A Case-Control Study Examining the Association between Travel and Deep Venous Thrombosis

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ABSTRACT

Background: This thesis explores the link between travel and deep venous thrombosis (DVT). While it is biologically plausible that prolonged travel is an independent risk factor for venous thromboembolic disease (VTE), epidemiological data to date are conflicting.

Aim: To determine whether there is a independent association between travel and DVT.

Methods: This was a multi-center case control study. Consecutive patients presenting to the vascular laboratory with clinically suspected DVT were eligible to participate. Cases were patients with confirmed DVT; controls were patients who had DVT ruled out. Travel history and clinical characteristics were determined though standardized interviewer-administered questionnaire. Genetic testing of Factor V Leiden and Prothrombin gene mutations were also performed. SAS was used to perform unconditional multivariate logistic regression analysis.

Results: There were 359 cases and 359 controls. The crude and adjusted odds ratios (OR) for travel and DVT were 1.15 (95%CI: 0.78, 1.69) and 1.51 (95%CI: 0.91, 2.50) respectively. Travel of $\geq$12 hours' duration had a higher OR estimate (2.82, 95%CI: 0.52, 15.24) than shorter travel durations (OR = 1.32, 95%CI: 0.63, 2.76), although this did not reach statistical significance. Analyzing plane and car travel separately showed that plane travel of $\geq$ 12 hours duration had a crude and adjusted OR of 8.22 (95%CI: 1.02, 66.05) and 7.10 (95% CI: 0.70, 72.35). No such association was found with long durations of car travel.

Interpretation: Plane travel appears to be a mild independent risk factor for DVT overall, although the adjusted OR does not achieve conventional levels of statistical significance. Plane travel durations of 12 hours or longer had the highest estimate of risk. This was not found to be true of car travel. These findings may have future implications regarding the use of thromboprophylaxis in travelers.

ABSTRACT

Introduction: Cette thèse explore le lien entre le voyage et la thrombophlébite profonde (TPP). Bien qu' il soit plausible qu' un épisode de voyage prolongé soit un facteur de risque indépendant pour la TPP, les données épidémiologiques à ce jour demeurent controversées.

Objectif : Déterminer s' il existe une association entre le voyage et la TPP.

Méthodologie: Une étude cas-témoin multi-centrique a été réalisée. Les patients présentant de façon consécutive au laboratoire vasculaire avec suspicion clinique de TPP étaient éligibles à participer à cette étude. Les cas étaient définis comme des patients avec TPP confirmée; les témoins comme des patients chez lesquels a TPP avait été éliminée. L'histoire de voyage et les caractéristiques cliniques ont été déterminés par le biais d'entrevues standardisées. Des tests génétiques pour le dépistage du Facteur V Leiden et de la mutation du gène de la Prothrombine ont été effectués. Le logiciel SAS a été utilisé pour réaliser les analyses. **Résultats:** Trois cent cinquante neuf cas et 359 témoins ont été recrutés. Les odds ratios (OR) non-ajustés et ajustés pour l' association entre le voyage et la TPP était 1.15 (95%CI: 0.78, 1.69) et 1.51 (95%CI: 0.91, 2.50) respectivement. Les épisodes de voyage de ≥12 heures avaient un OR plus élevé (2.82, 95%CI: 0.52, 15.24) que ceux de < 12 heures (OR = 1.32, 95%CI: 0.63, 2.76). Toutefois, cette différence n'était pas statistiquement significative. L'analyse séparé des épisodes de voyage par avion et voiture a montré que les voyages en avion de ≥12 heures avaient des OR non-ajustés et ajustés de 8.22 (95%CI: 1.02, 66.05) et 7.10 (95% CI: 0.70, 72.35) respectivement. Aucune association n' a été observée avec les voyages en voiture. **Conclusion:** Les voyages en avion semble représenter un faible risque indépendant pour la TPP malgré le fait que le OR n'a pas atteint une valeur statistique significative. Les voyages en avion de plus de 12 heures semble comporter le plus haut risque. Cette association ne semble pas présente pour le voyage en automobile. Ces résultats pourraient mener à de nouvelles recommendations en ce qui a trait à la thromboprophylaxie chez les voyageurs.

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LVO

1. INTRODUCTION

This thesis project explores the link between travel and venous thromboembolism (VTE). The association between prolonged periods of sitting and VTE was first described by Simpson during World War II among people sitting in air-raid shelters in London.(1) In recent years, the risk of VTE following air travel, the so-called 'economy-class syndrome',(2) has received extensive media coverage, especially following the high profile case of a young woman who died from a pulmonary embolism (PE) after disembarking from a flight from Australia to England.(3) It has been the subject of a threatened class-action law-suit in Australia,(4) and international aviation authorities are interested in evidence to guide them in airline policy making. In addition to its link to air travel, an understanding of the association between VTE and prolonged sitting during long distance ground travel, including car, bus and train is also of interest. Given the millions of people traveling yearly, the subject of travel and VTE is one of significant public health importance.

2. BACKGROUND

2.1 Overview of venous thromboembolic disease

A brief general review of the epidemiology and pathophysiology of VTE is presented followed by a systematic review of the literature on the association between VTE and travel. Venous thromboembolic disease consists of thrombus formation within the venous circulation, which manifests in the periphery as venous thrombosis or in the lung as a PE. Thrombosis of superficial veins can result in painful thrombophlebitis and varicosities, but is usually a benign condition. Thrombosis of the deep veins of limbs, known as deep venous thrombosis (DVT) represents a far more serious condition. DVT can also lead to local morbidities such as pain, limited mobility and in some cases permanent oedema known as the post-phlebitic syndrome. The most serious complication of DVT is PE, which can be lethal and has an estimated hospital case-fatality rate of 5 – 12%.(5;6)

The incidence of VTE varies greatly in different patient populations depending on age as well as the presence or absence of established risk factors, as will be described subsequently. The estimated incidence of DVT in the overall population is 48 – 159/100 000 per year, or almost 400 000 cases yearly in the United States, while the estimated incidence of PE is 23/100 000 per year.(6;7) Because of its high incidence and its associated morbidity and mortality, VTE risk factors, prevention and treatment strategies are subjects of active ongoing research.

2.2 Diagnosis of DVT

The diagnostic process for DVT includes clinical evaluation and/or d-dimer blood testing followed by imaging modalities. While clinical assessment and subsequent stratification into low, moderate and high probability categories is fairly accurate, alone it is insufficient for the

diagnosis of DVT, which must be confirmed by imaging testing.(8) The two main imaging modalities used today to diagnose DVT are venography and venous ultrasound. Venography is considered the reference standard diagnostic technique, and consists of contrast dye injection into a foot vein. Visualisation of intraluminal filling defects in at least two views is diagnostic for DVT.(9;10) However, venography is associated with pain, high cost and inconvenience. As a result, the current diagnostic procedure of choice is the venous ultrasound, a non-invasive test. Components of ultrasound testing include B mode imaging and a colour Doppler component.(11) Several criteria are noted during examination of the deep veins, but non-compressibility of the vein is considered to be the definitive diagnostic criterion for DVT.(9) Other features suggestive of a DVT include Doppler changes in colour analysis, intraluminal appearance and flow changes with respiration.(12) In symptomatic patients, the sensitivity and specificity of ultrasonography is over 95% for DVTs above the knee (i.e. proximal DVT).(10;11) However, ultrasound is sub optimal for the diagnosis of isolated below knee DVT (i.e. distal DVT).(10) Distinguishing between proximal and distal DVT is clinically important as proximal DVT has a higher predilection for progression to PE than distal DVT. For this reason, negative ultrasounds in the context of high clinical suspicion should be verified either by venogram or with a repeated ultrasound one week later to ensure that a calf DVT has not extended above the knee.(13) The second limitation of venous ultrasound is its inaccuracy in diagnosing asymptomatic DVT.(14) In this context, a venogram is also preferred. However, the clinical significance of an asymptomatic DVT is unclear.

2.3 Pathophysiology of Venous Thromboembolic Disease

Venous thrombosis occurs whenever there is excess in activation of blood coagulation over natural anticoagulant mechanisms. This was first conceptualized by Virchow in 1856 in his famous triad which postulated that thrombosis is caused by one or more broad categories of:

stasis, hypercoaguability or endothelial damage.(15) Almost 150 years later, many specific inherited and acquired risk factors for VTE have since been characterized, but all fit into one or more of Virchow's categories. However, not all factors increase the risk of thrombosis to an equal degree, and can conceptually be thought of as strong (relative risk (RR) ≥10), moderate (RR 2- 9) and weak (RR < 2) risk factors.(16)

2.3.1 Inherited Risk Factors for Thrombosis

There are a growing number of recognized genetic mutations that, via different pathways, result in a hypercoagulable state. As a group, they are referred to as the hereditary thrombophilias. First discovered were deficiencies in the natural anticoagulants antithrombin, protein C and protein S. These deficiencies are associated with a high incidence of thrombosis. For example, ~ 55% of people with antithrombin deficiency will suffer a thrombotic event in their lifetime.(17) However, these disorders are only found in approximately 2 – 3% of all people with venous thrombi.

Factor V Leiden is a more recently described hereditary thrombophilia, where a single point mutation in the factor V gene causes factor V to be resistant to inactivation by activated protein C, with a resultant increased risk of thrombosis.(18) Subsequent population studies have determined that Factor V Leiden mutation is present in 5% of people of northern European descent, but only a subset of carriers develop thrombotic events.(19) It is found in approximately 15% of patients presenting with DVT, and its presence is associated with a 4 – fold increase in the risk of DVT.(20) It is unclear at the present why some people, even within the same family, have thrombotic events, while others remain event-free.

The Prothrombin G20210A mutation is another cause of hereditary thrombophilia that is present in 2% of the general population and in approximately 20% of patients with VTE. It is associated with a 2.8 fold increased risk of thrombosis.(21) Additional hereditary thrombophilias are elevated levels of Factor VIII and Factor XI.(22-24) Undoubtedly, new hereditary thrombophilias will be described in the future as this is a rapidly growing field.

2.3.2 Acquired Thrombotic Risk Factors

A large number of physiologic states and medical conditions are also associated with the development of thrombosis. These include malignancy, surgery, trauma, pregnancy and medications such as oral contraceptives (OCP) and hormonal replacement therapy (HRT).(25-27)

The association between malignancy and thrombosis has long been known, and was first described by Trousseau in 1865. The risk of thrombosis in patients with malignancy varies greatly, depending on the tumour histological subtype, the presence of metastasis, level of patient disability and treatment-related aspects such as chemotherapeutic agents and radiotherapy.(28-30) Overall, malignancy is a moderate risk factor for thrombosis.

Similarly, surgery is recognised as an important risk factor for VTE. The level of risk depends on the duration and type of surgery. Certain types of surgeries, notably lower extremity orthopaedic surgery, warrant routine prophylactic perioperative anticoagulation due to the 50% risk of VTE in the absence of prophylaxis.(16) The duration of elevated VTE risk after surgery is unknown, but may be as long as three months.

