considered in most studies of VTE prognosis

Competing events occur when an outcome (e.g., death) other than the primary outcome under study (e.g., recurrent VTE) occurs, which changes the future probability of the occurrence of an outcome [23]. In standard Kaplan-Meier analysis, a censoring event (e.g., loss to follow-up) assumes that the primary outcome of interest would occur after the censoring event with sufficient follow-up duration [23]. Furthermore, conventional survival analysis employs the assumption of non-informative censoring, meaning that participants who remain in the study have the same future risk for the occurrence of the primary outcome as those who have been censored . While it is possible to consider competing events as censoring events, there are two drawbacks to this approach [23]. First, due to the possible imbalance in risk profiles between participants who died during follow-up compared to those who survived until occurrence of the primary endpoint, the assumption of non-informative censoring may be violated. Second, even if competing events are assumed to be independent, censoring participants when competing events occur would violate the assumption that the primary outcome of interest would occur with sufficient follow-up duration (as would be the assumption with loss to follow-up) [23]. Competing risk of death is an important consideration in studies involving older adults which, when not accounted for, often results in overestimation of disease incidence [24]. While a recent meta-analysis of randomized controlled

trials reported an all-cause mortality following unprovoked VTE at 1% during study follow-up, rates of all-cause mortality in non-randomized studies, often conducted within routine clinical practice, are approximately 10-fold higher: the prospective Cleveland cohort reported a 17% risk of all-cause mortality at 1 year [17], whereas an Olmsted County, Minnesota inception VTE cohort reported a 36% risk of death over the same period. Using national administrative databases in Sweden, Sogaard *et al* showed a 15% risk of all-cause mortality within 1 year of VTE diagnosis in an unselected population [25], which mirrors findings of a study using administrative data from Quebec, Canada [26]. Crucially, these risks far exceed the risk of recurrent fatal PE after anticoagulant cessation, which is estimated at 0.17 per 100 person-years or 1.5% at 10 years in recent meta-analyses [12, 27].Mortality rates after VTE were lower among cohorts of younger compared to older individuals even with long-term follow-up [28].

In settings where the competing risk of death is high over the duration of follow-up, standard Kaplan-Meier approaches overestimate the incidence of disease occurrence [23], with a 1.4-fold effect based on a recent systematic review and meta-analysis [29]. This was confirmed by Parpia *et al* using data from the CLOT trial, which compared six months of low molecular weight heparin to warfarin in the treatment of cancer-associated thrombosis, where overall mortality was 40% at end of follow-up [30]. Application of competing risk methods to analyze the CLOT trial data resulted in a lower absolute risk difference between the low molecular weight heparin and warfarin arms, from 8.5% with standard Kaplan-Meier methods to 6% with use of the cumulative incidence function [30].

In addition to producing inflated estimates of incidence associated with the primary outcome under study, differences in competing risks of all-cause mortality *between* candidate predictors may bias their prognostic impact on the outcome of interest with the use of Kaplan-Meier survival analysis

or Cox regression modeling. This is especially the case if the candidate predictors are associated with both the outcome of interest (e.g., recurrent VTE) and the competing outcome (e.g., all-cause mortality). For example, Ay *et al* used data from the Vienna Cancer and Thrombosis Study to evaluate whether the predictive characteristics of D-dimer quartiles for cancer-associated VTE would be modulated by incorporating all-cause mortality as a competing outcome. Comparing the Cox proportional hazards model based on the Kaplan-Meier approach and the Fine and Gray sub-distribution model based on the competing risk approach, they found a numerically lower hazard ratio for D-dimer as a predictor of cancer-associated VTE with competing risk modelling (hazard ratio 2.47, 95% CI 1.67 – 3.65 vs. hazard ratio 2.85, 95% CI 1.92-4.21) [31]. This suggests that models using D-dimers to predict VTE may produce biased estimates of relative risk (e.g. hazard ratios) if the competing risk of mortality is unaccounted for.

1.4 The interaction between age, sex, and site of index VTE on risk of recurrence is underexplored

While the overall incidence of VTE is similar between males and females, there are specific age-related considerations. For example, the risk of first VTE is 2- to 3-fold higher among females up to 50 years of age compared to males matched by age, whereas this pattern is reversed after age 50 [32]. In a post-hoc analysis of the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis (MEGA) study that accounted for the contribution of reproductive risk factors, Roach and colleagues noted a 2-fold increase in the risk of incident VTE among males compared to females, even among those aged <50 years [33]. This higher propensity to VTE among males, in turn, is reflected in a 1.4-fold higher risk of recurrence following time-limited anticoagulant therapy for unprovoked VTE compared to females [34]. Nonetheless, the

relationship between age, sex and risk of recurrence remains under-explored, including whether the protective effect of sex on VTE recurrence remains uniform across age groups.

Similarly, the impact of age on the relationship between index site of VTE (isolated PE, isolated DVT or PE+DVT) and recurrent VTE is unclear. While patients with a first unprovoked isolated PE experience lower risk of recurrent VTEs compared to those with isolated DVT or DVT + PE as their presenting VTE sites [35], whether this pattern persists across age groups has not been evaluated.

1.5 Thesis Objectives

The objectives of this thesis are two-fold:

a) To evaluate and synthesize existing literature on the risk of all-cause mortality by age following completion of limited-duration anticoagulation for a first episode of unprovoked VTE.

b) To evaluate the risk of VTE recurrence after completion of limited-duration OAC therapy by age, with death as a competing event using data from a prospective cohort study.

1.6 Thesis Structure

The thesis is composed of two manuscripts. In the first (Chapter 2), I will present the methodology and results of a systematic review and meta-analysis on the age-, sex- and index VTE-specific risk of all-cause mortality over a span of 10 years following anticoagulant discontinuation for a first unprovoked VTE. In the second manuscript (Chapter 3), I will present the impact of all-cause mortality as a competing outcome to age-specific risks of recurrent VTE and illustrate the differential impact of age on VTE recurrence according to sex and site of index VTE. In the final

chapter, I will discuss the clinical implications of these intercalated component manuscripts and present future research directions.

1.7 References

1. Goldhaber SZ, Bounameaux H: **Pulmonary embolism and deep vein thrombosis**. *Lancet* 2012, **379**(9828):1835-1846.
2. Barco S, Valerio L, Ageno W, Cohen AT, Goldhaber SZ, Hunt BJ, Iorio A, Jimenez D, Klok FA, Kucher N *et al*: **Age-sex specific pulmonary embolism-related mortality in the USA and Canada, 2000-18: an analysis of the WHO Mortality Database and of the CDC Multiple Cause of Death database**. *Lancet Respir Med* 2021, **9**(1):33-42.
3. Yusuf HR, Tsai J, Atrash HK, Boulet S, Grosse SD: **Venous thromboembolism in adult hospitalizations - United States, 2007-2009**. *Morbidity and Mortality Weekly Report* 2012.
4. Raskob GE, Angchaisuksiri P, Blanco AN, Büller H, Gallus A, Hunt BJ, Hylek EM, Kakkar TL, Konstantinides SV, McCumber M *et al*: **Thrombosis: A Major Contributor to Global Disease Burden**. *Seminars in Thrombosis and Hemostasis* 2014, **40**(7):724-735.
5. Shekelle PG, Pronovost PJ, Wachter RM, McDonald KM, Schoelles K, Dy SM, Shojania K, Reston JT, Adams AS, Angood PB *et al*: **The top patient safety strategies that can be encouraged for adoption now**. *Ann Intern Med* 2013, **158**(5 Pt 2):365-368.
6. Anderson FA, Jr., Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, Forcier A, Dalen JE: **A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study**. *Arch Intern Med* 1991, **151**(5):933-938.

7. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd: **Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study**. *Arch Intern Med* 1998, **158**(6):585-593.

8. White RH: **The Epidemiology of Venous Thromboembolism**. *Circulation* 2003, **107**(90231):4I--8.

9. Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T: **A prospective study of the incidence of deep-vein thrombosis within a defined urban population**. *J Intern Med* 1992, **232**(2):155-160.

10. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, Roy P-M, Fine MJ: **Derivation and Validation of a Prognostic Model for Pulmonary Embolism**. *American Journal of Respiratory and Critical Care Medicine* 2005, **172**(8):1041-1046.

11. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J: **Incidence and mortality of venous thrombosis: a population-based study**. *J Thromb Haemost* 2007, **5**(4):692-699.

12. Khan F, Rahman A, Carrier M, Kearon C, Weitz JI, Schulman S, Couturaud F, Eichinger S, Kyrle PA, Becattini C *et al*: **Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: Systematic review and meta-analysis**. *The BMJ* 2019, **366**:l4363.

13. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, Hutten BA, Jaff MR, Manja V, Schulman S *et al*: **American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism**. *Blood Adv* 2020, **4**(19):4693-4738.

14. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, Huisman MV, Kearon C, King CS, Knighton AJ *et al*: **Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report**. *Chest* 2021, **160**(6):e545-e608.

15. Rodger MA, Kahn SR, Wells PS, Anderson DA, Chagnon I, Le Gal G, Solymoss S, Crowther M, Perrier A, White R *et al*: **Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy**. *CMAJ* 2008, **179**(5):417-426.

16. Eischer L, Eichinger S, Kyrle PA: **Age at first venous thromboembolism and risk of recurrence: a prospective cohort study**. *Medicine (Baltimore)* 2009, **88**(6):366-370.

17. Beyth RJ, Cohen AM, Landefeld CS: **Long-term outcomes of deep-vein thrombosis**. *Arch Intern Med* 1995, **155**(10):1031-1037.

18. de Winter MA, van Es N, Buller HR, Visseren FLJ, Nijkeuter M: **Prediction models for recurrence and bleeding in patients with venous thromboembolism: A systematic review and critical appraisal**. *Thromb Res* 2021, **199**:85-96.

19. Rodger MA, Le Gal G, Anderson DR, Schmidt J, Pernod G, Kahn SR, Righini M, Mismetti P, Kearon C, Meyer G *et al*: **Validating the HERDOO2 rule to guide treatment duration for women with unprovoked venous thrombosis: Multinational prospective cohort management study**. *BMJ (Online)* 2017, **356**:j1065.

20. Tosetto A, Testa S, Martinelli I, Poli D, Cosmi B, Lodigiani C, Ageno W, De Stefano V, Falanga A, Nichele I *et al*: **External validation of the DASH prediction rule: a retrospective cohort study**. *J Thromb Haemost* 2017, **15**(10):1963-1970.

21. Tosetto A, Iorio A, Marcucci M, Baglin T, Cushman M, Eichinger S, Palareti G, Poli D, Tait RC, Douketis J: **Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH)**. *J Thromb Haemost* 2012, **10**(6):1019-1025.

22. Weingarz L, Schwonberg J, Schindewolf M, Hecking C, Wolf Z, Erbe M, Weber A, Lindhoff-Last E, Linnemann B: **Prevalence of thrombophilia according to age at the first manifestation of venous thromboembolism: results from the MAISTHRO registry**. *Br J Haematol* 2013, **163**(5):655-665.

23. Wolkewitz M, Cooper BS, Bonten MJ, Barnett AG, Schumacher M: **Interpreting and comparing risks in the presence of competing events**. *BMJ* 2014, **349**:g5060.

24. Berry SD, Ngo L, Samelson EJ, Kiel DP: **Competing risk of death: an important consideration in studies of older adults**. *J Am Geriatr Soc* 2010, **58**(4):783-787.

25. Søgaard KK, Schmidt M, Pedersen L, Horváth–Puhó E, Sørensen HT: **30-Year Mortality After Venous Thromboembolism**. *Circulation* 2014, **130**(10):829-836.

26. Tagalakis V, Patenaude V, Kahn SR, Suissa S: **Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort**. *Am J Med* 2013, **126**(9):832 e813-821.

27. van der Wall SJ, van der Pol LM, Ende-Verhaar YM, Cannegieter SC, Schulman S, Prandoni P, Rodger M, Huisman MV, Klok FA: **Fatal recurrent VTE after anticoagulant treatment for unprovoked VTE: a systematic review**. *Eur Respir Rev* 2018, **27**(150).

28. Reitter S, Laczkovics C, Waldhoer T, Mayerhofer M, Vutuc C, Pabinger I: **Long-term survival after venous thromboembolism: a retrospective selected cohort study among young women**. *Haematologica* 2010, **95**(8):1425-1428.

29. Lacny S, Wilson T, Clement F, Roberts DJ, Faris P, Ghali WA, Marshall DA: **Kaplan-Meier survival analysis overestimates cumulative incidence of health-related events in competing risk settings: a meta-analysis**. *J Clin Epidemiol* 2018, **93**:25-35.

30. Parpia S, Julian JA, Thabane L, Lee AY, Rickles FR, Levine MN: **Competing events in patients with malignant disease who are at risk for recurrent venous thromboembolism**. *Contemp Clin Trials* 2011, **32**(6):829-833.

31. Ay C, Posch F, Kaider A, Zielinski C, Pabinger I: **Estimating risk of venous thromboembolism in patients with cancer in the presence of competing mortality**. *J Thromb Haemost* 2015, **13**(3):390-397.

32. Scheres LJJ, van Hylckama Vlieg A, Cannegieter SC: **Sex-specific aspects of venous thromboembolism: What is new and what is next?** *Res Pract Thromb Haemost* 2022, **6**(4):e12722.

33. Roach RE, Lijfering WM, Rosendaal FR, Cannegieter SC, le Cessie S: **Sex difference in risk of second but not of first venous thrombosis: paradox explained**. *Circulation* 2014, **129**(1):51-56.

34. McRae S, Tran H, Schulman S, Ginsberg J, Kearon C: **Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis**. *Lancet* 2006, **368**(9533):371-378.

35. Kovacs MJ, Kahn SR, Wells PS, Anderson DA, Chagnon I, G LEG, Solymoss S, Crowther M, Perrier A, Ramsay T *et al*: **Patients with a first symptomatic unprovoked**

deep vein thrombosis are at higher risk of recurrent venous thromboembolism than patients with a first unprovoked pulmonary embolism. *J Thromb Haemost* 2010, **8**(9):1926-1932.

CHAPTER 2: Long-Term Risk of All-Cause Mortality Following Anticoagulant Cessation for Unprovoked Venous Thromboembolism: A Systematic Review and Meta-Analysis

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Background: While guidelines recommend long-term anticoagulation after the first diagnosis of unprovoked venous thromboembolism (VTE), benefits and harms associated with this approach remain unclear particularly among older adults at risk of non VTE-related mortality. While death is a competing event to recurrent VTE, the long-term risk of all-cause mortality following anticoagulant discontinuation has not been systematically quantified.

Aims: 1) To examine risks of all-cause mortality following anticoagulant cessation among patients with a first episode of unprovoked VTE, with stratification by age at treatment discontinuation and sex. 2) To determine the contribution of fatal pulmonary embolism (PE) on mortality in this population.

Methods: We performed a systematic review using MEDLINE, EMBASE, and CENTRAL to include randomized trials and prospective cohorts reporting recurrent VTE and all-cause mortality following anticoagulant discontinuation among patients with a first unprovoked VTE. Participants must have completed ≥3 months of initial treatment before anticoagulant discontinuation. Primary endpoint was incidence of all-cause mortality across age categories (<50 years, 50–64 years, 65–74 years, ≥75 years) at 1-, 2-, 5- and 10-years following anticoagulant discontinuation. We also determined the proportion of deaths attributable to fatal PE.

Results: We identified 12 studies with 14,523 person-years of follow-up. Cumulative incidence of all-cause mortality was 1.9% (95% CI 1.0-3.1), 4.3% (95% CI 2.1-7.3), 8.6% (95% CI 4.4–14.0) and 14.0% (95% CI 6.8–23.1) at 1, 2, 5 and 10 years following anticoagulant

discontinuation, respectively. All-cause mortality risks increased with age, with the highest risk observed among males ≥75 years at time of anticoagulant discontinuation. Fatal PE comprised 16.5% (95% CI 9.5 – 25.0) of mortality events.

