Venous Thromboembolism: Lifetime risk and novel risk factors

A DISSERTATION

SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL

OF THE UNIVERSITY OF MINNESOTA

BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

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March 2015

ACKNOWLEDGEMENTS

This research was supported by a training grant in cardiovascular disease epidemiology and prevention, funded by the National Institutes of Health. This fellowship has significantly enhanced my doctoral training experience.

I could not have completed this research without the support of a great many people. I would first like to thank my advisor, Aaron Folsom. Thank you for taking me on as a mentee, not only at the doctorate level, but also at the master's level. Undoubtedly you were an influence in my choice to continue my education with a doctorate in the first place. I recognize and appreciate the countless hours you have spent teaching and guiding; thank you for your thorough comments, quick turnaround times, and for always challenging me to achieve. I have learned much from you, including a passion for research.

A huge thank you to Pam Lutsey, who has served as an informal mentor to me throughout my master's and doctorate programs. Thank you for a countless number of things, including guiding my data analyses back before I knew how to do data analyses, sharing your expertise on every paper I have led, and being a role model to aspire to.

Thank you to Alvaro Alonso and Saonli Basu, who have each offered their expertise through serving on my doctoral committee. Alvaro, thank you for having an open door policy, and always finding time to discuss methodology and answer questions. Saonli, thank you for contributing your statistical expertise and your time.

And, finally, thank you to the other CVD fellows and Faye Lopez for feedback on presentations, always finding time to answer questions, and for making my experience enjoyable.

DEDICATION

This dissertation is dedicated to my husband, David Bell. I like to say he has done everything but my dissertation during this time. I am eternally grateful for his love, encouragement, and support…and of course for making me laugh.

ABSTRACT

Deep vein thrombosis and pulmonary embolism are viewed as different manifestations of the same disease process, termed venous thromboembolism (VTE). VTE represents a significant source of mortality and morbidity.

The first two manuscripts of this dissertation use data from two large, prospective cohort studies: the Cardiovascular Health Study (CHS) and the Atherosclerosis Risk in Communities (ARIC) study. We followed participants, aged 45–64 years in ARIC and ≥65 in CHS at baseline (1987-89 in ARIC, 1989-90 and 1992–93 in CHS), for incident VTE (through 2011 and 2001 in ARIC and CHS, respectively).

In manuscript 1, we estimated the lifetime risk and 95% confidence interval of incident VTE, using data from CHS and ARIC. We used a modified Kaplan-Meier method, accounting for the competing risk of death. We calculated that 1 in 12 middle-aged adults develop VTE in their lifetime. This estimate of lifetime risk may be useful to promote awareness of VTE and guide decisions at both clinical and policy levels.

Manuscripts 2 and 3 aimed to identify and clarify novel risk factors for VTE. The etiology of VTE is not fully understood, especially in contrast to atherothrombosis. Further identification of VTE risk factors may yield pathophysiological insights into the disease that could eventually provide new prevention or treatment options.

In manuscript 2, we quantified the association between orthostatic hypotension (OH) at baseline and VTE, using data from ARIC and CHS. In CHS, there was a positive association between incident VTE and OH (Hazard ratio for total VTE = 1.74 (95% confidence interval: 1.20-2.51)). In contrast, there was no association between OH and

VTE in ARIC. In conclusion, community-dwelling older adults with OH have a moderately increased risk of VTE. These results were not replicated in a population-based middle-aged cohort.

In manuscript 3, we conducted a systematic review and meta-analysis to quantify the association between diabetes and VTE. We identified 19 eligible studies. The pooled relative risk for the association of diabetes with VTE was 1.10 (95% confidence interval: 0.94-1.29). This literature-based systematic review and meta-analysis supports either no association or a very modest positive one between diabetes and VTE in the general population. Diabetes is unlikely to play a major role in VTE development.

Table of Contents

LIST OF TABLES……..……ix

LIST OF FIGURES…….……xi

PREFACE……...……...xiii

CHAPTER 1: Venous thromboembolism - definitions and clinical aspects……..……..1

A. Deep vein thrombosis 1

B. Pulmonary embolism 1

C. Sequelae of venous thromboembolism 2

D. Diagnosis of venous thromboembolism 2

E. Treatment of venous thromboembolism 5

F. Hospital-based prevention of venous thromboembolism 5

CHAPTER 2: Epidemiology of venous thromboembolism……..……6

A. Incidence 6

B. Mortality 6

C. Recurrence 7

CHAPTER 3: Major risk factors for venous thromboembolism……..……8

A. VTE susceptibility 8

B. Venous thromboembolism is a multi-causal disease 8

C. Transient acquired risk factors[53] 10

D. Constant acquired risk factors[53] 12

E. Genetic risk factors[51] 14

F. Knowledge of venous thromboembolism risk factors is incomplete 16

CHAPTER 4: Detailed methods……17

A. Overview..... 17

B. The Cardiovascular Health Study and the Atherosclerosis Risk in Communities Study .. 17

C. Expanded methods for manuscript 1 19

D. Expanded methods for manuscript 3 20

CHAPTER 5: Manuscript 1 - Lifetime risk of venous thromboembolism in two cohort studies..27

A. Introduction..... 27

B. Methods 28

C. Results..... 31

D. Discussion..... 32

CHAPTER 6: Manuscript 2 - Orthostatic hypotension and risk of venous thromboembolism in two cohort studies……...42

A. Introduction..... 42

B. Methods 43

C. Results..... 48

D. Discussion..... 51

CHAPTER 7: Manuscript 3 - Diabetes mellitus and venous thromboembolism: A systematic review and meta-analysis……58

A. Introduction..... 58

B. Methods 58

C. Results..... 62

D. Discussion 64

CHAPTER 8: Summary……..77

A. Manuscript 1 77

B. Manuscript 2 78

C. Manuscript 3 79

D. Overall Conclusions 80

REFERENCES……...81

APPENDICES……..104

LIST OF TABLES

CHAPTER 3: Major risk factors for venous thromboembolism

Table 3.1: Major venous thromboembolism risk factors……....9

CHAPTER 5: Manuscript 1 - Lifetime risk of venous thromboembolism in two cohort studies

Table 5.1: Baseline characteristics of ARIC and CHS participants……..36

Table 5.2: Age-specific incidence rates of VTE per 1,000 person-years, ARIC and CHS……37

Table 5.3: Lifetime risk (95% CI) of VTE, ARIC……38

Table 5.4: ARIC follow-up restricted to 2001: Incidence rates of VTE per 1,000 person-years, ARIC and CHS……..……..39

CHAPTER 6: Manuscript 2 - Orthostatic hypotension and risk of venous thromboembolism in two cohort studies

Table 6.1: Baseline characteristics of ARIC and CHS participants according to baseline orthostatic hypotension status……55

Table 6.2: HRs (95% CIs) for incident VTE among participants with OH at baseline compared to those without…….56

Table 6.3: Stratified by baseline characteristics, adjusted HRs (95% CIs) for incident total VTE among participants with orthostatic hypotension at baseline compared to those without……...57

CHAPTER 7: Manuscript 3 - Diabetes mellitus and venous thromboembolism: A systematic review and meta-analysis

Table 7.1: Characteristics of cohort studies that reported the relation between diabetes and VTE……68

Table 7.2: Characteristics of case-control studies that reported the relation between diabetes and VTE……...70

Table 7.3: Meta-regression and stratified analysis of studies on the association between diabetes and venous thromboembolism…….75

LIST OF FIGURES

CHAPTER 1: Venous thromboembolism - definitions and clinical aspects

Figure 1.1: A diagnostic algorithm for suspected VTE……..…...3

CHAPTER 3: Major risk factors for venous thromboembolism

Figure 3.1: Virchow's Triad……..……....8

Figure 3.2: Venous thromboembolism: a multi-causal disease……10

CHAPTER 5: Manuscript 1 - Lifetime risk of venous thromboembolism in two cohort studies

Figure 5.1: Cumulative risk of VTE at selected index ages…….40

Figure 5.2: Cohort- and age- specific VTE incidence rates by time period of VTE ascertainment…….41

CHAPTER 7: Manuscript 3 - Diabetes mellitus and venous thromboembolism: A systematic review and meta-analysis

Figure 7.1: Forest plot of study-specific and pooled relative risks (95% Cis) for venous thromboembolism, comparing those with diabetes to those without diabetes……...72

Figure 7.2: Forest plot of study-specific and pooled relative risks (95% Cis) for **provoked** venous thromboembolism, comparing those with diabetes to those without diabetes……..73

Figure 7.3: Forest plot of study-specific and pooled relative risks (95% Cis) for **unprovoked** venous thromboembolism, comparing those with diabetes to those without diabetes……74

Figure 7.4: Meta-analysis estimates and 95% confidence intervals, omitting one study at a time to assess the influence of any single study on the random-effects pooled estimate.....76

PREFACE

The dissertation begins with background information on venous thromboembolism (VTE): definitions, clinical aspects, epidemiology, and risk factors. Then, three original manuscripts are presented. The objectives of the manuscripts are to 1) calculate the lifetime risk of VTE overall and stratified by subgroups of interest, 2) quantify the association between orthostatic hypotension and VTE, and 3) perform a systematic review and meta-analysis to quantify the association between diabetes mellitus and VTE.

CHAPTER 1: Venous thromboembolism - definitions and clinical aspects

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are viewed as different manifestations of the same disease process, termed venous thromboembolism (VTE).

A. Deep vein thrombosis

A DVT is a blood clot, or thrombus, that forms in a large vein. Although most DVTs occur in the legs, they can occur in other locations, such as the arms[1]. We focused on DVTs that occur in the legs, since they differ in important ways - including epidemiology, diagnosis, and treatment - from DVTs that occur in other locations. A DVT may cause swelling, pain, tenderness, discoloration, or redness in the affected leg due to the block in venous blood flow[2].

B. Pulmonary embolism

About two-thirds of patients with VTE present with symptoms or signs of DVT and about one-third present with its complication, pulmonary embolism[3,4]. A PE begins when a thrombus from a DVT dislodges – becoming an embolus – and travels through the blood stream. The embolus continues to travel through the circulation until it reaches an artery that is smaller in diameter than it, at which time it will become lodged and block distal blood flow. When this happens within the pulmonary artery or one of its branches, it is termed a pulmonary embolism[5]. If there is an insufficient collateral supply of blood, tissue necrosis occurs. Symptoms depend on size and location of the lodged PE, but can include shortness of breath, expectoration of bloody sputum, cyanosis, pleuritic chest

pain, and cough[5,6]. PE can cause acute right heart failure, shock, acute respiratory compromise, pulmonary infarction, and – in rare cases – sudden death[5,67].

C. Sequelae of venous thromboembolism

Post-thrombotic syndrome[8] and chronic thromboembolic pulmonary hypertension[9] can be sequelae of VTE.

Post-thrombotic syndrome - which can manifest as chronic calf swelling and, in severe cases, venous ulcers - is a common complication after a DVT[8]. Among patients newly diagnosed with DVT of the leg, 43% of patients (166 out of 387) developed post-thrombotic syndrome within two years. Of those who developed post-thrombotic syndrome, it was mild in 30%, moderate in 10% and severe in 3%[10]. Post-thrombotic syndrome is a costly disease[11] that can have negative effects on quality of life and productivity[12].

Chronic thromboembolic pulmonary hypertension, defined as a mean pulmonary artery pressure > 25 mmHg that persists 6 months after a diagnosis of PE, occurs in 2-4% of patients diagnosed with PE[9,13,14]. It results in shortness of breath, which can be debilitating, during both exertion and rest[9,15]. Life expectancy among patients with chronic thromboembolic pulmonary hypertension can be short; many die of sudden cardiac death[15].

D. Diagnosis of venous thromboembolism

Typically, a diagnostic algorithm comprised of a series of tests guides the diagnosis of DVT or PE (**Figure 1.1.**). Use of a validated diagnostic algorithm is associated with better outcomes and is thus highly recommended[16].

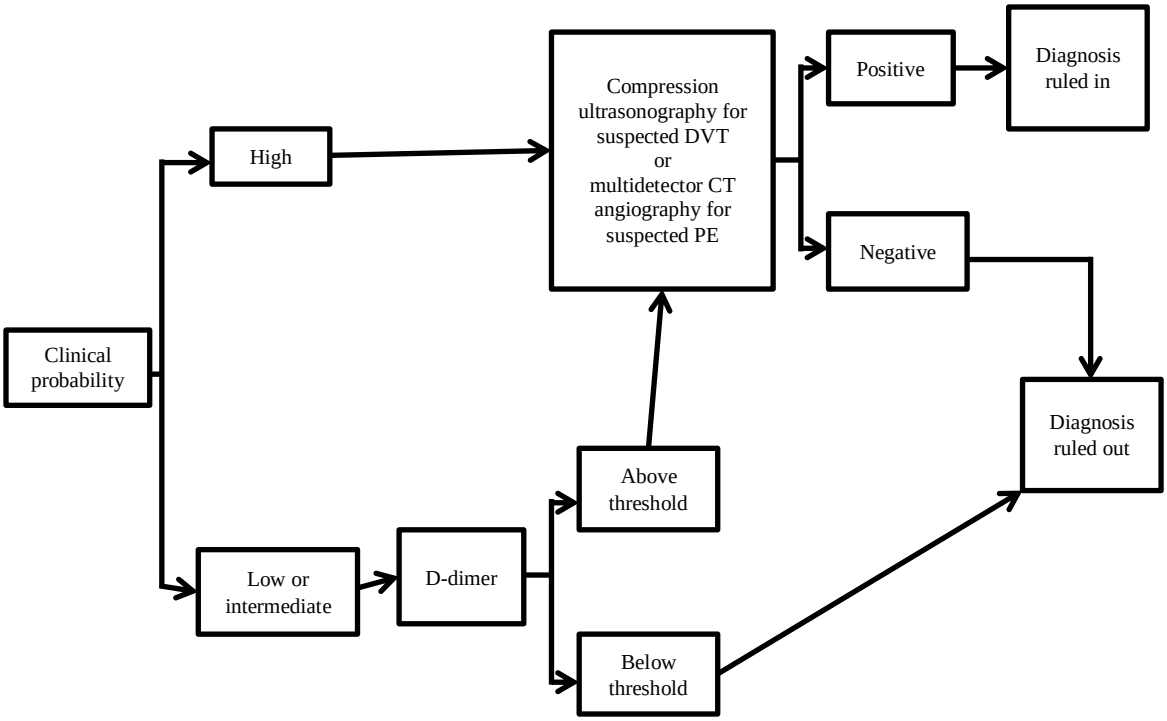


Figure 1.1. (from article by Goldhaber et al.[8]). A diagnostic algorithm for suspected VTE.

Clinical assessment of probability. The work-up for a diagnosis of VTE begins with a clinical assessment of VTE probability[15]. Probability of VTE can be assessed empirically, with prediction rules, or scores. Common scores are the Wells score for DVT[17] or PE[18], and the revised Geneva score[19] for the diagnosis of PE. Clinical probability assessments categorize patients who potentially have VTE as high, intermediate, or low probability of VTE. Patients categorized as high or intermediate probability may receive anticoagulant treatment as they await the results of diagnostic tests[15].

Fibrin D-dimer test. In patients with a low or intermediate probability of VTE, a VTE diagnosis can be largely ruled out with a fibrin D-dimer test. A D-dimer test reports

the concentration of fibrin D-dimer in the blood. Fibrin D-dimer is a degradation product of cross-linked fibrin, which is present in blood clots. Therefore, a patient with acute VTE usually has an elevated concentration of fibrin D-dimer in the blood. The D-dimer test has low specificity and high sensitivity (more than 95%), making it effective at excluding, but not confirming, a diagnosis[15]. Therefore, in patients with low or intermediate probability, a negative (below a threshold, usually of 500 µg/L) D-dimer test can safely rule out a VTE diagnosis[20]. If a patient tests positive on the D-dimer test, he or she goes on per the algorithm to receive either compression ultrasonography for suspected DVT or a CT angiography for suspected PE.

CT angiography for suspected PE. If a patient with suspected PE is deemed high probability or tests positive on a D-dimer test, CT angiography is performed[15]. CT angiography provides an image of the pulmonary artery and its branches, along with information on blood flow[5]. It is has acceptable sensitivity and specificity[21]. CT angiography has largely replaced older tests for PE, including the ventilation/perfusion scan and pulmonary angiography[2,15].

Compression ultrasonography for suspected DVT. If a patient with suspected DVT is deemed high probability or tests positive on a D-dimer test, compression ultrasonography is performed to image the veins in the leg. If a venous segment cannot be compressed with an ultrasonography probe, it is considered diagnostic of DVT[15]. Compression ultrasonography is both sensitive and specific for proximal (above the knee) DVT[2]. Compression ultrasonography has largely replaced older tests for DVT, including doppler ultrasound, impedence plethysmography, and radiological venogram[2,15].

E. Treatment of venous thromboembolism

Treatment of VTE has several aims: 1) to prevent DVT recurrence; 2) to prevent a thrombus from forming distal to the existing embolus or thrombus; 3) to prevent PE in those with DVT only; and, in certain situations, 4) to accelerate fibrinolysis[2,5]. Anticoagulants are the mainstay of VTE treatment. Anticoagulant options include heparin or low-molecular-weight heparin, vitamin K antagonists (e.g., warfarin), direct factor Xa inhibitors, and direct factor IIa inhibitors[22]. There is strong evidence that treatment with anticoagulants reduces mortality and recurrence in patients with PE, and recurrence in patients with DVT[23–25]. Patients with a contraindication to anticoagulants may be treated with an inferior vena cava filter, which is inserted into the vena cava and can prevent pulmonary emboli[2,22].

F. Hospital-based prevention of venous thromboembolism

The National Quality Forum recommends that hospitalized patients be screened for VTE risk, given that many hospitalized patients are high-risk[26]. The American College of Chest Physicians has set forth recommendations regarding who should receive VTE prophylaxis based on a patient's level of risk[27]. Recommended prophylaxis can include ambulation, anticoagulant use, intermittent pneumatic compression, graduated compression stockings, or a combination of the aforementioned[28].

CHAPTER 2: Epidemiology of venous thromboembolism

Importantly, VTE incidence and mortality may be greatly underreported due to the silent nature of the disease and the low rate of autopsies in the United States[28,29].

A. Incidence

In developed countries, VTE affects an about 1-3 in 1000 for the first time, per year[3,30–32]. This incidence rate varies by population characteristics. VTE incidence rises exponentially with age: from approximately 1 per 10,000 until age 45, then dramatically increasing to 5-6 per 1,000 by age 80[32–35]. Males and females have approximately the same incidence of VTE, with the exception of women of reproductive age; women of reproductive age have a slightly greater incidence of VTE than their male counterparts due to the increase in VTE risk factors – pregnancy, the postpartum period, and use of oral contraceptives – during this time period[32,36–38]. Asians and Hispanics have a lower incidence of VTE than whites, while African Americans have a higher incidence[39,40]. It is not clear why these racial and ethnic differences in VTE incidence exist.

B. Mortality

DVT alone is not often fatal. Its complication PE is a significant source of cardiovascular disease mortality, behind only heart attack and stroke[15]: 60,000 die from PE each year in the United States[2]. For perspective, this is more people than die in the United States each year from breast cancer, AIDS, or motor vehicle accidents (40,200; 14,499; and 42,116, respectively)[33,41]. PE is the leading cause of preventable death in hospitals[42] and a leading cause of maternal mortality[43] in the United States.

Mortality within a month of diagnosis occurs in about 6% of DVT cases and 12% of PE cases, with the highest risk of death in those with cancer[3,32,35]. A registry from 52 hospitals in seven countries in Europe and North America reports a 3-month case-fatality rate for PE of 17%[44]. Prognostic factors associated with death within three months of a PE diagnosis include old age, cancer, chronic obstructive pulmonary disease, congestive heart failure, tachypnea, right ventricular hypokinesis on echocardiography, and systolic arterial hypotension[44]. Long-term mortality among those with a PE diagnosis is substantial; an Australian registry reports that 36% of patients died within approximately four years of a PE diagnosis. This is 2.5 times the mortality rate in age and sex-matched people from the general population[45].

C. Recurrence

VTE recurrence is common. Approximately 30% of patients develop recurrent VTE within 10 years of the initial event; risk of recurrence is highest within 6-12 months of the initial VTE event[46–48]. Risk factors for VTE recurrence include active cancer, advanced age, obesity, male gender, and neurological disease with leg paresis[32,46–49]. Patients with transient risk factors, such as surgery, often have lower rates of recurrence than other patients[50].