Recent trauma is also associated with VTE. A population based study demonstrated that trauma increases the risk approximately 13-fold.(31) The level of risk is dependent on the sites of injury and the degree of patient immobility, and is influenced by endothelial injury from the trauma and activation of coagulation as a result of the injury. (32)

Immobility is another notable VTE risk factor. Immobility often occurs as a result of other medical or surgical conditions (e.g. postoperative state, congestive heart failure, etc), but can also be isolated, as in the case of limbs paralysed by stroke.(33) The VTE rate in paralysed limbs is notably higher than in the non-paralysed limb.

Several medications are associated with an increased risk of VTE. These include oral contraceptive pills (OCP), hormone replacement therapy (HRT) and tamoxifen. Users of second and third generation OCP have a 3 –4 times increased risk of VTE compared with non-users.(34) Similarly, the Heart and Estrogen/Progestin Replacement Study (HERS), a large randomized trial of HRT users versus placebo, recently reported a 2.7 fold increase in VTE risk in women on HRT. (35)

Many risk factors lead to venous thrombosis via a combination of Virchow's mechanisms. For example, pregnancy which carries a 3 – 5 fold increased risk of thrombosis compared with non-pregnant individuals.(36) It is associated with lower limb venous stasis as documented by Doppler flow studies and is also a hypercoagulable state as evidenced by increased levels of coagulation factors, decreased levels of coagulation inhibitors and reduced fibrinolytic activity.(37)

Thrombotic risk factors can also interact with each other to greatly increase the risk of thrombosis. For example, the combination of heterozygosity for the Factor V Leiden mutation (RR = 7) and oral hormonal contraceptives (RR = 4) increases the relative risk of thrombosis to 35.(38;39)

2.4 Clinical Importance of Recognising Thrombosis Risk Factors

Treatment and prophylaxis guidelines based on the results of clinical trials take thrombosis risk factors into account when issuing recommendations. For example, a woman with a history of a previous DVT can be followed during pregnancy clinically without heparin prophylaxis, but the presence of any hereditary thrombophilia requires the serious consideration of prophylactic treatment with unfractionated or low molecular heparin.(40) In summary, increased understanding of thrombotic risk factors has been instrumental in identifying subsets of people at higher risk of thrombosis for whom prevention in the form of lifestyle modification or anticoagulant prophylaxis may be warranted.

2.5 Travel and Thrombosis

2.5.1 Biologic evidence

Long distance travel has long been proposed as a risk factor for thrombosis. Possible mechanisms include venous stasis with all types of travel, and additionally dehydration, hypoxia, use of sleeping pills and hypobaric conditions inducing a hypercoagulable state with airline travel.(41) This has led to the conceptual division of risk factors of air travel into "cabin-related" and "patient related".(42)

It is conceptually plausible that prolonged and cramped seating in any form of travel leads to venous stasis. A widely quoted study from the 1950's that examined venous flow in non-

travelers demonstrated that venous flow in the legs is two thirds lower when sitting compared to lying down.(43)

Dehydration from low humidity cabin conditions and alcohol intake during airline flights have been hypothesized to cause increased plasma viscosity, with a resultant increased risk for thrombosis. However, a small study of healthy individuals in simulated air travel conditions showed a net average fluid gain of 1.15 L with no detectable increase in plasma viscosity, which refutes this hypothesis. (44)

The induction of a possible hypercoagulable state during airline travel due to the hypobaric conditions has also been examined. A study by Bendz et al simulated airline travel conditions to identify whether travel leads to a hypercoagulable state.(41) Twenty healthy male volunteers were subjected to a hypobaric chamber that simulated air travel conditions, but were instructed to walk and consume water in order to isolate the hypobaric effect on coagulation. The investigators found evidence of activation of coagulation with significant increases in levels of prothrombin fragments 1 + 2, thrombin-antithrombin complex, activated Factor VII activity and reduction in factor VII antigen. The same authors subsequently studied 12 healthy males under the same conditions, but administrated low molecular weight heparin prior to the hypobaric chamber exposure.(45) Under these conditions there was no activation of coagulation. These studies were small, uncontrolled and unblinded. However, they lend some credibility to air travel as a candidate risk factor for thrombosis, as well as suggest the potential beneficial role of thromboprophylactic therapy.

2.5.2 Epidemiological Studies on Travel and VTE

Despite the common belief that travel is a risk factor for DVT and the indirect evidence presented above, available epidemiological data on this association is conflicting (46-54), and editorials have called for additional studies to clarify the issue.(55-59) The definitive study would be a blinded controlled trial of subjects randomized to travel or no travel, with a diagnostic investigation for DVT performed at baseline and after the interventions by operators who are blinded to assignment group. However, it is not ethical to conduct a randomized study with the intent to prove harm. Furthermore, given the low expected incidence of VTE following travel, this study would require tens of thousands of people to observe enough VTE events to calculate precise estimates of risk. Such a study is not feasible from ethical, financial or logistical standpoints. Given this obstacle, the main published studies addressing this issue to date have been case control studies, which have unfortunately reached opposing conclusions. Two cohort studies and two small randomized controlled trials have also been published, but their interpretation is limited by significant design weaknesses. Travel exposure in all studies has been assessed by subject recall using a questionnaire format.

These studies were found by a systematic search of Medline for English language articles published between January 1, 1966 and September 1, 2004 containing the term travel in combination with one of the following: thrombosis, venous thrombosis, venous thromboembolus, deep vein thrombosis or pulmonary embolus. This resulted in finding a total of 410 articles. Many were review articles, case reports and editorials. The main findings of the eight (8) studies found, as well as their strengths and weaknesses are outlined below.

The first study was a case control study by Ferrari et al (n = 320), which found that the odds ratio (OR) for the association between travel of more than 4 hours and DVT was 3.98 (95% CI

1.9 – 8.4).(47) However, several potential biases could have influenced the results. Firstly, the control patients were hospitalised cardiac patients, whose mobility and potential to travel may have been significantly limited. Also, it is unknown whether the study subjects or the interviewers were blinded to the study hypothesis and the control/case status of the patient. Furthermore, the odds ratio was not adjusted for known VTE risk factors that may have been confounders or effect modifiers, despite the baseline differences between control and case patients. Finally, the analysis did not distinguish between different travel modalities or examine the effects of increased travel duration.

A large case control study by Samama et al (n = 988) used age and sex matched controls. The study showed that the odds ratio for the association between recent "prolonged travel" and DVT was 2.35 (95%CI 1.45 – 3.8).(51) However, the duration of travel that constituted "long haul" travel was not specified. Furthermore, only univariate analysis was carried out, and thus travel was not established as an independent risk factor. The case patients were much more likely to have had a history of prior DVT, pregnancy and CHF than the controls, further strengthening the need for a multivariate analysis with adjustment for confounders. This study also produced some unlikely results, such as finding that the use of oral contraceptives and smoking were protective for DVT. As in Ferrari's study, separate risk estimates were not provided for different modalities or durations of travel.

The third case control study by Kraaijenhagen et al (n = 788) found no association between travel and DVT, with an odds ratio of 0.7 (95% CI 0.3 – 1.4) between all types of travel and DVT.(49) The authors examined different modalities of transportation: plane, car or train, and were able to calculate separate estimates of risk for travel in general as well as air travel alone, controlling for known risk factors. For any travel of greater than 3 hours' duration, there was

no increased risk of thrombosis found (OR = 1.0, 95% CI 0.3 – 3.0). Air travel of greater than 3 hours' duration was also not associated with an increased risk of DVT (OR = 0.7, 95% CI 0.3 – 1.4). Strengths of the Kraaijenhagen et al study include the administration of a standardised questionnaire prior to ultrasound testing for DVT, and the performance of ultrasound by technicians who were blinded to the questionnaire data. However, the odds ratio calculations in the Kraaijenhagen study are based on very small numbers of patients with a history of travel (9 patients in the DVT group versus 43 in the non-DVT group). Also, the investigators did not examine the relationship between increasing duration of travel and DVT; rather, travel was examined as a binary exposure. Finally, the assessment of other VTE risk factors in cases and controls did not include thrombophilia testing.

Lastly, a population-based study conducted by Lapostolle et al found a positive association between increasing air travel duration and severe PE. (52) The authors reviewed the medical records of all passengers that presented with symptoms suggestive of PE during flight or on arrival at the Charles de Gaulle airport in Paris who were then brought to this airport's referring hospital. Details on class of travel, travel distance and duration were obtained for passengers with objectively confirmed PE. The incidence rate of severe PE was calculated using the number of all passengers arriving at the Charles de Gaulle airport over the study period as the denominator. It was also possible to calculate the incidence of severe PE for increasing travel durations, as the place of origin for all passengers was available. The incidence of severe PE increased with increasing travel time, ranging from 0.00 for travel of less than 3 hours' duration to 4.77 PEs/million arrivals for travel of more than 12 hours' duration. The major strength of this study was the large number of travelers, which allowed for precise calculations. Weaknesses included the inability to control for confounding factors due to the study design. Also, there was no adjustment made for the fact that passengers travelling

for longer durations had a longer observation period than those traveling for shorter durations, and, therefore, could have a higher incidence of PE regardless of travel exposure. Finally, the inclusion of passengers who presented during or immediately following their flight may have resulted in an underestimation of the PE incidence as the authors would miss anyone with milder symptoms, or those passengers who presented hours to weeks later at different hospitals.

Other observational studies that have examined the association between travel and VTE include two case control studies (46;50), a population based cohort study (52;60) and a prospective randomized study (61). Details regarding control selection, case selection, travel definition, control for confounders and results of these studies are summarized in Table 1. They also come to opposing conclusions as to whether or not travel is associated with VTE.

There has also been a randomized interventional study on the efficacy of elastic stockings (ES) in the prevention of travel-associated DVT. In this study, patients over age 50 years with no VTE risk factors were randomized to no intervention or to ES for the duration of a flight. The study found that 10% of patients without ES developed asymptomatic calf DVT following flights of greater than 8 hours as compared to 0% of patients randomized to ES. Several authors have raised concerns regarding both the accuracy of Doppler assessment by unblinded technicians, the clinical significance of asymptomatic DVT, and the accuracy of ultrasound imaging for isolated DVT in the calf.(55;62) In summary, the available data on the risk of VTE associated with travel remains inconclusive, and support the conduct of a large, well controlled study.

2.6 Conclusion

In conclusion, while there are theoretical reasons to support that prolonged travel is a risk factor for VTE, the epidemiological data remain unclear. Studies to date have been limited by small numbers of travelers, inadequate control for confounders or unblinded exposure assessment. Given the large and increasing number travelers internationally and the availability of safe and effective thromboprophylaxis, it is important to firmly establish if, to what extent, and for who, travel is a risk factor for DVT.