Conclusion: Patients with unprovoked VTE experience substantial risks of mortality following anticoagulant discontinuation; however, less than 20% of such events were related to fatal PE. All-cause mortality needs to be considered in shared decision-making about duration of anticoagulant treatment, especially among patients ≥75 years.

Anticoagulant treatment duration for venous thromboembolism (VTE) is predicated on the balance between risks of recurrent VTE and major bleeding both on and off anticoagulation, as well as case fatality associated with each scenario [1]. Patients who discontinue anticoagulation after a first episode of unprovoked VTE have recurrence rates of 16% at two years and 36% at 10 years [2]. Recognizing these high risks of thrombotic recurrence, major guidelines recommend long-term anticoagulation in this setting [3, 4].

Competing events occur when an outcome (e.g., death) other than the primary endpoint under study (e.g., recurrent VTE) occurs, which changes the future probability of the occurrence of the primary endpoint [5]. In settings where competing risk of death is high over the duration of follow-up, standard survival analysis using Kaplan-Meier approaches overestimate the incidence of disease occurrence [5, 6].

Despite the crucial role of mortality as a competing event to recurrent VTE, the long-term risk of all-cause mortality among patients with unprovoked VTE who stopped anticoagulation has not been systematically evaluated. We therefore conducted a systematic review and meta-analysis to quantify the risk of all-cause mortality after up to 10 years after discontinuing anticoagulation among patients with an unprovoked VTE, with a specific focus on patient's age, sex, and index site of VTE (DVT and/or PE). In addition, we sought to understand the contribution of fatal recurrent pulmonary embolism on long-term all-cause mortality in these patients.

METHODS

The study protocol was established *a priori* in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) Statement, and our methods have been reported in full previously [2].

Eligibility, Search Strategy and Study Selection

A comprehensive literature search was undertaken using Medline, Embase, CENTRAL and SCOPUS to include studies enrolling adults (aged 18 years and above) with a first episode of objectively confirmed, symptomatic deep vein thrombosis (DVT) and/or pulmonary embolism (PE) that is unprovoked as defined by the International Society on Thrombosis and Haemostasis criteria [7], who stopped anticoagulation after completing at least 3 months of anticoagulation. We performed backward searching of included studies by examining reference lists of included reports to identify additional eligible studies. Two independent reviewers screened titles, abstracts and full text articles in duplicate, with conflicts resolved through consensus discussion. We included randomized controlled trials and prospective cohort studies; retrospective cohort and case-control studies were excluded. Reports that included patients with VTE provoked by a major transient or persistent risk factor, or those with VTE in association with malignancy were excluded, unless a subgroup with unprovoked VTE was specifically analyzed and reported. As the goal of this systematic review and meta-analysis was to understand the competing risk of all-cause mortality among those who stopped OACs after time-limited treatment, we excluded patients on long-term anticoagulation following their index unprovoked VTE.

Screening of titles, abstracts and full text articles was performed in duplicate by two independent reviewers. Screening was performed using Covidence (Alfred Hospital, Melbourne, Australia),

and a full text eligibility form was used to document inclusion and exclusion criteria for full text article screening. Reasons for full text exclusion were recorded and reported in the PRISMA flow diagram.

Data Collection and Quality Assessment

A data extraction form was pilot tested in Microsoft Excel 2021 to record author, publication year, study design, number of patients included, patient demographics, distribution of index VTE (isolated DVT, isolated PE, PE + DVT), definition of unprovoked VTE, follow-up period, and outcomes of interest. Where studies reported age- and sex-specific subgroup data, they were extracted separately. Data extraction was performed in duplicate. We presented key characteristics of the included studies both in narrative summary and in a table summary. Key outcome measures included: number of patients at risk, the corresponding number of patient-years of follow-up, and all-cause mortality (including fatal PE). If an eligible study did not provide age- and sex-specific subgroup data on all-cause mortality, we contacted the study authors for clarification.

Consistent with our prior work [2], we used the Newcastle-Ottawa scale to complete the risk of bias assessment at the individual study level for the primary outcome [8].

Data Synthesis

A key aim of the study was to generate a pooled estimate of the absolute risk of all-cause mortality over time intervals of 1, 2, 5, and 10 years following the index unprovoked VTE diagnosis. Prior to proceeding with a meta-analysis, we assessed the included studies for heterogeneity of age among included participants and study design. Data were pooled using the DerSimonian and Laird

random-effects model, with weighting based on inverse variance of the effect estimate. Statistical heterogeneity was assessed through visual inspection of effect size estimates and 95% CI, and via calculation of the I^2 statistic. Two-tailed $p < 0.05$ was considered statistically significant. Where included trials contained more than one treatment group (e.g., different anticoagulant dosages), these were collapsed into a single interventional arm.

Incidence rates of mortality (in 100 person-years) were categorized into four intervals: year 1, year 2, years 3-5 and years 6-10. Cumulative incidence (in %) of all-cause mortality after 2, 5 and 10 years of follow-up were estimated using incidence rates for each time interval as follows:

$$\textit{Year 1 incidence} \times \textit{year 2 incidence} \times (\textit{year 3-5 incidence})^3 \times (\textit{year 5-10 incidence})^5$$

Incidence rates for years 3-5 and years 5-10 were used for determining cumulative incidences after 5 and 10 years respectively. Using the same approach, we used upper and lower bounds of 95% confidence intervals (CIs) of incidence rates to determine the respective 95% CI bounds of cumulative incidence.

We evaluated the contribution of fatal PE events to all-cause mortality during long-term follow-up of patients following anticoagulant cessation for unprovoked VTE, by calculating the proportion of fatal PE to total number of deaths during follow-up. Finally, we performed *a priori* subgroup analyses of all-cause mortality based on age of included participants (<50 years, 50-64 years, 65-74 years, or ≥75 years), sex, and initial site of VTE (DVT vs. PE vs. PE + DVT).

RESULTS

A total of 1,284 records were identified by the literature search, supplemented by 8 additional records identified via additional sources. Of these, 850 were screened by title and abstract

following removal of duplicates. Ninety-two abstracts proceeded to full-text review, after which 26 studies were deemed potentially relevant for inclusion in the systematic review. After study authors were contacted for data clarification, we obtained data (including unpublished data) for the analysis of all-cause mortality for 12 studies (**Figure 1**).

Characteristics of Included Studies

Of the 12 studies included in this systematic review [9-20], 8 were randomized controlled trials and 4 were prospective cohort studies, with a combined number of 5,010 patients with a first episode of unprovoked VTE who stopped anticoagulation after ≥3 months of initial treatment (**Table 1**). All studies followed patients for at least 1 year from the time of anticoagulant cessation. Ten of the 12 included studies followed patients for up to 2 years from anticoagulant cessation, while 8 and 5 studies had up to 5 and 10 years of follow-up respectively. All studies used *a priori*-defined criteria to diagnose VTE recurrence (**Table 1**), and overall risk of bias was considered low by the Newcastle-Ottawa Scale (**Supplemental Table 1**). All studies assessed suspected outcome events (e.g., recurrent VTE, including fatal PE) through independent adjudication.

Mean age in the included studies ranged from 53 to 69. Two studies exclusively enrolled patients with proximal DVT as their index VTE event [13, 20], while another two studies exclusively enrolled patients with PE, either with or without concomitant DVT [10, 17]. Among studies that included both sites of index VTE, the proportion of isolated DVT vs. PE (+/- DVT) was variable (**Table 1**).

Risk of All-Cause Mortality

268 patients with a first episode of unprovoked VTE who stopped anticoagulation died during 14,523 person-years of follow-up, corresponding to an incidence rate of 1.85 deaths per 100 person-years in the entire cohort. The pooled incidence of all-cause mortality per 100 person-years in the overall cohort was 2.1 (95% CI 1.3-3.3) in year 1, 2.4 (95% CI 1.2-4.3) in year 2, 1.8 (95% CI 1.0-2.7) in years 3-5, and 1.2 (95% CI 0.5-2.2) in years 5-10.

The cumulative incidence of all-cause mortality was 4.6% (95% CI 2.4% - 7.5%) at the end of year 2, 9.5% (95% CI 5.4%-14.8%) at the end of year 5, and 15.0% (95% CI 7.8% - 23.8%) at the end of year 10.

Impact of Age and Sex

Individuals with a first unprovoked VTE who were <50 years at the time of anticoagulant discontinuation had a 0.7% risk of all-cause mortality (95% CI 0.2% - 1.7% among males; 95% CI 0.2% – 1.5% among females) in the first year after anticoagulation discontinuation (**Table 2**). However, the incidence of death increased in an age-dependent fashion, where 5.1% (95% CI 2.7% – 8.2%) and 6.6% (95% CI 4.4% – 9.2%) of males and females aged ≥75 years at the time of treatment cessation died within in the first year (**Table 3**).

While there was no difference in pooled incidence of all-cause mortality between males (2.1 per 100 person-years, 95% CI 1.2 – 3.2) and females (1.8 per 100 person-years, 95% CI 1.0 – 2.8), the effect of age on the risk of all-cause mortality was especially pronounced among males ≥75 years at time of anticoagulant cessation, who had a 10-year cumulative incidence of all-cause mortality

of 62.6% (95% CI 38.6% - 80.9%), compared to females in the same age stratum who had a 47.9% (95% CI 23.4% - 73.2%) risk of all-cause mortality (**Table 3**).

Impact of Initial VTE Site

There was no difference in the 10-year cumulative incidence of all-cause mortality among patients whose index presentation involved isolated proximal DVT (16.7%, 95% CI 9.2% - 26.0%), isolated PE (11.9%, 95% CI 4.1% - 24.8%) or proximal DVT with PE (9.6%, 95% CI 3.4% - 18.3%). Risk of all-cause mortality was also consistent between sites of index VTE when stratified by age groups (**Table 3, Supplemental Figure 1**).

Contribution of Fatal PE to All-Cause Mortality

Of 268 deaths that occurred across all studies, 52 were classified as fatal PE. The pooled proportion of all-cause mortality events attributable to fatal PE was 15.9% (95% CI 9.4% to 23.7%). The contribution of fatal PE to all-cause mortality was consistent among males (23.3%, 95% CI 14.4% - 33.7%) and females (13.5%, 95% CI 6.0% - 23.4%). In addition, there was no difference in the proportion of deaths attributable to fatal PE among decedents aged <50 years (25.0%, 95% CI 5.5% - 57.2%), 50-64 years (17.1%, 95% CI 7.2% - 32.1%), 65-74 years (29.6%, 95% CI 19.3% – 41.6%), and ≥75 years (19.1%, 95% CI 12.4% – 25.8%).

DISCUSSION

In this systematic review and meta-analysis of 12 studies with over 14,000 patient-years of follow-up, we observed a pooled incidence of all-cause morality of 1.9 events per 100 person-years of follow-up. The risk of all-cause mortality was age-dependent particularly among those aged >75

years at the time of anticoagulant cessation: in this group, the 10-year cumulative incidence of death was 49.1%, 18-fold higher compared to those aged <50 years. Crucially, more than 5 in 6 all-cause mortality events occurred due to causes other than PE.

Our results are consistent with a recent meta-analysis of randomized controlled trials that evaluated extended anticoagulant treatment for VTE, which reported an incidence of 1% for all-cause mortality after a median follow-up duration of 12 months [21]. However, the risk of death observed in our study is higher than in cohort studies that followed patients from the time of index VTE diagnosis. For example, a prospective Cleveland cohort reported a 17% risk of all-cause mortality at 1 year [22], which mirrors findings of a study using administrative data from Quebec, Canada [23]. The discrepancy between our findings and these cohorts likely reflects the elevated risk of early mortality after VTE diagnosis, treatment-related bleeding, as well as detection of occult malignancy [24], all of which are higher at VTE diagnosis or within the first 3 months of treatment [25-27]. This highlights the potential broad application for our findings, which may inform the prognosis of patients who have completed at least 3 months of anticoagulation for unprovoked VTE, without a strong indication for ongoing anticoagulant treatment (e.g., detection of occult malignancy or a potent thrombophilia).

Although individuals with unprovoked VTE who have completed ≥3 months of therapeutic anticoagulation appear to have a lower incidence of all-cause mortality compared to those with a new diagnosis of VTE, they appear to have a higher risk of all-cause mortality compared to the general population matched by age. For example, the cumulative incidence of death among patients at age 65-74 years who stopped anticoagulation was 22.8% at 10 years. In comparison, 10-year risks of all-cause mortality in the general population in Canada, Austria and Italy,

coordinating countries of 3 studies with longest study follow-up included the meta-analysis, were 13.7%, 14.6% and 12.1% respectively [28, 29]. Using national administrative databases in Sweden, Søgaard *et al* showed an increase in all-cause mortality following a VTE diagnosis that remained elevated for up to 30 years [30]. In the study, rate ratios for 10-year all-cause mortality between those diagnosed with unprovoked DVT and PE, compared to their age- and sex-matched controls in the general population, were 1.36 and 1.41 respectively, mirroring our findings [30]. Our findings highlight the importance of identifying the cause of excess mortality risk after a diagnosis of unprovoked VTE, and mitigating modifiable risk factors that contribute to this survival disparity.

The high cumulative Incidence of all-cause mortality observed in our study, especially those among individuals aged ≥75 years at the time of anticoagulant cessation, raises important questions on the impact of the occurrence of death (as a competing event) on analyses which examine rates of recurrent VTE. For example, the cumulative incidence of all-cause mortality at 2 years following anticoagulant cessation in our study was 13.6% among those aged ≥75 years. In comparison, a prospective cohort study of 240 elderly VTE patients (mean age 74 years) at the time of anticoagulant discontinuation for an unprovoked VTE reported a 16.2% risk of recurrence over a follow-up of 2 years [33]. Similarly, another prospective registry of 7,208 patients aged ≥75 years at time of anticoagulant discontinuation observed a 10.6% risk of recurrence at 1.5 years following anticoagulant cessation [34]. Competing risk of death is an important consideration in studies involving older adults which, when not accounted for, often results in overestimation of disease incidence [35]. In settings where competing risk of death is high over the duration of follow-up, standard Kaplan-Meier approaches overestimate the incidence of disease occurrence [5], with a 1.4-fold effect based on a recent systematic review and meta-analysis [6]. This was

confirmed by Parpia *et al* using data from the CLOT trial, which compared low molecular weight heparin to warfarin for the treatment of cancer-associated thrombosis in which overall mortality was 40% at end of follow-up [36]. A re-analysis of the CLOT trial data using competing risk methods showed a decrease in the absolute risk difference between the low molecular weight heparin and warfarin arms, from 8.5% with standard Kaplan-Meier method to 6% with use of the cumulative incidence function [36]. Therefore, our results highlight the need to consider the competing risk of all-cause mortality when estimating the risk of recurrent VTE in research and in the clinic, especially among elderly patients aged ≥75 years.

Our study has several strengths. Drawing on over 14,000 patient-years of follow-up specifically of patients who have completed ≥3 months of therapeutic anticoagulation, we examined long-term risk of all-cause mortality specific to patients with unprovoked VTE who stopped anticoagulant treatment. Furthermore, by limiting our meta-analysis to prospective studies with rigorous inclusion criteria and independent adjudication of outcomes during follow-up we were able to accurately capture the index VTE events at enrolment and fatal PE events during follow-up. This overcomes criticisms of prior studies that evaluated all-cause mortality following VTE diagnosis, which have largely used administrative databases: while comprehensive and population-based, they inherently suffer from misclassification bias due to potential coding errors as it relates to cohort identification and assessment of fatal PE events.