CHAPTER 3: Major risk factors for venous thromboembolism

A. VTE susceptibility

VTE is a condition that begins with a blood clot within a vein. In normal physiology, blood does not clot within the vascular system. However, one or a combination of the following abnormalities can lead to clotting in the arteries or veins: blood slowing or stasis, injury to the blood vessel wall, or hypercoagulability[5]. These three broad categories are termed Virchow's triad (**Figure 3.1.**) and provide the theoretical cornerstone for understanding thrombosis susceptibility. Risk factors for VTE tend to involve at least one element of Virchow's triad. Most risk factors for VTE fall into the "hypercoagulability" or "blood slowing or stasis" categories.

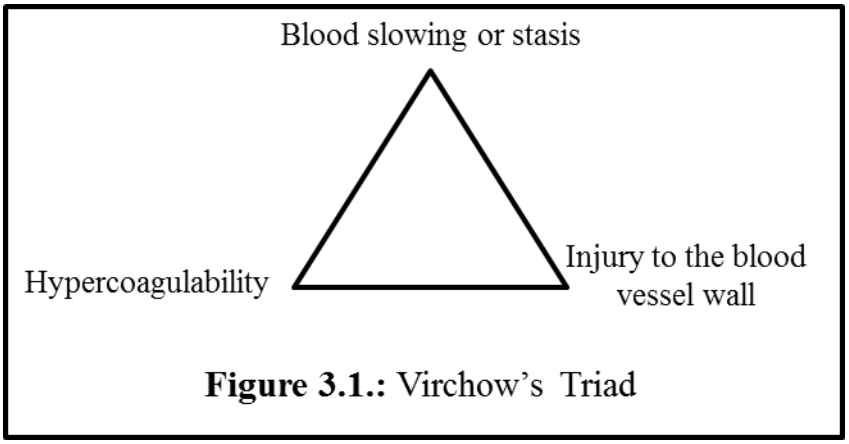


Figure 3.1.: Virchow's Triad

B. Venous thromboembolism is a multi-causal disease

VTE is a multi-causal disease, usually involving an interplay of genetic and acquired risk factors. Acquired risk factors tend to involve blood stasis and genetic risk factors tend to involve hypercoagulability; although, exceptions exist. Acquired risk factors can further be broken down into two categories: constant and transient over time (**Table 3.1.**). Transient acquired risk factors may act as triggers, whereas constant

acquired risk factors become part of an individual's intrinsic thrombosis risk.

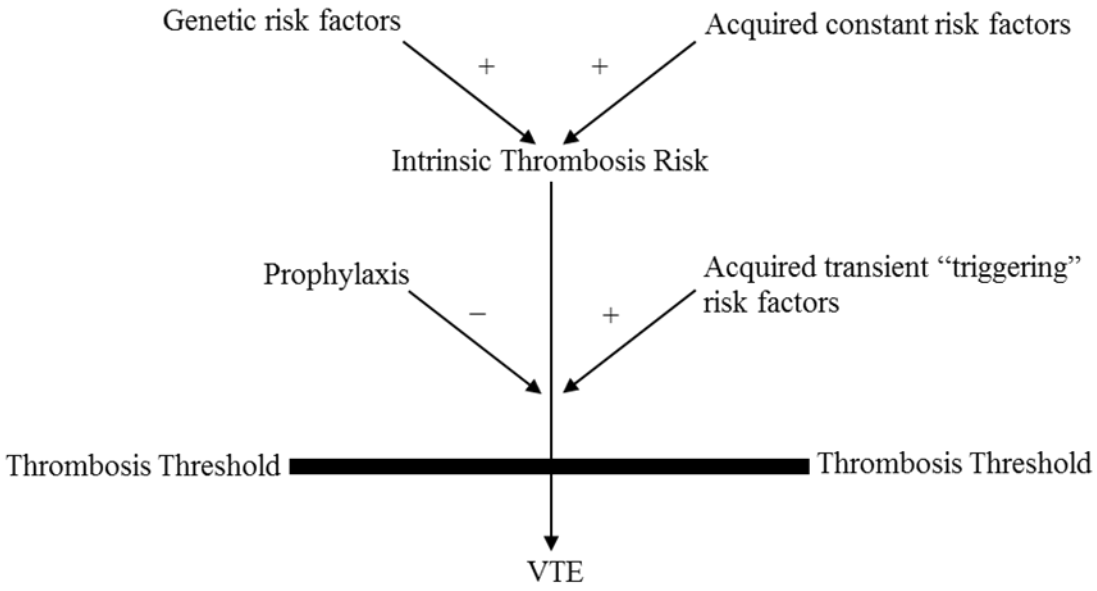
Table 3.1. Major venous thromboembolism risk factors

Acquired		Genetic
Transient	**Constant**	
Major and orthopedic surgery	Advanced age	Factor V Leiden
Trauma	Antiphospholipid antibodies	Prothrombin 20210A
Cancer	Obesity	Non-O blood group
Pregnancy and the postpartum period	Oral contraceptives and hormone therapy	Deficiencies of antithrombin, protein C, or protein S
Immobilization (i.e. bed rest, paralysis, plaster casts, or extended travel)		Elevated procoagulant levels (may be a mix of acquired and genetic)
Hospitalization		

Adapted from Rosendaal et al.[51]

It is hypothesized that a thrombosis threshold exists (**Figure 3.2.**), as many VTE risk factors are common and do not necessarily lead to VTE, and many patients with VTE have multiple risk factors[52].

Figure 3.2. Venous thromboembolism: a multi-causal disease.
Adapted from Rosendaal (1999), Cushman (2007), and a PowerPoint slide provided by AR Folsom.



C. Transient acquired risk factors[53]

Major and orthopedic surgery. Major and orthopedic surgery are strong risk factors for VTE. A surgical patient is at risk of VTE both due to an increase in coagulation factors that can occur in response to tissue injury and due to blood stasis incurred from the inactivity associated with surgery[5]. More than 50% of patients undergoing surgery may develop VTE unless they receive anticoagulants as prophylaxis[53–57]. However, given that it is now commonplace for VTE prophylaxis to be prescribed after major and orthopedic surgery, the risk of VTE in postoperative patients has decreased[53]. Still, surgery represents a major cause of VTE; patients who receive VTE prophylaxis and undergo a high-VTE-risk surgery experience VTE at a rate of 1-3%[58].

Trauma. Trauma is a strong risk factor for VTE. In a prospective study of patients with trauma - spinal injury, head trauma, pelvic fractures, femoral fractures, or tibial fractures - admitted to a trauma unit, almost 60% (201 out of 349) developed leg DVT in the absence of VTE prophylaxis[59].

Immobilization. Immobilization - such as bed rest, paralysis, plaster casts, and extended travel - is a strong risk factor for VTE[53]. During prolonged periods of immobilization or a cramped position the pumping action of the calf musculature, which promotes venous return, is impaired. The ensuing blood stasis promotes DVT[5,53].

Hospitalization. Patients who are hospitalized often have at least one risk factor for VTE (e.g., immobility, trauma, surgery).

Pregnancy and the postpartum period. Interestingly, pregnancy and the postpartum period have been known risk factors for VTE for centuries. Doctors referred to leg DVT as "milk leg" due to the white appearance of the thrombosed leg; the public health message at the time advocated for breastfeeding to prevent milk leg[60].

Pregnancy and the postpartum period are strong risk factors for VTE. Two retrospective cohort studies report the incidence of DVT in women during pregnancy and the post-partum period to be about 0.7 per 1,000 deliveries[61,62]. This is approximately a 10-fold higher risk of VTE compared to all women of reproductive age[63].

Cancer. Cancer is a strong risk factor for VTE. MEGA, a large population-based case-control study in the Netherlands, reports the risk of first leg DVT or PE to be 7-fold (95% CI: 5.2-8.6) higher in people with cancer versus people without cancer[64].

Although it is not entirely clear why cancer is a risk factor for VTE, it is likely that several factors are involved: 1) The tumor itself could increase risk of VTE through the release of humoral factors that induce a procoagulant state[53]; 2) cancer can lead to immobility, a known risk factor for VTE; 3) cancer treatment may have prothrombotic effects[65,66]; and 4) large tumors may obstruct veins and lead to thrombosis[67,68].

D. Constant acquired risk factors[53]

Advanced age. Age is one of the strongest risk factors for VTE[33,53,69,70]. A population-based prospective cohort study reports the risk of VTE over 8 years of follow-up to be 12-fold (95% CI: 5.35-29.7) higher in the very old as compared to a middle-aged population[69].

It is uncertain why age is a strong risk factor for VTE. However, plausible explanations exist. Other risk factors for VTE become more prevalent with advanced age (e.g., immobility and obesity) and could contribute to an age-VTE association. In addition, venous valves and muscular tone of the legs can deteriorate with age; both would contribute to poor venous return and could increase risk of VTE[53]. It is likely that these factors interact to contribute to the increased risk of VTE seen with advanced age.

Antiphospholipid antibodies. Phospholipids are required for blood to clot. However, the body can erroneously identify phospholipids as foreign substances and form antiphospholipid antibodies[71]. Antiphospholipid antibodies are a moderately strong risk factor for VTE. This is somewhat counterintuitive, as one would think an attack on a protein essential for blood clotting would cause a bleeding disorder. However, this is not the case and it is not clear why[53]; the Leiden Thrombophilia Study, a population-based

case-control study, reports the risk of first DVT to be 3-fold higher (95% CI: 1.2-10.9) in the presence of the lupus anticoagulant – a subgroup of antiphospholipid antibodies - as compared to people without this antiphospholipid antibody[72]. Other studies have reported a statistically significant, albeit also imprecise, higher risk of VTE in those with antiphospholipid antibodies[73,74].

Presence of antiphospholipid antibodies is somewhat rare. However, the exact prevalence is not well-established. In two studies of healthy individuals, the first reported a prevalence of 0% (0 out of 117)[74], while the other reported a prevalence of 2% (6 out of 300)[75].

Obesity. Obesity is a moderately strong risk factor for VTE[70]. Prospective cohort and case-control studies concur that the risk of VTE is 2- to 3-fold higher in obese individuals compared to those who are not obese[69,76–78]. Potential mechanisms are ill-defined, but possible explanations include 1) body size, which could have a physical impact on venous return; and 2) increases in coagulation and inflammation, which are associated with obesity, could increase VTE risk[70]. However, a large population-based case-control study reports that the obesity-VTE relation is not explained by differences in levels of factor VIII, fibrinogen, factor IX or D-dimer[78].

Oral contraceptives and hormone therapy. The use of oral contraceptives is a moderately strong risk factor for VTE[53]. A large, multicenter hospital-based case-control study reports the risk of VTE to be higher in women using oral contraceptives compared to those not using in both European and non-European countries: Odds ratios of 4.15 (95% CI: 3.09-5.57) and 3.25 (95% CI: 2.59-4.08), respectively[79]. It is important to remember that the incidence rate of VTE is low in young women - less than 1 per 10,000

per year - so even a quadrupling of risk equates to a low absolute risk of VTE: 2 to 3 per 10,000 per year in oral contraceptive users[63]. Despite the low absolute risk, because of the high prevalence of oral contraceptive use, it is the most common cause of VTE in women of reproductive age[53].

The use of hormone therapy is a moderately strong risk factor for VTE; studies demonstrate VTE risk is 2- to 4-fold higher in those who use hormone therapy compared to those who do not[53,80–83].

The estrogen found in oral contraceptives and hormone therapy may at least partially explain the increased risk of VTE; estrogen can stimulate the generation of coagulation factors, mildly increasing blood coagulability[5,84–87].

E. Genetic risk factors[51]

Factor V Leiden. A mutation in clotting factor V is known as factor V Leiden; it causes resistance to activated protein C[88] - a natural anticoagulant - and is a moderately strong risk factor for VTE. Heterozygous and homozygous carriers have a 5-fold and 50-fold, respectively, higher risk of VTE than those who are not carriers[89]. The mutation is a common variant; approximately 5% of whites are carriers[88]. It is less common in other races.

Prothrombin 20210A. A specific mutation in part of the prothrombin gene is known as prothrombin 20210A. It causes elevated production of prothrombin (i.e., coagulation factor II), a protein that is required for fibrin formation and thus clot formation[90]. Carrying the variant prothrombin 20210A is a moderately strong risk factor for VTE; a population-based case-control study reports heterozygous carriers have an

almost 3-fold (95% CI: 1.4-5.6) higher risk of VTE than those who are not carriers[91]. The mutation is a common variant - with a prevalence of more than 1% - that is found almost exclusively in whites[91].

Deficiencies of coagulation inhibitors. Antithrombin, protein C, and its cofactor protein S are natural coagulation inhibitors. A deficiency in any one of these inhibitors can be inherited through genetic mutations and is a strong risk factor for VTE[53]. Deficiencies are rare, affecting less than 1% of the population[92,93]. Due to their rareness, most research has been from family studies; heterozygous carriers with a familial deficiency have a 10-fold higher risk of VTE than those without a deficiency[94–96]. However, outpatient-based case-control studies (i.e., not family-based) report only a 2- to 5-fold higher risk of VTE in carriers of a deficiency vs. non-carriers[97,98]. It is unknown why this discrepancy exists; it is hypothesized that patients with familial deficiencies have other predisposing factors as well[99–101].

Non-O blood group. Having a non-O ABO blood group is a moderately strong risk factor for VTE[102,103]. A systematic review and meta-analysis reports that those with a non-O blood group have a 2- to 3-fold higher risk of VTE than people with an O blood group[102]. It is hypothesized that those with an O blood group have higher clearance of von Willebrand factor - a protein involved in blood clotting - than other blood groups and thus, lower subsequent factor VIII levels and VTE risk[104].

Findings from genome-wide association studies. Many potential genetic risk factors for VTE have been identified in genome-wide association studies; single nucleotide polymorphisms across the F5[105–107], ABO[105,106], GP6[105,108], CYP4V2[105,108],

F11[106,107,109], FGG[106,109], SERPINC1[108], KNG1[110], STXBP5[111], vWF[111], and protein C[107,112,113] genes have been implicated as potential risk factors. Many of these single nucleotide polymorphisms are common and modulate proteins that affect coagulation, anticoagulation, fibrinolysis, and antifibrinolysis. Although knowledge of each weak to moderately strong genetic risk factor by itself may have no clinical utility, it is hypothesized that knowledge of many such genetic risk factors could lead to a genetic risk score with clinical utility[51].

Elevated procoagulant factor levels. Elevated procoagulant factor levels are moderately strong risk factors for VTE. Individuals with the highest levels of certain procoagulant factors - prothrombin, factor VIII, factor IX, factor XI, thrombin activatable fibrinolysis inhibitor, and fibrinogen - have a 2- to 3-fold higher risk of VTE than the rest of the population[91,104,114–116]. Although it is not clear the extent that the environment versus genetics affect most procoagulant factor levels, it is likely a combination[53].

F. Knowledge of venous thromboembolism risk factors is incomplete

Although numerous risk factors for VTE have been identified, the etiology of VTE is not fully understood, especially in contrast to atherothrombosis. Further identification of VTE risk factors may yield pathophysiological insights into the disease that could eventually provide new prevention or treatment options.

CHAPTER 4: Detailed methods

A. Overview

Because chapters five through seven are formatted as concise manuscripts, details of the methods are omitted from these chapters. We elaborate on a few sections here.

B. The Cardiovascular Health Study and the Atherosclerosis Risk in Communities Study

All three manuscripts utilize data from two large, prospective cohort studies: the Cardiovascular Health Study (CHS)[117] and the Atherosclerosis Risk in Communities (ARIC)[118] study, which have similar protocols.

Between 1987–89, ARIC recruited and examined 15,792 participants aged 45–64 years living in four US communities: Forsyth County, NC; Jackson, MS (African Americans only); suburban Minneapolis, MN; and Washington County, MD[118]. Response rates for the baseline exam were 46% in Jackson and 65 to 67% at other clinic sites; differences between respondents and non-respondents have been described[119].

CHS sampled from Medicare lists, recruited, and examined 5,888 community-dwelling participants aged ≥ 65 years living in four US communities (Pittsburgh (Allegheny County), PA; Forsyth County, NC; Sacramento County, CA; and Washington County, MD) between 1989-90 and 1992–93 (African Americans only)[117]. The response rate for the baseline exam was 61% of those eligible; differences between respondents and non-respondents have been described[117].

Venous thromboembolism ascertainment in ARIC and CHS. Incident VTE was defined as the first occurrence of a validated deep vein thrombosis in the leg or pulmonary embolism from baseline through the end of follow-up: December 31, 2011 for the ARIC Study and December 31, 2001 for CHS.

In ARIC, follow-up consisted of annual phone calls and clinic visits every three years. In CHS, follow-up consisted of alternating clinic visits and phone calls every six months. Hospitalizations were identified through participant report in both studies, through Medicare records in CHS, and though surveillance of community hospitals' discharge lists in ARIC[32].

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) discharge codes from all identified hospitalizations were recorded to identify possible cases of VTE. Records with ICD-9-CM discharge codes (where x can take any value) 38.7 (procedure code), 415.1, 415.1X, 451, 451.1, 451.1X, 451.2, 451.8, 451.8X, 451.9, 453, 453.X, 453.XX, 996.7, 996.7X, 997.2, or 999.2 were considered to indicate possible VTE. The records were copied and independently reviewed by two physicians using standardized criteria, with differences resolved by discussion[32].

Definite deep vein thrombosis was defined as a positive venogram, duplex ultrasound, or autopsy. Probable deep vein thrombosis was defined as a positive Doppler examination or impedance plethysmography. Definite pulmonary embolism was defined as a positive pulmonary angiogram, ventilation/perfusion scans indicating "high probability" of pulmonary embolism or at least two segmental perfusion defects without ventilation defects, computed tomography, or autopsy[32]. Repeat classification has shown excellent repeatability.

VTE events were categorized as provoked or unprovoked. Provoked VTE was defined as occurring within 90 days of major trauma, surgery, marked immobility, or within 1 year of active cancer. Unprovoked were all other confirmed VTE cases[32].

C. Expanded methods for manuscript 1

Here are a few details of the statistical methods used in manuscript 1, titled 'Lifetime risk of venous thromboembolism in two cohort studies'.

Estimation of cumulative incidence using a modified Kaplan-Meier method. Cumulative incidence is defined as the proportion of people who develop an event over a certain time period[120]. As tends to be the case in prospective cohort studies with a long period of follow-up, not all individuals in ARIC and CHS were followed for the entire duration. Therefore, we used a modified Kaplan-Meier approach to approximate cumulative incidence[121] (i.e., lifetime risk and its confidence interval).

Accounting for the competing risk of death. A competing risk is defined as an event that either hinders the observation of or changes the probability of the event of interest[122]. In manuscript 1, VTE is the event of interest and non-VTE-related death is a competing risk. The standard Kaplan-Meier analysis treats an individual who died during the study as censored and will overestimate the cumulative incidence of the event of interest; it wrongly assumes this person could still experience a VTE event, when in fact the probability of a VTE event has changed to zero[121]. More appropriately, the lifetime risk analysis should condition on being alive; this can be achieved by treating death as its own event of interest. Thus, each participant will be classified as either a VTE event,

censored (lost to follow-up, or the end of follow-up), or a non-VTE-related death: whichever came first.

Cumulative incidence is defined as the proportion of people who develop an event over a certain time period[120]. We used the Practical Incidence Estimators SAS Macro[121] to estimate the future risk of incident VTE conditional on survival (alive and free of VTE) to selected index ages and by study. Notably, index age is not the same as age at the baseline CHS and ARIC exams. Participants are considered at risk at a given index age as long as they are enrolled in the study, alive, and free of VTE at that age. For example, a participant who was 45 at ARIC's baseline exam will begin to contribute person-years to the index-age-55 category when he or she turns 55, given that he or she is still alive and free of VTE. Conversely, a participant who is 55 at ARIC's baseline exam will begin to contribute person-years to the index-age-45 category after 10 years, at age 55 (i.e., the participant will not contribute person-years between the ages of 45 and 55 because he or she was not part of the ARIC study during this time period). Equations and details of calculations have been described elsewhere[121].

D. Expanded methods for manuscript 3

Here are details of the statistical methods used in manuscript 3, titled 'Diabetes mellitus and venous thromboembolism: A systematic review and meta-analysis'.