Author	Case selection	Control selection	Control for confounders	Travel type	Travel Duration	Result (95% CI)	Net Result
Arya (50)6)	185 patients; DVT	383 patients; DVT suspected but ruled out	No	All Air	> 3 hours > 3 hours + ≥1 VTE risk factor > 3 hours > 8 hours	1.4 (0.7 – 2.6) 2.7 (1.3 – 6.4) 1.2 (0.6 – 2.8) 1.3 (0.6 – 2.8)	Negative
Ferrari (47)3)	160 patients; DVT / PE	160 patients; hospitalised.	No	All	> 4 hours	3.98 (1.9 – 8.4)	Positive
Hosoi (46)2)	101 patients; DVT	106 patients; DVT suspected but ruled out	No	All Air	> 3 hours > 3 hours	1.3 (0.6 – 2.8) 0.8 (0.3 – 1.9)	Negative
Kraaijenhagen et al (49)5)	186 patients; DVT	602 patients; DVT suspected but ruled out	Yes	All Air	> 3 hours > 5 hours > 3 hours	0.7 (0.3 – 1.4) 0.4 (0.1 – 1.3) 1.0 (0.3 – 3.0)	Negative
Lapostolle* (52)8)	56 patients; PE	135.29 million travellers	No	Air	< 5000 km 5000 – 7499 km 7500 – 9999 km > 10 000 km	0.11 (0.01 – 0.71/10^6) 0.40 (0.19 – 0.79/10^6) 2.66 (1.83 – 3.79/10^6) 4.77 (2.66 – 8.41/10^6)	Positive
Martinelli (63)9)	210 patients; DVT / PE	210 study subjects; friends of cases	Yes	Air	Any > 8 hours Travel + HRT Travel + OCP	2.1 (1.1 – 4.0) 1.0 (0.9 – 9.5) 16.8 (3.8 – 74.7) 23.4 (2.6 – 211.2)	Positive
Perez* Rodriguez (60)6)	16 patients; PE	41 million travellers	No	Air	Any < 6 hours 6 – 8 hours > 8 hours	0.39 (0.20 – 0.58/10^6) 0.00 (NA) 0.25 (0 – 0.75 /10^6) 1.65 (0.81 – 2.49/10^6)	Positive
Samama (51)7)	636 patients; DVT	636 patients; with influenza	No; sex, age matched	All	Not stated	2.35 (1.45 – 3.80)	Positive

Legend:
DVT: deep vein thrombosis
HRT: hormone replacement therapy
All travel : plane, car, train.
PE : pulmonary embolus
OCP : oral contraceptives

* Incidence density calculations

3. METHODS

The study described in this thesis was a substudy to the VEnous Thrombosis Outcomes Study, a multicenter FRSQ-funded prospective cohort study examining the predictors of postphlebitic syndrome during long term follow-up of patients with an objectively confirmed lower extremity DVT. The Venous Thrombosis Outcomes study will herein be referred to as the VETO study. This present case control study will be referred to as the RT-DVT study (Recent Travel and DVT study).

3.1 Study objectives and hypothesis of the RT-DVT study

Overall objectives:

To determine, among patients presenting to the vascular laboratory with suspected DVT, whether there is a greater odds of exposure to travel in the month prior to presentation in patients with confirmed DVT as compared to patients in whom DVT is ruled out.

Specific objectives:

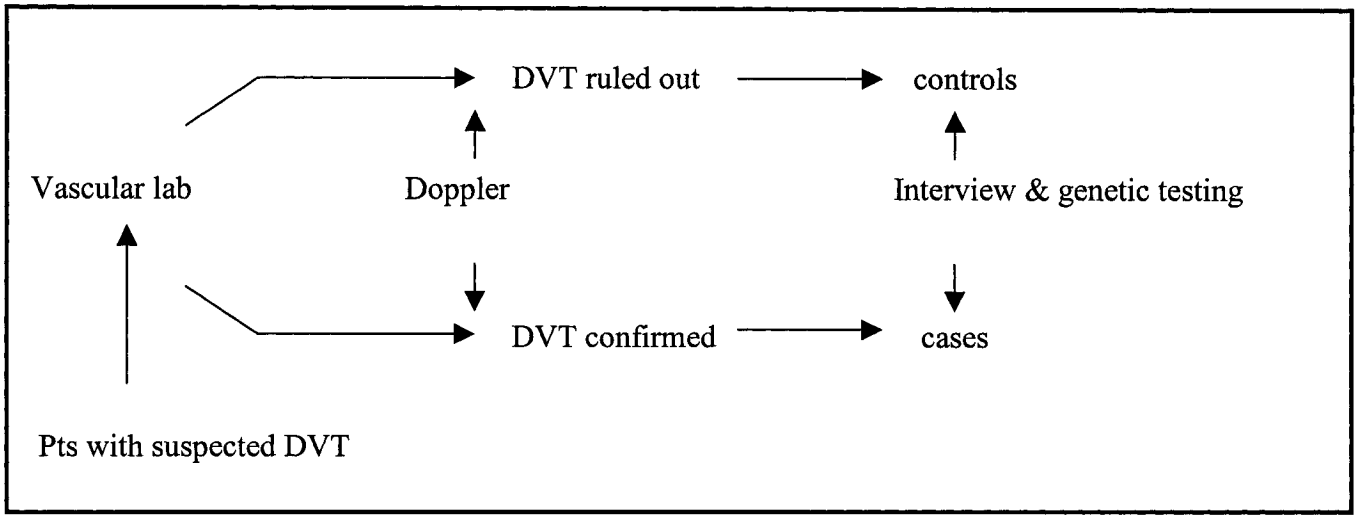
- To determine the strength and direction of association between recent travel and DVT among patients presenting to the vascular laboratory with suspected DVT.
- To evaluate the association between travel and DVT according to different travel modalities and different travel durations.
- To evaluate the role of confounding and effect modification on the association between DVT and travel.

3.2 Research design and rationale

For the purposes of public health policy and clinical decision making, it is vital to determine whether travel is a risk factor for DVT. As discussed in Chapter 2 - Background, studies to date have been conflicting and have had significant methodological limitations. The ideal study would involve a controlled trial with randomization to varied lengths of travel, with diagnostic investigation for DVT performed by blinded assessors at baseline and after the travel intervention. As mentioned previously, given the low expected incidence of DVT, as the population incidence of DVT is only about 1 per 1000 per year,(64) such a study would require hundreds of thousands of travellers to observe enough DVT events to calculate precise estimates of risk, and is not feasible from ethical, financial or logistical standpoints. Such a study would also have problems of generalizability since people consenting to participate as study subjects would likely be different that the usual individual. The case control design is appropriate to assess risk factors for conditions that are relatively rare.

As such, we conducted a multi-center case-control study to test our hypotheses regarding the association between DVT and travel (Figure 3.1). Eligible study recruits were those patients presenting to vascular laboratories with suspected DVT. Both inpatients and outpatients were eligible for participation. Case patients were patients with DVT (obtained from the VETO study) while control patients were patients who had DVT ruled out (recruited for the purposes of this study). Travel history and clinical information on confounders was determined though a 10 – 20 minute interviewer-administered questionnaire after objective testing for DVT. Genetic testing of the two most common inherited thrombophilias, Factor V Leiden and Prothrombin gene mutation, was also performed.

Figure 3.1: RT-DVT Study Design Overview



3.3 The VETO study

The VETO cohort of patients was the source of case patients for the RT-DVT study. This section will outline the subjects and methods used in the VETO study in order to subsequently understand the study population and possible sources of bias of the RT-DVT study.

3.3.1 Aim of the VETO study:

The main goals of the VETO study were to determine the point prevalence of post-phlebitic syndrome two years after the occurrence of acute DVT, as well as to identify clinical predictors of the post-phlebitic syndrome.

3.3.2 VETO Study population:

Source population:

This was a multi-center Quebec study that recruited study subjects at seven participating hospitals: the Montreal General Hospital, Jewish General Hospital, Hôpital Notre Dame, St.

Mary's Hospital, Hôpital Maisonneuve Rosemont and Centre Hospitalier Universitaire du Quebec-Laval (CHUL).

Patients screened:

Beginning in April 2001 and continuing until June 2002, consecutive patients from any outpatient department, presenting to the vascular laboratory in any of the above mentioned hospitals with clinically suspected acute DVT that was subsequently objectively confirmed by Doppler ultrasonography were screened for potential inclusion into the VETO study.

Eligibility criteria:

Screened patients were eligible for participation provided that they were:

1. 18 years of age or older.
2. Able to provide consent (that is, exclusion of incompetent persons).
3. Able to speak in either English or French. Most data was collected from an orally administered questionnaire. Therefore, it was vital to have unhindered oral communication with the study recruits.

Exclusion criteria:

1. Geographic inaccessibility preventing follow-up. The goal of the VETO study was to determine the frequency and causes of the post-phlebitic syndrome as a long term consequence of acute DVT. Geographic inaccessibility would be a major hindrance to follow-up, and result in incomplete follow-up data.
2. Estimated life expectancy less than one years' duration as determined by the patient's primary physician. The goal of the VETO study was long term follow-up of patients with DVT for the development of post-phlebitic syndrome. This

exclusion criterion was necessary to prevent loss of long term outcome data secondary to the death of study patients.

Study patients:

Overall 359 patients were prospectively enrolled in the VETO study.

3.3.3 Study flow:

All potential study recruits were screened for eligibility by an onsite study research assistant. Eligible patients who consented to participate in the study had baseline information collected on a large number of variables. This included demographic data; clinical characteristics of the acute DVT episode; active medical conditions; medication use; previous episodes of VTE; and presence of potential DVT precipitants, including type and duration of travel the last month. The patients were subsequently followed at 1, 4, 8, 12 and 24 months after enrolment for further information regarding costs, quality of life, and post-thrombotic syndrome symptomatology. Finally, blood samples for the genetic testing of Factor V Leiden and Prothrombin gene mutations were collected from each patient.

3.4 RT-DVT study

The RT-DVT study was a case-control design substudy of the VETO cohort study that was implemented specifically for the purpose of this thesis project.

3.4.1 Aim of the RT-DVT study:

The goals of the RT-DVT study were described in section 3.1. The primary goal was to determine, among patients presenting to the vascular laboratory with suspected DVT, whether

there is a greater odds of exposure to travel in patients with confirmed DVTs as compared to patients in whom DVT is ruled out.

3.4.2 Study population:

Source population:

The source population for the RT-DVT study was patients presenting to the vascular laboratories of participating hospitals (the Montreal General Hospital, Jewish General Hospital, Hôpital Notre Dame, St. Mary's Hospital, Hôpital Maisonneuve Rosemont and Centre Hospitalier Universitaire du Quebec (CHUL) for the investigation of clinically suspected lower limb DVT. That is, patients with clinically suspected DVT who subsequently had this diagnosis confirmed or ruled out by Doppler ultrasonography. Patients evaluated in any inpatient or outpatient department at the participating hospitals were eligible.

3.4.3 Identification of cases

Cases for RT-DVT were the 359 consecutive patients with DVT enrolled into the VETO prospective cohort study between April 2001 to July 2002 at the seven participating Quebec hospitals mentioned previously, i.e. patients presenting to the vascular laboratory with a clinical suspicion of acute DVT that was objectively confirmed by Doppler ultrasonography.

3.4.4. Identification of controls

Controls for RT-DVT were those patients presenting to the vascular laboratory with suspected DVT who were subsequently found to be free of DVT by venous Doppler ultrasonography. The control patients were 359 consecutive patients without DVT enrolled from May 1 2003 to August 20 2003 specifically for the RT-DVT study. For convenience and cost issues, controls were sought at only two of the hospitals which recruited case patients - the Jewish General

Hospital and Hôpital Notre Dame. These hospitals were chosen as they were felt to be representative of the social and age demographics of the hospitals listed above.