Nonetheless, our study is subject to several limitations. First, included studies did not enrol a contemporaneous cohort of patients without VTE, which limits the interpretation of all-cause mortality risks relative to the general population. However, our results suggest that analyses which account for the competing risk of death may inform treatment decisions by providing more accurate estimates of the risk of recurrent VTE, particularly in older individuals. Second, specific

causes of death apart from fatal PE were not captured in our meta-analysis, a topic that has been evaluated in prior studies. Third, the definition of PE-related mortality among clinical studies involving VTE has been heterogenous to date (Supplementary Appendix 4) and only recently been harmonized [37], which may limit the effect estimate of proportion of all-cause mortality events that are attributable to fatal PE. Finally, our study was not designed to assess risks of major bleeding and all-cause mortality among patients who continued anticoagulant treatment for unprovoked VTE, which serve as competing events for the risk of recurrent VTE that are future topics of research.

In summary, patients with unprovoked VTE who completed at least 3 months of therapeutic anticoagulation had substantial risk of all-cause mortality at 10 years after anticoagulant cessation, especially among individuals aged ≥ 75 years. However, fatal PE comprised less than 1 in 6 deaths. These findings provide rigorous estimates to inform the prognosis of patients with unprovoked VTE and serve as an impetus for future evaluation of all-cause mortality as a competing event to VTE recurrence among patients with a first unprovoked DVT or PE.

REFERENCES

1. Rodger MA, Le Gal G: **Who should get long-term anticoagulant therapy for venous thromboembolism and with what?** *Blood Advances* 2018, **2**(21):3081-3087.
2. Khan F, Rahman A, Carrier M, Kearon C, Weitz JI, Schulman S, Couturaud F, Eichinger S, Kyrle PA, Becattini C *et al*: **Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: Systematic review and meta-analysis**. *The BMJ* 2019, **366**:l4363.

3. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, Hutten BA, Jaff MR, Manja V, Schulman S *et al*: **American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism**. *Blood Adv* 2020, **4**(19):4693-4738.
4. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, Huisman MV, Kearon C, King CS, Knighton AJ *et al*: **Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report**. *Chest* 2021, **160**(6):e545-e608.
5. Wolkewitz M, Cooper BS, Bonten MJ, Barnett AG, Schumacher M: **Interpreting and comparing risks in the presence of competing events**. *BMJ* 2014, **349**:g5060.
6. Lacny S, Wilson T, Clement F, Roberts DJ, Faris P, Ghali WA, Marshall DA: **Kaplan-Meier survival analysis overestimates cumulative incidence of health-related events in competing risk settings: a meta-analysis**. *J Clin Epidemiol* 2018, **93**:25-35.
7. Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing GJ, Kyrle PA: **Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH**. *Journal of Thrombosis and Haemostasis* 2016, **14**(7):1480-1483.
8. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P: **The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses**. In.; 2014.
9. Palareti G, Legnani C, Cosmi B, Guazzaloca G, Pancani C, Coccheri S: **Risk of venous thromboembolism recurrence: High negative predictive value of D-dimer**

performed after oral anticoagulation is stopped. *Thrombosis and Haemostasis* 2002, **87**(01):7-12.

10. Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, Imberti D, Poggio R, Ageno W, Pogliani E *et al*: **Extended oral anticoagulant therapy after a first episode of pulmonary embolism**. *Ann Intern Med* 2003, **139**(1):19-25.
11. Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, Cushman M, Moll S, Kessler CM, Elliott CG *et al*: **Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism**. *N Engl J Med* 2003, **348**(15):1425-1434.
12. Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, Iotti M, Tormene D, Simioni P, Pagnan A: **The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients**. *Haematologica* 2007, **92**(2):199-205.
13. Prandoni P, Prins MH, Lensing AW, Ghirarduzzi A, Ageno W, Imberti D, Scannapieco G, Ambrosio GB, Pesavento R, Cuppini S *et al*: **Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis: a randomized trial**. *Ann Intern Med* 2009, **150**(9):577-585.
14. Investigators. E: **Oral Rivaroxaban for Symptomatic Venous Thromboembolism**. *New England Journal of Medicine* 2010, **363**(26):2499-2510.
15. Brighton TA, Eikelboom JW, Mann K, Mister R, Gallus A, Ockelford P, Gibbs H, Hague W, Xavier D, Diaz R *et al*: **Low-dose aspirin for preventing recurrent venous thromboembolism**. *N Engl J Med* 2012, **367**(21):1979-1987.

16. Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, Bianchi M, Moia M, Ageno W, Vandelli MR *et al*: **Aspirin for preventing the recurrence of venous thromboembolism**. *N Engl J Med* 2012, **366**(21):1959-1967.

17. Couturaud F, Sanchez O, Pernod G, Mismetti P, Jego P, Duhamel E, Provost K, Dit Sollier CB, Presles E, Castellant P *et al*: **Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism**. *JAMA* 2015, **314**(1):31.

18. Rodger MA, Scarvelis D, Kahn SR, Wells PS, Anderson DA, Chagnon I, Le Gal G, Gandara E, Solymoss S, Sabri E *et al*: **Long-term risk of venous thrombosis after stopping anticoagulants for a first unprovoked event: A multi-national cohort**. *Thromb Res* 2016, **143**:152-158.

19. Kyrle PA, Kammer M, Eischer L, Weltermann A, Minar E, Hirschl M, Heinze G, Eichinger S: **The long-term recurrence risk of patients with unprovoked venous thromboembolism: an observational cohort study**. *J Thromb Haemost* 2016, **14**(12):2402-2409.

20. Couturaud F, Pernod G, Presles E, Duhamel E, Jego P, Provost K, Pan-Petesch B, Sollier CBD, Tromeur C, Hoffmann C *et al*: **Six months versus two years of oral anticoagulation after a first episode of unprovoked deep-vein thrombosis. The PADIS-DVT randomized clinical trial**. *Haematologica* 2019, **104**(7):1493-1501.

21. Mai V, Guay C-A, Perreault L, Bonnet S, Bertoletti L, Lacasse Y, Jardel S, Lega J-C, Provencher S: **Extended Anticoagulation for VTE: A Systematic Review and Meta-Analysis**. *Chest* 2019, **155**(6):1199-1216.

22. Beyth RJ, Cohen AM, Landefeld CS: **Long-term outcomes of deep-vein thrombosis**. *Arch Intern Med* 1995, **155**(10):1031-1037.

23. Tagalakis V, Patenaude V, Kahn SR, Suissa S: **Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort**. *Am J Med* 2013, **126**(9):832 e813-821.

24. van Es N, Le Gal G, Otten HM, Robin P, Piccioli A, Lecumberri R, Jara-Palomares L, Religa P, Rieu V, Rondina M *et al*: **Screening for Occult Cancer in Patients With Unprovoked Venous Thromboembolism: A Systematic Review and Meta-analysis of Individual Patient Data**. *Ann Intern Med* 2017, **167**(6):410-417.

25. Gussoni G, Frasson S, La Regina M, Di Micco P, Monreal M, Investigators R: **Three-month mortality rate and clinical predictors in patients with venous thromboembolism and cancer. Findings from the RIETE registry**. *Thromb Res* 2013, **131**(1):24-30.

26. Laporte S, Mismetti P, Decousus H, Uresandi F, Otero R, Lobo JL, Monreal M, Investigators R: **Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry**. *Circulation* 2008, **117**(13):1711-1716.

27. Castellucci LA, Cameron C, Le Gal G, Rodger MA, Coyle D, Wells PS, Clifford T, Gandara E, Wells G, Carrier M: **Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis**. *JAMA* 2014, **312**(11):1122-1135.

28. **Life tables: Life tables by country** [https://www.who.int/data/gho/data/indicators/indicator-details/GHO/gho-ghe-life-tables-by-country]

29. **Life expectancy and other elements of the complete life table, three-year estimates, Canada, all provinces except Prince Edward Island.** [https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310011401]

30. Søgaard KK, Schmidt M, Pedersen L, Horváth–Puhó E, Sørensen HT: **30-Year Mortality After Venous Thromboembolism**. *Circulation* 2014, **130**(10):829-836.

31. Flinterman LE, van Hylckama Vlieg A, Cannegieter SC, Rosendaal FR: **Long-term survival in a large cohort of patients with venous thrombosis: incidence and predictors**. *PLoS Med* 2012, **9**(1):e1001155.

32. Prandoni P, Bilora F, Marchiori A, Bernardi E, Petrobelli F, Lensing AW, Prins MH, Girolami A: **An association between atherosclerosis and venous thrombosis**. *N Engl J Med* 2003, **348**(15):1435-1441.

33. Mean M, Breakey N, Stalder O, Alberio L, Limacher A, Angelillo-Scherrer A, Fontana P, Beer HJ, Rodondi N, Aujesky D *et al*: **Thrombophilia and outcomes of venous thromboembolism in older patients**. *Res Pract Thromb Haemost* 2023, **7**(1):100015.

34. Prandoni P, Gabara C, Bilora F, Aibar J, Pesavento R, Villalobos A, Campello E, Miguel PL, Tormene D, Monreal M *et al*: **Age over 75 does not increase the risk of recurrent venous thromboembolism: Findings from the RIETE registry**. *Thromb Res* 2023, **222**:16-19.

35. Berry SD, Ngo L, Samelson EJ, Kiel DP: **Competing risk of death: an important consideration in studies of older adults**. *J Am Geriatr Soc* 2010, **58**(4):783-787.

36. Parpia S, Julian JA, Thabane L, Lee AY, Rickles FR, Levine MN: **Competing events in patients with malignant disease who are at risk for recurrent venous thromboembolism**. *Contemp Clin Trials* 2011, **32**(6):829-833.

37. Kraaijpoel N, Tritschler T, Guillo E, Girard P, Le Gal G. Definitions, adjudication, and reporting of pulmonary embolism-related death in clinical studies: A systematic review. J Thromb Haemost. 2019;17(10):1590-1607.

Table 1: Characteristics of included studies.

Source (year)	**Study Design**	**No. of patients with first unprovoked VTE**	**Male** (%)	**Age, years** (Range or SD)	**Unprovoked VTE Definition[a]** (minor transient risk factors included)	**Number and site of index VTE**	***Follow-up Duration, years**	**Overall Risk of Bias**
Palareti *et al* Palareti et al. (2002) [9]	Cohort	162	50.0	67 (12-91)	ISTH	137 proximal DVT; 25 PE + DVT	2	Low
WODIT-PE Agnelli et al. (2003) [10]	RCT	181			ISTH	72 PE; 109 PE + DVT		Low
Arm 1		91	41.6	61.0 (15.5)			2	
Arm 2		90	39.4	62.9 (16.3)			2	
PREVENT Ridker et al. (2003) [11]	RCT	140	52.9	67.7 (7.3)	Not occurring within 90 days after surgery or trauma	100 proximal DVT +/- PE; 40 unspecified VTE	2	Low
Prandoni *et al* Prandoni et al. (2007) [12]	Cohort	864	45.2	66.0 (16-96)	ISTH	735 proximal DVT +/- PE; 129 PE	10	Low
AESOPUS Prandoni et al. (2009) [13]	RCT	151	57.6	69.0 (21-89)	ISTH	151 proximal DVT	2	Low
EINSTEIN-Extension Bauersachs et al. (2010) [14]	RCT	465	58.5	57.6 (16.2)	ISTH	267 proximal DVT; 144 PE; 46 PE + DVT	1	Low
ASPIRE Brighton et al. (2012) [15]	RCT	822			ISTH	468 proximal DVT; 231 PE; 114 PE + DVT		Low
Arm 1		411	54	54 (15.8)			2	
Arm 2		411	55	55 (16)			2	

WARFASA Becattini et al. (2012) [16]	RCT	402			ISTH	252 proximal DVT; 55 PE; 95 PE + DVT		Low
Arm 1		197	61.9	62.1 (15.1)			2	
Arm 2		205	65.8	61.9 (15.3)			2	
PADIS-PE Couturaud et al. (2015) [17]	RCT	371			ISTH (exogenous estrogen)	259 PE; 112 PE + DVT		Low
Arm 1		187	55.1	57.3 (17.4)			3	
Arm 2		184	42.5	58.7 (16)			2	
REVERSE Rodger et al. (2016) [18]	Cohort	663	51.4	53.2 (18-95)	ISTH (exogenous estrogen)	346 proximal DVT; 194 PE; 123 PE + DVT	10	Low
AUREC Kyrle et al. (2016) [19]	Cohort	685	66.0	53 (14)	ISTH	349 proximal DVT; 336 PE with or without DVT	10	Low
PADIS-DVT Couturaud et al. (2019) [20]	RCT	104			ISTH (exogenous estrogen)	104 proximal DVT		Low
Arm 1		54	72.2	61.5 (14.5)			3	
Arm 2		50	62.0	59.0 (17.2)			2	

ISTH, International Society on Thrombosis and Haemostasis; RCT, randomized controlled trial; SD, standard deviation; y, years.

[a] "ISTH" is listed for studies judged to have defined unprovoked VTE, as closely as possible, as VTE occurring in the absence of ISTH defined persistent or major transient provoking risk factors.[10] The minor transient risk factors included in the definition of unprovoked VTE are listed in brackets after "ISTH".

[b] As applicable to the studied intervals of year 1, year 2, years 3-5, and years 5-10.

Table 2: Age-specific incidence of all-cause mortality after anticoagulant discontinuation among males and females with a first unprovoked VTE.