Search strategy. Studies were included in this review if they 1) were case-control or cohort design and 2) reported an effect estimate (odds ratio, relative risk, or hazard ratio) between diabetes mellitus (any definition - including self-report, glucose measurement, or medical records) and VTE (defined as deep vein thrombosis and/or

pulmonary embolism) in humans or provide enough information to calculate an effect estimate and its standard error. Studies were excluded if:

- They had no original data.
- DVTs were solely outside of the leg (PE not excluded). Risk factors can differ depending on where the deep vein thrombosis occurs.
- The entire study population was affected by a specific medical condition (e.g. cancer) or procedure.
- VTEs were solely recurrent. Risk factors can be different for a recurrent versus first-time VTE.
- The exposure was solely type 1 diabetes mellitus. A more precise specification of the exposure allowed us to focus on potential confounders of a type 2 diabetes-VTE association, which likely differ from confounders of a type 1 diabetes-VTE relation.

Investigator E.J.B. consulted with a biomedical librarian to develop the search strategy. E.J.B. conducted the search. We searched PubMed, Web of Science, and CINAHL databases. The database search included both keywords and headings, explosion searching, and truncated words related to diabetes mellitus, venous thromboembolism, pulmonary embolism, and deep vein thrombosis. The search cutoff date was December 31, 2013. No language restrictions were applied. We queried experts to identify any additional studies, including unpublished material.

Duplicates were removed, titles and abstracts of records were screened for relevance, and records that obviously did not meet the eligibility criteria were excluded.

The full-text of remaining records was obtained to assess eligibility. Exclusions of full-text articles were reported in an exclusion log, with reason for exclusion. We manually reviewed reference lists of review articles and eligible articles to identify additional eligible studies. In the situation of multiple articles from the same study, the article that had the best adjustments for potential confounders was used.

Data abstraction. We abstracted effect estimates (odds ratios, relative risks, or hazard ratios) and their standard errors for the association between diabetes and VTE. When a standard error was not reported, it was derived from data provided in the manuscript. We sought effect estimates that adequately controlled for potential confounders. As a quality control measure, we checked reported effect estimates against other information in the manuscript, such as graphs and other text, for inconsistencies. If an inconsistency was found, the corresponding author was queried to obtain the correct information.

Establishing a common measure of effect. Since VTE is relatively rare, we were able to ignore the distinctions between various types of effect estimates (e.g. hazard ratios, relative risks, and odds ratios)[123]. We represented and interpreted effect estimates as relative risks (RRs) for this review.

Controlling for confounding. We considered an effect estimate as adequately controlled for potential confounders if it 1) statistically adjusted for race (or only primarily involved one race group), age, and a measure of body size; or 2) demonstrated that a lack of statistical adjustment had little effect on findings. We queried the corresponding authors of papers without adequately controlled results in an attempt to obtain results that did account for a measure of body size, age, and race.

Notably, biases of the effect estimates remain even under our definition of an "adequately controlled" effect estimate. These biases are related to methods of measurement (e.g., estimating body mass index using self-report versus direct measurement) and modeling (e.g., modeling age as bands versus continuous) variables. We discussed the effect of these potential biases on our summary effect estimate - including hypothesized direction and strength - in the discussion section of manuscript 3.

Qualitative methods. Characteristics of eligible studies were presented in tabular form.

Choosing random versus fixed-effects statistical models to calculate the pooled RR. A meta-analysis is simply a weighted average of different study results. There are two weighting-schemes employed for meta-analyses, each with their own assumptions: random-effects[124] and fixed-effects[123]. It remains controversial which weighting scheme is best. The random-effects model assumes that the observed effect estimates from the studies included in the meta-analysis represent a random sample from a distribution of the true effect of diabetes on VTE risk. In contrast, the fixed-effects model assumes that the differences between study results are solely due to the play of chance. This is a very strong assumption, as there are usually a multitude of differences between studies, including different methodologies and populations. Thus, we chose the random-effects model, which is typically more conservative in that it produces wider confidence intervals[125].

Statistical tests for between-study heterogeneity. We reported statistical tests for between-study heterogeneity alongside the pooled RR.

We calculated an overall homogeneity test p-value from Cochran's Q statistic. Rejecting the null hypothesis signifies that the estimates differ more than expected if chance alone were at play[124], which suggests important between-study differences. However, a limitation of this test is its low power[125]. Knowing this, we used a higher cutoff for statistical significance: 0.1.

We also calculated I^2, a measure of the percentage of heterogeneity that is due to between-study differences, as opposed to sampling variation[126]. Typically, an I^2 value of 25-50% is interpreted as low heterogeneity, 50-75% as moderate heterogeneity, and ≥75% as high heterogeneity. However, these values are relative to the total amount of heterogeneity.

Funnel plot symmetry. A funnel plot[125] was generated to provide a visual assessment of whether treatment effects were associated with study size. A fixed-effects model was used to derive a summary estimate for the funnel plot because a random-effects model gives relatively more weight to smaller studies and thus is more affected if publication bias is present[127]. If bias is not present, the plot should resemble a symmetrical inverted funnel. However, a certain amount of asymmetry is expected by chance, making funnel plot interpretation difficult. We also statistically checked for funnel plot asymmetry using the Begg[128] and Egger tests[129] tests, keeping in mind that the sensitivity of the tests are low in meta-analyses based on less than 20 studies[130].

Sources of asymmetry in funnel plots can be 1) selection bias, including publication bias or biased meta-analysis inclusion criteria; 2) true heterogeneity in effect that systematically varies by study size, perhaps due to differences in population characteristics; 3) data irregularities that systematically vary by study size, including

differences in methodology (e.g., the way measurements were made) and analyses (e.g., statistical adjustment for confounding); and 4) chance[125]. An asymmetric funnel plot cannot distinguish which reason led to its asymmetry. However, unless an assumption is made that asymmetry was produced by chance alone - an untestable assumption - it is inappropriate to interpret an overall effect estimate if there is funnel plot asymmetry.

Meta-regression. We used meta-regression to examine heterogeneity between studies by regressing the log RR on several pre-specified study characteristics: study design (case-control, cohort), level of confounding (adequately controlled, not adequately controlled), and measurement of diabetes (included glucose measurement, no glucose measurement).

We used a random-effects model for the meta-regression[131], and used an algorithm for restricted maximum likelihood estimation of between-study variance[132]. We chose not to use fixed-effects meta-regression because it assumes that all heterogeneity can be explained by the covariates in the model and can lead to a substantially inflated type I error rate when this assumption is violated[132,133]. Random-effects meta-regression does not require this assumption. The Knapp-Hartung[134] variance estimator was used, as it produces a false-positive rate close to the nominal value of .05[133]. Therefore, statistical significance was considered $p < 0.05$ for the meta-regressions.

We calculated the ratio of RR (95% CI) from the meta-regression, which is an estimate of the average RR in studies with one characteristic to the average RR of studies with another characteristic.

Stratified analyses. We calculated a random-effects pooled RR and a corresponding homogeneity p-value within each stratum.

CHAPTER 5: Manuscript 1 - Lifetime risk of venous thromboembolism in two cohort studies

A. Introduction

A recent Surgeon General's report[28] called to "inform health care professionals and administrators about the problem of DVT/PE [deep vein thrombosis/pulmonary embolism] in terms of mortality [and] morbidity" and to "raise consumer awareness about DVT/PE and the magnitude of the burden caused by these conditions." Indeed, there is a case for raising awareness of DVT and PE, collectively termed venous thromboembolism (VTE): A telephone survey of the general population found that only a quarter of respondents had even heard of DVT, and fewer than 1 in 10 had any knowledge of its symptoms or risk factors[41]. Additionally, evidence-based guidelines for VTE prophylaxis are inconsistently implemented in the health care system[28], and experts identified "lack of awareness of DVT risk" among physicians and other health care professionals as a barrier to prophylaxis[41]. Of course, VTE represents a large source of morbidity and mortality, so prevention is important[135]. Promoting awareness of VTE may be an important next step for VTE prevention and treatment.

Lifetime risk estimates of VTE - defined as the cumulative incidence of VTE between an index age and death - could help in promoting awareness of VTE. Lifetime risk of disease is more easily interpretable than some other formats of risk information (e.g., the annual incidence rate)[136,137]. In addition, lifetime risk estimates allow for easy comparison of burden between diseases, and hence can be an important tool to guide decisions at both clinical and policy levels.

To our knowledge, no estimates of the lifetime risk of VTE exist. Therefore, we calculated the lifetime risk of VTE using data from two large, prospective cohort studies: the Cardiovascular Health Study (CHS)[117] and the Atherosclerosis Risk in Communities (ARIC)[118] study, which have similar protocols.

B. Methods

Study population

Between 1987–89, ARIC recruited and examined 15,792 participants aged 45–64 years living in four US communities: Forsyth County, NC; Jackson, MS (African Americans only); suburban Minneapolis, MN; and Washington County, MD[118]. Response rates for the baseline exam were 46% in Jackson and 65 to 67% at other clinic sites; differences between respondents and non-respondents have been described[119].

CHS sampled from Medicare lists, recruited, and examined 5,888 community-dwelling participants aged ≥ 65 years living in four US communities (Pittsburgh (Allegheny County), PA; Forsyth County, NC; Sacramento County, CA; and Washington County, MD) between 1989-90 and 1992–93 (African Americans only)[117]. The response rate for the baseline exam was 61% of those eligible; differences between respondents and non-respondents have been described[117].

We excluded individuals from all analyses if they had a history of VTE or anticoagulant use at baseline (n = 347 in ARIC, 419 in CHS); were of a race other than African American or white (due to small numbers) (n = 48 in ARIC, 38 in CHS); in ARIC, were African American from Washington County or Minneapolis suburbs (due to

small numbers) (n = 55); or had missing data on any variable included in the main analysis (n excluded in ARIC = 1,157: 25 missing body mass index (BMI) measurements, 547 missing factor V Leiden status, 340 missing prothrombin G20210A status, 238 missing blood group measurements, and 7 missing sickle cell trait measurements; n excluded in CHS = 17 missing BMI measurements). Our final sample size for statistical analyses was 14,185 in ARIC and 5,414 in CHS. The Institutional Review Boards of the collaborating institutions approved both studies. We obtained informed consent from all participants before inclusion in the study.

Venous thromboembolism ascertainment

Incident VTE was defined as the first occurrence of a validated DVT or PE from baseline through the end of follow-up: December 31, 2011 for the ARIC Study and December 31, 2001 for CHS.

Hospitalizations were identified through participant report in both studies, through Medicare records in CHS, and though surveillance of community hospitals' discharge lists in ARIC[32]. Possible VTEs were identified using hospital discharge ICD codes and validated by physician review using standardized criteria[32]. VTE events were categorized as provoked or unprovoked. Provoked VTE was defined as occurring within 90 days of major trauma, surgery, marked immobility, or within 1 year of active cancer. Unprovoked were all other confirmed VTE cases.

Baseline measurements

Age, race, sex, and history of VTE were self-reported in both studies. BMI was calculated as weight (kg) divided by height $(m)^2$; obesity was defined as BMI $\geq$ 30. In

ARIC only, factor V Leiden[138], prothrombin G20210A[91], ABO blood group[139], and hemoglobin S genotype[140] were measured as previously described.

Statistical analyses

Analyses were performed using SAS (version 9.2, SAS Institute, Cary, North Carolina). Because age-specific incidence rates (IRs) differed by cohort, all analyses were stratified by cohort. We computed person-years of follow-up from the date of the baseline examination to whichever came first: VTE event, death, loss to follow-up, or the end of follow-up. Person-years of follow-up were allocated to 5-year age-specific groups. Age-specific VTE IRs per 1,000 person-years were calculated by dividing the age-specific number of incident VTE events by age-specific person-years of follow-up, and multiplying this number by 1,000.

Lifetime risk was approximated as the cumulative incidence[120] of VTE through age 85, because many ARIC participants were not older than 85 at the end of follow-up. We used the Practical Incidence Estimators SAS Macro[121] to estimate the remaining lifetime risk of incident VTE conditional on survival (alive and free of VTE) to selected index ages, and then repeated the estimation stratified by subgroups: sex, race, obesity status at baseline, factor V Leiden, prothrombin G20210A, blood group, and sickle cell trait. These variables were chosen because they are risk factors for VTE in the general population. As tends to be the case in prospective cohort studies with a long period of follow-up, not all individuals in ARIC and CHS were followed for the entire duration. To account for this, we used a modified Kaplan-Meier approach to approximate cumulative incidence[121] (i.e., lifetime risk and its confidence interval). We adjusted lifetime risk estimates for the competing risk of death[121,122]. Thus, each participant was classified as

either a VTE event, censored (loss to follow-up or the end of follow-up), or a non-VTE-related death, whichever came first.

Because age-specific VTE IRs varied by cohort, we conducted sensitivity analyses to explore these differences. We restricted ARIC's follow-up to 2001 to match CHS' and calculated IRs. We also investigated the effect of cohort and time period of VTE ascertainment on IRs by plotting cohort- and age-specific IRs by time period.

C. Results

At baseline, the mean age of ARIC participants was 54 years, approximately 50% were female, one-quarter were African American, and one-quarter were obese. In comparison, the CHS cohort at baseline was older (mean age of 73), had a similar sex distribution, a lower proportion of African Americans, and a lower proportion of participants who were obese (**Table 5.1.**).

After the index age of 45 years, ARIC participants developed 728 VTE events over 288,535 person-years of follow-up. After the index age of 65 years, CHS participants developed 172 VTE events over 54,207 person-years of follow-up. As evidenced by sparse person-years, few ARIC participants have been followed past age 85, and few CHS participants survived past age 95. Incidence rates of VTE increased exponentially across increasing age groups. Notably, the age-specific rates in ARIC were higher than for CHS (**Table 5.2.**).

Conditional on survival (alive and free of VTE) to age 45, the remaining lifetime risk of VTE in ARIC was 8.1% (95% confidence interval: 7.1-8.7). There was little

difference in lifetime risk of VTE by sex. Particularly high-risk groups were African Americans, with a lifetime risk (95% confidence interval) of 11.5% (8.8-13.1), participants who were obese at baseline (10.9% (8.7-12.3)), participants with factor V Leiden (17.1% (11.4-21.4)), and participants with sickle cell trait or disease (18.2% (3.8-25.1)) (**Table 5.3.**).

As expected, remaining lifetime risk of VTE decreased across increasing index ages, reflecting the shorter life expectancy and period at risk of older participants. The lifetime risk estimates for CHS were about half those for ARIC (Lifetime risk at index age 65: ARIC – 7.1%, CHS – 3.9%; lifetime risk at index age 75: ARIC – 5.2%, CHS – 2.6%) (**Figure 5.1.**).

At least part of this difference by cohort may relate to ARIC, but not CHS, having follow-up for 2002-2011. When the follow-up for ARIC was restricted to 2001 to match that for CHS, the IRs were more similar (**Table 5.4.**). Additionally, when we compared cohort- and age-specific IRs by time period of VTE ascertainment, the IRs per 1,000 person years were similar by study (≤1995, 65-74 yrs: ARIC = 2.1, CHS = 1.8; 1996-2001, 65-74 yrs: ARIC = 2.9, CHS = 3.2; 1996-2001, 75-84 yrs: ARIC = 3.9, CHS = 3.6), and age-specific IRs of VTE increased across increasing time periods of VTE ascertainment (**Figure 5.2.**).

D. Discussion

1 in 12 middle-aged adults in ARIC developed VTE by age 85. High-risk groups were African Americans (1 in 9), those with obesity (1 in 9), those with factor V Leiden

(1 in 6), and those with sickle cell trait or disease (1 in 5). The lifetime risk of VTE decreased with age, as expected, but still remained relatively high at older ages. IRs and lifetime risk estimates differed between ARIC and CHS; these differences were largely explained by differences in time period of VTE ascertainment, with IRs of VTE being higher in recent years.

The lifetime risk of VTE is substantial, although lower than for other major cardiovascular diseases. At age 40 years, the lifetime risk estimates of coronary heart disease are 1 in 2 for males and 1 in 3 for females[141]; atrial fibrillation, 1 in 4[142]; and congestive heart failure, 1 in 5[143]. At age 55, the lifetime risk estimates of stroke are 1 in 6 for males and 1 in 5 for females[144]. At age 40 years, the lifetime risk of breast cancer is 1 in 8 for females[145].

Differences in IRs and lifetime risk estimates between ARIC and CHS may be explained by changes over time in how VTE was ascertained. Computed tomographic pulmonary angiography (CTPA) - a highly sensitive imaging technique to detect PE - was introduced in 1998; CTPA largely and rapidly replaced other tests for PE[146]. Thought to be in large part a result of the introduction of CTPA, PE incidence in the US increased substantially after 1998[147]. In concordance, our data shows a sharp increase in IRs during the time period that CTPA was adopted (**Figure 5.1.**). Of course, if VTE IRs truly increase over time or the detection of VTE becomes more sensitive, estimates of lifetime risk will correspondingly increase.

Other possible explanations for the observed differences between ARIC and CHS exist. Baseline exclusions and self-selection could have made the CHS cohort healthier in old age than ARIC, for whom exclusions were 20 years earlier and thus included more

unhealthy people by age 65 plus. Also, ARIC had a higher proportion of African Americans (.26 versus .15) and participants with obesity (.27 versus .19) compared to CHS. However, race- and obesity- specific IRs did not explain the discrepancies between cohorts (data not shown).

Our estimates of lifetime risk of VTE are, of course, only generalizable to US populations similar to ARIC. Participants in this study were exclusively African American or white, so results may not generalize to other race groups. Asians and Hispanics in the US have lower incidence rates of VTE than whites, while African Americans have higher rates[39,40]. The lifetime risk estimates represent population averages; an individual's estimated risk of VTE will vary depending on the presence or absence of various factors.

Strengths of this study include a prospective design; two large, population-based biracial samples with a wide geographic distribution in the United States; VTE validation; and a long period of follow-up. Drawbacks of this study warrant discussion as well. Participants were exclusively African American or white, so results may not generalize to other race groups. IRs and lifetime risk estimates were unadjusted for other variables, raising the possibility that differences in these metrics between risk subgroups were due to differences in the distribution of other unidentified variables. The estimated lifetime VTE risk of 8% is a global estimate, integrating both chronic and acute risk factors into a single metric. Although we studied the lifetime risk of some general population risk factors for VTE that operate across the life-course (e.g, obesity, race, and genetic variants), we were less able than clinical studies to assess the lifetime risk after cancer, surgery, immobilization, or other medical conditions. However, lifetime risk

estimates may be less applicable to patients with transient risk factors, such as surgery. Additionally, it is likely that we underestimated the incidence of VTE, and thus lifetime risk, in these cohorts. As in most studies, fatal and undiagnosed VTEs would have been under-ascertained. Further, cases of VTE treated solely in outpatient settings were not captured, although an ARIC pilot study found that outpatient treatment of VTE was still rare through 2005 (data not available through 2011). And finally, approximating lifetime risk estimates as the cumulative incidence of VTE through age 85 assumed that nobody developed VTE after age 85.

In conclusion, 1 in 12 middle-aged adults develop VTE in their lifetime. This estimate of lifetime risk may be useful to promote awareness of VTE and guide decisions at both clinical and policy levels.

Table 5.1. Baseline characteristics of ARIC and CHS participants.

Characteristics (means or prevalences)	ARIC (N = 14,185)	CHS (N = 5,414)
Age, years ± SD	54.1 ± 5.8	72.8 ± 5.6
Male, %	44.7	42.8
African American, %	26.1	15.7
Obese[1], %	27.2	19.3
Factor V Leiden, % AA or AG[2]	4.5	N/A
Prothrombin G20210A, % AA or AG[2]	2.2	N/A
Non-O group blood type, %	57.5	N/A
HbS genotype among African Americans, % AS (sickle cell trait) or SS (sickle cell disease)[3]	6.9	N/A

Baseline ARIC Study: 1987-89.

Baseline CHS: 1989-90 and 1992-93.

ARIC, Atherosclerosis Risk in Communities study; CHS, Cardiovascular Health Study; HbS, hemoglobin S; SD, standard deviation.

[1]Obesity is defined as a body mass index of ≥ 30.

[2]AA: homozygous mutant, AG: heterozygous mutant.

[3]AS: heterozygosity for hemoglobin S, SS: homozygosity for hemoglobin S. HbS genotype was measured in ARIC African Americans only (N = 3,704).