Eligibility criteria:

In order for cases and controls in RT-DVT to be as comparable as possible other than the presence or absence of DVT, the VETO inclusion and exclusion criteria were used during the screening and recruitment of all study controls. That is, eligible controls were those from any inpatient or outpatient department that were:

1. 18 years of age or older.
2. Able to provide consent .
3. Able to communicate in either English or French.

Exclusion criteria:

1. Geographic inaccessibility preventing follow-up.
2. Estimated life expectancy less than one years' duration as determined by the patients' primary physician.
3. A patient with a known acute pulmonary embolus coming for Doppler testing of DVT. These patients already had diagnosed VTE disease, and would thus be inappropriate control subjects.

Note: As for VETO cases, we did not exclude patients with a history of prior VTE. This enabled us to look at prior VTE as a potential predictor or effect modifier.

In summary, the RT-DVT study population consisted of 359 case patients obtained from the VETO cohort, and 359 controls prospectively recruited expressly for the RT-DVT study.
The RT-DVT study protocol is described in detail over the next few pages.

3.4.5 Outcome definition: ultrasound for the diagnosis of deep venous thrombosis

The outcome ascertained was the presence or absence of DVT as diagnosed by venous duplex Doppler ultrasonography.

While the venogram is considered the 'gold standard' for DVT diagnosis, the test is painful and costly and clinically outdated at most centers. The initial diagnostic procedure of choice in all participating hospitals is the venous ultrasound, a non-invasive test .(13) Published trials show venous ultrasound to have a positive predictive value of 97% and a negative predictive value of 98% for DVT above the knee.(11)

As per standard diagnostic criteria, DVT was considered to be present when there was a lack of compressibility of the examined veins.(9;12) DVT was considered to be absent when there was full compressibility of examined veins. The veins examined extend from the inguinal ligament to the lower calf, as defined by the inferior border of the gastronemius muscle. As per standard criteria, 'deep' veins are veins that have an adjacent arterial supply, as assessed by ultrasonography.

3.4.6 Exposure definition: travel history

The exposure of interest was travel within the past month. The modality of travel (car, bus, train or plane) and the total duration of travel in hours were also assessed. If travel occurred more than once during the time period of interest, the longest trip was used as the exposure rather than cumulative travel, in order to allow assessment of the association between consecutive hours of travel time and DVT. The exposure to travel was obtained by questionnaire administered by a trained interviewer. To create a reference point, the

interviewer stated the date and month that corresponded to the time included in the previous one month's history. The potential effect of cumulative travel time on its association with DVT was not examined.

The interviewers were trained to administer the questionnaire in a standardized fashion. In order to limit the possibility of bias in the ascertainment of travel by the interviewers and differential recall bias by the patients, they remained unaware of the exact study hypothesis.

3.4.7 DNA analysis

The Factor V Leiden mutation and the Prothrombin G20210A mutation were measured in all study subjects who consented to undergo genetic testing for this specific purpose. Genetic material in the form of DNA is identical in all cells in an individual. Classically, DNA is collected by drawing 5cc of blood from a peripheral vein. The blood is spun to form a precipitate and the DNA-containing white blood cells are separated, the DNA extracted, and testing performed for the presence of Factor V Leiden and the Prothrombin G20210A mutations (65). This procedure was performed in the case patients as part of the VETO study. There are minor complications that may occur during the drawing of blood from a peripheral vein including echymosis and mild pain, and there is added inconvenience to the participant of having to wait at the blood drawing center for blood to be drawn. It was felt that these minor complications and inconveniences should be avoided in the control subjects. Therefore, DNA was collected by performing a toothpick scrape of the inner cheek (buccal swab) of patients (66). The cells were then placed in a test tube containing 1cc of sterile 0.9% saline solution. This solution was spun down and DNA extracted from buccal epithelial cells to perform testing for the detection of Factor V Leiden and the Prothrombin gene mutations. The buccal swab yields less DNA than blood samples on average, but identical genetic information.

3.4.8 Data collection

Information on a number of different variables was collected identically in cases and controls of the RT-DVT study. These included

Demographic information:

- Age
- Sex
- Patient location (inpatient vs. outpatient)
- Patient education level
- Patient employment
- Height and weight

Medical History:

- Comorbid medical conditions including hypertension, diabetes mellitus, hypercholesterolemia, asthma, COPD, ischemic heart disease, stroke and congestive heart failure.
- Medication use including the use of hormone replacement therapy, oral contraceptives, antiestrogen/antiandrogen drugs, aspirin, warfarin, heparin, non-steroidal anti-inflammatory agents and antiplatelet agents within 30 days of presentation.
- Smoking status
- Prior history of VTE events
- Family history of VTE

Potential DVT triggers:

- Cancer, including site, year of diagnosis and whether it was active.
- Surgery within the previous 3 months
- Leg trauma within the previous 3 months
- Immobilization within the previous 3 months

- Travel within the previous month
- Pregnancy or early postpartum period (less than 6 weeks)

Definitions utilized for determination of the presence of the above medical conditions:

Cancer

Patients were asked whether a diagnosis of cancer (excluding non-melanomatous skin cancer) had been made at any time in the past; its location; whether it was currently active; whether it had metastasized; if they were currently receiving treatment. Sensitivity and specificity for self report of invasive cancers by questionnaire as compared to chart review has been validated.(67)

Recent surgery or immobilization

Patient were asked for exposure to surgery requiring general anesthesia of 30 minutes or more within four weeks prior to presenting. Immobilization for any reason (sickness, injury, etc) requiring 24 or more consecutive hours in bed in the past month was also recorded.

Oral contraceptives and hormone replacement (HRT)

Patients were asked about current use of oral contraceptives and hormone replacement therapy. Current use was defined by the use of any brand taken at any dose, more days than not (>50%) within the past month. Questionnaire extraction of this data has been validated.(68)

Pregnancy

Patients were asked for pregnancy or postpartum status (up to and including six weeks postpartum).

Previous deep venous thrombosis or pulmonary embolus

Patients were asked about previous objectively diagnosed deep venous thrombosis or pulmonary embolus at any time in the past. Lay terms such as 'blood clot' were used. If this was not spontaneously recalled, the patients were questioned regarding the use of anticoagulants 'blood thinners' in the past, with its treatment indications. Obtaining DVT history by patient interview as compared to chart review has been shown to be valid .(69)

Family history of venous thromboembolism

Patients were asked if they had first or second degree relatives that had suffered from objectively diagnosed pulmonary embolus or deep venous thrombosis.

Known inherited thrombophilia

For cases, blood samples were drawn for DNA collection and testing of Factor V Leiden and Prothrombin mutations as part of the VETO study at the four month follow-up visit. For control subjects, DNA was collected through buccal swabs by trained personnel. The validity of extracting DNA from buccal swabs compares favorably to blood samples, although the DNA yield is lower.(65;70) The molecular genetic laboratory at the Jewish General Hospital performed standard DNA extraction and testing for the detection of the two mutations on all study patients. Heterozygosity (one abnormal gene copy), homozygosity (both abnormal gene copies) and double heterozygous state (one abnormal copy of each) for these polymorphisms was documented.

Appendix 2 provides the RT-DVT English consent form and Appendix 3 provides a copy of the English RT-DVT questionnaire.

3.5 Study setting

3.5.1 Training and supervision of research assistants

Three bilingual research assistants were hired specifically for the purpose of recruiting controls for the RT-DVT study. They all had a science background, and underwent a one week supervised training period by myself with graduated independence in work responsibilities. This training included a didactic lecture on general medical research ethics as well as pathophysiology of venous thromboembolic disease. The specific study hypothesis regarding DVT and travel was not revealed to the research assistants to ensure that data gathering occurred in a blinded fashion with minimal chance for bias. Subsequently, both the French and English language consent forms and the data gathering sheet (questionnaire – Appendix 2) were explained item by item, with each item of the questionnaire being operationalized. The research assistants then observed several structured clinical interviews using the consent and questionnaire in the patient-preferred language, and they subsequently requested consent and performed the structured interview on additional volunteer patients. Data from these interviews were not used as part of the data analysed for the RT-DVT study. Finally, the research assistants were shown how to perform buccal swab testing with the use of toothpicks for the purposes of collecting genetic material. The research assistants, vascular laboratory technicians and the study subjects undergoing the questionnaire were kept blinded to the specific study hypothesis by being informed that the aim of the study was "to further study risk factors for DVT".

At the study onset, the research assistants performed the screening for eligibility, consent, study subject interview and buccal swab testing under direct observation for two days. After that time, random visits were performed by myself several times weekly. There were also weekly team meetings to discuss any issues or concerns arising directly from the study. The research assistants had continual access to either Dr. Susan Kahn or me via pager for any problems or questions.

The research assistant salaries were funded by a pilot project grant from the Fonds de Recherche en Sante du Quebec as well as by an unrestricted educational grant from Aventis Canada.

3.5.2 Study flow

Vascular technicians or vascular physicians performed vascular Doppler studies on all patients referred to the vascular laboratory with a clinical suspicion of lower extremity DVT as per standard technique. They were blind to the study hypothesis during the recruitment period of cases (recruited during the main VETO study) and controls (recruited non-concurrently during the RT-DVT substudy).

For the VETO study (recruitment of cases), when a patient had a positive study the medical personnel performing the Doppler study identified the patient as a potential study candidate, and signalled the VETO research assistant to verify eligibility, request consent from eligible patients, and perform the VETO baseline questionnaire over a 10 to 20 minute period and draw blood for genetic studies on successful study recruits. Data on demographic information, medical history, medications and exposure to various thrombosis risk factors was collected from the study subjects. For each medical problem, both official medical terms and layman

terms were used (for example, "myocardial infarct" and "heart attack" or "COPD" and "smoker's asthma"). Further clarification was given to the patients as needed. The medical chart was consulted if the patient was unsure of any information.

For the recruitment of controls, when a patient had a negative vascular study, the medical personnel performing the Doppler study identified the patient as a potential study candidate, and signalled the RT-DVT research assistant. The research assistant verified eligibility, requested consent from eligible patients, performed the RT-DVT questionnaire (identical to the VETO baseline questionnaire), and took a buccal swab sample for genetic studies. All patients had one copy of their signed consent form placed in their patient record, one kept for study purposes, and a third given to the patient.

3.5.3 Avoidance of bias

Recall bias:

Since the aim of the RT-DVT study was to determine if recent travel was a risk factor for DVT, it was crucial to minimize any potential for differential recall bias between cases and controls. This was achieved by ensuring both cases and controls had been referred to the vascular lab for identical reasons (i.e. suspicion of DVT). Therefore, determination of case or control status differed only by the result of the ultrasound. Also, differential recall of travel exposure was minimized by administering the identical questionnaire in the same manner at comparable times in the investigation of both the case and control subjects. That is, all patients had clinically suspected DVT with subsequent referral for vascular studies, and all patients had equal time to reflect on possible exposures to risk factors, including travel.