Interval of Follow-up After Discontinuing Anticoagulation	Male				Female			
	Age <50 y	Age 50–64 y	Age 65–75 y	Age >75 y	Age <50 y	Age 50–64 y	Age 65–75 y	Age >75 y
Year 1								
Events, n	3	7	15	13	1	3	4	25
Person-years, n	581.1	764.7	409.0	252.7	527.5	356.1	403.2	356.5
Incidence rate per 100 person-years (95% CI)	0.7 (0.2 - 1.7)	1.1 (0.5 - 2.0)	3.4 (1.9 – 5.5)	5.1 (2.7 – 8.2)	0.7 (0.2 - 1.5)	1.5 (0.5 – 3.0)	1.5 (0.5 - 2.9)	6.6 (4.4 – 9.2)
Year 2								
Events, n	2	7	14	22	1	2	5	24
Person-years, n	441.3	571.3	333.1	157.1	487.6	300.9	279.8	368.4
Incidence rate per 100 person-years (95% CI)	0.6 (0.1 - 1.6)	1.4 (0.5 – 2.8)	4.7 (2.7 -7.2)	9.7 (4.2 – 17.2)	0.6 (0.1 – 1.5)	1.2 (0.3 - 2.8)	2.2 (0.9 – 4.1)	6.9 (4.3 – 10.0)
Years 3–5								
Events, n	2	8	8	20	1	4	7	22
Person-years, n	708.1	902.8	455.8	207.0	744.2	480.0	456.0	451.6
Incidence rate per 100 person-years (95% CI)	0.5 (0.1 - 1.1)	1.1 (0.5 - 1.9)	2.0 (1.0 - 3.5)	9.8 (6.2 – 14.1)	0.3 (0.0 - 0.8)	1.3 (0.5 – 2.5)	2.0 (0.9 – 3.4)	5.3 (3.4 – 7.5)
Years 6–10								
Events, n	2	7	5	7	0	1	7	8
Person-years, n	709.6	640.2	213.5	83.6	619.2	437.4	277.0	152.6
Incidence rate per 100 person-years (95% CI)	0.5 (0.0 - 1.6)	1.3 (0.6 - 2.3)	2.8 (1.1- 5.5)	9.7 (4.4 - 16.9)	0.0 (0.0 - 0.5)	0.4 (0.0 - 1.2)	2.9 (1.3 - 5.2)	7.0 (1.5 – 16.1)

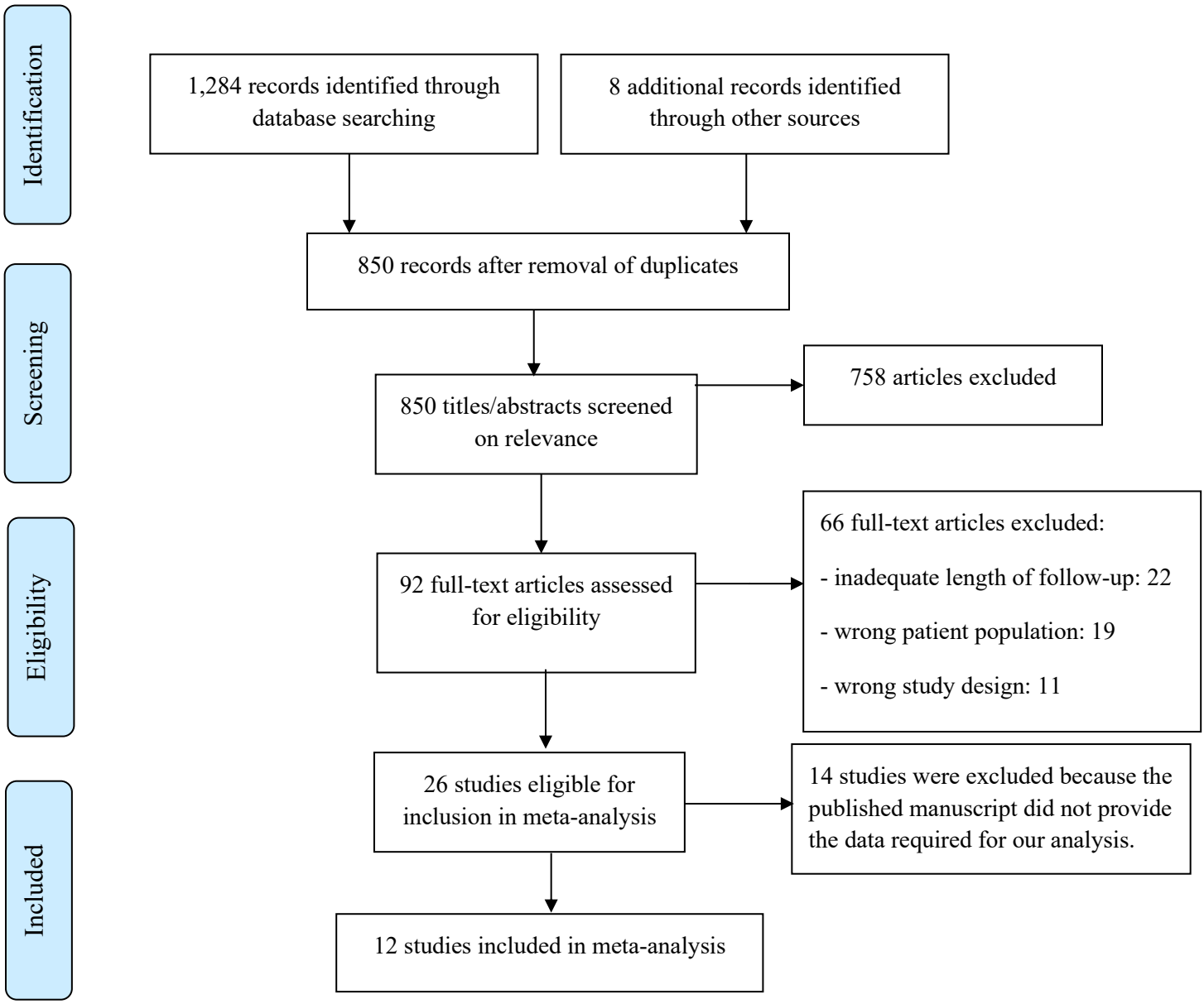
Table 3. Age-specific cumulative incidence of all-cause mortality by sex and site of index VTE

	Year 2	Year 5	Year 10
Males			
<50 years	1.4 (0.3 – 3.1)	2.7 (0.6 – 6.2)	4.8 (0.6 – 13.2)
50-64 years	2.5 (1.0 – 4.8)	5.7 (2.5 – 10.0)	11.7 (5.3 – 20.0)
65-74 years	8.0 (4.5 – 12.3)	13.5 (7.2 – 21.3)	25.2 (12.0 – 40.6)
≥75 years	14.3 (6.8 – 24.0)	37.2 (23.2 – 51.9)	62.3 (38.6 – 80.9)
Females			
<50 years	1.3 (0.3 – 3.0)	2.1 (0.4 – 5.3)	2.7 (0.4 – 7.8)
50-64 years	2.8 (0.8 – 5.8)	6.6 (2.3 – 12.7)	8.3 (2.4 – 17.7)
65-74 years	3.6 (1.4 – 6.9)	9.3 (4.1 – 16.1)	21.6 (10.0 – 35.7)
≥75 years	13.1 (8.6 – 18.0)	26.1 (17.6 – 35.4)	48.5 (23.4 – 73.2)
Isolated DVT			
<50 years	0.9 (0.2 – 2.1)	3.0 (0.6 – 6.9)	5.2 (1.0 – 12.5)
50-64 years	1.0 (0.2 – 2.4)	4.9 (1.5 – 10.4)	9.6 (3.1 – 19.2)
65-74 years	2.9 (0.9 – 5.9)	10.4 (4.4 – 18.3)	21.5 (9.8 – 35.7)
≥75 years	9.6 (6.5 – 13.2)	32.5 (21.5 – 44.3)	56.6 (24.2 – 85.4)

Isolated PE			
<50 years	1.6 (0.3 – 4.1)	2.4 (0.3 – 6.7)	3.1 (0.3 – 9.8)
50-64 years	3.6 (1.1 – 7.5)	6.2 (1.7 – 13.2)	9.8 (2.0 – 22.6)
65-74 years	6.6 (2.2 – 13.0)	12.6 (4.0 – 24.7)	26.6 (5.5 – 58.8)
≥75 years	12.0 (5.7 – 20.2)	27.6 (13.5 – 43.8)	42.2 (13.7 – 75.7)

DVT, deep vein thrombosis; PE, pulmonary embolism

Figure 1: Flow Diagram of Study Identification and Selection.



SUPPLEMENTAL APPENDIX

Appendix 1. Literature Search Strategy

1. Venous Thromboembolism/
2. Venous Thrombosis/
3. Pulmonary Embolism/
4. ven* thrombos*.tw
5. ven* thromboe*.tw
6. pulmonary embol*.tw
7. DVP.mp
8. or/1-7
9. Anticoagulants/
10. Warfarin/
11. Rivaroxaban/
12. Dabigatran/
13. Heparin/
14. Heparin, Low-Molecular Weight/
15. Factor Xa Inhibitors/
16. vitamin k antagonist.tw
17. VKA.tw
18. Aspirin/
19. ASA.tw
20. or/9-19
21. 8 and 20
22. Secondary Prevention/

23. Recurrence/

24. Randomized Controlled Trial/

25. Cohort Studies/

26. 24 or 25

27. 22 or 23

28. 21 and 27

29. 26 and 28

30. 21 and 26 and 27

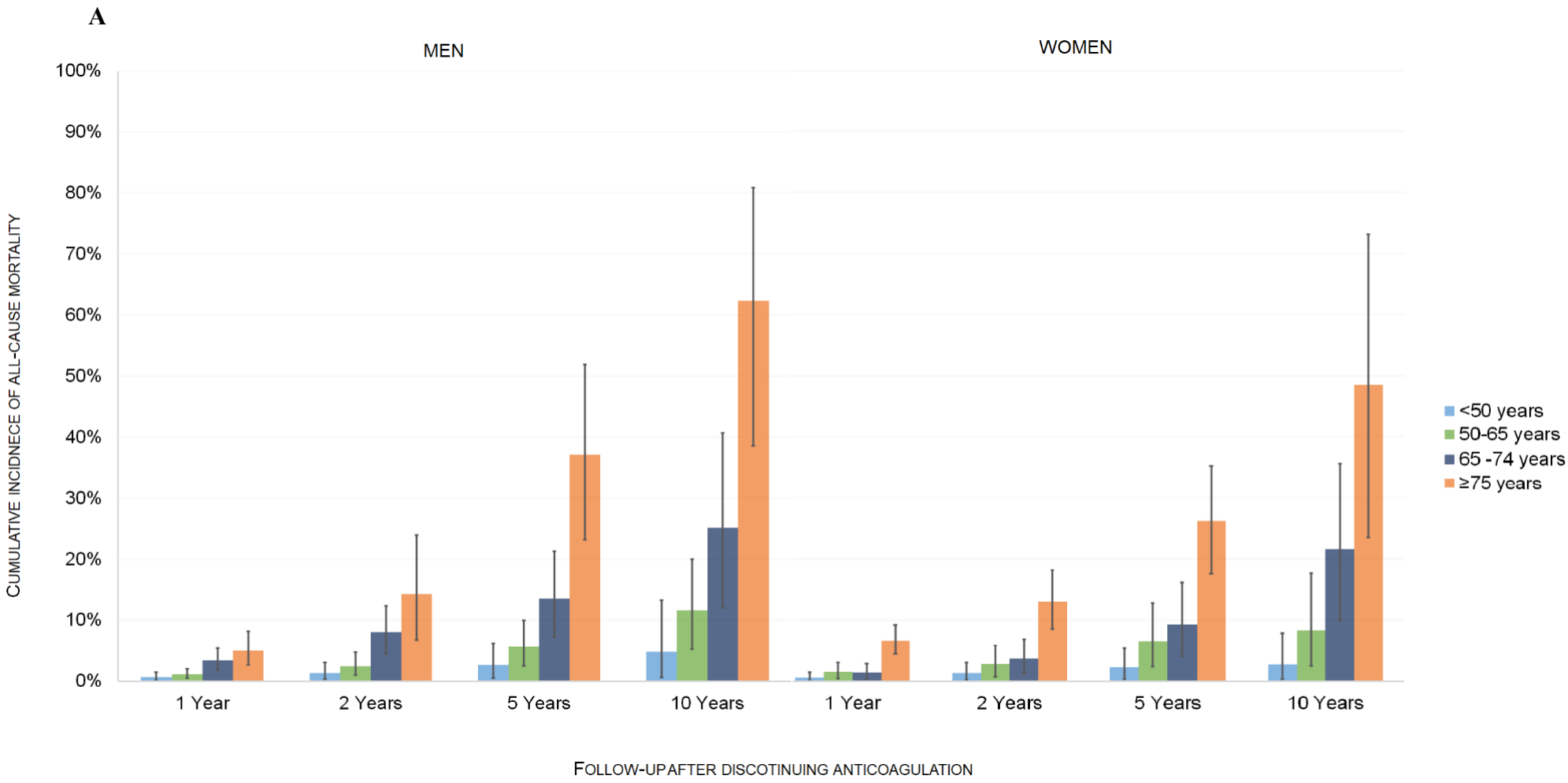
Appendix 2. Modified Newcastle-Ottawa Scale Risk of Bias Assessment.

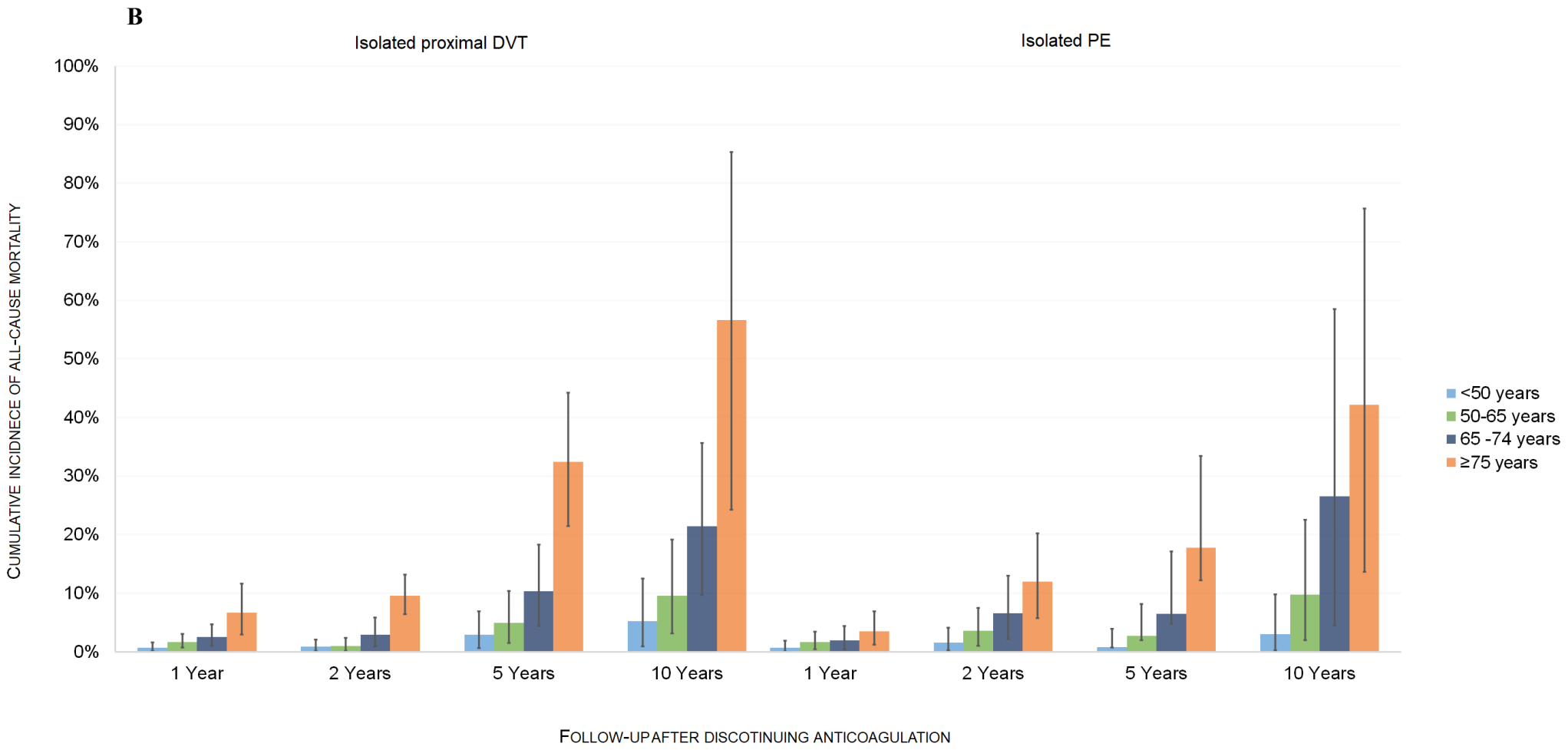
Newcastle-Ottawa scale was modified to our study objectives, and to exclude comparability as our objective was to generate a summary estimate of prognosis.