Table 5.2. Age-specific incidence rates of VTE per 1,000 person-years, ARIC and CHS.

	ARIC (N = 14,185)			CHS (N = 5,414)		
Age group	**# of VTE cases**	**Person-years**	**Incidence rates of VTE**	**# of VTE cases**	**Person-years**	**Incidence rates of VTE**
45-49	6	11,517	0.5	-	-	-
50-54	15	30,127	0.5	-	-	-
55-59	45	46,562	1.0	-	-	-
60-64	106	60,075	1.8	-	-	-
65-69	168	60,664	2.8	4	4,819	0.8
70-74	165	43,301	3.8	38	14,145	2.7
75-79	132	24,622	5.4	47	17,353	2.7
80-84	80	10,121	7.9	43	11,320	3.8
85-89	11	1,548	7.1	31	4,986	6.2
90-94	0	1	0.0	8	1,358	5.9
95-99	-	-	-	1	205	4.9
100-104	-	-	-	0	22	0.0

Baseline through end of follow-up in the ARIC Study = 1987-89 through 2011.

Baseline through end of follow-up in CHS = 1989–90 through 2001.

ARIC, Atherosclerosis Risk in Communities study; CHS, Cardiovascular Health Study; HbS, hemoglobin S; venous thromboembolism (VTE).

Table 5.3. Lifetime risk (95% CI) of VTE, ARIC.

	Lifetime risk of VTE (95% CI), %
Total	8.1 (7.1, 8.7)
Sex	
Male	7.7 (6.3, 8.6)
Female	8.4 (7.0, 9.3)
Race	
white	6.9 (5.9, 7.7)
African American	11.5 (8.8, 13.1)
Obesity status at baseline[1]	
Obese	10.9 (8.7, 12.3)
Not obese	7.0 (5.9, 7.7)
Factor V Leiden[2]	
AA or AG	17.1 (11.4, 21.4)
GG	7.6 (6.6, 8.3)
Prothrombin G20210A[2]	
AA or AG	6.3 (1.6, 9.7)
GG	8.1 (7.1, 8.8)
Blood type	
Non-O group blood type	8.9 (7.5, 9.8)
O group blood type	7.0 (5.5, 7.9)
HbS Genotype among African Americans[3]	
AS (sickle cell trait) or SS (sickle cell disease)	18.2 (3.8, 25.1)
No S	11.0 (8.3, 12.5)

Lifetime risk is to age 85, conditional on survival free of VTE to age 45, with death free of VTE considered a competing event.
Baseline through end of follow-up in the ARIC Study = 1987-89 through 2011.
[1]Obesity is defined as a body mass index ≥ 30.
[2]AA: homozygous mutant, AG: heterozygous mutant, GG: wild type.
[3]HbS genotype was measured in ARIC African Americans only (N = 3,704). AS: heterozygosity for hemoglobin S, SS: homozygosity for hemoglobin S, No S: wild type.
ARIC, Atherosclerosis Risk in Communities study; CI, confidence interval; HbS, hemoglobin S; VTE, venous thromboembolism.

Table 5.4. ARIC follow-up restricted to 2001: Incidence rates of VTE per 1,000 person-years, ARIC and CHS.

	ARIC (N = 14,185)			CHS (N = 5,414)		
Age group	# of VTE cases	Person-years	Incidence rates of VTE	# of VTE cases	Person-years	Incidence rates of VTE
45-49	6	11,517	0.5	-	-	-
50-54	15	30,127	0.5	-	-	-
55-59	43	45,229	1.0	-	-	-
60-64	62	45,670	1.4	-	-	-
65-69	71	32,751	2.2	4	4,819	0.8
70-74	49	15,755	3.1	38	14,145	2.7
75-79	7	2,920	2.4	47	17,353	2.7
80-84	0	2	0.0	43	11,320	3.8
85-89	-	-	-	31	4,986	6.2
90-94	-	-	-	8	1,358	5.9
95-99	-	-	-	1	205	4.9
100-104	-	-	-	0	22	0.0

Baseline (1987-89) through **2001** in the ARIC Study.

Baseline (1989–90) through end of follow-up (2001) in CHS.

ARIC, Atherosclerosis Risk in Communities study; CHS, Cardiovascular Health Study; VTE, venous thromboembolism.

Figure 5.1. Cumulative risk of VTE at selected index ages (A) by cohort and, in ARIC, for race- and sex-specific groups (B-E), with death considered a competing event. Lifetime risk for a given index age is cumulative risk through 85 years of age. ARIC, Atherosclerosis Risk in Communities study; CHS, Cardiovascular Health Study; VTE, venous thromboembolism.

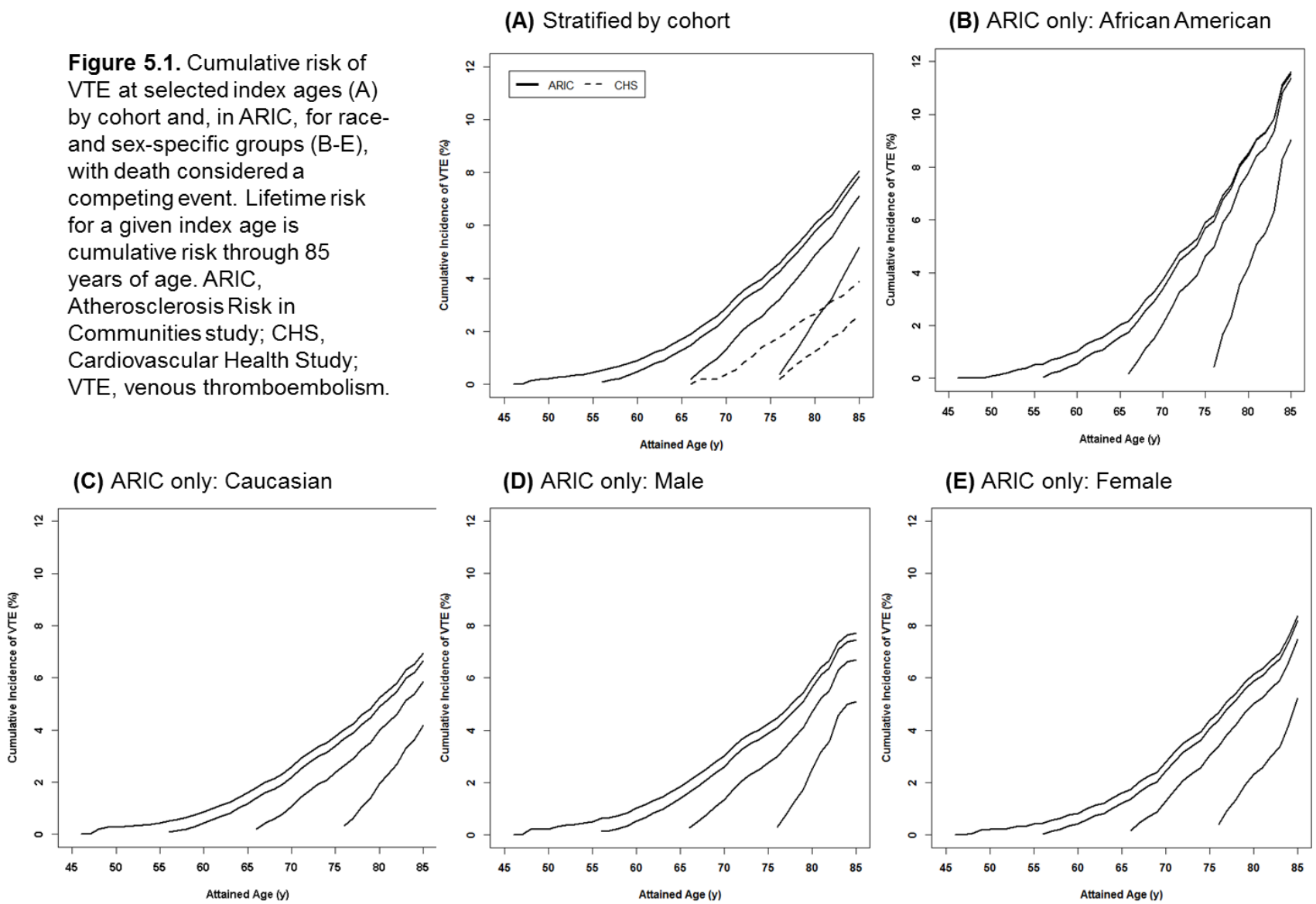
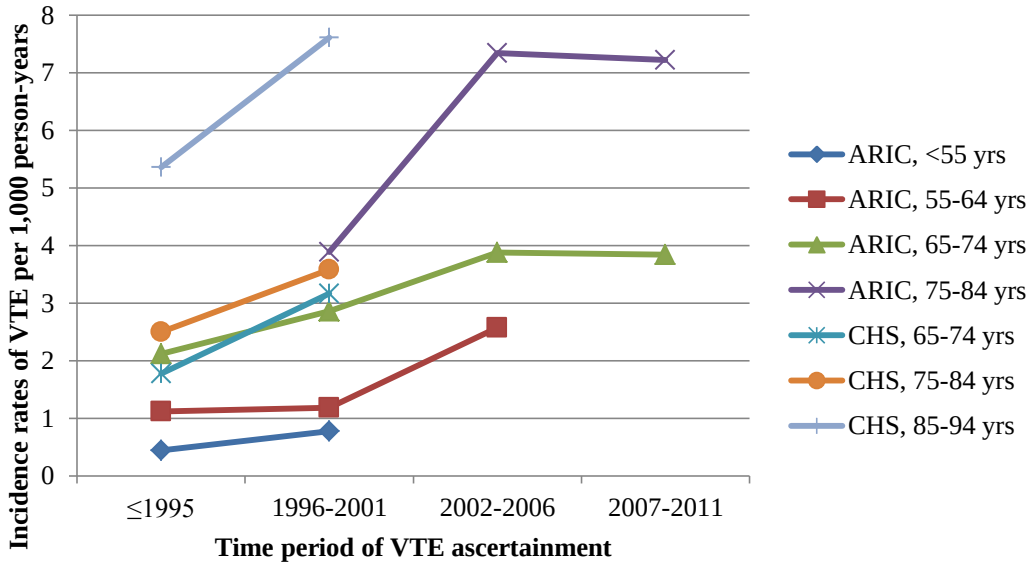


Figure 5.2. Cohort- and age- specific VTE incidence rates by time period of VTE ascertainment.



CHAPTER 6: Manuscript 2 - Orthostatic hypotension and risk of venous thromboembolism in two cohort studies

A. Introduction

Orthostatic hypotension (OH) is a common condition in older adults. A current consensus statement has defined OH as a reduction in systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of at least 10 mmHg within 3 minutes of standing[148]. OH is not part of a singular disease process, but rather a sign that can result from a variety of pathologies. If cerebral blood flow is affected, OH can cause dizziness, blurred vision, chronic fatigue, fainting, or pain in the neck and shoulders[149].

When standing upright, about 500 to 1000 mL of blood is redistributed due to gravity. This causes venous pooling in the lower extremities, which reduces venous return[149,150]. The normal physiological response is to activate compensatory mechanisms that maintain arterial pressure in the upper body for adequate perfusion, which causes a reduction in venous pooling and an increase in venous return[149,150]. Conversely, in an individual with OH, at least one of the compensatory mechanisms is impaired. Blood pressure drops upon standing and venous pooling in the legs is sustained for a longer duration[149,150]. Blood pooling can increase venous thromboembolism (VTE) risk[151]. Therefore, a reasonable hypothesis is that OH may increase VTE risk through an increased duration of venous pooling.

Although it is known that VTE risk is related to physical characteristics of the leg that affect venous return - such as varicose veins[47] and leg length[152] - to our knowledge no study has examined the relation between OH and VTE risk. We were able to examine

the relation using data from two large, prospective cohort studies: the Cardiovascular Health Study (CHS) and the Atherosclerosis Risk in Communities (ARIC) study.

Therefore, our aim was to quantify the association between OH and VTE (leg deep vein thrombosis or pulmonary embolism). We hypothesized that OH is positively associated with incident VTE.

B. Methods

Study population

Between 1987–89, ARIC recruited and examined 15,792 participants aged 45–64 years living in four US communities: Forsyth County, NC; Jackson, MS (African Americans only); suburban Minneapolis, MN; and Washington County, MD[118]. Response rates for the baseline exam were 46% in Jackson and 65 to 67% at other clinic sites; differences between respondents and non-respondents have been described[119].

CHS sampled from Medicare lists, recruited, and examined 5,888 community-dwelling participants aged ≥ 65 years living in four US communities (Pittsburgh (Allegheny County), PA; Forsyth County, NC; Sacramento County, CA; and Washington County, MD) between 1989-90 and 1992–93 (African Americans only)[117]. The response rate for the baseline exam was 61% of those eligible; differences between respondents and non-respondents have been described[117].

Individuals were excluded from all analyses if they had a history of VTE or anticoagulant use at baseline (n = 347 in ARIC, 419 in CHS); in ARIC, were African American from Washington County or Minneapolis suburbs (due to small numbers) (n =

55); had missing data on any variable included in the analysis (n excluded in ARIC = 2,910: 2,469 missing OH measurements, 6 missing body mass index (BMI) measurements, 5 missing self-perceived health status, 7 missing leg length, 105 missing diabetes status, 238 missing history of coronary heart disease status, 27 missing history of stroke status, and 53 missing hypertension status; n excluded in CHS = 442: 247 missing OH measurements, 14 missing BMI measurements, 11 missing self-perceived health status, 93 missing leg length, 47 missing diabetes status, 21 missing history of stroke status, 2 missing hypertension status, 6 missing seated DBP measurements, and 1 missing seated SBP measurement); or were of a race other than African American or white (due to small numbers) (n = 0 in both ARIC and CHS due to previous exclusions). The final sample size for statistical analyses was 12,480 in ARIC and 5,027 in CHS. Both studies were approved by the Institutional Review Boards of the collaborating institutions and informed consent was obtained from all participants before inclusion in the study.

Notably, 2,469 participants in ARIC were missing a measurement of OH at baseline, most of whom attended the baseline exam in the first six months of the ARIC study, before the postural blood pressure measurement protocol was implemented. We excluded these participants from this study, and considered whether selection bias would be present as a result. However, participants were randomly assigned examination dates, and those with a measurement of OH were not significantly different than those without a measurement in terms of seated SBP, anthropometric variables, or age, race, and sex distributions[153]. Therefore, it is reasonable to believe that participants in this study represent a sub-sample of the entire ARIC cohort.

VTE ascertainment

Incident VTE was defined as the first occurrence of a validated deep vein thrombosis in the leg or pulmonary embolism from baseline through the end of follow-up: December 31, 2011 for the ARIC Study and December 31, 2001 for CHS.

Hospitalizations were identified through participant report in both studies, through Medicare records in CHS, and though surveillance of community hospitals' discharge lists in ARIC[32]. Possible VTEs were identified using hospital discharge ICD codes and validated by physician review using standardized criteria[32]. VTE events were categorized as provoked or unprovoked. Provoked VTE was defined as occurring within 90 days of major trauma, surgery, marked immobility, or within 1 year of active cancer. Unprovoked were all other confirmed VTE cases.

Measuring and modeling OH.

In both CHS and ARIC, OH was defined as an SBP reduction upon standing of at least 20 mmHg, a DBP reduction of at least 10 mmHg, or both[148]. In addition, participants in CHS who needed to abort the OH measurement procedure due to dizziness, lightheadedness, or faintness during standing were classified as having OH.

At ARIC's baseline visit, after 20 minutes of resting in the supine position, blood pressure was measured supine approximately every 30 seconds for 2 minutes (2-5 measurements, 90% of participants had ≥4 measurements) using a Dinamap 1846 SX automated oscillometric device. Participants then stood, held hands on the chest, and blood pressure was measured repeatedly for the first 2 minutes after standing (2–5 measurements, 91% of participants had ≥4 measurements)[154]. Blood pressure change in

ARIC was defined as the first supine blood pressure measurement minus the last standing blood pressure measurement (approximately two minutes after standing).

At CHS' baseline visit, after at least 20 minutes of resting in the supine position, blood pressure was measured supine using a mercury sphygmomanometer (Baumanometer, W.A. Baum Co., Copiague, N.Y.) according to a standardized protocol following recommendations[155]. Participants then stood for 3 minutes (unless feelings of dizziness, lightheadedness, or faintness occurred during standing, at which point the OH measurement procedure was immediately aborted), after which they rested a hand on a stand positioned at heart level, and blood pressure was measured. Blood pressure change in CHS was defined as the supine blood pressure measurement minus the 3 minute standing blood pressure measurement.

Baseline measurements.

Variables measured similarly in CHS and ARIC: Age, race, sex, history of VTE, and perception of general health were self-reported. BMI was calculated as weight (kg) divided by height $(m)^2$. Torso length was estimated as the difference between seated height and stool height; leg length was estimated as the difference between standing height and torso length. Medication use was identified from prescription bottles[156]. 'Use of medications that might induce OH' was defined as use of antihypertensives, anti-psychotics, antidepressants, anti-cholinergics, narcotics, nitro compounds, or sedatives[157]. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL (7 mmol/L), nonfasting blood glucose ≥ 200 mg/dL (11.1 mmol/L), a self-report of physician diagnosis, and/or current medication use for diabetes. Seated blood pressure was measured using a random-zero sphygmomanometer; the last two of three blood pressure measurements were

averaged. Hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or taking antihypertensive medications.

Variables measured differently in CHS and ARIC: In ARIC, prevalent coronary heart disease was defined as 1) ECG evidence of a previous myocardial infarction, or 2) a self-reported history of coronary revascularization or myocardial infarction; prevalent heart failure was defined as signs and symptoms of heart failure by the Gothenburg questionnaire[158]. In CHS, prevalent coronary heart disease, prevalent heart failure, and prevalent stroke were based on self-report, which was validated with information from the baseline examination, medical records, or from physician questionnaires[159].

Statistical analyses.

Analyses were performed using SAS (version 9.2, SAS Institute, Cary, North Carolina). A p-value of <0.05 on a two-tailed test was considered statistically significant. We statistically evaluated difference in the OH relation with VTE by study: In a dataset that contained both studies, we ran a VTE model that included the OH variable, a cohort variable (CHS, ARIC), and a multiplicative interaction term (OH*study). Because the interaction term indicated statistically significant differences in the OH-VTE relation by cohort (p-value = 0.02), all analyses were stratified by cohort and reasons for potential differences were explored. Baseline participant characteristics were presented by OH status. We computed person-years of follow-up as time elapsed from the baseline examination to whichever came first: VTE event, death, loss to follow-up, or the end of follow-up (December 31, 2001 in CHS and December 31, 2011 in ARIC). VTE incidence rates were calculated by dividing the number of VTE events by person-years of follow-

up, and 95% confidence intervals (CIs) were obtained using Rothman's Episheet (krothman.hostbyet2.com/Episheet.xls).

Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% CIs for incident VTE (total, provoked and unprovoked) in relation to OH status (yes/no), using those without OH as the referent. We verified the proportional hazards assumption through inspection of ln(–ln) survival curves by OH status. Model 1 was adjusted for age (continuous), race (African American, white), and sex (male, female). Model 2, our main model, was adjusted for variables in Model 1 plus BMI (continuous), self-perceived health status (excellent, very good, good, fair, poor), and leg length (continuous). Further inclusion of variables known to be risk factors for VTE and/or associated with OH - seated DBP, seated SBP, smoking status, estimated glomerular filtration rate, factor VIII, sex/hormone therapy use, history of heart failure, diabetes status, use of medications that can induce OH, and history of cancer - did not appreciably change point estimates, and thus were not included in our final model. Analyses were also stratified by variables of interest.

We conducted sensitivity analyses in which we 1) restricted follow-up time to ten years, 2) excluded participants with VTE events within 90 days of marked immobility or active cancer, 3) in CHS, further adjusted Model 2 HRs for frailty (measured in CHS cohort only), and 4) excluded VTE events from the first five years after baseline.