Ascertainment bias:

Bias due to differential ascertainment of travel exposure as well as of other medical and demographic data between cases and controls was avoided for controls by blinding the trained interviewers and vascular technicians to the RT-DVT study hypothesis. Blinding for cases was achieved as the RT-DVT (i.e. focus on travel) substudy was not yet underway at the time of their interviews.

Misclassification bias:

There was also potential for misclassification of case and control status, that is a case patient being misclassified as having a DVT when in fact they did not. Because of the very high positive predictive value of the Doppler ultrasound test (97%), this was unlikely. Of greater concern was the potential for misclassification of controls as having no DVT when in fact they did. That is, misclassification of a control due to a false negative test. This could have occurred since the Doppler ultrasound has limited sensitivity for the detection of calf vein DVT. However, this remains an unlikely cause of significant misclassification in this study. In the context of high clinical suspicion of DVT and a negative ultrasound study, recommendations include either performing a venogram, or repeating a Doppler in several days' time. This is to detect DVT extension, as calf vein DVTs can extend to more proximal deep veins over the course of several days, becoming detectable at that point. Since the research assistants were present during all hours that the vascular laboratory was open, any patient scheduled for a repeat test was seen, and if the follow-up study was positive the patient was not used as a control. Additional testing of patients with a high clinical suspicion of DVT was performed either by serial ultrasonography or venography at the discretion of the attending physician rather than mandated by the research protocol.

3.5.4 Data collection and storage

The coordinating center for the VETO study and the RT-DVT VETO substudy was the Center for Clinical Epidemiology and Community Studies at the JGH. All data was retained in duplicate - original paper form at the recruitment site, and a second paper copy at the central coordinating center. Forms were kept in a locked office in a secured department. Data was entered onto a computer database at the JGH. Each patient was assigned a unique study identification number by the coordinating center that allowed anonymity of information. Data access was restricted to the study personnel only, and was stored in a locked office with secure access. Data entry was performed at the JGH by a data entry manager using the subject study numbers only. Data entry was performed by duplicate entry for all study patients in the RT-DVT study to minimize data entry errors. Those performing data entry were blind to the study hypothesis. Each site was informed of the occurrence of missing data, and attempts were made to retrieve this data by reaching the patient or reviewing the hospital chart.

3.5.5 Ethical considerations

The RT-DVT study received ethics approval as a VETO substudy at the McGill University Faculty of Medicine Institutional Review Board, the Jewish General Hospital Research Ethics Committee and the Notre Dame Hospital Research Ethics Committee. Patient participation was voluntary, with the right to withdraw consent at any time. The interview and data management took place in such a way that maintained patient confidentiality.

Patients were required to provide a second, separate consent for genetic testing of two common clotting defects: Factor V Leiden and the Prothrombin G20210A mutation. These genetic polymorphisms are common, present in more than 5% of the population.(71;72) During their lifetime, only a fraction of people with either mutation will suffer from thrombotic events.

Because of this, current recommendations do not advocate any intervention in patients who have these mutations but have never had DVT. Results were discussed with the study subject at their request. The genetic material was collected for the specific purpose of this study only.

3.6 Data analysis and statistical methods

3.6.1 Sample size

Considerations for sample size depend on the desired power and targeted significance level of the relationship between the main outcome and exposure variables. The number of independent variables that will likely be included in the regression analysis model must also be taken into consideration. The number of case patients for the RT-DVT study was predetermined by the VETO study, at 359. Using a 20% estimated prevalence of travel in case patients from a previous case control study,(51) with 359 cases and 359 controls we would be able to detect a relative risk of 1.5 with a Type I error of 0.05 and 87% power.

The ratio of cases to controls for purposes of power, and matching (or not) of controls to cases on certain variables must also be decided in the planning stages of a study. The case to control ratio commonly varies between 1:1 up to 1:4, and is decided on a study to study basis depending on feasibility issues such as estimated number of cases that will be recruited, and cost and time involved. The statistical power of a study increases as the number of controls per case increases. However, when the number of cases is large, a ratio of 1:1 is often selected, since the recruitment of additional controls represents significant cost and time considerations in return for a limited statistical benefit. For this reason we decided to recruit control patients to achieve a 1:1 ratio with case patients.

Another decision regarding recruitment of controls was whether or not to choose matched controls. Matching on variables known to be associated with case status can increase the power of the analysis. The decision influences the type of statistical analysis performed (unconditional versus conditional logistic regression analysis), and must again take into consideration the cost and time factors involved in finding controls who match on one or additional variables to the case patients. In this study, the control patients were unmatched due to cost and time constraints for control recruitment

3.7.2 Statistical Analysis

Univariate analysis:

Proportions of affected individuals in each group were used to describe the distribution of discrete variables. Proportions between cases and controls were compared using χ^2 tests, and their differences are presented using 95% confidence intervals.

For continuous variables, means were compared between cases and controls using the Student t-test, with differences in means expressed by 95% confidence intervals, and standard deviations calculated using standard formulae.

For variables with skewed distributions, medians and interquartile ranges were used instead of means and standard deviations as these provide a better overall summary of the distribution for the variable in question. Cases and controls were compared using the Wilcoxon rank sum for comparison of non parametric data.

Odds ratios (ψ) for the risk of exposure to travel in cases compared with controls were calculated via the PROC LOGISTIC option in SAS. However, while the crude association

between travel and DVT was calculated, this relationship can be deceiving if other clinical variables are not taken into account. These variables, which modify the exposure/outcome association, are termed confounders. A confounder is a variable that is related to both the exposure and to the outcome. Confounding can be taken into account either in the design or analysis stages of a study. In the design stage, one can restrict study subjects to one level of a confounder (for example, studying a disease only in non-smokers if smoking is considered a confounder), or match controls with cases on the confounding variable. In the analysis stage, a confounder can be identified and taken into account either with stratified analysis or by using a modeling approach. In the present study, modeling by including the potential confounding variables in logistic regression analysis was used, as there were multiple potential confounders, thus making the other approaches unfeasible. Each independent variable that was a priori deemed to be a predictor of both DVT and travel on a clinical basis or through review of previous studies, and hence a possible confounder (listed in Tables 3.1 through 3.6), was analyzed individually using the PROC LOGISTIC function in SAS to generate a crude odds ratio for its relationship with the dependent variable DVT. The β parameters were estimated by SAS using maximum likelihood estimation, and the effect of each variable on predicting outcome was evaluated. A p-value < 0.1 was considered to indicate association with DVT. In this study a linear logistic regression model was assumed. For this reason, linearity in the logit for continuous variables was verified by measuring and plotting their interquartile medians.

Bivariate analysis:

A correlation matrix of all independent variables was generated to identify any highly correlated variables that would indicate potential problems with colinearity. Stratified analysis was carried out with the individual exposure variables on the outcome (DVT) to assess for the possibility of confounding or effect modification. Confounding was identified when there was

a significant difference in odds ratios (10% difference) calculated in a crude analysis versus a Mantel-Haenzel estimate.

Multivariate analysis:

Multivariate modeling using unconditional logistic regression with PROC LOGISTIC was performed by forward stepwise addition of variables judged to be important predictors of DVT on either clinical grounds, a p ≤ 0.1 on univariate analysis or bivariate analysis. Travel (all forms combined), plane travel and car travel were each separately analyzed as a dichotomous (yes/no) outcome variable as well as a categorical outcome variable using the method described below. Categorical travel duration cut-points were selected *a priori* with different travel destinations in mind in the following manner: ≤ 3 hours: short haul flights, 3 – 6 hours intra-continental flights, 6 – 12 hour medium duration flights, ≥ 12 hours long haul flight. Analysis of travel as a continuous measure ($0 \rightarrow \infty$) to was not possible, as data for travel of $\leq$ 3 hours duration were grouped together as three hours or less.

General guidelines for linear regression recommend having at least 10 observations per variable added to a model to avoid over-modeling and creating a model that is non-reproducible outside of one particular data set. Although there is no such rule for logistic regression, conservatively this ratio should be greater than 10:1, given that the dependent variable is binary and is thus less informative. Therefore, with 359 cases it was decided *a priori* that no more than 35 variables were to be tested or modeled. The contribution of possible confounders identified through stratified analysis was further assessed by the variation in β that resulted from addition of the confounding variable to the model. Effect modification was identified when the β coefficients for the interaction term was significant defined as a p value less than 0.05. Several models were generated, and the model with the best fit was

chosen. Goodness-of-fit was evaluated by the Hosmer-Lemishaw procedure via the LACKFIT procedure. Acceptance of the Hosmer-Lemeshow null hypothesis with a p-value of greater than 0.05 is one indicator suggesting an appropriately fitted model. Outliers in the final model were assessed via DFBETA and IPLOTS, which assesses the leverage of every observation. Extreme values assessed with these methods can identify whether any individual study subject has a large influence on the results of the model. SAS software (SAS Institute version 8.2) was used to perform the analyses described above.

CHAPTER 3. METHODS: TABLES

TABLE 3.1: OUTCOME VARIABLE

Variable Description	Variable Definition	Variable Type	Variable Coding
Case status for DVT	Noncompressibility of deep veins and/or visualization of intraluminal thrombus by Doppler examination	Dichotomous	Case = 1 Control = 0

TABLE 3.2: EXPOSURE VARIABLES

Variable description	Variable Definition	Variable Type	Variable Coding
Recent travel	Travel by car, train or plane within a month prior to presentation	Dichotomous	No = 0 Yes = 1
Recent travel	As above	Dummy variables	≤3 hrs 3 – 6 hrs 6 - 12 hrs > 12 hrs

TABLE 3.3: PREDICTOR VARIABLES, DEMOGRAPHIC

Variable Description	Variable Type	Variable Coding
Patient age	Continuous	Age in years
Patient age	Dichotomous	Age in years ≤65 = 0 Age in years ≥65 = 1
Gender	Dichotomous	Male = 0 Female = 1

TABLE 3.4: PREDICTOR VARIABLES, GENERAL HEALTH CONDITIONS

Variable Description	Variable Type	Variable Coding
Body Mass Index	Continuous	Mean +/- SD
Smoking status	Dichotomous	No = 0 Yes = 1
Congestive heart failure	Dichotomous	No = 0 Yes = 1
Diabetes	Dichotomous	No = 0 Yes = 1

TABLE 3.5: PREDICTOR VARIABLES, ACQUIRED DVT PRECIPITANTS

Variable Description	Variable Definition	Variable Type	Variable Effect	Variable Coding
Cancer	Cancer of any site, as described above;	Dummy	C or EM	No cancer Cancer, ever Cancer, active
Recent surgery	Surgery under general anesthesia of longer than 30 minutes within the past four weeks.	Dichotomous	C or EM	No = 0 Yes = 1
Immobilization	72 or more consecutive hours confined to bed in previous month.	Dichotomous	C or EM	No = 0 Yes = 1
Oral contraceptive	Any hormonal OCP use in past month more than 50% of days.	Dichotomous	C or EM	No = 0 Yes = 1
HRT	HRT use in the past month more than 50% of days.	Dichotomous	C or EM	No = 0 Yes = 1
Pregnancy	Currently pregnant or within 6 weeks of postpartum period.	Dichotomous	C or EM	No = 0 Yes = 1
Previous VTE	Objective diagnosis, at any time in the past, of either a pulmonary embolus or deep venous thrombosis.	Dichotomous	C or EM	No = 0 Yes = 1