	Selection			**Outcome**			**TOTAL**
	Ascertainment of Exposure (Consecutive patients with unprovoked VTE)	Representativeness (Patients have completed at least 3 months of initial anticoagulation)	Demonstration that no patients had recurrent VTE at start of follow-up	Primary Outcome Assessment of Recurrent VTE	Acceptable length of follow-up	Adequacy of follow-up (>90%)	
Palareti *et al* Palareti et al. (2002)	1	1	1	1	1	1	
WODIT-PE Agnelli et al. (2003)	1	1	1	1	1	1	
PREVENT Ridker et al. (2003)	1	1	1	1	1	1	
Prandoni *et al* Prandoni et al. (2007)	1	1	1	1	1	1	
AESOPUS Prandoni et al. (2009)	1	1	1	1	1	1	
EINSTEIN-Extension Bauersachs et al. (2010)	1	1	1	1	1	1	
ASPIRE	1	1	1	1	1	1	

Brighton et al. (2012)							
WARFASA Becattini et al. (2012)	1	1	1	1	1	1	
PADIS-PE Couturaud et al. (2015)	1	1	1	1	1	1	
REVERSE Rodger et al. (2016)	1	1	1	1	1	1	
AUREC Kyrle et al. (2016)	1	1	1	1	1	1	
PADIS-DVT Couturaud et al. (2019)	1	1	1	1	1	1	

Appendix 3. Cumulative incidence of all-cause mortality after anticoagulant cessation for first unprovoked VTE by sex (A) and index site of VTE (B).




B
Isolated proximal DVT
Isolated PE
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
CUMULATIVE INCIDNECE OF ALL-CAUSE MORTALITY
1 Year
2 Years
5 Years
10 Years
1 Year
2 Years
5 Years
10 Years
FOLLOW-UPAFTER DISCOTINUING ANTICOAGULATION
<50 years
50-65 years
65 -74 years
≥75 years

Appendix 4. Definition of fatal pulmonary embolism used among included studies.

Study	Definition
Palareti *et al* **Palareti et al. (2002)**	Not specified
WODIT-PE **Agnelli et al. (2003)**	Not specified
PREVENT **Ridker et al. (2003)**	Not specified
Prandoni *et al* **Prandoni et al. (2007)**	Not specified
AESOPUS **Prandoni et al. (2009)**	Confirmed at autopsy, preceded immediately before death by objectively confirmed pulmonary embolism or venous thrombosis, or was a sudden death that could not be explained by a disease or condition other than pulmonary embolism
EINSTEIN-Extension **Bauersachs et al. (2010)**	Objective diagnostic testing, autopsy, or death which could not be attributed to a documented cause and for which pulmonary embolism could not be ruled out (unexplained death)
ASPIRE **Brighton et al. (2012)**	Not specified
WARFASA **Becattini et al. (2012)**	Not specified
PADIS-PE **Couturaud et al. (2015)**	Autopsy-confirmed PE, objectively confirmed PE on imaging before death, Sudden death for which PE cannot be ruled out
REVERSE **Rodger et al. (2016)**	Not specified
AUREC **Kyrle et al. (2016)**	Not specified
PADIS-DVT **Couturaud et al. (2019)**	Not specified

CHAPTER 3: Recurrence after Anticoagulant Cessation in Unprovoked Venous Thromboembolism by Age: Impact of Mortality as a Competing Outcome

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Abstract

Background

While guidelines recommend long-term anticoagulation after a first diagnosis of unprovoked venous thromboembolism (VTE), the generalizability of this approach to older adults at higher risk of all-cause mortality remains uncertain. We sought to evaluate age-specific risks of VTE recurrence after anticoagulant cessation, accounting for death as a competing event.

Methods

We analyzed the REVERSE cohort to determine VTE recurrence rates among patients with a first unprovoked event who stopped anticoagulation at 6 months, with stratification by age (<50 years, 50-64 years, 65-74 years, ≥75 years) and sex using Kaplan-Meier and cumulative incidence function (CIF) approaches.

Results

Among 664 patients, 38 (5.7%) died over a median follow-up of 5.7 years. Incidence of mortality was high among males ⩾75 years (8.3 vs. 1.1 per 100 patient-years in the overall cohort). In this group, the cumulative incidence of recurrent VTE was numerically lower with competing risk methods (27.9% CIF vs. 49.8% Kaplan-Meier). However, VTE recurrence rates at 1 year exceeded 5% with either method (9.8% CIF vs. 8.2% Kaplan-Meier). Females 65 - 74 years at the time of anticoagulant cessation had a higher VTE recurrence risk compared to females <50 years (hazard ratio 2.8, 95% CI 1.4 - 5.5). There was no impact of age on the risk of recurrent VTE among males.

Conclusion(s)

Long-term risk of recurrence after anticoagulant cessation among older males with unprovoked VTE differs by nearly 20% when accounting for death as competing event. The impact of age on the risk of VTE recurrence differs between males and females, highlighting the need for sex-specific risk stratification.

Take home points:

- Risk of all-cause mortality is high among males ≥75 years after anticoagulant cessation for unprovoked VTE, and use of a competing risk model produced lower estimates of long-term VTE recurrence.
- Among males with a first unprovoked VTE, the risk of recurrence after anticoagulation cessation did not differ by age.
- Among females with a first unprovoked VTE, the risk of VTE recurrence was highest among those aged ≥65 years at time of anticoagulant cessation, including females with age as the only risk factor under the HERDOO2 model.

Venous thromboembolism (VTE), comprising of deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third leading cause of cardiovascular mortality after myocardial infarction and stroke [1]. Half of all VTEs are not attributable to a transient or persistent risk factor, thus classifying them as unprovoked [2]. Among patients with unprovoked incident VTEs, recurrence rates are 16% at two years and 36% at 10 years after discontinuing anticoagulation [3]. While major guidelines recommend long-term anticoagulation in patients with unprovoked VTE owing to the high risk of thrombotic recurrence [4, 5], approximately 70% of females and 60% of males with unprovoked VTE will not experience recurrence after completing a time-limited duration of antithrombotic therapy [3].

Despite the well described association between age and the risk of incident VTE [6-8], the relationship between age and risk of recurrent VTE is conflicting among studies to date [9-11]. Ascertaining the relationship between age and recurrent VTE is crucial, as increasing age is a well-established risk factor for anticoagulant-associated major bleeding in the setting of secondary VTE prevention and carries a case fatality that is three times that of recurrent VTE [3, 12, 13]. A key aspect to accurate determination of age-specific disease outcomes is the risk of all-cause mortality: globally, the 5-year probability of all-cause mortality for an individual at 40 and 80 years are 1.4% and 33% respectively, a greater than 20-fold difference [14]. This is crucial, as death acts as a competing event to the occurrence recurrent VTE [15]. When the risk of all-cause mortality as a competing event is high, standard Kaplan-Meier approaches overestimate the incidence of disease occurrence [15].

Given the inconsistency in the relationship between age and risk of recurrent VTE after first episode of unprovoked VTE, we sought to determine the risk of recurrent VTE by age strata in a

prospective cohort of patients with first episode of unprovoked VTE who stopped anticoagulation after 6 months, while accounting for all-cause mortality as a competing risk.

Materials and Methods

Study population

We used long-term follow-up data from the REVERSE study, an international, multi-centre prospective clinical decision-rule derivation study that included unselected patients from 12 tertiary care centres [9, 17]. Patients were included if they had a first episode of unprovoked, objectively identified VTE treated with 5-7 months of VKA (target International Normalized Ratio 2-3), and did not have recurrent events during the treatment period.

Unprovoked VTE was defined as an event occurring in the absence of a leg fracture or lower extremity plaster cast, immobilization for more than 3 days, or surgery using a general anesthetic in the 3 months prior to the index VTE event, and without diagnosis of malignancy in the prior 5 years [18]. Patients were excluded if they were unable or unwilling to consent, were under the age of 18 years, had already discontinued anticoagulant therapy, required ongoing anticoagulation for reasons other than VTE or were geographically inaccessible for follow-up. Patients with recurrent unprovoked VTE, or a previously known high-risk thrombophilia were excluded. High-risk thrombophilia was defined as known deficiency of protein S, protein C or antithrombin, known persistently positive anticardiolipin antibodies (>30 U/mL), a known persistently positive lupus anticoagulant or two or more known defects (e.g. homozygous for factor V Leiden [FVL] or prothrombin gene mutation [PGM], or compound heterozygous for FVL and PGM).

After obtaining written informed consent, patients underwent data collection including demographic characteristics, risk factors for VTE at time of index event, family history of VTE, history of previous secondary VTE, and baseline imaging.

Follow-up and outcomes

After the first study visit, patients were instructed to stop their anticoagulant treatment and to contact study personnel if they developed symptoms of recurrent VTE during follow-up. Patients were followed in clinic every 6 months and asked about symptoms of VTE recurrence. Patients with symptoms suggestive of recurrent DVT or PE underwent respective imaging modalities. Imaging tests at the time of suspected recurrent event were compared with baseline imaging conducted at the time of study enrollment. All suspected VTE recurrence and deaths were centrally adjudicated by assessors blinded to the predictor data.

The primary outcome of the study was confirmed recurrent VTE over 18 months of study follow-up (based on objective imaging).

Data analysis

We assessed baseline characteristics of patients by age categories (<50 years, 50-64 years, 65-74 years, ≥75 years), based on dichotomous age cut-offs used in two externally validated clinical prediction tools [9, 16]. To determine the predictive value of age thresholds, we first determined recurrence rates among patients within each age stratum after 1, 2 and 5 years of follow-up using Kaplan-Meier and cumulative incidence function (CIF) methods. Among female patients, we further stratified recurrence rates based on presence of additional clinical risk factors (HERDOO2 score <2 or ≥ 2) [9]. To account for the competing risk of all-cause mortality on age-specific

recurrence estimates, we derived estimates of recurrent VTE at 1, 2 and 5 years of follow-up using the cumulative incidence function.

Next, to determine the impact of death as competing event on the relationship between of age and risk of recurrent VTE, we analyzed the data using 2 regression models, Cox proportional hazards model and Fine and Gray sub-distribution hazard competing risk models to determine the hazard ratio of VTE recurrence at each age stratum, with patients aged <50 years serving as reference group. In general, two regression models that account for competing risks exist: the cause-specific hazard model and the sub-distribution hazard (Fine and Gray) model. The cause-specific hazard model generates the *rate* at which a specific event occurs among those who are currently event-free (e.g., *hazard*), and is suitable for assessment of etiologic associations. Meanwhile, the Fine and Gray sub-distribution hazard model directly determines the effect of covariates on the *incidence* of disease; it is therefore suited for prognostic research in which the *risk* of disease (rather than its hazard) is of primary interest [19]. We assessed whether absolute risks of VTE recurrence varies between CIF compared to Kaplan-Meier methods, and whether crude hazard ratios generated using the Cox proportional hazards model diverge from those generated by the Fine and Gray sub-distribution model.

Results

Patients

A total of 664 patients were enrolled and followed in the REVERSE study across 12 centres between October 2001 and March 2006 (**Figure 1**). Median follow-up was 5.7 years (IQR 1.5 – 8.0 years), and 40 (6.0%) of participants were on an anti-platelet agent (aspirin, clopidogrel or dipyridamole) at the time of their enrolment. Baseline characteristics of patients are shown in

Table 1. Compared to females <50 years at the time of index VTE diagnosis, females >75 years had higher rates of isolated DVT, features of post-thrombotic syndrome, and D-dimer >250 ng/mL (**Table 1**). On the other hand, there was a decrease in BMI among males and females with each increase in age category (**Table 1**). Overall, females with two or more HERDOO risk factors rose from 22.9% among those <50 years at the time of anticoagulation cessation to 91.3% among those aged >75 years (**Table 1**).

All-Cause Mortality

Among 664 patients enrolled and followed-up after anticoagulant cessation for a first episode of provoked VTE, 38 (5.7%) died over 3,318 patient-years of follow-up, corresponding to an incidence rate of 1.14 deaths per 100 person-years (95% CI 0.81 to 1.57 per 100 person-years). The risk of all-cause mortality remained consistent up to 10 years of follow-up, with incidence per 100 person-years of 1.67 (95% CI 0.80 to 3.04) in year 1, 0.78 (95% CI 0.21 to 2.00) in year 2, 1.18 (95% CI 0.65 to 1.97) in years 3-5 and 0.99 (95% CI 0.47 to 1.81) in years 5-10 following anticoagulant cessation. The cumulative incidence of all-cause mortality was 2.4% (95% CI 1.0% - 5.0%) after 2 years, 5.8% (95% CI 2.9% -10.5%) after 5 years, and 10.4% (95% CI 5.2% – 18.3%) after 10 years.

The 10-year cumulative incidence of all-cause mortality rose in an age-dependent manner: 43.9% (95% CI 16.7% – 75.7%) among individuals ≥75 years at the time of their anticoagulant cessation, compared to 1.0% over the same period among those aged <50. While the cumulative incidence of mortality did not differ by sex in the overall cohort (**Table 2**), the disparity in all-cause mortality between males and females widened with increasing age, such that it was highest at 59.0% (95%

CI 14.2% - 96.8%) among males ≥75 years at time of anticoagulant cessation compared to 35.5% (95% CI 7.3 – 76.8%) among females in this age stratum (**Figure 2**).

There was no difference in the risk of all-cause mortality by site of index VTE (**Table 2**).

Overall Recurrent VTEs

Over the course of study follow-up, 165 patients experienced recurrent VTE consisting of 93 isolated DVTs, 43 isolated PEs, 25 PEs with DVTs, and 2 fatal PEs. The case fatality rate of recurrent PE was 2.9% (95% CI 0.4% – 9.9%), while the contribution of fatal PE to all-cause mortality events was 5.3% (95% CI 0.6% - 17.7%).

The cumulative incidence of recurrent VTE was similar when using Kaplan-Meier and CIF estimates for most age groups (**Table 2**). However, males ≥75 years at the time of anticoagulant cessation had a numerically lower incidence of recurrent VTE at 8 years when the CIF method was used with competing risk modeling (30.8%, 95% CI 18.0% – 52.7%), compared to Kaplan-Meier methods (49.8%, 95% CI 26.6% – 78.4%, **Figure 2**). However, the 1-year risk of recurrent VTE did not differ significantly using either approach (9.8% with CIF vs. 8.2% with Kaplan-Meier**,** **Table 2**).

Impact of Age on Recurrent VTE

Using males and females <50 years at the time of anticoagulant cessation as reference, we found consistent hazard ratios for recurrent VTE in each age- and sex-specific stratum using either the cause-specific hazards model or the Fine and Gray regression model (**Table 3**). This included males ≥75 years with the highest cumulative incidence of all-cause mortality (cause-specific HR 0.71, 95% 0.35-1.44 vs. Fine and Gray HR 0.59, 95% CI 0.30-1.17).

Overall, we did not detect an association between age at anticoagulant cessation on risk of recurrent VTE among males (**Table 3**). On the other hand, females between 65 and 74 years of age at time of their anticoagulant cessation had higher risk of VTE recurrence compared to those <50 years (hazard ratio 2.8, 95% CI 1.4 - 5.5, p<0.01, **Table 4** and **Figure 2**). The relationship between age and risk of recurrent VTE persisted even among those with 0 or 1 risk factors for recurrence (hazard ratio 11.34, 95% CI 1.27 - 101.66 for recurrence between <50 years and 65-74 years, **Table 4**).

Discussion

In this cohort study of over 600 patients who systematically stopped OAC treatment for their first episode of unprovoked VTE, we observed more than 50% risk of all-cause mortality among males aged ≥75 years over a median follow-up was 5.7 years following anticoagulant cessation. Correspondingly, the long-term risk of recurrent VTE among individuals reaching end of the 8-year follow-up period in this group differed by over 20% when survival analysis accounted for death as a competing event. However, the risk of recurrent VTE at 1 year exceeded the 5% acceptable thresholds proposed by the International Society on Thrombosis and Haemostasis for anticoagulant discontinuation regardless of the methodology used. Therefore, accounting for all-cause mortality as a competing risk is unlikely to alter management decisions surrounding anticoagulant duration following a first unprovoked VTE. Finally, females ≥65 years had higher risk of VTE recurrence compared to those <50 years, even among those identified to be at low risk by the HERDOO2 model.