C. Results

At baseline, the mean age of ARIC participants was 54 years, approximately 50% were female, one-quarter were African American, and the prevalence of OH was 7.5%. In comparison, the CHS cohort at baseline was older (mean age = 73), had a lower proportion of African Americans, a similar sex distribution, and a higher prevalence of OH (18.2%). Several baseline characteristics - age, diabetes mellitus, history of heart failure, history of coronary heart disease, history of stroke, self-perceived health status, hypertension, use of medications that may induce OH, and seated SBP - were positively associated with OH. Sex, race, BMI, leg length and seated DBP did not substantially differ by OH status (**Table 6.1.**). Among those with OH, the mean drop in SBP upon standing was 23.7 and 20.3 mmHg (ARIC and CHS, respectively). In contrast, the mean drop in DBP upon standing among those with OH was only 4.7 and 7.5 mmHg (ARIC and CHS, respectively), indicating that more participants fit the criteria for OH due to a 20 mmHg or more SBP reduction upon standing rather than a DBP reduction of 10 mmHg or more.

VTE events for this analysis included venous thrombosis in the leg and/or pulmonary embolism. Over a median follow-up time of 17.8 years (245,620 person-years), 568 ARIC participants had VTE events (41 had OH at baseline, 527 did not have OH); over a median follow-up time of 11.6 years (47,655 person-years), 148 CHS participants had VTE events (39 had OH at baseline, 109 did not have OH). In ARIC, the crude incidence rate (95% CI) of VTE per 1,000 person-years was 2.54 (1.85-3.41) in those with OH and 2.30 (2.11-2.50) in those without OH; in CHS, the crude incidence rate (95% CI) of VTE per 1,000 person-years was 4.76 (3.44-6.44) in those with OH and 2.76 (2.28-3.32) in those without OH (**Table 6.2.**).

The association of OH with VTE differed between ARIC and CHS (p-value for interaction by study = 0.02). In ARIC, HRs for incident VTE (total, provoked, and unprovoked) among participants with OH at baseline compared to those without were approximately 1.0 in both regression models and by VTE type, indicating no association (**Table 6.2.**). In CHS, there was a positive association between incident VTE and OH status in both models (Model 2 HR for total VTE = 1.74 (95% CI: 1.20-2.51)), greater for provoked than unprovoked VTE.

We stratified analyses by subgroups of interest - many of which are causes of OH - and calculated HRs and 95% CIs (**Table 6.3.**). Most stratum-specific HRs for total VTE were not statistically different from each other, although power to detect a difference was low. However, the OH-VTE relation was marginally statistically different by 1) history of stroke status in ARIC (HR = 2.87 (95% CI: 0.83-9.92) in those with a history of stroke and 0.90 (95% CI: 0.64-1.26) in those without a history of stroke, p-value for interaction by stratum = 0.05), and 2) self-reported health status in ARIC (HR = 0.73 (95% CI: 0.47-1.14) in those with a self-reported health status of excellent, very good or good and 1.56 (95% CI: 0.97-2.53) in those with a self-reported health status of fair or poor, p-value for interaction by stratum = 0.04). In CHS, the OH-VTE HRs were qualitatively different by history of stroke (HR = 34.26 (95% CI: 2.06-570.7) in those with a history of stroke and 1.60 (95% CI: 1.09-2.35) in those without a history of stroke, p-value for interaction by stratum = 0.10).

Sensitivity analyses

Results did not appreciably change if we restricted follow-up time to 10 years so that VTEs – particularly in ARIC – were closer to the baseline OH measurement (HR =

1.02 (95% CI: 0.56-1.85) in ARIC and 1.55 (95% CI: 1.04-2.32) in CHS). Results also remained similar after excluding participants with VTE events within 90 days of marked immobility (HR = 1.50 (95% CI: 0.86 -2.62) in ARIC and 2.02 (95% CI: 0.88-4.66) in CHS) or active cancer (HR = 1.16 (95% CI: 0.67-2.01) in ARIC and 2.27 (95% CI: 1.07-4.82) in CHS) in an attempt to remove these potential confounding variables. When we adjusted for Model 2 covariates plus frailty (measured in the CHS cohort only), the HR was mildly attenuated compared to Model 2 alone, but still statistically significant (HR = 1.64 (95% CI: 1.10-2.45). Results also did not appreciably change when we excluded VTE events from the first five years after baseline (HR = 0.95 (95% CI: 0.68-1.34) in ARIC and 1.98 (95% CI: 1.23-3.19) in CHS).

D. Discussion

In the population-based CHS cohort of older adults, those with OH at baseline had approximately a 70% higher risk of incident total VTE than those without OH at baseline, nominally greater for provoked than unprovoked VTE. In contrast, there was no association between OH and VTE in the ARIC study of initially middle-aged adults. Results did not appreciably change in several sensitivity analyses. In ARIC, the OH-VTE relation was marginally statistically different by history of stroke status (higher in those with a history of stroke) and self-reported health status (higher in those with worse self-reported health status). In CHS, OH-VTE estimates were qualitatively different by history of stroke stratum (also higher in those with a history of stroke). However, a large number of statistical tests were performed and, thus, subgroup analyses should be interpreted as hypothesis-generating and need to be replicated elsewhere.

We are unsure why the relation of OH with VTE differed between ARIC and CHS. This difference was not explained by longer follow-up time in ARIC, as results were similar when we restricted follow-up time to 10 years. To verify the OH-VTE relation in CHS was independent of confounding variables, we not only adjusted for several VTE risk factors, but we also conducted analyses that excluded participants with VTE events within 90 days of marked immobility or within 1 year of active cancer. Since the association remained, it is likely that these variables did not confound our results. Further, when we excluded VTE events from the first five years after baseline, the association remained similar, making it unlikely that an undetected condition at baseline (e.g., cancer) could explain the association. It is possible, but untestable, that discrepancies in arm position contributed to the different results between ARIC and CHS: CHS used a Mayo stand for arm support at heart level and ARIC had hands placed on the chest. In a previous study, OH was detected in 18.2% of participants when an arm stand at heart level was used, but in only 6% of the same participants when the arm was placed at the participant's side[160]. Having one's arms in the incorrect position (not at heart level) overestimates standing blood pressure presumably due to a hydrostatic effect[161], and therefore underestimates the prevalence of OH[160]. It is also possible, but untestable, that discrepancies in timing of standing blood pressure measurements contributed to the different results between ARIC and CHS. Indeed, if longer duration of venous pooling is a risk factor for VTE - as it is shown to be for long-distance travel[162] - then a drop in blood pressure that remains 3 minutes after standing, as in CHS, would be expected to have a stronger relation with VTE than a drop in blood pressure only 2 minutes or less after standing, as in ARIC. Future research could examine the relation between "delayed

OH" - a variant of OH that occurs beyond three minutes of standing[148] - and VTE. Delayed OH is at least as prevalent as the "classical" OH that we measured in this study[163] and some believe[164] that the optimal time duration of orthostatic challenge for the diagnosis of OH is longer than the 3 minutes called for in the consensus definition.

If our findings are real, they could be explained through the increased duration of venous pooling associated with OH. The venous system of the legs is a large capacitance system, and upon standing from supine position, blood pools. This results in a decrease in venous return to the heart or a decrease in cardiac output. To maintain cardiac output, the normal physiological response is to activate compensatory mechanisms: an interplay between neurohumoral effects, the skeletal muscle pump, neurovascular compensation, and cerebral blood flow regulation[149,150]. These compensatory mechanisms cause a reduction in venous pooling and increase in venous return[149,150]. Conversely, in an individual with OH, at least one of the compensatory mechanisms is impaired and there is an increased duration of venous pooling[149,150]. Blood pooling (i.e. venous stasis) is an element of Virchow's Triad – which includes factors that are thought to contribute to thrombosis – and can increase VTE risk[151].

Methodological aspects of OH measurement deserve further consideration. The diagnosis of OH is only moderately reproducible[165–167]. Transient factors that can influence OH include immobility, hydration, time of day, and food intake[148]. Participants of both ARIC and CHS were from the community and ambulatory at baseline, so it seems reasonable that neither immobility nor dehydration had a major effect on OH measurements. Non-standardization of these factors may have led to some misclassification of OH, but it seems unlikely that these factors varied based on VTE

status. Therefore, misclassification of OH would have most likely biased hazard ratios towards the null.

Strengths of this study include the prospective design; a large, biracial sample with a wide geographic distribution in the United States; characterization of important potential confounders at baseline; and VTE validation. In addition to issues of OH measurement, described above, other weaknesses of our study warrant discussion. Participants were exclusively African American or white, so results may not generalize to other race groups. We had only a single measurement of OH, and follow-up was long. Participants who developed OH during follow-up were not detected; this misclassification would typically attenuate hazard ratios toward the null. As in most studies, undiagnosed VTEs would have been under-ascertained. Further, cases of VTE treated solely in outpatient settings were not captured, although an ARIC pilot study found that outpatient treatment of VTE was still rare through 2005 (data not available through 2011). And finally, despite adjustment for numerous risk factors, it is possible that residual confounding influenced our findings.

In conclusion, community-dwelling older adults with OH have a moderately increased risk of VTE. These results were not replicated in a population-based middle-aged cohort. Although the burden of VTE is high, its incidence is still too low to merit VTE prophylaxis in elderly patients with OH, especially since the causality of the OH-VTE association is uncertain. Future studies should try to replicate findings using standard methods of measurement of OH[164], and could examine the relation between delayed OH and VTE.

Table 6.1. Baseline characteristics of ARIC and CHS participants according to baseline orthostatic hypotension status.

	ARIC		CHS	
Characteristics (means or prevalences)	**Orthostatic Hypotension (N = 934)**	**No Orthostatic Hypotension (N = 11,546)**	**Orthostatic Hypotension (N = 915)**	**No Orthostatic Hypotension (N = 4,112)**
Age, years ± SD	56.3 ± 5.7	53.9 ± 5.7	73.5 ± 5.7	72.6 ± 5.5
Male, %	47.0	45.2	43.5	43.0
African American, %	29.9	26.1	15.2	16.6
Diabetes mellitus, %	20.7	11.3	18.6	15.9
History of heart failure, %	12.4	9.7	11.5	10.4
History of coronary heart disease, %	7.4	4.5	17.8	13.5
History of stroke, %	4.2	1.5	5.8	4.1
Body mass index, kg/m^2 ± SD	27.9 ± 5.9	27.6 ± 5.2	26.1 ± 4.5	26.8 ± 4.7
Self-perceived health status - fair/poor, %	30.5	17.9	28.3	23.0
Leg length, cm ± SD	80.2 ± 5.6	80.0 ± 5.8	79.2 ± 6.1	79.6 ± 5.7
Hypertension, %	52.4	32.8	67.9	64.4
Use of medications that might induce orthostatic hypotension, %	48.2	33.1	66.8	61.9
Seated systolic blood pressure, mmHg ± SD	128.1 ± 21.5	120.7 ± 18.7	137.8 ± 23.6	136.1 ± 21.3
Mean change in systolic blood pressure upon standing, mmHg ± SD	-23.7 ± 11.7	2.5 ± 10.6	-20.3 ± 14.3	-1.1 ± 9.9
Seated diastolic blood pressure, mmHg ± SD	75.1 ± 12.2	73.4 ± 11.1	69.1 ± 11.9	71.1 ± 11.1
Mean change in diastolic blood pressure upon standing, mmHg ± SD	-4.7 ± 8.2	4.9 ± 6.1	-7.5 ± 10.4	3.4 ± 7.5

Baseline ARIC Study: 1987-89

Baseline CHS: 1989-90 and 1992-93

ARIC, Atherosclerosis Risk in Communities; CHS, Cardiovascular Health Study; SD, standard deviation

Table 6.2. HRs (95% CIs) for incident VTE among participants with OH at baseline compared to those without.

	ARIC		CHS	
	Orthostatic Hypotension (N = 934)	**No Orthostatic Hypotension (N = 11,546)**	**Orthostatic Hypotension (N = 915)**	**No Orthostatic Hypotension (N = 4,112)**
Total VTE				
Crude IR (95% CI)[a]	2.54 (1.85, 3.41)	2.30 (2.11, 2.50)	4.76 (3.44, 6.44)	2.76 (2.28, 3.32)
N total VTE events	41	527	39	109
Model 1 HR (95% CI)[b]	1.05 (0.76, 1.45)	1 (referent)	1.70 (1.18, 2.45)	1 (referent)
Model 2 HR (95% CI)[c]	0.97 (0.70, 1.33)	1 (referent)	1.74 (1.20, 2.51)	1 (referent)
Unprovoked VTE				
N unprovoked VTE events	11	204	11	45
Model 2 HR (95% CI)[c]	0.67 (0.36, 1.23)	1 (referent)	1.14 (0.59, 2.21)	1 (referent)
Provoked VTE				
N provoked VTE events	30	323	28	64
Model 2 HR (95% CI)[c]	1.16 (0.80, 1.69)	1 (referent)	2.19 (1.40, 3.44)	1 (referent)

[a] Rate/1000 years.

[b] Model 1 is adjusted for age, sex, and race.

[c] Model 2 is adjusted for model 1 covariates, body mass index, self-perceived health status, and leg length.

ARIC, Atherosclerosis Risk in Communities Study; CHS, Cardiovascular Health Study; CI, Confidence interval; HR, Hazard ratio; IR, incidence rate; OH, Orthostatic hypotension; VTE, venous thromboembolism.

Table 6.3. Stratified by baseline characteristics, adjusted[a] HRs (95% CIs) for incident total VTE among participants with orthostatic hypotension at baseline compared to those without.

	ARIC			CHS		
Strata	**# of VTE events/Total # in stratum**	**HR (95% CI)**	**P-value for interaction by stratum[b]**	**# of VTE events/Total # in stratum**	**HR (95% CI)**	**P-value for interaction by stratum[b]**
Overall	568/12,480	0.97 (0.70, 1.33)	N/A	148/5,027	1.74 (1.20, 2.51)	N/A
Age <55 years	243/6,629	0.65 (0.33, 1.26)	0.18	0	N/A	N/A
Age ≥55 years	325/5,851	1.14 (0.79, 1.65)		100	N/A	
Age <70 years	100	N/A	N/A	45/1,725	2.07 (1.06, 4.05)	0.38
Age ≥70 years	0	N/A		103/3,302	1.61 (1.03, 2.50)	
Female	317/6,825	1.08 (0.72, 1.62)	0.43	80/2,862	2.09 (1.28, 3.39)	0.29
Male	251/5,655	0.85 (0.51, 1.45)		68/2,165	1.40 (0.78, 2.49)	
African American	192/3,296	1.25 (0.75, 2.10)	0.41	35/822	1.09 (0.44, 2.71)	0.23
white	376/9,184	0.87 (0.58, 1.31)		113/4,205	1.99 (1.32, 2.99)	
Diabetes	76/1,493	0.85 (0.39, 1.86)	0.62	29/825	1.81 (0.81, 4.07)	0.78
No Diabetes	492/10,987	0.99 (0.70, 1.4)		119/4,202	1.69 (1.11, 2.57)	
History of heart failure	75/1,231	0.85 (0.37, 1.97)	0.73	15/531	1.25 (0.34, 4.63)	0.45
No history heart failure	493/11,249	0.98 (0.69, 1.38)		133/4,496	1.81 (1.23, 2.67)	
History of coronary heart disease	20/584	N/A	0.95	12/717	1.95 (0.50, 7.56)	0.55
No history of coronary heart disease	548/11,896	1.03 (0.75, 1.42)		136/4,310	1.83 (1.24, 2.68)	
History of stroke	13/207	2.87 (0.83, 9.92)	0.05	6/221	34.26 (2.06, 570.7)	0.10
No history stroke	555/12,273	0.90 (0.64, 1.26)		142/4,806	1.60 (1.09, 2.35)	
Body mass index <25 kg/m^2 at baseline	127/4,206	1.05 (0.55, 2.01)	0.63	40/1,946	1.55 (0.77, 3.15)	0.79
Body mass index ≥25 kg/m^2 at baseline	441/8,274	0.96 (0.67, 1.39)		108/3,081	1.79 (1.16, 2.77)	
Self-reported health status - excellent/very good/good	428/10,131	0.73 (0.47, 1.14)	0.04	105/3,821	1.84 (1.18, 2.86)	0.75
Self-reported health status - fair/poor	140/2,349	1.56 (0.97, 2.53)		43/1,206	1.56 (0.80, 3.05)	
Use of medications that might induce OH	223/4,269	1.09 (0.71, 1.69)	0.54	86/3,156	1.90 (1.19, 3.04)	0.52
No use of medications that might induce OH	345/8,211	0.86 (0.53, 1.38)		62/1,871	1.50 (0.82, 2.74)	
Hypertension	242/4,271	1.16 (0.78, 1.72)	0.21	91/3,270	1.57 (0.98, 2.54)	0.53
No hypertension	326/8,209	0.71 (0.41, 1.24)		57/1,757	2.02 (1.12, 3.63)	
Leg length ≥ 80 cm	319/6,433	0.82 (0.52, 1.29)	0.27	75/2,428	1.96 (1.16, 3.30)	0.61
Leg length < 80 cm	249/6,047	1.19 (0.76, 1.86)		73/2,599	1.52 (0.90, 2.58)	

[a]HRs adjusted for age, sex, race, body mass index, self-perceived health status, and leg length.

[b]Multiplicative interactions of orthostatic hypotension with strata were evaluated by including cross-product terms in the models (dataset contained both strata).
Study- and stratum-specific HRs were computed from separate statistical models ran by study and stratum.
ARIC, Atherosclerosis Risk in Communities Study; CHS, Cardiovascular Health Study; CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism.

CHAPTER 7: Manuscript 3 - Diabetes mellitus and venous thromboembolism: A systematic review and meta-analysis

A. Introduction

Diabetes has been proposed as a risk factor for venous thromboembolism (VTE). However, reported associations of diabetes with VTE are inconsistent, and many measures of association were not adjusted for body fat, a known confounder of the association of type 2 diabetes mellitus and VTE. Two previous systematic reviews exist: Both estimated a 1.4-fold increased risk of VTE for persons with diabetes compared to persons without[168,169]. However, neither adequately accounted for potential confounders of the diabetes-VTE association, making it impossible to know whether the observed increased risk in VTE is due to diabetes, other VTE risk factors associated with diabetes, or both. Further, some research studies, both published[170–174] and unpublished, were not included in either review. Thus, an updated systematic review and meta-analysis was warranted to utilize current research, account for important potential confounders of the diabetes-VTE relation, and try to explain inconsistencies in research findings. Therefore, our aim was to perform a systematic review and meta-analysis to quantify the association between diabetes mellitus (type 1 or 2) and VTE (deep vein thrombosis (DVT) or pulmonary embolism (PE)). We hypothesized that diabetes is positively associated with VTE before and after adjustment for potential confounding variables.

B. Methods

We followed the Meta-analysis of Observational Studies in Epidemiology Guidelines[175] throughout this review.

Selection criteria

Studies were included in this review if they 1) were case-control or cohort design and 2) reported an effect estimate between diabetes mellitus (any definition - including self-report, glucose measurement, or medical records) and VTE (defined as DVT and/or PE) in humans or provided enough information to calculate an effect estimate and its standard error. Studies were excluded if 1) they had no original data; 2) DVTs were solely outside of the leg (PE not excluded), because risk factors can differ depending on where the DVT occurs; 3) VTEs were solely recurrent, because risk factors can be different for a recurrent versus first-time VTE; or 4) the entire study population was affected by a specific medical condition (e.g. cancer) or procedure, because we were interested in studies that were broadly representative of general populations.

Search strategy

Investigator E.J.B. consulted with a biomedical librarian to develop the search strategy. E.J.B. searched the PubMed, Web of Science, and CINAHL databases. The database search included both keywords and headings, explosion searching, and truncated words related to diabetes mellitus, venous thromboembolism, pulmonary embolism, and deep vein thrombosis (see **Appendix 1** for full text of search string). The search cutoff date was July 31, 2014. No language restrictions were applied. We queried experts to identify additional studies, including unpublished material. We manually reviewed reference lists of review articles and eligible articles to identify additional eligible studies.

Data abstraction

We abstracted estimates of association (odds ratios, relative risks, or hazard ratios) between diabetes and VTE, and their standard errors. When a standard error was not reported, it was derived from data provided in the article. Since VTE is relatively rare, we were able to ignore the distinctions between various types of effect estimates[123]. Thus, we represented and interpreted all effect estimates as relative risks (RRs) for this review.