* C = confounder, EM = effect modifier

TABLE 3.6: PREDICTOR VARIABLES, HEREDITARY DVT PRECIPITANTS

Variable Description	Variable Definition	Variable Type	Variable effect	Variable Coding
Family history of VTE	First degree family member with VTE in past.	Dichotomous	C or EM	No = 0 Yes = 1
Factor V Leiden mutation	Genetic testing for the Factor V Leiden mutation.			
	- Homozygous	Dichotomous	EM	No = 0 Yes = 1
	- Heterozygous	Dichotomous		No = 0 Yes = 1
Prothrombin mutation	Genetic testing for Prothrombin G20210A.			
	- Homozygous	Dichotomous	EM	No = 0 Yes = 1
	- Heterozygous	Dichotomous		No = 0 Yes = 1
Double heterozygote	Finding of heterozygous state for both Factor V Leiden and Prothrombin mutations.	Dichotomous	EM	No = 0 Yes = 1

4. RESULTS

Control population for analysis

As described in the Methods section, for reasons of cost and convenience controls were recruited from two (JGH, HND) of the seven centers that recruited cases. These two centers were selected as they were felt to serve patient populations representative of all seven centers. Furthermore 46% of all case subjects had been recruited from these 2 centers. Tables 4.15 and 4.16 show the comparison of the demographic descriptors, medical conditions and DVT risk factors of cases recruited from the JGH and HND sites (n = 165) as compared to the case group as a whole (n = 359). Given the absence of evidence that the cases recruited at the JGH and HND sites were different from cases as a whole, we believe that the controls, recruited at the JGH and HND sites are likely to be representative of controls that would have been recruited at all seven sites.

4.1 Univariate analysis

4.1.1 Demographic Variables (Table 4.1)

The RT-DVT case control study recruited 359 cases and 359 controls. The baseline characteristics of the two groups of patients are presented in Table 4.1. Cases were younger than controls (55.8 +/- 14.3 years versus 64.8 +/- 16.0 years respectively; p = <0.001), and had a higher proportion of males (50.1% of cases versus 34.8% of controls; p = <0.0001). The BMI was similar among cases and controls (27.3 +/- 5.4 versus 27.5 +/- 6.7 respectively; p = 0.78) as was the proportion of current smokers (18.4% versus 15.3% respectively; p = 0.27). The distribution of inpatient and outpatients was also similar between the two groups with 67.4% outpatients among cases as compared to 68.5% among controls (p = 0.75). Finally, cases were significantly more educated than controls with 55.6% of cases having at least some university education as compared to 38.2% of controls (p = <0.0001).

TABLE 4. 1: DEMOGRAPHIC DATA

Variable	Cases n = 359	Controls n = 359	95% CI of difference	p-Value
Age (years), mean +/- SD	55.8 +/-14.8	64.8 +/- 16.0	6.8, 11.2	<0.001
Sex (% male)	180/359 (50.1%)	125/359 (34.8%)	8.3, 22.3%	<0.0001
BMI, mean +/- SD	27.3 +/-5.4	27.5 +/- 6.7	- 0.7, 1.1	0.78
Smoker	66/359 (18.4%)	55/359 (15.3%)	- 2.4, 8.6%	0.27
Patient location (% outpatient)	242/359 (67.4%)	246/359 (68.5%)	- 5.7, 7.9%	0.75
Education				
None	2/359 (0.6%)	6/359 (1.7%)		
Grade school	34/359 (9.5%)	74/359 (20.6%)		
High school	123/359 (34.3%)	142/359 (39.6%)		<0.0001
Some university	120/359 (33.4%)	67/359 (18.7%)		
University degree	80/359 (22.2%)	70/359 (19.5%)		

4.1.2 General medical conditions (Table 4.2)

General medical conditions were all significantly more common in the control as compared to case subjects, as shown in Table 4.2.

TABLE 4.2: GENERAL MEDICAL CONDITIONS

Variable	Cases n = 359	Controls n = 359	95% CI of difference	P-value
Stroke	11/359 (3.1%)	30/358 (8.4%)	1.9, 8.7%	0.0022
Heart failure	12/359 (3.3%)	39/358 (10.9%)	3.9, 11.3%	<0.0001
Hyperlipidemia	72/359 (20.0%)	109/358 (30.4%)	4.1, 16.7%	0.0015
Diabetes	29/359 (8.1%)	77/358 (21.4%)	8.3, 18.3%	<0.0001
COPD	14/359 (3.9%)	27/358 (7.5%)	0.3, 7.0 %	0.0365

4.1.3 Acquired DVT precipitants: (Table 4.3)

Cases had significantly more acquired conditions previously shown in population-based studies to be associated with an increased risk of DVT. These included a previous history of either DVT or PE (21.8% cases versus 14.5% of controls, p = 0.011), immobility (22.1% versus 9.5%, p = <0.0001), recent surgery (28.0% versus 17.8%, p = 0.0012) and recent trauma (17.3% versus 8.9%, p = 0.0009). Among women, cases were also more likely to be taking oral contraceptives (14.0% versus 1.3%, p = <0.0001) and hormone replacement therapy (28.5% versus 10.3% respectively, p = 0.001). Two conditions were equally prevalent in cases and controls; pregnancy in 4.5% and 4.0% (p = 0.95) of women and currently active cancer in 12.5% and 10.6% (p = 0.29), respectively.

TABLE 4.3: ACQUIRED DVT PRECIPITANTS

Variable	Cases N = 359	Controls N = 359	OR (95%CI)	P- value
Previous VTE	78/358 (21.8%)	52/359 (14.5%)	1.65 (1.12, 2.43)	0.011
Immobility	79/358 (22.1%)	34/359 (9.5%)	2.67 (1.73,4.12)	<0.0001
Recent surgery	100/357 (28.0%)	64/359 (17.8%)	1.80 (1.26,2.57)	0.0012
Recent trauma	62/358 (17.3%)	32/359 (8.9%)	2.11 (1.34, 3.32)	0.0009
OCP †	25/179 (14.0%)	3/234 (1.3%)	12.50 (3.71, 42.12)	<0.0001
HRT †	51/179 (28.5%)	24/234 (10.3%)	3.49 (2.05, 5.94)	0.001
Cancer diagnosis	78/359 (21.7%)	77/359 (21.4%)	1.20 (0.72,1.46)	0.93
Presently active	45/359 (12.5%)	38/359 (10.6%)	1.21 (0.77,1.92)	0.29
Pregnancy †	8/177 (4.5%)	9/234 (4.0%)	0.97 (0.37,2.55)	0.95

Note: † Denominator = women

4.1.4 Hereditary DVT precipitants (Table 4.4)

A positive family history of VTE was present in 33.7% of cases as opposed to only 16.8% of controls. Similarly, significantly more cases were positive for the Factor V Leiden mutation than control subjects (15.5% versus 7.0%). Prothrombin gene mutation was more common in case patients (5.3% of cases compared to 1.3% of controls), but this difference was not statistically significant. Homozygosity for Factor V Leiden and Prothrombin mutations as well as double heterozygous states (ie presence of both Factor V Leiden and Prothrombin mutations in a single subject) were all uncommon conditions, and there was no significant difference in the presence of these mutations between cases and controls.

TABLE 4.4: HEREDITARY DVT PRECIPITANTS

Variable	Cases n = 359	Controls n = 359	OR (95%CI)	P-value
Family history‡	105/311 (33.8%)	60/358 (16.8%)	2.53 (1.76, 3.64)	<0.0001
Factor V Leiden †				
heterozygous	45/300 (15.0%)	19/273 (7.0%)	2.37 (1.35, 4.16)	0.0058
homozygous*	1/300 (0.3%)	0/273 (0%)	-	1.0
Prothrombin†				
heterozygous	16/301 (5.3%)	1/80 (1.3%)	4.44 (0.58, 33.96)	0.1175
homozygous	0/301 (0%)	0/80 (0%)	-	-
Double heterozygote†* (Factor V Leiden + Prothrombin)	3/299 (1.0%)	0/74 (0%)	-	1.0

* Fisher's exact test used
† Denominator includes only subjects for whom genetic data was available
‡ Denominator includes only subjects for whom data was known by subjects

4.1.5 DVT Protective Variable

Information was also collected on the use of warfarin medication, an anticoagulant that is a strong protector against DVT formation. There was a significantly lower proportion of cases taking warfarin than controls (4.5% versus 12.8% , p-value <0.0001).

4.1.6 Travel exposure (Table 4.5 and Figures 1 and 2)

Travel by car, plane, train or other modality within four weeks of presenting to the vascular laboratory with suspected DVT represents the main exposure variable. Both duration (in hours) and type of travel were assessed. On univariate analysis (Table 4.5), there was no significant difference in a history of travel between cases and controls (18.9% versus 16.4%, p-value 0.37). This was true when all types of travel were examined together as well as when separated into car, plane or other modes of travel. For example, plane travel was reported by 7.2% of cases versus 4.7% of controls (p =0.16). Travel duration was also analyzed in a categorical fashion from short trips through to extended travel durations. There was no significant difference between cases and controls in any category of travel duration of up to 12 hours. However, there was a trend of more cases than controls who underwent travel of ≥12 hours (3.3% versus 1.1%, p= 0.07). The Chi square for trend of overall travel (all forms) was 0.09. This is also shown graphically in a scatterplot diagram (Figure 4.1). When plane travel was examined alone, a similar pattern emerged, with a difference between cases and controls seen only with durations of travel of ≥12 hours (Table 4.5 and Figure 4.2). The Chi square for the trend of plane travel of all durations was 0.09. In contrast, when car travel was examined alone, there was no difference between cases and controls in travel of any duration (Chi Square for trend 0.89).