All-cause mortality is important to consider when estimating the risk of VTE recurrence, particularly among older individuals. Competing events occur when an outcome (e.g., death) other

than the primary outcome under study (e.g., recurrent VTE) occurs, which alter the future probability of the occurrence of this outcome [15]. The competing risk of death is particularly important to consider when rates are high as in studies involving older adults as analyses that do not account for the competing risk of death may overestimate the incidence of recurrent events [20]. Our findings are comparable to a recently completed systematic review and meta-analysis of 12 studies that reported 62.6% risk of all-cause mortality at 10 years following anticoagulation cessation for a first unprovoked VTE [Part 1 of thesis].

In addition to producing inflated estimates of disease incidence, differences in competing risks of all-cause mortality across strata of a candidate predictor variable may bias its effect on prognosis when Kaplan-Meier or Cox proportional hazards modeling are used for analysis. This is especially the case if the candidate predictor (e.g., age) is associated with both the outcome of interest (e.g., recurrent VTE) and the competing outcome (e.g., all-cause mortality). For example, Ay *et al* used data from the Vienna Cancer and Thrombosis Study to evaluate whether the predictive characteristics of D-dimer quartiles for cancer-associated VTE would be modulated by incorporating all-cause mortality as a competing outcome. Comparing the Cox proportional hazards model based on the Kaplan-Meier approach and the Fine and Gray sub-distribution model based on the competing risk approach, they found a numerically lower hazard ratio for D-dimer as a predictor of cancer-associated VTE with competing risk modelling (hazard ratio 2.47, 95% CI 1.67 – 3.65 vs. hazard ratio 2.85, 95% CI 1.92-4.21) [21]. This suggests that models that do not consider the competing risk of all-cause mortality may produce biased prognostic estimates.

The risk of all-cause mortality as a competing risk to recurrent VTE was highest among males ≥ 75 years. While we found a numerically lower risk of recurrent VTE over the entire follow-up period using competing risk modeling compared to standard survival analysis (e.g. Kaplan-Meier

and Cox regression) in this subgroup of patients at the time of anticoagulant cessation, their 1- and 5-year risks of VTE recurrence exceeded recommended thresholds to consider anticoagulant cessation nonetheless [18]. This may be due to the higher risk of recurrence early after anticoagulant discontinuation [3], at which point the competing risk of death is unlikely to contribute substantially to short- and medium-term risks of VTE recurrence in absence of significant life-limiting comorbidities. However, all-cause mortality as a competing event among individuals with >50% anticipated 1-year risk of death remains relevant: recently, a risk calculator has been derived and validated that stratifies individuals from 1.5% to 98.1% risk of all-cause mortality within 6 months [22]. Given limited data that suggest no reduction in thromboembolic events and increased risk of mortality among home palliative care recipients who continued anticoagulation [23], tailoring long-term anticoagulation for secondary VTE prevention based on expected life expectancy in a shared decision-making remains a prudent approach.

We identified different patterns of age specific VTE recurrence rates between males and females. While age was not a predictor of VTE recurrence among males, we observed lower risk of VTE recurrence among females who stopped anticoagulation <65 years compared to those ≥65 years. This may reflect differences in pathophysiology of thromboembolism between males and females, whereby endogenous or exogenous hormonal exposure masks an intrinsically lower thrombotic threshold among females, specifically those <50 years of age at VTE diagnosis [24, 25]. Accordingly, females with index VTE diagnosed ≥65 years were rarely classified as low risk by the HERDOO2 model in prospective derivation and validation studies [9, 26], and those harboring age as the sole risk factor for VTE recurrence had higher risk of VTE recurrence compared to their counterparts <50 years of age [26]. Therefore, clinicians need to recognize higher risks of

recurrence associated with unprovoked VTEs diagnosed after age 65 among females, even among those considered “low risk” by the HERDOO2 model.

By following an all-comer group of patients who uniformly underwent anticoagulation cessation following six months of therapy for an incident unprovoked VTE, the REVERSE study offers important insights while guarding against selection bias in most observational studies on VTE recurrence. Nonetheless, there are several limitations. First, some effect size estimates were imprecise with wide 95% confidence intervals, due to sample size of the REVERSE study. Nonetheless, the study had extended follow-up and was able to adequate capture the association between age and increased risk of recurrent VTE among females. Second, the definition of fatal PE used in the REVESE study, with enrolment spanning 2001 and 2006, may not be reflective of the recently standardized definition [27]. However, the contribution of fatal PE to all-cause mortality reported in our study was consistent with findings from a recently published meta-analysis, where overwhelming majority of fatal events after anticoagulant cessation was not related to PE recurrence. Finally, the REVERSE study excluded patients with known high-risk thrombophilias, and our conclusions therefore cannot be extended to this group.

In summary, among 664 patients with unprovoked VTE who discontinued OACs for a first episode of unprovoked VTE after 6 months of anticoagulant therapy, we found high risk of all-cause mortality among males ≥75 years at the time of anticoagulant cessation. When regression analysis accounted for all-cause mortality as a competing event, we did not observe a difference in the long-term cumulative incidence of VTE recurrence at 1 year and 5 years compared to standard survival analysis. The risk of recurrent VTE among females was observed among those ≥65 years at the time of anticoagulant cessation, even among those without post-thrombotic syndrome and negative D-dimer. Competing risk modelling in settings with high risk of short-term mortality, such as in

the palliative care setting, represents an ongoing research need to understand the optimal duration of anticoagulant therapy in unprovoked VTE.

References

1. Goldhaber SZ, Bounameaux H: **Pulmonary embolism and deep vein thrombosis**. *Lancet* 2012, **379**(9828):1835-1846.
2. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J: **Incidence and mortality of venous thrombosis: a population-based study**. *J Thromb Haemost* 2007, **5**(4):692-699.
3. Khan F, Rahman A, Carrier M, Kearon C, Weitz JI, Schulman S, Couturaud F, Eichinger S, Kyrle PA, Becattini C *et al*: **Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: Systematic review and meta-analysis**. *The BMJ* 2019, **366**:l4363.
4. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, Hutten BA, Jaff MR, Manja V, Schulman S *et al*: **American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism**. *Blood Adv* 2020, **4**(19):4693-4738.
5. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, Huisman MV, Kearon C, King CS, Knighton AJ *et al*: **Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report**. *Chest* 2021, **160**(6):e545-e608.

6. Anderson FA, Jr., Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, Forcier A, Dalen JE: **A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study**. *Arch Intern Med* 1991, **151**(5):933-938.

7. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd: **Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study**. *Arch Intern Med* 1998, **158**(6):585-593.

8. White RH: **The Epidemiology of Venous Thromboembolism**. *Circulation* 2003, **107**(90231):4I--8.

9. Rodger MA, Kahn SR, Wells PS, Anderson DA, Chagnon I, Le Gal G, Solymoss S, Crowther M, Perrier A, White R *et al*: **Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy**. *CMAJ* 2008, **179**(5):417-426.

10. Eischer L, Eichinger S, Kyrle PA: **Age at first venous thromboembolism and risk of recurrence: a prospective cohort study**. *Medicine (Baltimore)* 2009, **88**(6):366-370.

11. Beyth RJ, Cohen AM, Landefeld CS: **Long-term outcomes of deep-vein thrombosis**. *Arch Intern Med* 1995, **155**(10):1031-1037.

12. Khan F, Tritschler T, Kimpton M, Wells PS, Kearon C, Weitz JI, Buller HR, Raskob GE, Ageno W, Couturaud F *et al*: **Long-Term Risk for Major Bleeding During Extended Oral Anticoagulant Therapy for First Unprovoked Venous Thromboembolism : A Systematic Review and Meta-analysis**. *Ann Intern Med* 2021, **174**(10):1420-1429.

13. Carrier M, Le Gal G, Wells PS, Rodger MA: **Systematic review: Case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism**. In.; 2010.

14. **Life tables: Life tables by country** [https://www.who.int/data/gho/data/indicators/indicator-details/GHO/gho-ghe-life-tables-by-country]

15. Wolkewitz M, Cooper BS, Bonten MJ, Barnett AG, Schumacher M: **Interpreting and comparing risks in the presence of competing events**. *BMJ* 2014, **349**:g5060.

16. Tosetto A, Testa S, Martinelli I, Poli D, Cosmi B, Lodigiani C, Ageno W, De Stefano V, Falanga A, Nichele I *et al*: **External validation of the DASH prediction rule: a retrospective cohort study**. *J Thromb Haemost* 2017, **15**(10):1963-1970.

17. Rodger MA, Scarvelis D, Kahn SR, Wells PS, Anderson DA, Chagnon I, Le Gal G, Gandara E, Solymoss S, Sabri E *et al*: **Long-term risk of venous thrombosis after stopping anticoagulants for a first unprovoked event: A multi-national cohort**. *Thromb Res* 2016, **143**:152-158.

18. Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing GJ, Kyrle PA: **Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH**. *Journal of Thrombosis and Haemostasis* 2016, **14**(7):1480-1483.

19. Austin PC, Lee DS, Fine JP: **Introduction to the Analysis of Survival Data in the Presence of Competing Risks**. *Circulation* 2016, **133**(6):601-609.

20. Berry SD, Ngo L, Samelson EJ, Kiel DP: **Competing risk of death: an important consideration in studies of older adults**. *J Am Geriatr Soc* 2010, **58**(4):783-787.

21. Ay C, Posch F, Kaider A, Zielinski C, Pabinger I: **Estimating risk of venous thromboembolism in patients with cancer in the presence of competing mortality**. *J Thromb Haemost* 2015, **13**(3):390-397.

22. Hsu AT, Manuel DG, Spruin S, Bennett C, Taljaard M, Beach S, Sequeira Y, Talarico R, Chalifoux M, Kobewka D *et al*: **Predicting death in home care users: derivation and validation of the Risk Evaluation for Support: Predictions for Elder-Life in the Community Tool (RESPECT)**. *CMAJ* 2021, **193**(26):E997-E1005.

23. Chin-Yee N, Gomes T, Tanuseputro P, Talarico R, Laupacis A: **Anticoagulant use and associated outcomes in older patients receiving home palliative care: a retrospective cohort study**. *CMAJ* 2022, **194**(35):E1198-E1208.

24. Scheres LJJ, van Hylckama Vlieg A, Cannegieter SC: **Sex-specific aspects of venous thromboembolism: What is new and what is next?** *Res Pract Thromb Haemost* 2022, **6**(4):e12722.

25. Roach RE, Lijfering WM, Rosendaal FR, Cannegieter SC, le Cessie S: **Sex difference in risk of second but not of first venous thrombosis: paradox explained**. *Circulation* 2014, **129**(1):51-56.

26. Rodger MA, Le Gal G, Anderson DR, Schmidt J, Pernod G, Kahn SR, Righini M, Mismetti P, Kearon C, Meyer G *et al*: **Validating the HERDOO2 rule to guide treatment duration for women with unprovoked venous thrombosis: Multinational prospective cohort management study**. *BMJ (Online)* 2017, **356**:j1065.

27. Tritschler T, Salvatore SP, Kahn SR, Garcia D, Delluc A, Kraaijpoel N, Langlois N, Girard P, Le Gal G: **ISTH definition of pulmonary embolism-related death and**

classification of the cause of death in venous thromboembolism studies: Validation in an autopsy cohort. *J Thromb Haemost* 2021, **19**(10):2514-2521.

Table 1. Baseline Characteristics

	Males				Females			
	<50 years (n=130)	50-64 years (n=124)	65-74 years (n=43)	≥75 years (n=44)	<50 years (n=157)	50-64 years (n=74)	65-74 years (n=45)	≥75 years (n=46)
Index VTE (%)								
Isolated DVT	56.9	54.0	62.8	65.9	39.5	44.6	55.6	60.9
Isolated PE	26.2	26.6	11.6	31.8	38.9	32.4	26.7	32.6
PE + DVT	16.9	19.4	25.6	2.3	21.7	23.0	17.8	6.5
Estrogen-associated					49.1	50.0	31.1	50.0
Oral contraceptive					30.6	23.0	13.3	23.9
Hormone replacement					18.5	27.0	17.8	26.1
Recurrence risk factors								
Hyperpigmentation	10.4	22.4	26.8	36.8	6.4	11.5	25.0	30.0
Edema	25.5	27.1	24.4	35.9	25.6	21.3	37.5	30.0
Redness	11.3	12.2	9.8	20.5	7.2	13.1	17.5	25.0
Hyperpigmentation, edema, redness (HER)								
Overall	32.1	46.7	39.0	56.4	29.6	31.2	50.0	57.5
Among index isolated DVT	39.1	58.1	40.7	65.4	49.1	30.8	60.9	45.8
Among index isolated PE	12.5	20	33.3	41.7	2.5	15.8	33.3	78.6
Among index PE + DVT	33.3	45.0	36.4	0	28.6	50.0	37.5	50.0

D-dimer >250 ng/mL	16.4	24.4	70.8	82.1	19.7	36.6	73.8	88.9
BMI (mean ± SD)	30.9 ± 7.0	30.2 ± 6.8	28.0 ± 3.4	27.4 ± 4.1	30.1 ± 9.2	30.0 ± 6.7	28.0 ± 5.2	26.2± 5.1
BMI >30	47.7	40.3	30.2	18.2	38.9	43.2	31.8	17.4
Factor V Leiden heterozygosity								
Overall	20.2	5.7	14.0	11.4	18.0	11.0	22.2	15.6
Among index isolated DVT	29.7	7.5	18.5	13.8	26.2	15.2	20.0	14.8
Among index isolated PE	5.9	3.0	0	7.1	11.5	0	25.0	13.3
Among index PE + DVT	9.5	4.2	9.1	0	14.7	17.7	25.0	33.3
Prothrombin gene mutation heterozygosity								
Overall	4.6	3.2	9.3	6.8	8.3	6.8	4.4	0
Among index isolated DVT	4.1	3.0	3.7	6.9	12.9	9.1	4.0	0
Among index isolated PE	5.9	6.1	0	7.1	3.3	0	8.3	0
Among index PE + DVT	4.6	0	27.3	0	8.8	11.8	0	0
HERDOO2 ≥2					22.9	31.1	84.4	91.3

Table 2. Cumulative incidence of VTE recurrence by age based on competing risk and Kaplan-Meier models.