We sought effect estimates that adequately controlled for potential confounders. We considered an effect estimate as adequately controlled for potential confounders if the study 1) statistically adjusted for race (or only involved primarily one race group, defined as a study population with ≥80% of a single race), age, and a measure of body size; or 2) demonstrated that a lack of statistical adjustment had little effect on findings. Race, age, and a measure of body size were required as the minimal adjustment set because we considered them the most likely confounders of the association of diabetes with VTE, since they are established risk factors for VTE and associated with diabetes[176,70,177–179,35,180,181]. We queried the corresponding authors of papers without adequately controlled results in an attempt to obtain results that did account for a measure of body size, age, and race. In the situation of multiple articles from the same study, the article that had the best adjustments for potential confounding was used.

Statistical analyses

We tabulated the eligible studies and described their characteristics. We investigated the degree of heterogeneity in effect estimates between studies by generating three forest plots: One included all unique study samples, and the other two stratified by

VTE type [provoked (defined as VTE occurring in a patient with an antecedent transient acquired risk factor for VTE) and unprovoked VTE]. Because of substantial qualitative and quantitative heterogeneity across studies, a random-effects[124] model was used to pool the effect estimates. We reported statistical tests for between-study heterogeneity: 1) An overall homogeneity test p-value from Cochran's Q statistic[124] and 2) I^2, a measure of the percentage of heterogeneity that was due to between-study differences, as opposed to sampling variation[126]. We considered statistical significance of Cochran's Q statistic as a p-value of <0.1 due to the test's low power[125]. We interpreted an I^2 value of 25-50% as low heterogeneity, 50-75% as moderate heterogeneity, and ≥75% as high heterogeneity.

To assess potential publication bias, we generated a funnel plot[125] to provide a visual assessment of whether treatment effects were associated with study size (manifested as funnel plot asymmetry). We used a fixed-effects model to produce the funnel plot since results are less affected than random-effects when publication bias is present[125]. We also statistically checked for funnel plot asymmetry using the Begg[128] and Egger tests[129].

We ran meta-regressions to examine heterogeneity between studies by regressing the log RR on several pre-specified study characteristics: study design (case-control; cohort), level of confounding (adequately controlled for age, body mass index (BMI), and race; not adequately controlled), and measurement of diabetes (included glucose measurement; no glucose measurement). Because a fixed-effects meta-regression requires the strong assumption that all heterogeneity can be explained by the covariates in the model[133,132], we used a random-effects model[131]. The Knapp-Hartung[134] variance estimator was used, as it produces a false-positive rate close to the nominal value of

.05[133]. Therefore, statistical significance was considered $p < 0.05$ for the meta-regressions. We calculated ratios of RRs and their 95% confidence intervals (CIs) from the meta-regressions, which is a ratio of the average RR in studies with one characteristic to the average RR of studies with another characteristic. We also calculated a random-effects pooled RR, and corresponding homogeneity p-value and I^2 within strata of the same pre-specified study characteristics.

We performed sensitivity analyses, omitting one study at a time to assess the influence of any single study on the pooled estimate. All statistical analyses were conducted using Stata software, version 12.1.

C. Results

The database search identified 2,224 publications through PubMed, 389 through CINAHL, and 1,727 through Web of Science. Of the publications identified through the database search, eight publications met the inclusion criteria[171,172,182–187] (See **Appendix 2** for a chart that depicts the flow of information through different phases of the review, and **Appendix 3** for the exclusion log). Additionally, we identified 8 publications[170,173,174,188–192] through manual review of reference lists of eligible articles and review articles[168,169,193–197], and 3 unpublished datasets (the REGARDS study[198], CHS[117] and the ARIC study[118]) through querying experts. In all, 19 unique studies met the selection criteria for this review: 11 cohort studies and 8 case-control studies. More-fully-adjusted RRs than originally published were obtained by author queries for 4 studies[173,182,185,189]. Notable details of data abstraction and analyses of unpublished data are described in **Appendix 4**.

Tables 7.1. and 7.2. report the characteristics of cohort and case-control studies, respectively, included in the review. Most studies (84%) were conducted in the United States or Northern Europe. Most (82%) of the cohort studies were population-based, whereas most (75%) of the case-control studies were hospital or clinic-based. The number of VTE events per study varied widely: from 38 to 2,137. Measurement of diabetes varied across studies, but just over half of studies relied on self-report only, while others used some variation of criteria including fasting or non-fasting glucose levels, physician diagnosis, oral glucose tolerance test, or use of diabetes medication. Notably, Sveinsdottir et al. defined diabetes as fasting glucose ≥100 mg/dl, whereas some other studies that used fasting glucose defined diabetes as ≥200 mg/dl. One study did not specify its method of diabetes measurement[172]. No study specifically distinguished between type 1 and type 2 diabetes, but presumably studies contained mostly type 2, given the relative frequencies of the two types. Just over half of studies controlled for age, BMI, and race: Only 2[171,32] out of 19 did not control for age, 7[170–172,174,187,190,192] did not control for BMI, and 1[173] did not control for race (**Figure 7.1.**).

Comparing those with diabetes to those without diabetes, the pooled RR for VTE was 1.10 (95% CI: 0.94-1.29) (**Figure 7.1.**). Figure 1 encompasses all 19 unique studies; 17 used total (provoked plus unprovoked) VTE as the outcome, whereas 2[173,192] used unprovoked VTE only as the outcome. Five studies also reported RR estimates for provoked VTE, and 8 for unprovoked. The pooled RR for provoked VTE only was 1.02 (95% CI: 0.75-1.39) (**Figure 7.2.**), and for unprovoked was 1.03 (95% CI: 0.68-1.57) (**Figure 7.3.**).

There were moderate levels of statistical heterogeneity between the 19 studies of diabetes and total VTE (I^2=59.7%, Cochran's Q p-value <0.0005), and between the 8 studies of diabetes and unprovoked VTE (I^2=66.1%, Cochran's Q p-value = 0.004). We observed low to moderate levels of heterogeneity between the 5 studies of diabetes and provoked VTE (I^2=45.5%, Cochran's Q p-value = 0.12). To evaluate potential sources of heterogeneity, we conducted pre-specified subgroup analyses that compared the RR estimates for studies by study design, method of diabetes measurement, and level of control for potential confounding variables (**Table 7.3.).** No significant differences in RRs were observed. Using all 19 studies, there was no indication of publication bias, as evidenced by non-significant Begg and Egger tests (p=0.12 and 0.25, respectively) and a relatively symmetric funnel plot (**Appendix 5**).

Sensitivity analyses indicated that the REGARDS study influenced the pooled estimate more than other studies (**Figure 7.4.**). When we excluded the REGARDS study, the pooled estimate increased slightly and just reached statistical significance [including REGARDS: 1.10 (95% CI: 0.94-1.29; excluding REGARDS: 1.16 (95% CI: 1.01-1.34)]. Although there was less statistical heterogeneity after excluding REGARDS, some heterogeneity did remain [including REGARDS: I^2=59.7%, Cochran's Q p-value <0.0005; excluding REGARDS: I^2=48.3%, Cochran's Q p-value = 0.01].

D. Discussion

This literature-based systematic review and meta-analysis supports either no association or a very modest positive association between diabetes and venous thromboembolism in the general population. Between-study heterogeneity was observed

and was not explained by study design, method of diabetes measurement, or level of adjustment for confounding. There was no evidence of publication bias.

The findings of our meta-analysis contradict two previous meta-analyses. Both estimated a 1.4-fold increased risk of VTE for persons with diabetes compared to persons without[168,169]. However, neither adequately accounted for potential confounders of the diabetes-VTE relation. The 2008 meta-analysis by Ageno et al.[168] did not account for age, body size, or race as potential confounding variables to the diabetes-VTE relation, making results difficult to interpret. Potential confounding was also an issue in the 2014 meta-analysis by Bai et al.[169]: Three quarters of the studies included did not adjust for a measure of body size. For the present meta-analysis, we queried corresponding authors of included studies that did not account for body size (n=11), asking for BMI-adjusted estimates. We received BMI-adjusted estimates for 4 studies. Three out of 4 of these studies were included, without adjustment for BMI, in the meta-analysis by Bai et al.; we wondered whether substituting the unadjusted for BMI-adjusted estimates would impact their results. It did: Bai et al. reported a pooled effect estimate of 1.36 (95% CI: 1.11-1.68) for analyses restricted to high-quality cohort studies, but when we substituted the 3 more fully-adjusted estimates, the positive association decreased to 1.24 (95% CI: 0.96-1.61), and lost statistical significance (Details of analysis in **Appendix 6**).

A sensitivity analysis indicated that the REGARDS Study influenced the pooled estimate more than other studies. The REGARDS Study - a large, prospective cohort study of whites and African Americans across the United States - reported an inverse association between diabetes and VTE [0.65 (95% CI: 0.46-0.91)]. Though untestable, the surprising inverse association could be at least partly explained by REGARDS' VTE

ascertainment methods, which possibly led to biased ascertainment of VTE. REGARDS predominantly captured VTE events through participant report; participants were queried in 2010-11 about past VTE events (as far back as 2003)[198]. Similar questionnaires have 98% specificity and >70% sensitivity for ascertaining VTE[199]. Then, medical records were retrieved so that potential VTE events could be validated. Notably, not all records could be retrieved, and the retrieval rate differed by race (79.5% overall retrieval rate, 72% among African Americans, 85% among whites)[198]. Thus, VTE ascertainment in REGARDS was not complete, and it is difficult to know how factors associated with under-ascertainment might bias an association between diabetes and VTE.

We chose to examine the relation between diabetes and VTE because diabetes has been proposed as a risk factor for VTE, the theoretical mechanism being that hyperglycemia contributes to elevated coagulation factors, and therefore impaired fibrinolysis (thrombus resolution) and increased likelihood of thrombosis[195,200]. Indeed, laboratory evidence suggests that high glucose levels 1) increase oxidative stress, which in turn increases gene transcription of coagulation factors; 2) degrade the glycocalyx layer of the endothelial wall, which releases coagulation factors and stimulates the coagulation cascade; and 3) increase glycation of proteins involved in coagulation and fibrinolysis, shifting their activity towards a procoagulant state[195]. However, our findings suggest that diabetes is unlikely to play a major role in VTE development.

This review has expanded on previous reviews by utilizing current research, including three large, unpublished data sources; and accounting for potential confounders of the diabetes-VTE relation, sometimes through obtaining effect estimates that were more fully-adjusted than originally published. Our review and analysis also has

limitations that warrant discussion. Only one investigator conducted the search, making it possible that the systematic review was more susceptible to selection bias. However, the search was conducted and data were abstracted according to a pre-specified protocol to minimize this risk. Also, we observed substantial qualitative and quantitative heterogeneity across studies, but could not explain it. Future research should attempt to pinpoint sources of heterogeneity; an individual participant data meta-analysis would be a particularly good design to explore heterogeneity, as this would remove heterogeneity from analyses, and meta-regressions could use patient-level (as opposed to study-level) data. And, finally, this review drives home the importance of accounting for potential confounding variables when examining the relation of diabetes with VTE. Notably, biases of the effect estimates likely remain even under our definition of an "adequately controlled" effect estimate. These biases were probably related to methods of measurement (e.g., estimating BMI using self-report versus direct measurement) and modeling (e.g., modeling age as bands versus continuous) variables. Confounding of a diabetes-VTE relation by BMI and age would likely bias an estimate upwards.

In conclusion, this literature-based meta-analysis supports a very modest positive or no association of diabetes with VTE risk in the general population. Diabetes is unlikely to play a major role in VTE development.

Table 7.1. Characteristics of cohort studies that reported the relation between diabetes and VTE.

First author, publication year	Study location	Source of participants	No. of participants (cases/ cohort size)	Period of recruit-ment	Follow-up time, years	Age at baseline, years	BMI at baseline, kg/m^2	Distribution by race	Measurement of diabetes	Outcome measure
Goldhaber (1997)	United States (Nurses' Health Study)	Female registered nurses	280/112,822	1976	Max: 16	Range: 30-55	Mean: 23.8	97.6% white	Self-report	PE
Cushman (2004)	United States (Women's Health Initiative)	Post-menopausal women from 40 clinical centers	243/16,608	1993-98	Mean: 5.6	Mean: 63.2, Range: 50-79	Mean: 28.4	84% white, 7% African American	Self-report	VTE
Glynn (2005)	United States (Physicians' Health Study)	Male physicians	358/18,662	1982	Median: 20.1	Range: 40-84	Mean ± SD: 24.9 ± 3.0	94% white	Self-report	VTE
Mahmoodi (2009)	Netherlands (PREVEND Study)	Inhabitants of Groningen, Netherlands	129/8,574	1997-98	Mean: 8.6	Mean ± SD: 49 ± 13	Mean ± SD: 26.1 ± 4.2	99% white	Fasting glucose level ≥126 mg/dL, nonfasting glucose level ≥200 mg/dL, or use of oral antidiabetic drugs. Insulin-dependent diabetes excluded.	VTE
Holst (2010)	Denmark (Copenhagen City Heart Study)	Inhabitants of Copenhagen, Denmark	969/18,954	1976-78, 1981-83, 1991-93, and 2002-03	Median: 19.5	Mean: 51.3	Mean: 25.0	>99% persons of Danish descent	Self-report or nonfasting glucose levels ≥200 mg/dL	VTE
Lutsey (2010)	Iowa (IWHS)	Iowa women from the state driver's list	2,137/40,377	1986	Max: 18	Range: 55–69	NS	99% white	Self-report	VTE
Brækkan (2012)	Norway (Tromsø Study)	Inhabitants of Tromsø, Norway	437/26,185	1994-95	Median: 10.8	Mean ± SD: 46 ± 5, Range: 25–97	Mean: 25.2	87.3% Norwegians, 1.6% of Sami ethnicity, 1.3% of Finnish descent, 2.2% of other ethnicities, and 7.6% without information about ethnicity	Self-report	VTE

First author, publication year	Study location	Source of participants	No. of participants (cases/ cohort size)	Period of recruit-ment	Follow-up time, years	Age at baseline, years	BMI at baseline, kg/m^2	Distribution by race	Measurement of diabetes	Outcome measure
Sveinsdottir (2013)	Sweden (Malmö Preventive Study)	Male inhabitants of Malmö, Sweden	398/6,068	1974-82	Mean: 26.2	Mean: 46.8	Mean: 25.0	Almost exclusively white	Fasting glucose level ≥6.1 mmol/l (110 mg/dl) or current use of any diabetes medication	VTE
Unpublished data from ARIC	United States	Middle-aged adults from 4 communities in the United States	775/15,234	1987-89	Median: 22.5	Mean ± SD: 54.1 ± 5.8	Mean ± SD: 27.7 ± 5.3	72.9% white, 27.1% African American	Fasting glucose level ≥126 mg/dl, non-fasting glucose level ≥200 mg/dl, physician diagnosis of diabetes, or current use of any diabetes medication	VTE
Unpublished data from CHS	United States	Medicare eligibility lists from 4 communities in the United States	175/5,469	1989-90 and 1992–93	Median: 11.6	Mean ± SD: 72.8 ± 5.6	Mean ± SD: 26.6 ± 4.7	83.7% white, 16.3% African American	Fasting glucose level ≥126 mg/dl, non-fasting glucose level ≥200 mg/dl, physician diagnosis of diabetes, or current use of any diabetes medication	VTE
Unpublished data from REGARDS	United States	African Americans and whites ≥45 years of age in the contiguous United States	246/25,948	2003-2007	Mean ± SD in African Americans: 4.6 ± 1.7; Mean ± SD in whites: 4.7 ± 1.6	Mean ± SD in African Americans: 64.1 ± 9.3; Mean ± SD in whites: 65.4 ± 9.5	Mean ± SD in African Americans: 30.8 ± 6.7; Mean ± SD in whites: 28.3 ± 5.6	59.0% white, 41.0% African American	Fasting glucose level ≥126 mg/dl, non-fasting glucose level ≥200 mg/dl, participant report of diabetes mellitus, or current use of any diabetes medication	VTE

ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CHS, Cardiovascular Heart Study; IWHS, Iowa Women's Health Study; NS, not specified; PE, pulmonary embolism; PREVEND, Prevention of Renal and Vascular End-stage Disease; REGARDS, Reasons for Geographic and Racial Differences in Stroke; VTE, venous thromboembolism..

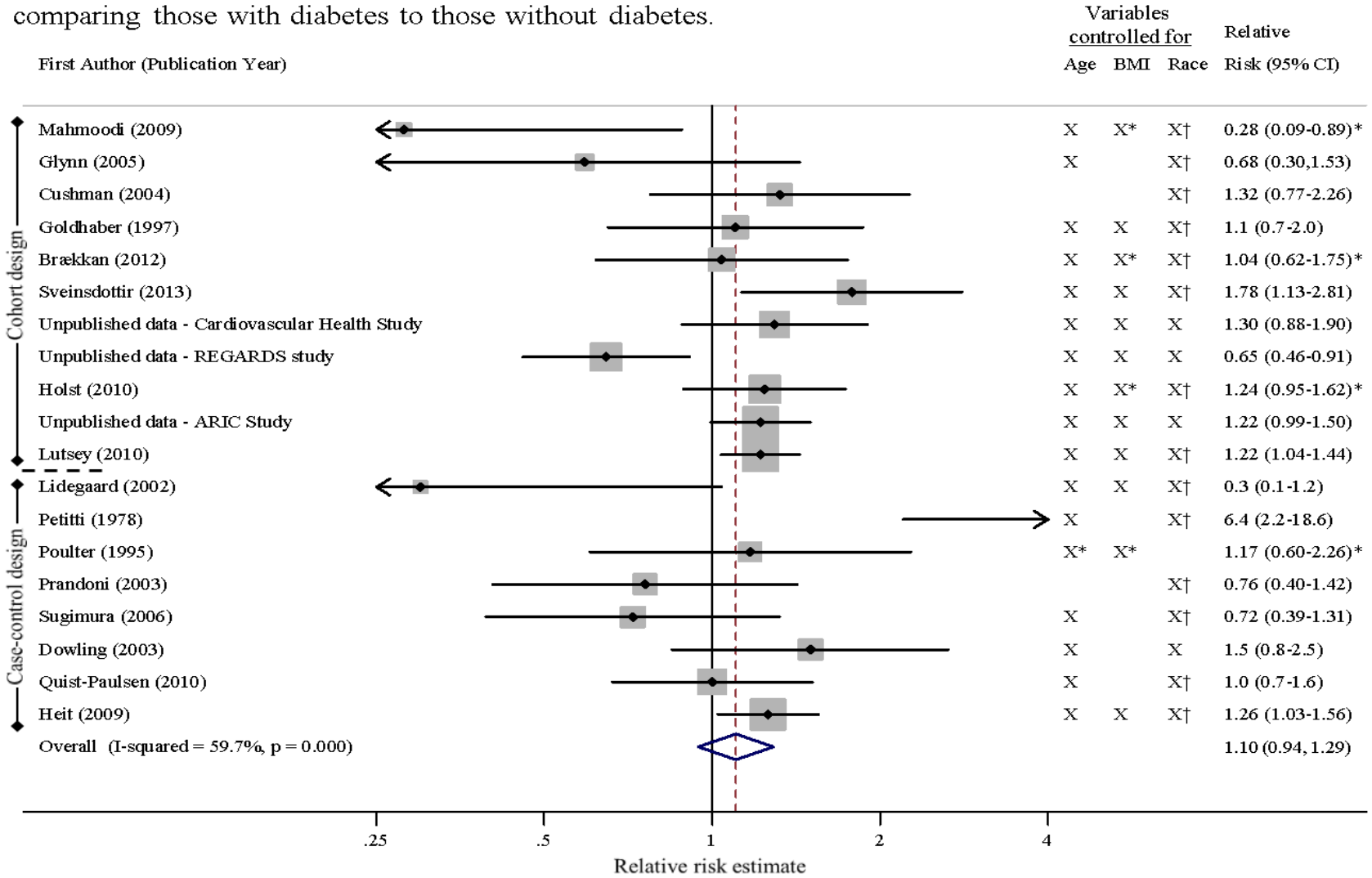
Table 7.2. Characteristics of case-control studies that reported the relation between diabetes and VTE.