TABLE 4.5 TRAVEL EXPOSURE[†]

Variable	Cases	Controls	P-Value
Travel (all forms)	66/359 (18.4%)	59/359 (16.4%)	0.48
Travel			
Car	35/359 (9.7%)	40/359 (11.1%)	0.47
Plane	26/359 (7.2%)	17/359 (4.7%)	0.16
Other[*]	5/359 (1.4%)	2/359 (0.6%)	0.26
Travel (all forms)[•]			
≤3 hours	19/359 (5.3%)	16/359 (4.7%)	0.60
3 - 6 hours	13/359 (3.6%)	12/359 (3.3%)	0.84
6 - 12 hours	22/359 (6.1%)	27/359 (7.5%)	0.46
> 12 hours[*]	12/359 (3.3%)	4/359 (1.1%)	0.07
Chi-square for trend			0.09
Plane travel[*]			
≤3 hours	4/359 (1.1%)	3/359 (0.9%)	1.0
3 - 6 hours	5/359 (1.4%)	2/359 (0.6%)	0.25
6 - 12 hours	9/359 (2.5%)	11/359 (3.1%)	0.82
>12 hours	8/359 (2.2%)	1/359 (0.3%)	0.04
Chi-square for trend			0.09
Car Travel[‡]			
≤3 hours	12/359 (3.3%)	13/359 (3.6%)	0.84
3 - 6 hours	7/359 (1.9%)	9/359 (2.5%)	0.61
6 - 12 hours	11/359 (3.1%)	15/359 (4.2%)	0.42
> 12 hours[*]	4/359 (1.1%)	3/359 (0.9%)	0.16
Chi-square for trend			0.89

[†] Travel refers to travel within 1 month of presenting with a suspected DVT.
[*] Fisher's exact test used.
[•] Travel all forms includes car, plane, boat and train.
[‡] Travel duration not available for one patient

Figure 4.1 Scatterplot of travel duration among study subjects who reported recent travel

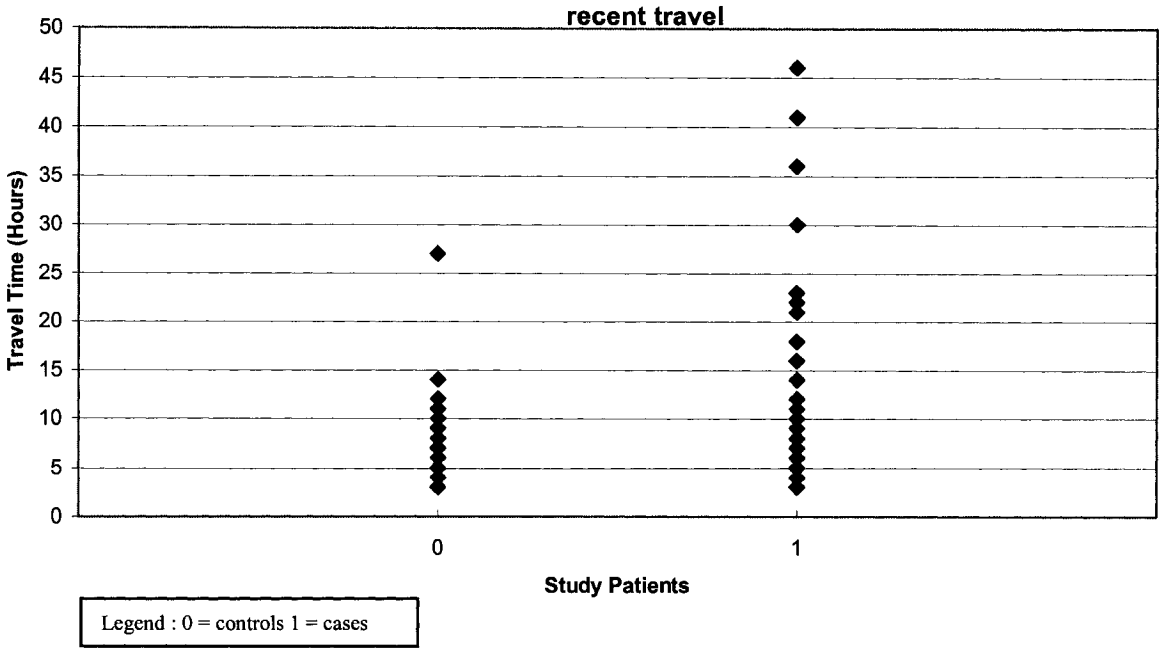
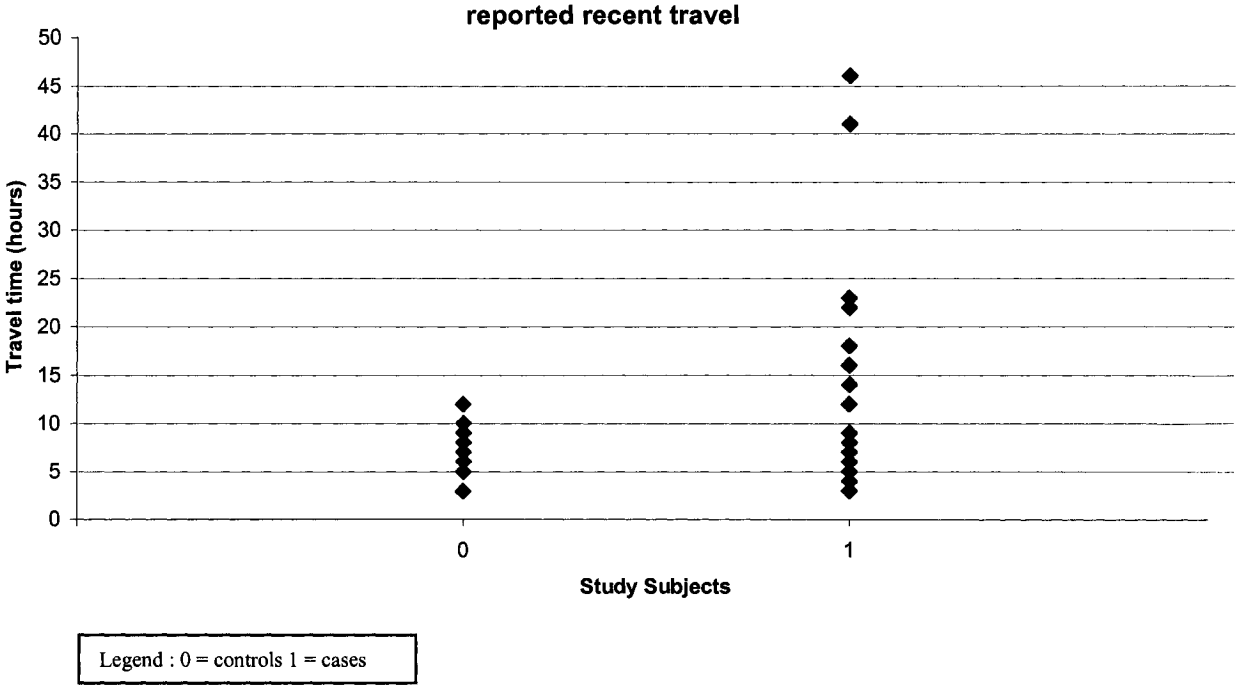


Figure 4.2: Scatterplot of plane trip duration among study subjects who reported recent travel



4.2 Bivariate analysis

4.2.1 Spearman's rank correlation (Table 4.6)

Spearman's nonparametric rank correlation, r, was calculated for all variables felt to be potential confounders or effect modifiers. An absolute r value ≥ 0.20 was considered to be an indicator of possibly important correlation, and as such a potential confounding variable.

There were few correlations of $|r| \geq 0.20$, as shown in Table 4.6, and they were largely those expected from substantive knowledge. These included a negative correlation between age and oral contraceptive use as well as age and education. Not surprisingly, recent surgery was correlated with both inpatient status and recent immobility. Currently active cancer was positively correlated with immobility. A family history of VTE was positively associated with case status. The inverse correlation between case status and age, however, was not expected.

TABLE 4.6: Spearman's rank correlation

	Case status	Inpatient Location	Age	Sex	Immob.	Cancer	Surgery	OCP	HRT	Family VTE	Warfarin	Hx of VTE	Travel	FVL	PT	Trauma	Education
Case status	1.0																
Inpatient Location	0.01	1.0															
Age	***-0.29***	0.11	1.0														
Sex	-0.15	-0.05	0.03	1.0													
Immobility	0.17	0.18	-0.15	0.02	1.0												
Cancer	0.09	0.02	-0.12	-0.03	***0.25***	1.0											
Surgery	0.12	***0.27***	-0.06	-0.10	***0.27***	0.08	1.0										
OCP	0.16	-0.10	***-0.30***	0.17	0.09	-0.05	-0.02	1.0									
HRT	0.12	0.00	-0.02	***0.29***	0.05	-0.02	0.01	-0.07	1.0								
Family Hx VTE	***0.20***	-0.10	-0.15	0.09	-0.03	0.13	-0.04	-0.01	0.11	1.0							
Warfarin	-0.15	0.15	0.12	-0.07	0.04	-0.10	0.07	-0.06	-0.01	-0.08	1.0						
Hx of VTE	0.09	-0.01	0.02	0.01	-0.03	-0.07	0.02	-0.09	-0.02	0.12	0.18	1.0					
Travel	0.03	-0.10	-0.11	-0.07	-0.08	-0.17	-0.07	-0.04	0.02	0.00	0.04	0.02	1.0				
FVL	0.13	-0.03	-0.11	0.06	-0.02	-0.10	0.00	0.16	0.02	0.05	0.02	0.13	-0.03	1.0			
Prothrombin	0.08	0.02	-0.07	0.00	-0.04	0.18	0.05	0.16	-0.01	0.09	-0.06	-0.04	-0.03	0.02	1.0		
Trauma	0.12	-0.05	-0.12	0.04	0.13	0.01	-0.01	0.09	0.03	0.10	-0.07	-0.05	0.06	-0.03	0.00	1.0	
Education	0.17	-0.17	**-0.38**	-0.07	0.00	0.11	-0.02	0.17	0.02	0.09	-0.11	0.05	0.16	-0.01	0.05	0.05	1.0

4.2.2 Stratified analysis

Stratified analysis was performed in order to further explore the possibility of confounding of the travel-DVT relationship. Variables chosen for stratified analysis were based on substantive knowledge of plausible effects as well as unexpected significant associations from univariate analysis for variables not firmly established as a predictor of case status from the literature, notably gender and education. Confounding in the stratified analysis would be suspected if there was a difference in proportion of between the two levels of the stratification variable to travel (all types), the main exposure variable.

Stratification on gender (Table 4.7):

All travel (but not plane travel alone) and recent surgery were more common in males than females, while a family history of VTE was more common in females than males. There were no sex differences noted for age, the presence of general medical conditions, active cancer, previous VTE, recent immobility or warfarin use.

TABLE 4.7: SELECTED VARIABLES IN MALES COMPARED TO FEMALES

Variable	Males	Females	P-value
Travel	63/305 (20.7%)	62/413 (15.0%)	0.05
Plane travel	19/305 (6.2%)	24/413 (5.8%)	0.81
Surgery	84/303 (27.7%)	80/413 (19.4%)	0.009
Family history of VTE	56/279 (20.1%)	109/391 (27.9%)	0.02

Stratification on education (Table 4.8):

Both all travel and plane travel were more common among more educated as compared to less educated study subjects. There was no difference among level of education for car travel.

TABLE 4.8: SELECTED VARIABLES BY LEVEL OF EDUCATION

Variable	Level of Education					p-Value
	None	Grade School	High School	Some university	University	
Travel	0/8 (0%)	14/108 (13.0%)	32/265 (12.1%)	38/187 (20.3%)	41/149 (27.5%)	0.0005
Plane travel	0/8 (0%)	3/108 (2.8%)	7/265 (2.6%)	13/187 (7.0%)	20/149 (13.4%)	0.0001
Car travel	0/8 (0%)	10/108 (9.3%)	24/265 (9.1%)	22/187 (11.8%)	19/149 (12.8%)	0.58

Stratification on age (Table 4.9):

Travel was significantly more common in subjects under 65 years of age. In addition, as could be expected, the presence of general medical conditions (listed in Table 4.2) were more common in those older as compared to those younger than 65 years of age. Several recognized risk factors for VTE were more common in those less than 65 years of age including immobility and a family history of VTE. Warfarin use was less common in those under 65 years of age. There was no significant difference among those under-

versus over- 65 years of age in those affected with active cancer or a personal history of VTE.