	Year 1 % (95% CI)			Year 5 % (95% CI)			End of Follow-Up % (95% CI)		
	Mortality	CIF	Kaplan-Meier	Mortality	CIF	Kaplan-Meier	Mortality	CIF	Kaplan-Meier
Males (N=341)									
<50 years (N=130)	0 (0 – 3.1)	16.0 (11.9 - 21.6)	14.9 (9.8 - 22.3)	0 (0 - 11.8)	36.6 (29.4 - 45.5)	35.5 (27.5 - 44.9)	1.7 (0.0 – 19.9)	46.4 (38.3 - 56.2)	47.3 (37.7 - 58.1)
50-64 years (N=124)	2.8 (0.6 – 7.8)	11.9 (8.3 - 17.0)	14.9 (9.7 - 22.6)	4.1 (0.6 – 18.1)	28.2 (21.0 - 37.9)	29.4 (21.8 - 38.9)	7.2 (1.0 – 27.4)	36.4 (28.7 - 46.3)	35.5 (27.0 - 45.6)
65-74 years (N=43)	2.6 (0.1 – 13.6)	14.6 (9.5 - 22.5)	15.1 (7.1 - 30.7)	2.6 (0.0 – 35.9)	33.8 (22.5 - 51.0)	42.1 (26.9 - 61.3)	14.7 (1.6 – 60.3)	43.2 (30.0 - 62.2)	46.2 (30.3 - 65.5)
≥75 years (N=44)	2.6 (0.0 – 13.9)	9.8 (5.4 - 17.8)	8.2 (2.7 - 23.3)	40.6 (13.4 – 74.7)	23.6 (12.5 - 44.7)	39.8 (19.9 - 68.6)	52.5 (13.9 – 92.7)	30.8 (18.0 - 52.7)	49.8 (26.6 - 78.4)
Females (N=322)									
<50 years (N=157)	0 (0 – 2.4)	4.7 (2.8 - 8.0)	3.9 (1.8 - 8.5)	0 (0 – 7.8)	11.6 (7.7 - 17.6)	10.4 (6.4 - 16.7)	0 (0 – 10.9)	15.1 (10.2 - 22.2)	15.3 (10.2 - 22.6)
50-64 years (N=74)	0 (0 – 5.1)	3.9 (1.9 - 8.0)	4.1 (1.3 - 12.2)	3.7 (0.5 - 21.8)	9.6 (4.7 - 19.4)	8.6 (3.9 - 18.1)	5.5 (0.5 - 29.7)	12.5 (6.4 - 24.1)	12.3 (6.3 - 23.3)
65-74 years (N=45)	8.1 (1.7 - 21.9)	12.7 (6.9 - 23.5)	16.9 (8.4 - 32.2)	15.5 (2.7 - 48.8)	29.2 (17.6 - 48.4)	38.8 (24.8 - 57.1)	19.9 (2.8 - 61.9)	36.7 (23.2 - 58.1)	38.8 (24.8 - 57.1)
≥75 years (N=46)	4.7 (0.6 - 16.0)	7.2 (3.4 - 15.3)	6.8 (2.2 - 19.7)	21.7 (5.1 - 53.3)	17.8 (9.2 - 34.4)	23.3 (12.1 - 42.1)	30.3 (6.4 - 69.3)	23.0 (13.5 - 41.1)	28.1 (15.1 - 48.4)
Isolated DVT (N=)									
<50 years (N=136)	0 (0 – 3.0)	11.8 (8.0 - 17.5)	12.1 (7.6 - 19.0)	0 (0 – 10.7)	29.7 (22.8 - 38.6)	27.8 (20.7 - 36.8)	1.5 (0 – 17.7)	38.4 (30.9 - 47.8)	40.0 (30.5 - 51.2)
50-64 years (N=100)	1.1 (0 – 6.0)	10.2 (6.7 - 15.6)	11.1 (6.3 - 19.2)	4.5 (0.4 - 20.9)	26.0 (19.1 - 35.5)	26.6 (18.5 - 37.1)	6.4 (0.5 - 29.2)	34.0 (24.9 - 46.3)	32.6 (23.6 - 44.0)

65-74 years (N=52)	7.0 (1.4 - 18.3)	12.4 (7.4 - 20.7)	12.4 (5.8 - 25.7)	10.2 (1.5 - 40.0)	31.0 (21.2 - 45.3)	37.0 (23.9 - 54.2)	18.6 (2.7 - 57.9)	39.9 (28.2 - 56.6)	43.0 (28.9 - 60.3)
≥75 years (N=57)	4.0 (0.5 - 13.8)	11.0 (6.7 - 18.0)	9.4 (4.0 - 21.2)	29.3 (8.9 - 60.5)	27.9 (17.1 - 45.5)	34.8 (21.1 - 53.7)	29.3 (8.9 - 71.5)	36.3 (24.2 - 54.3)	44.5 (28.2 - 64.7)
Isolated PE (N=)									
<50 years (N=95)	0 (0 - 3.9)	3.6 (1.8 - 7.1)	3.2 (1.0 - 9.6)	0 (0 - 12.7)	8.2 (4.0 - 16.5)	8.8 (4.5 - 16.9)	0 (0 - 17.0)	10.4 (5.4 - 20.4)	10.1 (5.4 - 18.7)
50-64 years (N=57)	3.9 (0.4 - 13.3)	6.1 (2.7 - 13.9)	7.3 (2.8 - 18.3)	3.9 (0.5 - 26.5)	13.4 (7.0 - 26.0)	13.2 (6.5 - 25.7)	8.6 (1.1 - 38.8)	17.2 (9.2 - 32.1)	17.5 (9.5 - 31.1)
65-74 years (N=17)	7.1 (0.2 - 33.6)	18.3 (8.2 - 40.8)	18.6 (6.4 - 47.4)	18.5 (0.5 - 67.9)	37.2 (21.1 - 65.5)	49.1 (26.2 - 77.6)	18.5 (0.5 - 67.9)	45.4 (27.8 - 74.4)	49.1 (26.2 - 77.6)
≥75 years (N=29)	0 (0 – 12.7)	4.5 (1.5 - 13.3)	4.2 (0.6 - 26.1)	32.1 (8.5 - 71.0)	10.0 (4.0 - 25.3)	4.2 (0.6 - 26.1)	51.2 (14.4 - 88.9)	12.9 (4.7 - 35.5)	21.9 (7.1 - 56.3)

DVT, deep vein thrombosis; PE, pulmonary embolism

Table 3. Impact of age on VTE recurrence following anticoagulant cessation after first unprovoked VTE, with or without use of competing risk methods.

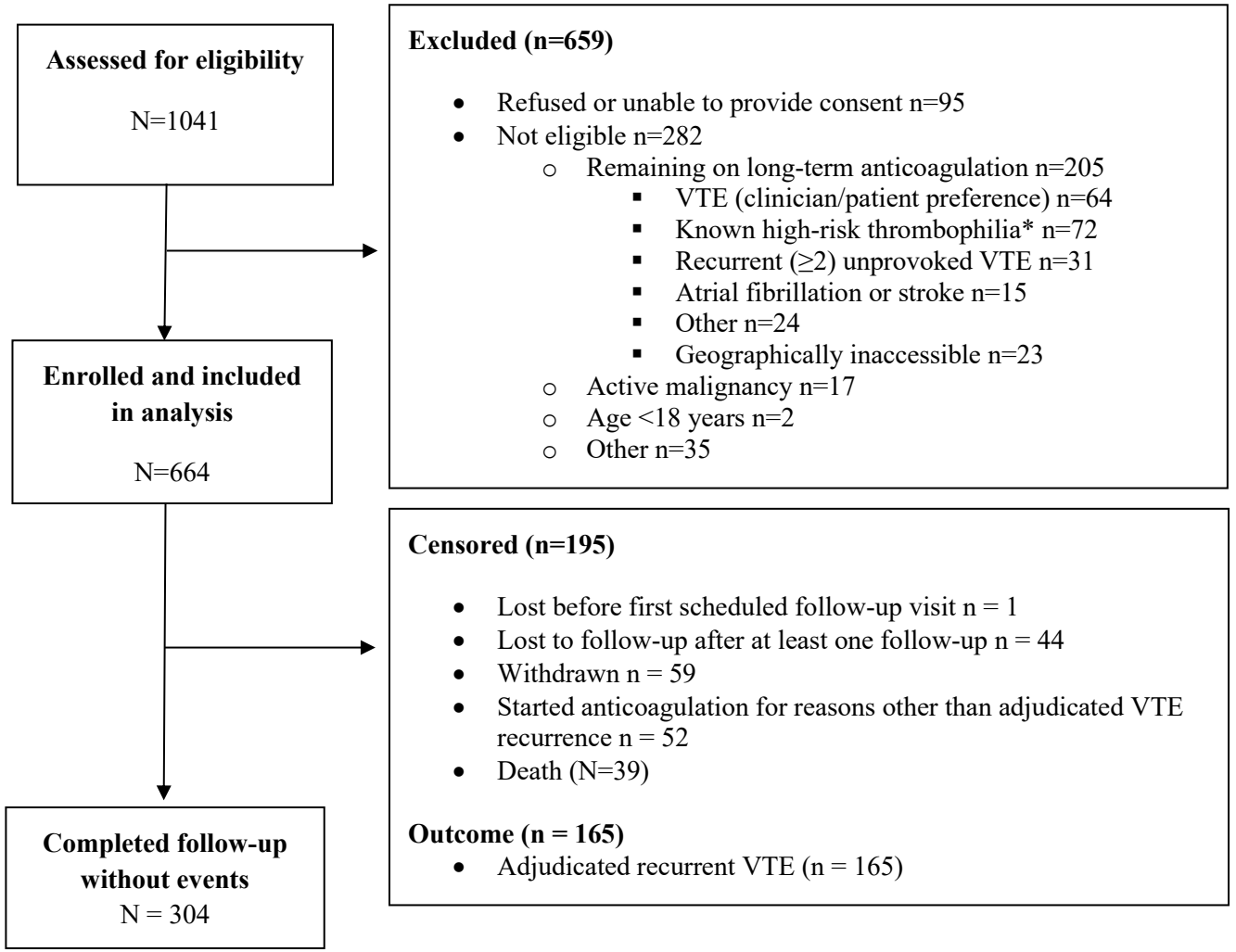
Timepoint	Analysis Type	Males (Hazard Ratio, 95 CI)				Females (Hazard Ratio, 95 CI)			
		<50 years	50-64 years	65-74 years	≥75 years	<50 years	50-64 years	65-74 years	≥75 years
1 Year	Fine & Gray	1.0 (Ref)	0.93 (0.49 - 1.80)	0.78 (0.29 - 2.06)	0.47 (0.14 - 1.57)	1.0 (Ref)	1.08 (0.27 - 4.28)	3.83 (1.25 - 11.80)§	1.73 (0.44 - 6.92)
	Cause-specific	1.0 (Ref)	0.95 (0.49 - 1.82)	0.79 (0.29 - 2.10)	0.48 (0.14 - 1.62)	1.0 (Ref)	1.08 (0.27 - 4.30)	3.96 (1.28 - 12.28)§	1.76 (0.4 - 7.03)
5 Years	Fine & Gray	1.0 (Ref)	0.75 (0.47 - 1.20)	0.93 (0.51 - 1.69)	0.53 (0.25 - 1.15)	1.0 (Ref)	0.87 (0.33 - 2.24)	3.54 (1.70 - 7.36)‖	1.73 (0.71 - 4.22)
	Cause-specific	1.0 (Ref)	0.77 (0.49 - 1.22)	0.95 (0.51 - 1.77)	0.58 (0.26 - 1.29)	1.0 (Ref)	0.87 (0.34 - 2.25)	3.82 (1.82 - 8.04)‖	1.86 (0.7 - 4.56)
Entire Follow-up Period	Fine & Gray	1.0 (Ref)	0.73 (0.48 - 1.11)	0.91 (0.52 - 1.58)	0.59 (0.30 - 1.17)	1.0 (Ref)	0.82 (0.36 - 1.84)	2.80 (1.42 - 5.52)‖	1.65 (0.76 - 3.56)
	Cause-specific	1.0 (Ref)	0.75 (0.4 - 1.14)	0.94 (0.53 - 1.66)	0.71 (0.35 - 1.44)	1.0 (Ref)	0.83 (0.37 - 1.87)	3.11 (1.58 - 6.13)‖	1.86 (0.85 - 4.07)

§ $p<0.05$ ‖ $p<0.01$

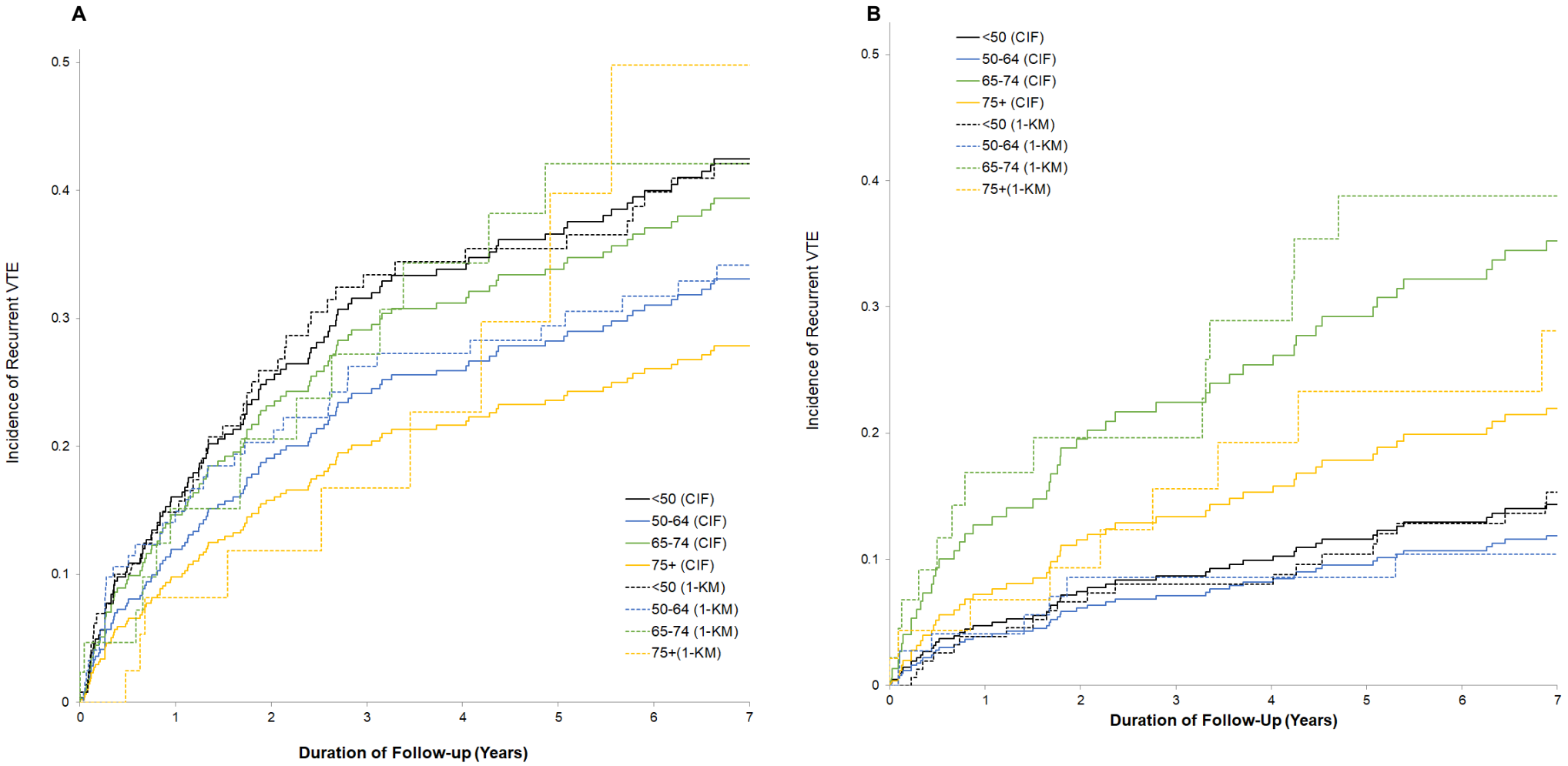
Table 4. Impact of age on VTE recurrence following anticoagulant cessation after first unprovoked VTE among females classified as low-risk by the HERDOO2 model.

	Year 1 % (95% CI)		Year 5 % (95% CI)		End of Follow-Up % (95% CI)	
	CIF	Kaplan-Meier	CIF	Kaplan-Meier	CIF	Kaplan-Meier
Females with HERDOO2 0-1 (N=)						
<50 years (N= 107)	1.1 (0.3 – 3.3)	0 (0 – 0)	4.8 (2.1 – 10.7)	4.2 (1.6 – 10.8)	7.5 (4.0 – 14.0)	7.7 (3.7 – 15.5)
50-64 years (N= 46)	1.0 (0.2 – 6.1)	2.1 (0.3 – 14.4)	4.6 (1.6 – 13.2)	4.4 (1.1 – 16.7)	7.2 (2.4 – 21.7)	7.3 (2.4 – 21.3)
65-74 years (N= 3)	6.6 (0.3 – 100)	33.3 (5.5 – 94.6)	26.1 (3.3 – 100)	33.3 (5.5 – 94.6)	38.3 (5.3 – 100)	33.3 (5.5 – 94.6)
≥75 years (N= 3)	5.3 (0.5 – 57.7)	0 (0 – 0)	22.9 (4.2 – 100)	33.3 (5.5 – 94.6)	32.6 (6.2 – 100)	33.3 (5.5 – 94.6)

Figure 1. STROBE diagram



VTE: venous thromboembolism. High-risk thrombophilia includes antiphospholipid antibody syndrome (n=41), protein C, protein S, or antithrombin deficiency (n=21), multiple thrombophilias (n=9)



CIF, cumulative incidence function; KM, Kaplan-Meier

Figure 2. Cumulative incidence of recurrent VTE among males (A) and females (B) using cumulative incidence and Kaplan-Meier methods.