First author, publication year	Study location	Source of cases	No. of participants (cases/ controls)	Source of controls	Period of recruitment	Response rate (cases/ controls), %	Age, years	Mean BMI ± SD in controls	Distribution by race	Measurement of diabetes	Outcome measure
Petitti (1978)	Walnut Creek, CA (Walnut Creek Contraceptive Drug Study)	Women who sought a general health check-up from Walnut Creek Clinic	38/8,174	Women who sought a general health check-up from Walnut Creek Clinic	1969-71	NS/NS	Range: 18-54	NS	Almost exclusively white	Self-report	Unprovoked VTE
Poulter (1995)	21 centers across Africa, Asia, Europe, and Latin America (WHO CCS Study)	Women admitted to participating hospitals	1,143/2,998	Women admitted to participating hospitals	1989-1993	>97/>98	Range: 20-44	23.8 ± NS	Race distribution not reported, but distribution by geographic area was: 36% European, 13% African, 8% Asian, 43% Latin American	Self-report	Unpro-voked VTE
Dowling (2003)	Atlanta, GA (GATE Study)	Patients admitted to 2 university-owned hospitals	370/250	Patients from a university-affiliated primary care clinic	1997-2001	57/49	Control mean: 49.5	26.1 ± NS	Controls: 36% African American, 64% white	Self-report	VTE
Lidegaard (2002)	Denmark	Women admitted to Danish hospitals	987/4,054	Women in Denmark's population registry	1994-98	87.2/89.7	Range: 15–44	22.2 ± NS	94% of women in Denmark are of Danish descent	Self-report	VTE

First author, publication year	Study location	Source of cases	No. of participants (cases/ controls)	Source of controls	Period of recruitment	Response rate (cases/ controls), %	Age, years	Mean BMI ± SD in controls	Distribution by race	Measurement of diabetes	Outcome measure
Prandoni (2003)	Padua, Italy	Outpatients admitted to University of Padua Medical School's institution	299/150	Outpatients admitted to University of Padua Medical School's institution	1996-2001	99/NS	Control mean ± SD: 65.4 ± 15.7	Obesity - number (%): 16 (10.7%)	90.7% Italian	Fasting glucose level ≥126 mg/dl on at least 2 occasions, ≥200 mg/dl after an oral glucose tolerance test, or current use of any diabetes medication	Proximal DVT
Sugimura (2006)	Japan	Patients admitted to university clinics and to hospitals with more than 100 beds	204/204	Patients admitted to university clinics and to hospitals with more than 100 beds	2004	NS/NS	Control mean ± SD: 64.3 ± 15.2	22.8 ± 3.8	98.5% Japanese	NS	PE
Heit (2009)	Olmsted County, Minnesota (Rochester Epidemiology Project)	Olmsted County residents	1,922/2,115	Olmsted County residents	1976-2000	NS/NS	Control mean ± SD: 64.6 ± 19.2	26.3 ± 5.3	96% white	Physician diagnosis in medical record	VTE
Quist-Paulsen (2010)	Nord-Trøndelag County, Norway (HUNT 2 Study)	HUNT 2 cohort	515/1,476	HUNT 2 cohort	1995-2001	NS/NS	Control mean ± SD: 66.3 ± 14.6	27.0 ± 4.2	>97% white	Self-report	VTE

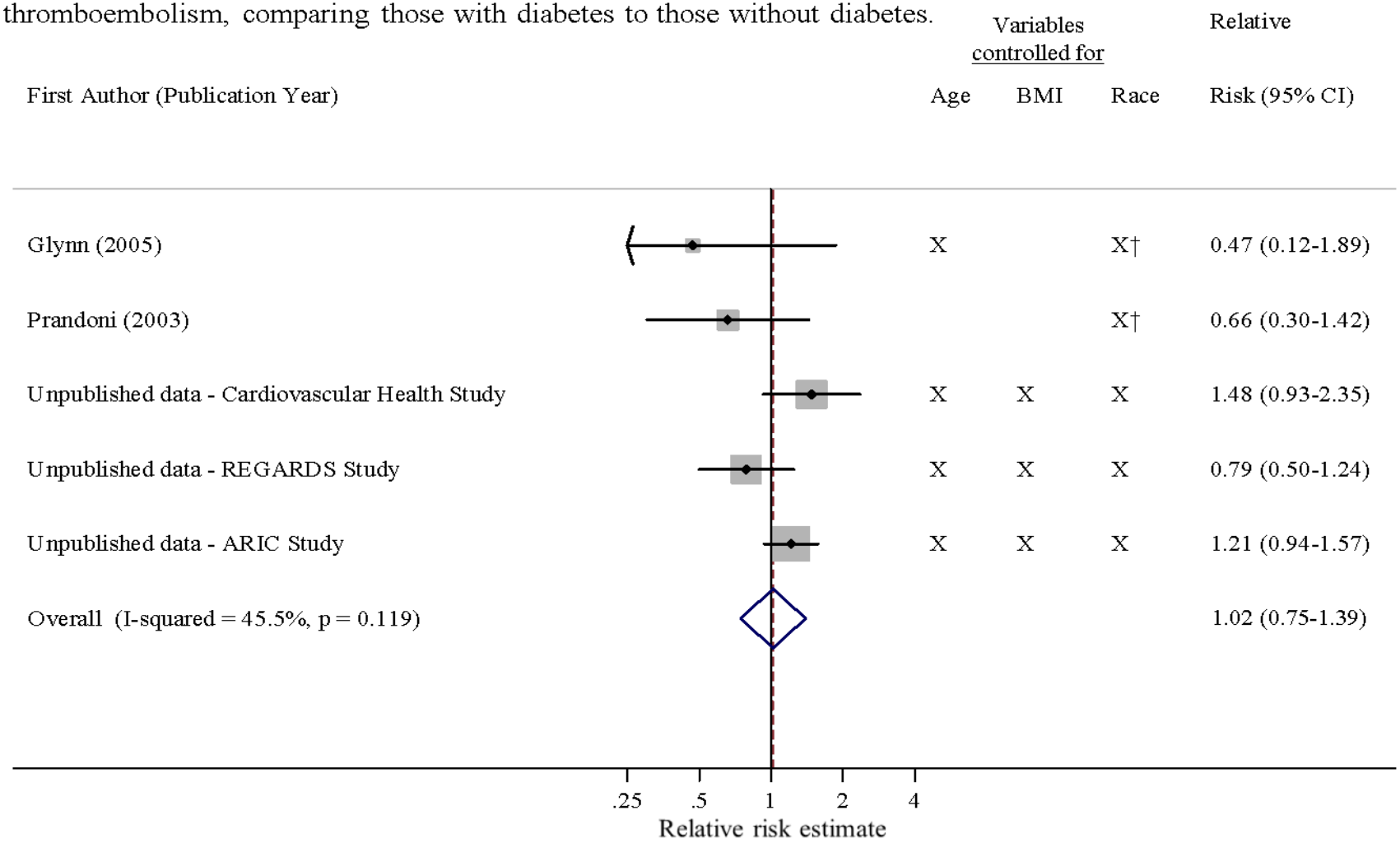
BMI, body mass index; DVT, deep vein thrombosis; GATE, Genetic Attributes and Thrombosis Epidemiology; NS, not specified; PE, pulmonary embolism; VTE, venous thromboembolism; WHO CCS, World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception.

Figure 7.1. Forest plot of study-specific and pooled relative risks (95% CIs) for venous thromboembolism, comparing those with diabetes to those without diabetes.



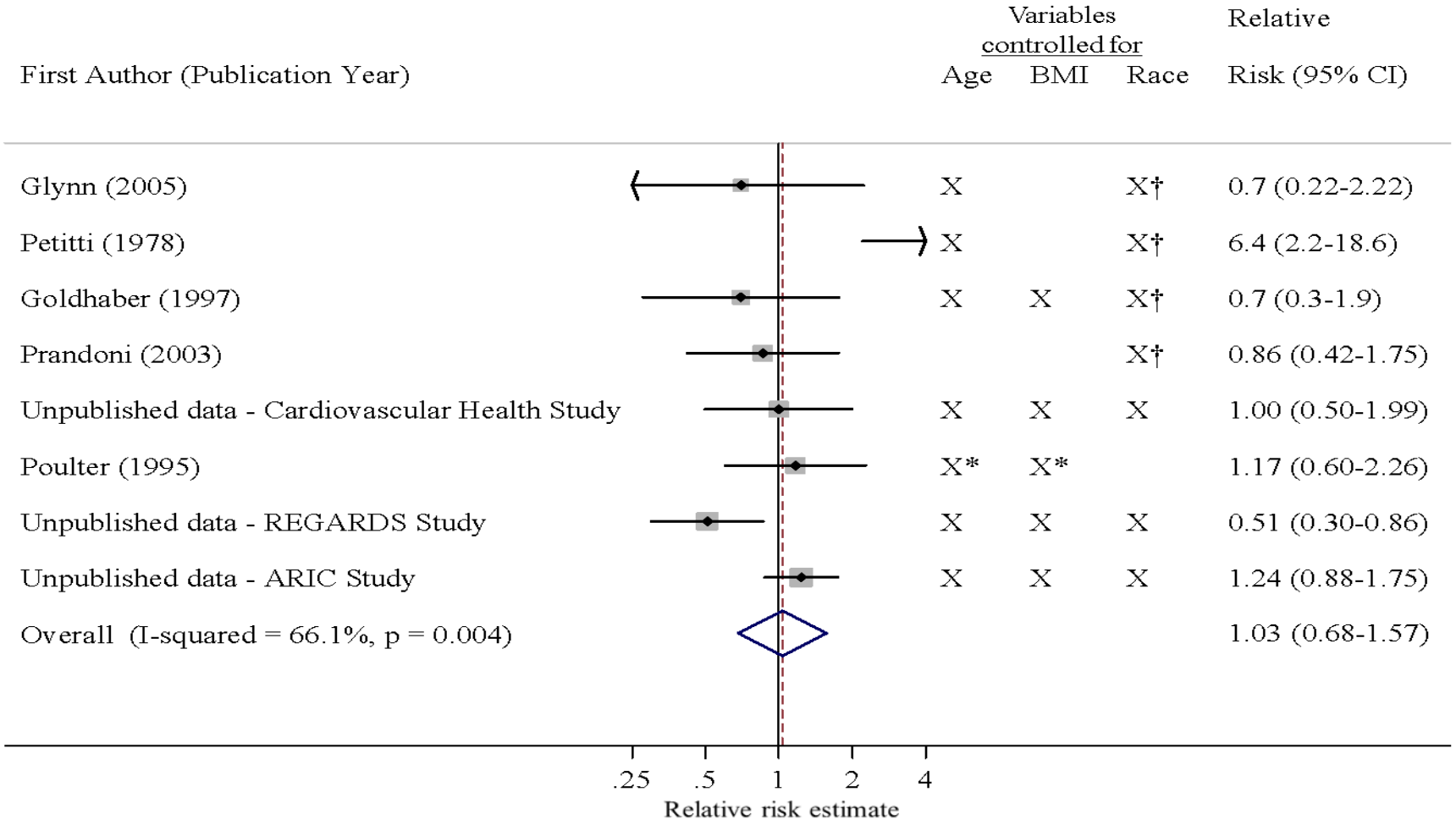
Each study is represented by a square and a horizontal line, which represents its relative risk and corresponding 95% CI, respectively. The area of the square is proportional to the weight of the study in the pooled analysis. The studies are sorted by weight in the plot and study design. The pooled random-effects estimate and its 95% CI are represented by a dashed vertical line and diamond. The vertical line at 1.0 indicates no effect of diabetes on venous thromboembolism risk. The table on the right side of the figure indicates whether the study-specific relative risks were controlled for potential confounding variables. BMI, body mass index; CI, confidence interval. *A more-fully-adjusted relative risk than originally published was obtained as a result of author query. †Study primarily involved one race-group, making statistical adjustment for race unnecessary.

Figure 7.2. Forest plot of study-specific and pooled relative risks (95% CIs) for **provoked** venous thromboembolism, comparing those with diabetes to those without diabetes.



Each study is represented by a square and a horizontal line, which represents its relative risk and corresponding 95% CI, respectively. The area of the square is proportional to the weight of the study in the pooled analysis. The studies are sorted by weight in the plot. The pooled random-effects estimate and its 95% CI are represented by a dashed vertical line and diamond. The vertical line at 1.0 indicates no effect of diabetes on venous thromboembolism risk. The table on the right side of the figure indicates whether the study-specific relative risks were controlled for potential confounding variables. BMI, body mass index; CI, confidence interval. †Study primarily involved one race-group, making statistical adjustment for race unnecessary.

Figure 7.3. Forest plot of study-specific and pooled relative risks (95% CIs) for **unprovoked** venous thromboembolism, comparing those with diabetes to those without diabetes.

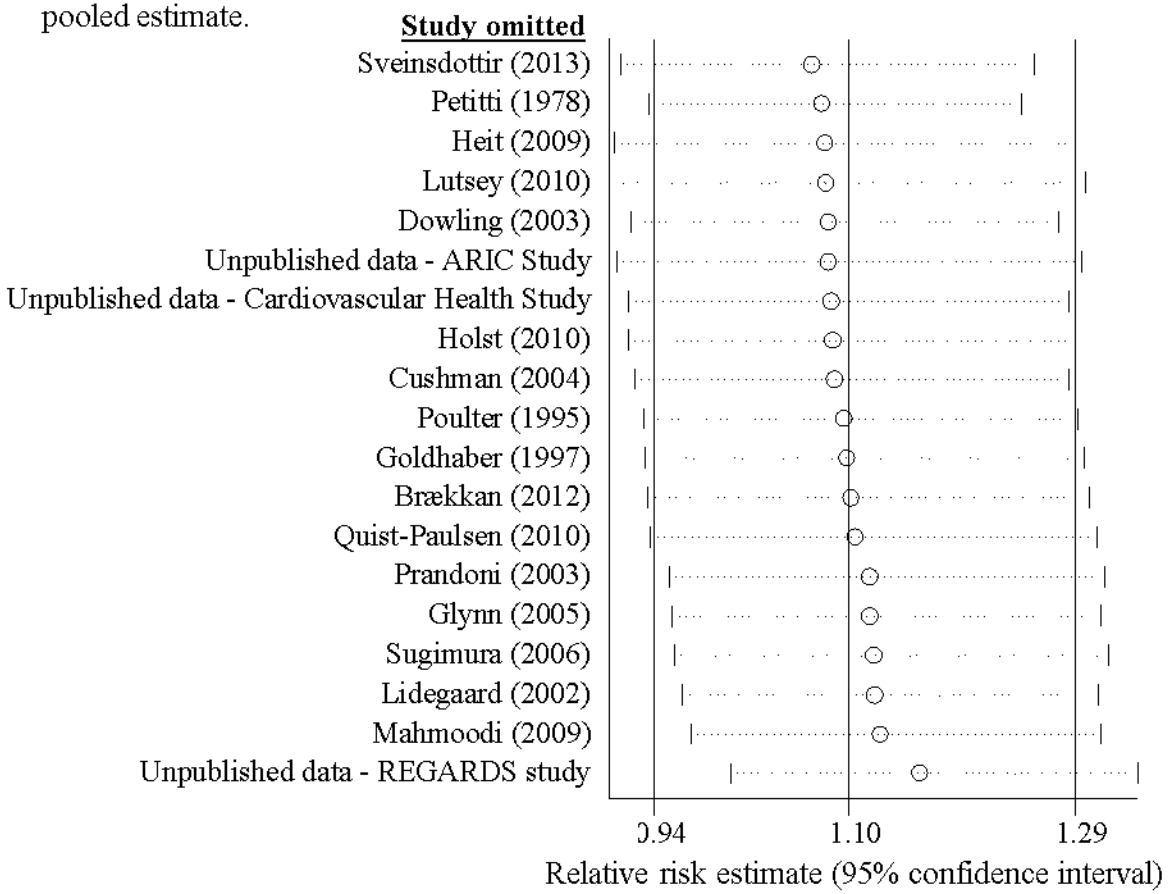


Each study is represented by a square and a horizontal line, which represents its relative risk and corresponding 95% CI, respectively. The area of the square is proportional to the weight of the study in the pooled analysis. The studies are sorted weight in the plot. The pooled random-effects estimate and its 95% CI are represented by a dashed vertical line and diamond. The vertical line at 1.0 indicates no effect of diabetes on venous thromboembolism risk. The table on the right side of the figure indicates whether the study-specific relative risks were controlled for potential confounding variables. BMI, body mass index; CI, confidence interval. *A more-fully-adjusted relative risk than originally published was obtained as a result of author query. †Study primarily involved one race-group, making statistical adjustment for race unnecessary.

Table 7.3. Meta-regression and stratified analysis of studies on the association between diabetes and venous thromboembolism

		Meta-regression	Stratified analysis		
Study Characteristics	**No. of studies**	**Ratio of RR (95% CI)**	**Random-effects summary RR (95% CI)**	**I^2**	**Homogeneity p-value**
Study design					
Cohort	11	0.98 (0.62-1.56)	1.10 (0.92-1.32)	58.7%	0.01
Case-control	8	1 (referent)	1.11 (0.79-1.55)	65.7%	0.005
Measurement of diabetes					
No glucose measurement	11	1.12 (0.72-1.75)	1.18 (0.98-1.43)	46.8%	0.043
Included glucose measurement	7	1 (referent)	1.03 (0.77-1.39)	73.4%	0.001
Level of confounding					
Not adequately controlled for age, BMI, and race	8	1.02 (0.64-1.62)	1.13 (0.80-1.61)	60%	0.02
Adequately controlled	11	1 (referent)	1.07 (0.90-1.27)	63%	0.003

Figure 7.4. Meta-analysis estimates and 95% confidence intervals, omitting one study at a time to assess the influence of any single study on the random-effects pooled estimate.



CHAPTER 8: Summary

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are viewed as different manifestations of the same disease process, termed venous thromboembolism (VTE). VTE represents a significant source of mortality and morbidity, and recurrence is common.

The overall objectives of this dissertation were to 1) calculate the lifetime risk of VTE overall and stratified by subgroups of interest, 2) quantify the association between orthostatic hypotension and VTE, and 3) perform a systematic review and meta-analysis to quantify the association between diabetes mellitus and VTE.

A. Manuscript 1

Greater public awareness of VTE may be an important next step for VTE prevention and treatment. The "lifetime risk" of VTE may be an easily interpretable format of risk information, permitting comparison with lifetime risks of other diseases. To our knowledge, no estimates of the lifetime risk of VTE exist. We sought to calculate the lifetime risk of VTE using data from two large, prospective cohort studies: the Cardiovascular Health Study (CHS) and the Atherosclerosis Risk in Communities (ARIC) study. We followed participants aged 45–64 years in ARIC (n=14,185) and ≥65 in CHS (n=5,414) at baseline visits (1987-89 in ARIC, 1989-90 and 1992–93 in CHS) for incident VTE (n=728 in ARIC through 2011 and n=172 in CHS through 2001). We estimated lifetime risks and 95% confidence intervals of incident VTE using a modified Kaplan-Meier method, accounting for the competing risk of death. At age 45, the

remaining lifetime risk of VTE in ARIC was 8.1% (95% confidence interval: 7.1-8.7). High-risk groups were African Americans (11.5% lifetime risk), those with obesity (10.9%), factor V Leiden (17.1%), or sickle cell trait or disease (18.2%). Lifetime risk estimates differed by cohort; these differences were explained by differences in time period of VTE ascertainment. In conclusion, 1 in 12 middle-aged adults develop VTE in their lifetime. This estimate of lifetime risk may be useful to promote awareness of VTE and guide decisions at both clinical and policy levels.

B. Manuscript 2

Although it is known that venous stasis increases VTE risk and that orthostatic hypotension (OH) can cause venous stasis, to our knowledge no study has examined the relation between OH and VTE risk. We sought to quantify the association between OH and VTE, again using data from CHS and the ARIC. We hypothesized that OH is positively associated with incident VTE. We measured OH - defined as a reduction in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 minutes of standing - in participants aged 45–64 years in ARIC (n=12,480) and ≥ 65 in CHS (n=5,027) at baseline visits (1987-89 in ARIC, 1989-90 and 1992–93 in the CHS), and followed participants for incident VTE (n=568 in ARIC through 2011 and n=148 in CHS through 2001). We calculated adjusted hazard ratios and their 95% confidence intervals for incident VTE (total, provoked and unprovoked) in relation to OH status. In CHS, there was a positive association between incident VTE and OH status (Hazard ratio for total VTE = 1.74 (95% confidence interval: 1.20-2.51)). In contrast, there was no association between OH and VTE in the ARIC study. In

conclusion, community-dwelling older adults with OH have a moderately increased risk of VTE. These results were not replicated in a population-based middle-aged cohort.

C. Manuscript 3

Some evidence suggests diabetes may be a risk factor for VTE but results are inconsistent. We conducted a systematic review and meta-analysis of case-control and cohort studies to quantify the association between diabetes mellitus and VTE. The database search included PubMed, Web of Science, and CINAHL through July 31, 2014. Additional studies were identified by contacting experts and through manual review of reference lists of review articles and articles eligible for this review. We abstracted relevant information, including relative risk estimates, from eligible articles. We pooled relative risks using a random-effects model. Between-study heterogeneity was explored with a forest plot, funnel plot, meta-regression, and a stratified analysis. Sensitivity analyses omitted one study at a time to assess the influence of any single study on the pooled estimate. We identified 19 studies that met our selection criteria. The pooled relative risk for the association of diabetes with VTE was 1.10 (95% confidence interval: 0.94-1.29). Between-study heterogeneity was observed and was not explained by study design, method of diabetes measurement, or level of adjustment for confounding. Sensitivity analyses indicated that one study influenced the pooled estimate more than other studies; when this study was excluded, the pooled estimate increased slightly and just reached statistical significance: 1.16 (95% confidence interval: 1.01-1.34)]. In conclusion, this literature-based systematic review and meta-analysis supports either no

association or a very modest positive one between diabetes and VTE in the general population. Diabetes is unlikely to play a major role in VTE development.

D. Overall Conclusions

This dissertation reports the lifetime risk of VTE, and the association between two novel risk factors and VTE. We believe this information will be useful in promoting awareness of VTE, and has contributed to our understanding of VTE etiology.

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APPENDICES

Appendix 1. Database search strategies,

Search 1: **PubMed**, searched through July 31, 2014

(diabetes mellitus[MeSH] OR diabet*) AND (venous thrombosis[MeSH] OR venous thromboembolism[MeSH] OR pulmonary embolism[MeSH] OR DVT OR PE OR VTE OR venous thromb* OR pulmonary embol* OR deep vein thromb*). Filters: Humans

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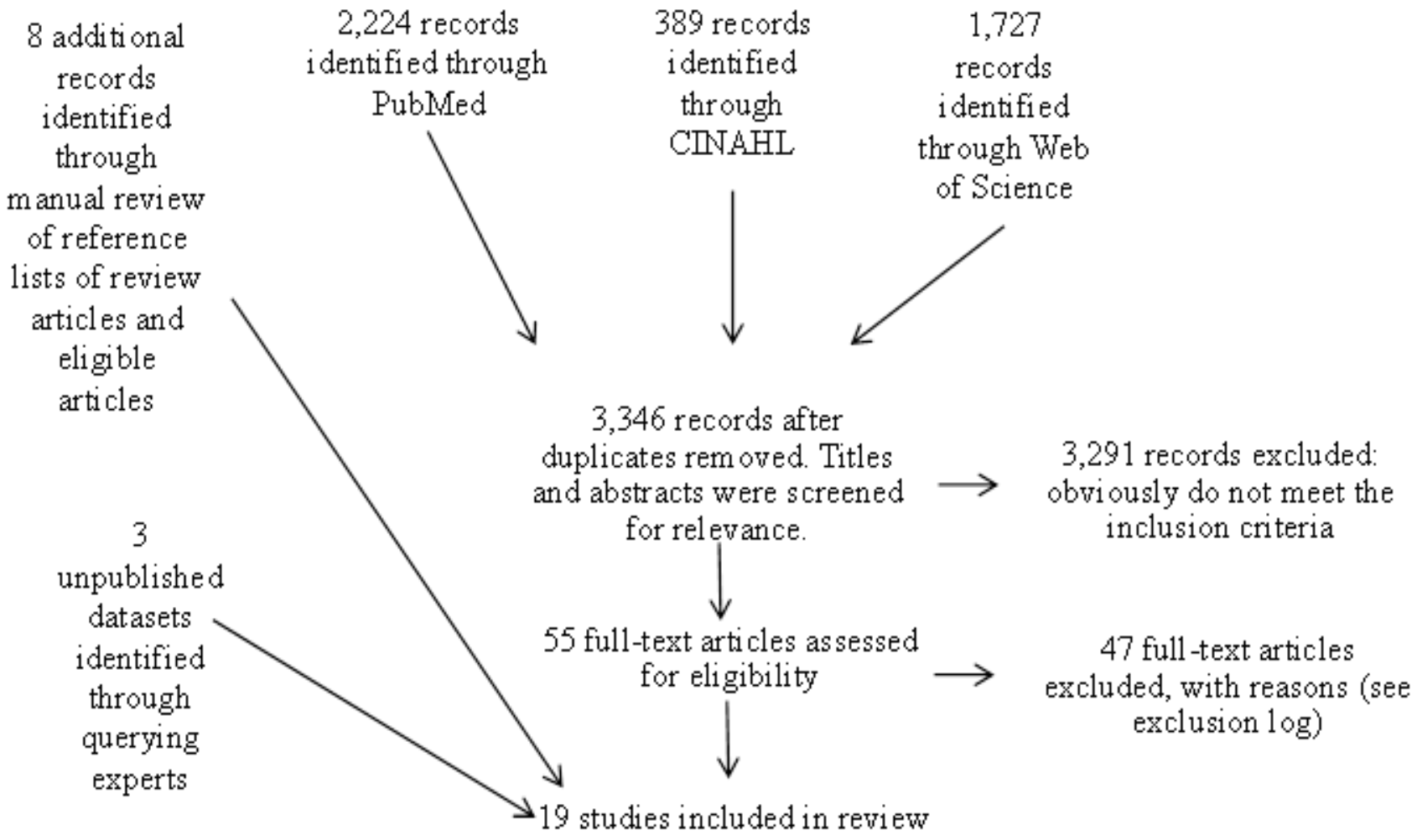
Search 2: Web of Science, searched through July 31, 2014

(diabet*) AND (DVT OR PE OR VTE OR venous thromb* OR pulmonary embol* OR deep vein thromb*). All words were searched for in topic.

Search 3: CINAHL, searched through July 31, 2014

((MH "Diabetes Mellitus+") OR diabet*) AND ((MH "Venous Thromboembolism+") OR (MH "pulmonary embolism+") OR (MH "Venous Thrombosis+") OR DVT OR PE OR VTE OR venous thromb* OR pulmonary embol* OR deep vein thromb*).

Appendix 2. Flow of information through the different phases of the systematic review.



Appendix 3. Exclusion log,

Investigator and year	Reason for exclusion
Liem, 2013[201]	DVTs were solely outside the leg
King, 2006[202]	DVTs were solely outside the leg
Barba, 2012[203]	The entire study population was affected by a specific medical condition or procedure: COPD hospitalized patients
Bergqvist, 1985[204]	The entire study population was affected by a specific medical condition or procedure: Patients undergoing transplantation for terminal renal failure
Darze, 2005[205]	The entire study population was affected by a specific medical condition or procedure: Severe heart failure patients admitted to a coronary care unit
Dennis, 2011[206]	The entire study population was affected by a specific medical condition or procedure: Immobile patients with stroke
Gandhi, 2009[207]	The entire study population was affected by a specific medical condition or procedure: Patients undergoing total knee replacement
Gangireddy, 2007[208]	The entire study population was affected by a specific medical condition or procedure: Surgical patients undergoing nine common general, vascular, and orthopedic operations
Hansen, 2001[209]	The entire study population was affected by a specific medical condition or procedure: Patients with antiphospholipid antibodies
Jones, 1983[210]	The entire study population was affected by a specific medical condition or procedure: Patients admitted to hospital with myocardial infarction, heart failure or stroke, or for abdominal surgery
Kapoor, 2010[211]	The entire study population was affected by a specific medical condition or procedure: Patients undergoing total hip or knee replacement
Krnic-Barrie, 1997[212]	The entire study population was affected by a specific medical condition or procedure: Patients with antiphospholipid syndrome
Lynch, 1988[213]	The entire study population was affected by a specific medical condition or procedure: Patients underwent total knee arthroplasty
Mahmoodi, 2008[214]	The entire study population was affected by a specific medical condition or procedure: Patients had nephrotic syndrome
Mraovic, 2010[215]	The entire study population was affected by a specific medical condition or procedure: Patients undergoing major orthopedic surgery
Ocak, 2011[216]	The entire study population was affected by a specific medical condition or procedure: Dialysis patients
Ramagopalan, 2011[217]	The entire study population was affected by a specific medical condition or procedure: People admitted to hospital with a range of immune-mediated diseases
Saarinen, 1995[218]	The entire study population was affected by a specific medical condition or procedure: Patients who underwent aortic and peripheral vascular

	procedures
Sairam, 2003[219]	The entire study population was affected by a specific medical condition or procedure: Patients with anticardiolipin antibodies
Salami, 2012[220]	The entire study population was affected by a specific medical condition or procedure: Orthotopic liver transplant recipients
Satoh, 2008[221]	The entire study population was affected by a specific medical condition or procedure: Patients with endometrial cancer
Shibuya, 2012[222]	The entire study population was affected by a specific medical condition or procedure: People with foot and ankle trauma
Simici, 1979[223]	The entire study population was affected by a specific medical condition or procedure: Patients who underwent surgery
Vresilovic, 1993[224]	The entire study population was affected by a specific medical condition or procedure: Osteoarthritic patients prophylaxed with low-dose coumadin after cemented total knee arthroplasty
Wang, 2000[225]	The entire study population was affected by a specific medical condition or procedure: Patients who underwent total knee arthroplasty
Wong, 2011[226]	The entire study population was affected by a specific medical condition or procedure: Patients who underwent total hip arthroplasty
Xu, 2008[227]	The entire study population was affected by a specific medical condition or procedure: Patients who underwent lower extremity surgery
Yegen, 2007[228]	The entire study population was affected by a specific medical condition or procedure: Patients who underwent lung transplantation
Yuan, 2004[229]	The entire study population was affected by a specific medical condition or procedure: Patients undergoing thoracotomy
Grady, 2000[230]	The entire study population was affected by a specific medical condition or procedure: Patients were postmenopausal women younger than 80 years of age who had coronary disease
Linnemann, 2008[231]	VTEs were solely recurrent
Hong, 2005[232]	The entire study population was affected by a specific medical condition or procedure: In this case-control study, the source population was consecutive patients with clinically suspected VTE admitted to a hospital. All patients were examined for VTE, with cases being those with a VTE confirmation and controls being randomly selected from those with VTE excluded.
Tsai, 2002[69]	Since we are using unpublished data from the CHS and ARIC studies with longer follow-up time than Tsai's report, we excluded it.
Tichelaar, 2011[233]	The entire study population was affected by a specific medical condition or procedure: In this case-control study, the source population was consecutive patients with clinically suspected VTE admitted to a hospital. All patients were examined for VTE, with cases being those with a VTE confirmation and controls being those with VTE excluded.
Hansson, 1999[234]	Did not provide enough information to calculate a relative risk
Ray, 2007[235]	The entire study population was affected by a specific medical condition or procedure: Persons aged 55 years of age or older with a history of

	symptomatic cardiovascular disease, or who had diabetes mellitus and at least one additional risk factor for atherosclerosis.
McColl, 2000[236]	Did not provide enough information to calculate a relative risk
Deguchi, 2005[237]	Did not provide enough information to calculate a standard error
Høibraaten, 1999[238]	Did not provide enough information to calculate a relative risk
Palosuo, 1997[239]	Did not report on an association between diabetes and VTE
Hirohashi, 2006[240]	Did not provide enough information to calculate a relative risk
Movahed, 2005[241]	The entire study population was affected by a specific medical condition or procedure: The control group was selected to have hypertension
Stein, 2009[242]	Cross-sectional design
Franks, 1992[243]	Cross-sectional design
Petrauskiene, 2005[244]	Did not provide enough information to calculate a relative risk
Lerstad, 2014[245]	Did not report on an association between diabetes and VTE
Mili, 2013[246]	This study was excluded because another study[190], using the same cohort and better adjustments for potential confounders, was included in this review.
Bell, 2013[247]	Since we are using unpublished data from the ARIC Study with longer follow-up time than Bell's report, we excluded it.

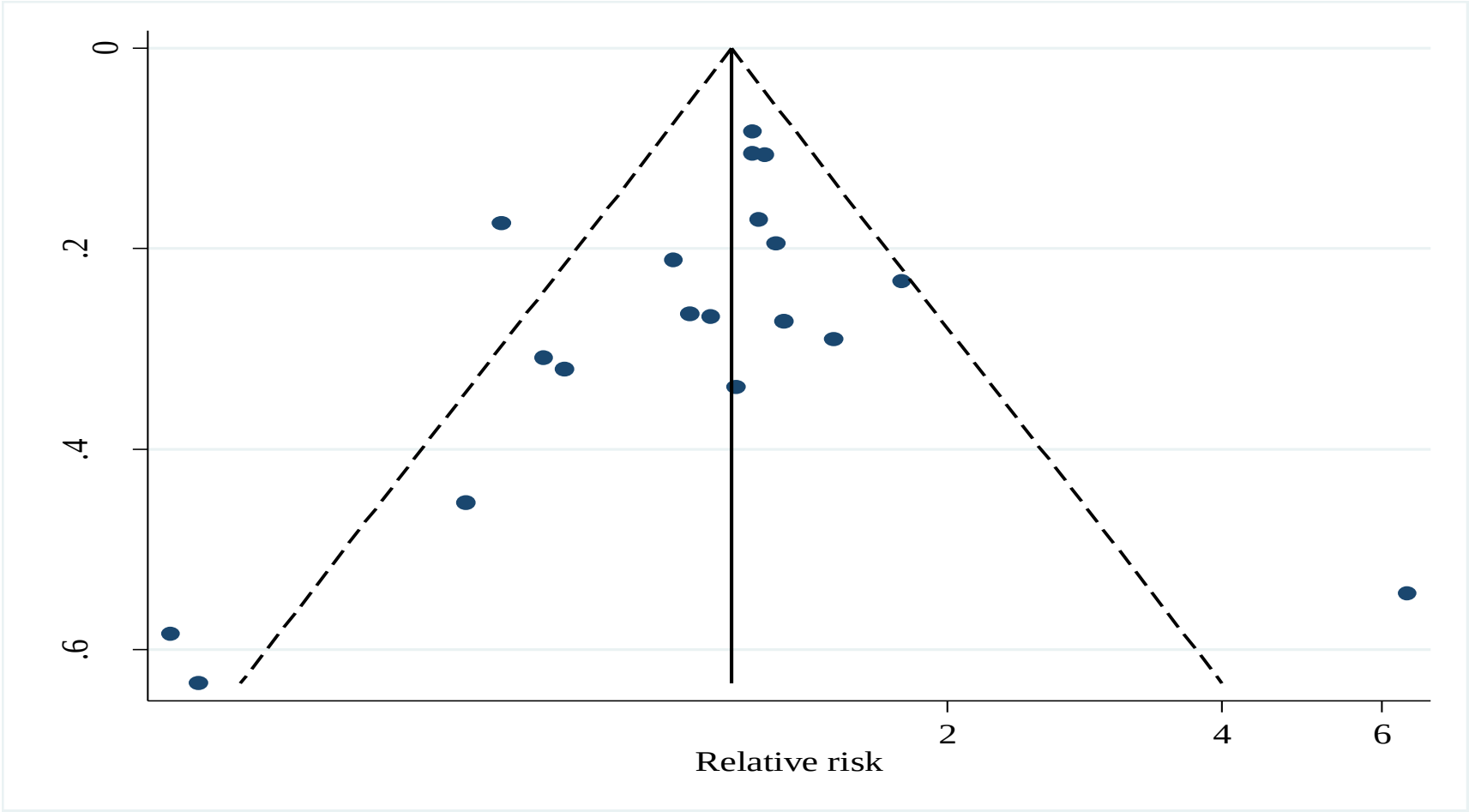
Appendix 4. Data abstraction methods by study

Investigator and year	Notable data abstraction methods
Goldhaber, 1997[183]	Mean BMI at baseline and distribution by race were not reported in Goldhaber's article (which used the Nurses' Health study cohort), but this information has been reported elsewhere for this cohort[248,249].
Cushman, 2004[174]	Method of diabetes measurement was not reported in Cushman's article (which used the Women's Health Initiative study cohort), but this information has been reported elsewhere for this cohort[250].
Glynn, 2005[187]	Mean BMI at baseline and distribution by race were not reported in Glynn's article (which used the Physicians' Health Study cohort), but this information has been reported elsewhere for this cohort[251,252].
Mahmoodi, 2009[189]	Distribution by race was not reported in Mahmoodi's article (which used the PREVEND Study cohort), but this information has been reported elsewhere for this cohort[253].
Brækkan, 2012[182]	Distribution by race was not reported in Brækkan's article (which used the Tromsø Study cohort), but this information has been reported elsewhere for this cohort[254].
Dowling, 2003[190]	Mean BMI in controls was approximated using data from Table 7.1.[190]: (0.03*18.5)+(0.32*21.7)+(0.36*27.5)+(0.29*30)
Heit, 2009[184]	Distribution by race was not reported in Heit's article (which created a nested case-control study within the Rochester Epidemiology Project cohort), but this information has been reported elsewhere for the entire cohort[255].
Quist-Paulsen, 2010[170]	Distribution by race was not reported in Quist-Paulsen's article (which created a nested case-control study within the HUNT 2 study cohort), but this information has been reported elsewhere for the entire cohort[256].
Unpublished data – ARIC[118] and CHS[117]	Individuals were excluded from all analyses if they had a history of VTE or anticoagulant use at baseline; in ARIC, were African American from Washington County or Minneapolis suburbs (due to small numbers); had missing data on any variable included in the analysis; or were of a race other than African American or white (due to small numbers). We used Cox proportional hazards regression to calculate diabetes-VTE hazard ratios and 95% confidence intervals adjusted for race (white, African American), sex, age (continuous), and BMI (continuous).
Unpublished data – REGARDS study[198]	Individuals were excluded from all analyses if they had a history of VTE or anticoagulant use at baseline, or had missing data on any variable included in the analysis. We used Cox proportional hazards regression to calculate diabetes-VTE hazard ratios and 95% confidence intervals adjusted for race, sex, age (continuous), and BMI (continuous).
Sveinsdottir, 2013[191]	Distribution by race was not reported in Sveinsdottir's article (which used data from the Malmö Preventive Project), but this information has been reported elsewhere[257].
Petitti,	Distribution by race was not reported in Petitti's article (which used data

1978[192]	from the Walnut Creek Contraceptive Drug Study), but this information has been reported elsewhere for this cohort[258].
Lidegaard, 2002[188]	Distribution by race was not reported in Lidegaard's article (which used women from Denmark's population registry), but the race distribution of women in Denmark has been reported[259].
Sugimura, 2006[172]	Distribution by race was not reported in Sugimura's article (which used patients admitted to Japanese university clinics and to hospitals with more than 100 beds), but the race distribution in Japan has been reported[260].
Prandoni, 2003[171]	Distribution by race was not reported in Prandoni's article (which used outpatients admitted to University of Padua Medical School's institution), but the race distribution of Padua has been reported[261].

Appendix 5. Funnel plot of the relative risk for venous thromboembolism according to diabetes st

The vertical line represents the summary estimate of relative risk, derived using a fixed-effects model. Diagonal dashed lines estimate the expected distribution of studies; 95% of studies should fall within these limits in the absence of heterogeneity. Neither the Begg nor Egger tests were significant (p=0.12 and 0.25, respectively).



Appendix 6. Details of updated random-effects meta-analysis of high-quality cohort studies from Bai et al.[169]

We used the "Meta-Analysis" tab from Rothman's Episheet (krothman.hostbyet2.com/Episheet.xls) to calculate an updated random-effects meta-analysis of high-quality cohort studies from Bai et al.[169], substituting the unadjusted for BMI-adjusted estimates when available. Below are the data we used for this updated meta-analysis, with highlights on the data that are different than the original meta-analysis by Bai et al.

Study	RR estimate	Lower bound of 95% CI	Upper bound of 95% CI	Relative weight
Bell et al. (A_{1c}<7.00%)	1.41	0.79	2.54	0.13
Bell et al. (A1c≥7.00%)	1.64	0.84	3.22	0.11
Braekkan	1.04	0.62	1.75	0.15
Goldhaber	1.10	0.70	2.00	0.13
Holst (both men and women)	1.24	0.95	1.62	0.27
Mahmoodi	0.28	0.09	0.89	0.04
Sveinsdottir	1.78	1.13	2.81	0.17
Pooled	**1.242**	**0.957**	**1.611**	**1**