CHAPTER 4: Integrated Discussion

While the estimated annual incidence of VTE is 115 cases per 100,000 population [1], its burden is heavily skewed by age: those ≥ 70 years are approximately 10-fold more likely to be diagnosed with first-episode VTE than those aged 20-44 years [2]. Recognizing the high rates of VTE recurrence after limited treatment duration with OACs [3], contemporary guidelines recommend long-term anticoagulation after the first episode of unprovoked VTE [4, 5].Whether this recommendation optimally balances the benefits associated with recurrent VTE prevention and harms associated with OAC-associated bleeding across age groups is unclear. As the risk of death from any cause increases with age, understanding the true incidence of thrombotic and bleeding complications across the lifespan requires competing risk analyses that have not been adequately addressed in VTE prognostic studies to date.

My thesis focused on quantifying the long-term risk of all-cause mortality following anticoagulant discontinuation for a first unprovoked VTE, as well as evaluating its impact on the estimation of recurrent VTE risk by age strata. The following three observations carry important clinical and research implications.

4.1 Cumulative incidence of all-cause mortality is high following time-limited anticoagulation for unprovoked VTE.

The systematic review and meta-analysis found high risks of all-cause mortality among individuals who stopped anticoagulation at age ≥75 years, especially males in whom this risk exceeded 50% at 10 years. Furthermore, this high mortality rate is not fully explained by the occurrence of fatal PE. Our findings support the need to account for the impact of death as a competing event in the estimation of recurrent VTE risk. Notably, after treatment for unprovoked PE the risk of all-cause

mortality was higher compared to the general population, underscoring the need for intervention of mutual risk factors between unprovoked VTE and all-cause mortality (e.g., hypercholesterolemia, elevated body mass index, occult malignancy).

4.2. Competing risk analysis did not impact short- to medium-term recurrence risks among those with a first unprovoked VTE.

In the REVERSE cohort analysis, we observed an attenuation in the long-term cumulative incidence of VTE from competing risk of mortality, in particular at the end of the 8-year follow-up. Nonetheless, risks of recurrent VTE at 1- and 5-years following anticoagulation cessation exceeded acceptable thresholds proposed by the International Society on Thrombosis and Haemostasis and therefore unlikely to alter management decisions surrounding anticoagulant duration following a first unprovoked VTE [6]. Therefore, the clinical impact of death as a competing event is likely limited in the setting of unprovoked VTE, due to the gradual accumulation of mortality risk over time.

On the other hand, the competing risk of mortality on recurrent VTE becomes relevant when the predicted 1-year risk of death exceeds 50% (e.g., palliative care). In such settings, the benefits and harms of anticoagulation are uncertain, with little data to guide frontline clinicians. With advent of prognostic scoring systems for all-cause mortality such as the RESPECT calculator [7], an integrated approach to VTE risk prediction in the palliative care setting that simultaneously accounts for life expectancy is needed to inform decisions on treatment duration in this vulnerable population [8].

4.3 Age, sex, and index site of VTE interact to inform risks of recurrence.

Beyond the impact of competing risk, we observed that the relationship between age and recurrent VTE was dependent on sex. In contrary to males in whom we did not observe a relationship between age and recurrent VTE risk, females >65 years had a markedly higher risk of VTE recurrence compared to those ≤65 years, including those classified as low-risk by the HERDOO2 criteria. Overall, there was an age-dependent "catch-up" phenomenon that attenuated the protective effect of female sex on VTE recurrence among those >65 years. Given the relationship between sex and age on risks of recurrent VTE, our findings highlight the importance of specific stratification tools beyond multivariable regression approaches that assume the effect of each candidate predictor to be uniform in the entire cohort [9].

The prognostic impact of index site of VTE (isolated DVT, isolated PE, or DVT+PE) had been mixed, in part based on whether DVT + PE is categorized as DVT or PE. While the presence of PE conferred an increased risk of recurrence in the Vienna prediction and VTE-PREDICT models [9, 10], these studies did not specify whether PE events were isolated or accompanied by concurrent DVT. On the other hand, the protective association conferred by *isolated* PE on risk of VTE recurrence, compared to DVT +/- PE as index presentation, had been observed in the REVERSE cohort and a recent meta-analysis [3]. In the present thesis, we identified the association between index site of VTE and risk of recurrence to be age-dependent: the protective effect of isolated PE only applied to patients <65 years. Notably, carriers of factor V Leiden (FVL heterozygotes) appear to have an increased propensity to DVT (with or without PE) compared to isolated PE, a phenomenon known as factor V Leiden paradox [11, 12]. Nonetheless, no study to date screened for lower extremity DVT among patients with symptomatic PE using *systematic* compression ultrasound and Doppler to identify a cohort with confirmed isolated PE for prognostic

evaluation. Furthermore, isolated PE was largely diagnosed using ventilation-perfusion scanning among the composite studies included in this thesis. As computed tomography pulmonary angiogram (CTPA) has largely replaced ventilation-perfusion scans as the diagnostic imaging modality of choice in suspected PE, the association of index VTE site and risk of recurrent VTE in the CTPA era remains an additional area of future inquiry. These findings, in turn, would inform whether clinicians should consider the role of systematic screening of symptomatic PE patients with lower extremity imaging to detect the presence of DVT, and vice versa (screening of patients with symptomatic DVT for PE).

4.4 Future Directions

To definitively understand the interaction between age, sex, and index site of VTE, we are undertaking a systematic review and meta-analysis to determine the effect of age at first unprovoked VTE on the risk for recurrence up to 10 years after discontinuing anticoagulation, with a specific focus on patient's sex and site of initial VTE. A key aim of the study will be to generate age-specific (<50 years, 50-64 years, 65-74 years, or ≥75 years) estimates of VTE recurrence risks over time intervals of 1, 2, 5, and 10 years after anticoagulant discontinuation. This project is currently ongoing as part of the Meta-Analysis of the long-term Risk of recurrent Venous thromboEmboLism after stopping anticOagulation for acute Unprovoked venous thromboembolism (MARVELOUS) collaboration (PROSPERO registration: CRD42017056309).

In addition, ways in which age and sex interact to modify risks of anticoagulant-associated major bleeding require further elucidation. While highly effective, major bleeding remains the most serious complication of anticoagulant therapy and is associated with a three-fold higher case fatality rate compared to recurrent VTE [3, 13, 14]. Despite the advent of direct oral anticoagulants

(DOACs) that reduce the risk of major bleeding compared to vitamin K antagonists in randomized controlled trials [15], their long-term net clinical benefit after unprovoked VTE among patients >65 years remains to be seen. For example, a recent systematic review and meta-analysis reported the 1-year incidence of major bleeding for DOAC- and VKA-treated patients >65 years to be 2.1 (95% CI 1.3 - 3.1) and 2.2 (1.5 - 3.0) per 100 person-years respectively [14]. In the same study, there was no risk difference in major bleeding between DOACs and VKA among males. While the incidence of major bleeding was numerically lower among females treated with DOACs (1.3 per 100 person-years, 95% CI 0.7 - 2.1) compared to VKA (2.4 per 100 person-years, 95% CI 1.8 - 3.1), they nonetheless exceed background rates of major bleeding in absence of anticoagulation (0.35 per 100 person-years) [16]. Despite randomized trial data showing an overall mortality benefit of DOACs over placebo for secondary prevention after unprovoked VTE [17], understanding the age- and sex-specific benefits and harms associated with anticoagulation for is crucial to adequately inform shared decision-making between clinicians and patients. This is especially relevant among the elderly population, in whom the use of low-dose DOACs as monotherapy may not be suitable due to concurrent coronary artery disease or atrial tachyarrhythmias [18-20].

Finally, our findings may not be generalizable to racialized minority populations who are under-represented in VTE research, including source studies that were part of this thesis. Although observational studies suggest that benefits and harms of anticoagulant treatment vary across ethnoracial and ancestral groups, ethnoracial representation is lacking within clinical studies of VTE [21]. For example, enrolment of non-White participants in contemporary VTE trials ranged from 4.9% to 30% among studies in which race or ethnicity was reported, while representation of

African American and Hispanic participants in contemporary anticoagulant trials ranged from 0.4% to 5.5% [21]. In the REVERSE study, only 8% of patients identified as non-White.

Limited inclusion of ethnoracially under-represented populations in VTE-related studies is in stark contrast to disease burden: for example, African American adults have a higher incidence of first-episode VTE and fatal PEs compared to those of European origin [22, 23]. Furthermore, rates of major bleeding differ among ethnoracial groups: individuals identifying as East Asian have higher rates of intracranial hemorrhage on OACs compared to other groups [24]. Therefore, we will aim to determine whether current clinical prediction tools effectively predict racialized minority patients who are at low risk of VTE recurrence to safety stop anticoagulation.

Overall, our future directions will advance the field of adult thrombosis medicine and anticoagulant safety by clarifying the prognosis of VTE among minority populations, refining the study of anticoagulant safety in a patient-centered manner, and informing future clinical and health system level decisions about anticoagulation for secondary VTE prevention in North America and beyond.

4.5 References

1. Wendelboe AM, Raskob GE: **Global Burden of Thrombosis: Epidemiologic Aspects**. *Circ Res* 2016, **118**(9):1340-1347.
2. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J: **Incidence and mortality of venous thrombosis: a population-based study**. *J Thromb Haemost* 2007, **5**(4):692-699.

3. Khan F, Rahman A, Carrier M, Kearon C, Weitz JI, Schulman S, Couturaud F, Eichinger S, Kyrle PA, Becattini C *et al*: **Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: Systematic review and meta-analysis**. *The BMJ* 2019, **366**:l4363.

4. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, Hutten BA, Jaff MR, Manja V, Schulman S *et al*: **American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism**. *Blood Adv* 2020, **4**(19):4693-4738.

5. Stevens SM, Woller SC, Baumann Kreuziger L, Bounameaux H, Doerschug K, Geersing GJ, Huisman MV, Kearon C, King CS, Knighton AJ *et al*: **Executive Summary: Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report**. *Chest* 2021, **160**(6):2247-2259.

6. Kearon C, Iorio A, Palareti G, Subcommittee on Control of Anticoagulation of the SSCotI: **Risk of recurrent venous thromboembolism after stopping treatment in cohort studies: recommendation for acceptable rates and standardized reporting**. *J Thromb Haemost* 2010, **8**(10):2313-2315.

7. Hsu AT, Manuel DG, Spruin S, Bennett C, Taljaard M, Beach S, Sequeira Y, Talarico R, Chalifoux M, Kobewka D *et al*: **Predicting death in home care users: derivation and validation of the Risk Evaluation for Support: Predictions for Elder-Life in the Community Tool (RESPECT)**. *CMAJ* 2021, **193**(26):E997-E1005.

8. Goedegebuur J, Abbel D, Accassat S, Achterberg WP, Akbari A, Baddeley E, Bax JJ, Becker D, Bergmeijer B, Bertoletti L *et al*: **Towards optimal use of antithrombotic**

therapy of people with cancer at the end of life: A research protocol for the development and implementation of the SERENITY shared decision support tool. *Thrombosis Research*.

9. de Winter MA, Buller HR, Carrier M, Cohen AT, Hansen JB, Kaasjager KAH, Kakkar AK, Middeldorp S, Raskob GE, Sorensen HT *et al*: **Recurrent venous thromboembolism and bleeding with extended anticoagulation: the VTE-PREDICT risk score**. *Eur Heart J* 2023, **44**(14):1231-1244.
10. Eichinger S, Heinze G, Jandeck LM, Kyrle PA: **Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model**. *Circulation* 2010, **121**(14):1630-1636.
11. Makelburg AB, Veeger NJ, Middeldorp S, Hamulyak K, Prins MH, Buller HR, Lijfering WM: **Different risk of deep vein thrombosis and pulmonary embolism in carriers with factor V Leiden compared with non-carriers, but not in other thrombophilic defects. Results from a large retrospective family cohort study**. *Haematologica* 2010, **95**(6):1030-1033.
12. Bounameaux H: **Factor V Leiden paradox: risk of deep-vein thrombosis but not of pulmonary embolism**. *Lancet* 2000, **356**(9225):182-183.
13. Carrier M, Le Gal G, Wells PS, Rodger MA: **Systematic review: Case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism**. In.; 2010.
14. Khan F, Tritschler T, Kimpton M, Wells PS, Kearon C, Weitz JI, Buller HR, Raskob GE, Ageno W, Couturaud F *et al*: **Long-Term Risk for Major Bleeding During Extended**

Oral Anticoagulant Therapy for First Unprovoked Venous Thromboembolism : A Systematic Review and Meta-analysis. *Ann Intern Med* 2021, **174**(10):1420-1429.

15. Van Es N, Coppens M, Schulman S, Middeldorp S, Büller HR: **Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: Evidence from phase 3 trials**. *Blood* 2014, **124**(12):1968-1975.

16. Khan F, Rahman A, Tritschler T, Carrier M, Kearon C, Weitz JI, Schulman S, Couturaud F, Becattini C, Agnelli G *et al*: **Long-Term Risk of Major Bleeding after Discontinuing Anticoagulation for Unprovoked Venous Thromboembolism: A Systematic Review and Meta-analysis**. *Thromb Haemost* 2022, **122**(7):1186-1197.

17. Mai V, Guay C-A, Perreault L, Bonnet S, Bertoletti L, Lacasse Y, Jardel S, Lega J-C, Provencher S: **Extended Anticoagulation for VTE: A Systematic Review and Meta-Analysis**. *Chest* 2019, **155**(6):1199-1216.

18. Hald EM, Enga KF, Lochen ML, Mathiesen EB, Njolstad I, Wilsgaard T, Braekkan SK, Hansen JB: **Venous thromboembolism increases the risk of atrial fibrillation: the Tromso study**. *J Am Heart Assoc* 2014, **3**(1):e000483.

19. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS *et al*: **Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease**. *N Engl J Med* 2017, **377**(14):1319-1330.

20. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A *et al*: **Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease**. *N Engl J Med* 2019, **381**(12):1103-1113.

21. Xu Y, Siegal DM, Anand SS: **Ethnoracial variations in venous thrombosis: implications for management, and a call to action**. *Journal of Thrombosis and Haemostasis* 2020.

22. White RH, Keenan CR: **Effects of race and ethnicity on the incidence of venous thromboembolism.** *Thrombosis research* 2009, **123 Suppl 4**(vrn, 0326377):S11-17.

23. Tang Y, Sampson B, Pack S, Shah K, Yon Um S, Wang D, Wang T, Prinz M: **Ethnic differences in out-of-hospital fatal pulmonary embolism**. *Circulation* 2011, **123**(20):2219-2225.

24. Shen AYJ, Yao JF, Brar SS, Jorgensen MB, Chen W: **Racial/Ethnic Differences in the Risk of Intracranial Hemorrhage Among Patients With Atrial Fibrillation**. *Journal of the American College of Cardiology* 2007, **50**(4):309-315.