TABLE 4.9: SELECTED VARIABLES IN PATIENTS UNDER 65 COMPARED TO OVER 65

Variable	Age < 65	Age ≥65	P-value
Travel	82/401 (20.4%)	43/317 (13.6%)	0.02
Plane travel	32/401 (8.0%)	11/317 (3.5%)	0.01
General medical conditions[†]	162/401 (40.4%)	224/317 (70.7%)	<.0001
Surgery	99/401 (24.7%)	65/315 (20.6%)	0.20
Immobility	80/401 (20.0%)	33/316 (10.4%)	0.0005
Family history of VTE	116/377 (30.8%)	49/293 (16.7%)	<.0001
Warfarin use	24/401 (6.0%)	38/316 (12.0%)	0.004

[†] General medical conditions include at least one of: stroke, CHF, hyperlipidemia, diabetes and COPD

Stratification by cancer:

No variable including travel was associated with presence of cancer.

4.2.3 Conclusions based on univariate and bivariate analysis

Findings on univariate and bivariate analysis help to identify probable confounding factors, which influences model building for multiple logistic regression analysis. My interpretation of these findings is as follows:

1. Gender. There exists case-control (73) and population-based (74) data to support male sex as a modest risk factor for VTE. In our study a higher proportion of males were also exposed to travel, the main exposure variable, as compared to females. Recent surgery, a major DVT risk factor, was also more common in males than females in this study group. Hence, sex was controlled for in the multivariate analysis.

2. Education. Higher education was associated with both case status and with travel, the main exposure variable. Hence, education was controlled for in the multivariate analysis.

3. Age. Population studies have consistently demonstrated that increasing age is a risk factor for DVT, in contrast to the findings in univariate analysis that cases were younger than controls. Travel was also more common in the younger age group. The apparent inverse association in our study was likely confounded by any one of a number of variables: There was a statistically significantly higher proportion of surgery, immobility and family history of VTE (which are DVT risk factors) and a statistically lower proportion of warfarin use (protective against DVT) in those younger than 65 years of age. Age was controlled for in the multivariate analysis as it was associated with the main exposure (travel) and outcome (DVT) variables.

4. Cancer. Univariate analysis did not demonstrate any association between cancer and case status or between cancer and travel. Therefore, cancer was unlikely to be a confounding factor in this study.

4.3 Multivariate analysis

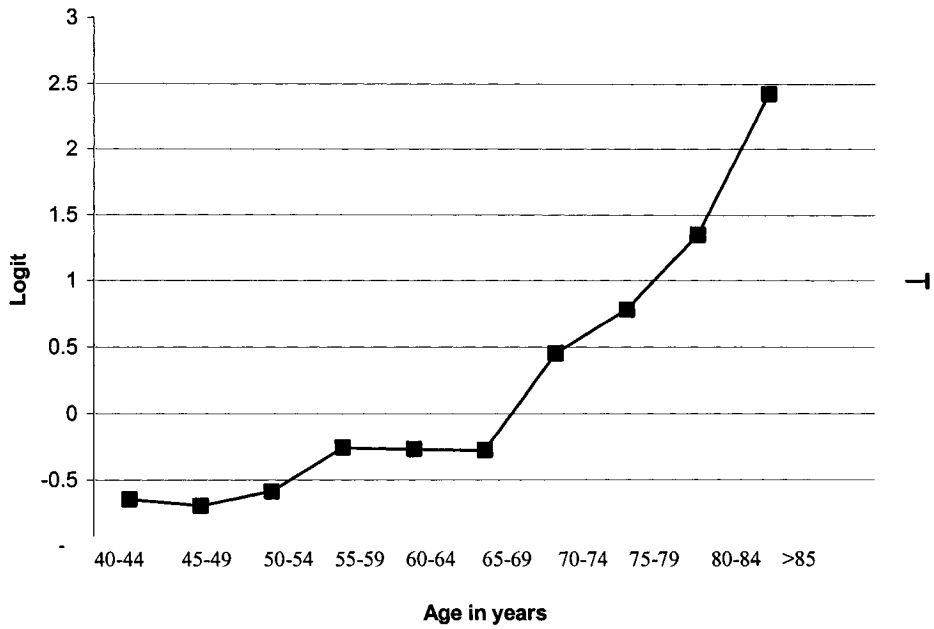
4.3.1 Logistic regression of the relationship between travel and DVT (Table 4.10)

Several models were constructed in order to examine whether travel as a binary or categorical outcome variable was associated with case status, and are illustrated in Table 4.10. Travel is compared as any travel versus none. Models were created to include confounders identified by univariate and bivariate analysis as well as those suspected on a substantive basis. Possible effect modifiers identified a priori were tested, but only included in the final model if found to contribute significantly to the overall model.

Model 1 calculated the crude association between travel and DVT, with an odds ratio of 1.15 (95%CI: 0.78,1.69).

Model 2 examined the association between travel and DVT adjusted for age and sex. Age was found to violate the linearity of the logit assumption. Age versus logit was calculated at 5 year intervals, and plotted as shown in Figure 3. Based on the change in slope of the logit at 65 years of age, the best fit for the observed graph was a division of age into those older and younger than 65 years of age. Adjusted for age and sex, the odds ratio for the association between travel and DVT was 0.97 (95%CI: 0.65, 1.44).

Figure 4.3: Logit of case status with respect to age



Model 3 examined the relationship between travel and DVT adjusted for age and sex as well as education, surgery, immobility, family history of VTE and warfarin use, all identified as potential confounders in bivariate analysis. The odds ratio for travel adjusting for these factors was 1.24 (95% CI: 0.80, 1.93).

TABLE 4.10: ASSESSMENT OF TRAVEL AS A RISK FACTOR FOR DVT

Variable	Odds Ratio	95% CI Intervals	Parameter Estimate	Standard Error	P-value
Travel: Model 1	1.15	0.78, 1.69	0.14	0.20	0.48
Travel: Model 2	0.97	0.65, 1.44	- 0.04	0.21	0.86
Travel: Model 3	1.24	0.80, 1.93	0.22	0.22	0.33
Travel: Model 4	Unstable	(see text)			
Travel: Model 5	1.51	0.91, 2.50	0.41	0.20	0.10

Legend:
Model 1: Crude association
Model 2: Adjusted for sex and age
Model 3: Adjusted for sex, age, education, surgery, immobility, family history, warfarin
Model 4: Adjusted for sex, age, education, surgery, immobility, family history, warfarin, cancer, FVL, PT mutation, previous VTE, OCP, HRT, trauma,
Model 5: Adjusted for sex, age, family history, Factor V Leiden, previous VTE, OCP, HRT, warfarin, immobility,trauma

No other confounders were suspected in bivariate analysis. However, Model 4 was created to include previously defined risk factors for DVT in order to examine the independent relationship of travel to DVT. These included age, gender, active cancer, family history of VTE, presence of Factor V Leiden, presence of Prothrombin gene mutations, personal history of VTE, HRT use, OCP use, warfarin use, immobility, recent trauma and recent surgery.

There was no reason to hypothesize that any of the variables were in the causal pathway between travel and DVT, and that as such controlling for them would result in overfitting. Due to a large number of missing data for some of these variables (n= 388 observations removed), this model produced unstable parameter estimates. Therefore, variables that

were non-significant contributors to the overall model according to the Wald Chi-square results were eliminated. These were education, active cancer, recent trauma and recent surgery. Data on the presence of the Prothrombin gene mutation was available for less than one third of control patients. This was the cause of most of the missing data, and this variable was therefore removed. A model with the aforementioned changes (Model 5; 152 missing observations) resulted in an odds ratio for travel of 1.51 (95%CI: 0.91, 2.50).

4.2.1.1 Effect modifiers

Potential effect modifiers were identified *a priori*, based on substantive knowledge derived from previous studies. OCP or HRT therapy by women were considered to be potential effect modifiers of the association between travel and DVT. In previous studies, oral contraceptive therapy was shown to dramatically increase thrombosis rates in women with Factor V Leiden.(39) Furthermore, another study examining the travel-VTE relationship identified OCP as an effect modifier that increased the risk of VTE 12-fold.(60)

Other potential effect modifiers that were examined included the presence of thrombophilia, active cancer or a personal or family history of VTE among people not concurrently on warfarin therapy. Effect modifiers were each tested in the model individually by the addition of a TRAVEL*VARIABLE variable to the model along with the variable of interest. OCP was examined as a possible effect modifier in female subjects of reproductive age, and HRT was examined among all female study subjects.

None were retained for the final model as none were found to contribute significantly to the model.

4.3.1.2 Regression Diagnostics

Goodness of fit for Model 5 was assessed by the Hosmer-Lemeshow procedure via the LACKFIT option in SAS as a regression diagnostic technique. Acceptance of the Hosmer-Lemeshow null hypothesis is one indicator suggesting an appropriately fitted model. The p-value for LACKFIT was 0.53, thereby suggesting acceptable goodness of fit via this statistical test.

Leverage was assessed by calculating the DFBETA's for Model 5, the final model. There were very few observations that were outliers (approx. 2%). Given the large sample size, it is unlikely that these data points influenced the findings to any significant degree, hence they were not removed.

4.3.1.3 Confounding

Suspected confounding by gender and age was not confirmed as shown by a lack of change in parameter from that found by crude association. Male sex and younger age were confirmed to be weak independent predictors of case status even after adjustment for suspected confounders. All variables included in the final model (Model 5) were significant determinants of case status according to Wald χ^2 . All others were retained in the model for substantive reasons.

4.3.2 Logistic regression for duration of travel (Table 4.11)

To evaluate the effect of increasing travel durations on case status, the above mentioned bivariate and multivariate analyses were repeated for travel classified in the following categories: 3 hours or less, 3 to 6 hours, 6 to 12 hours and more than 12 hours in order to evaluate short, medium, long and prolonged travel durations.

Table 4.11 shows the crude estimation of risk for varying travel durations. Up to 12 hours' duration, the odds ratio estimates and their 95% CI center approximately around 1.0. For travel durations of longer than 12 hours however, the odds ratio was considerably higher (OR= 5.63, 95%CI: 1.24, 25.61). Due to the small number of travelers reporting prolonged durations of travel, the confidence intervals were wide.

Adjustment for potential confounding factors determined that travel of over 12 hours' duration had an odds ratio point estimate that was higher (OR = 2.82) than shorter travel durations, but due to the inclusion of multiple variables and a small number of prolonged duration travelers the 95% CI were no longer significant (95%CI: 0.52, 15.24) (Model 2). The Hosmer-Lemeshow test for the model was 0.16, suggesting goodness of fit.

TABLE 4.11: MULTIVARIATE ANALYSIS WITH INCREASING TRAVEL DURATIONS

Variable	Odds Ratio	95% CI Intervals	Parameter Estimate	Standard Error	P-value
Travel : Model 1					
≤3 hours	1.22	0.61, 2.41	0.20	0.35	0.57
3 - 6 hours	1.11	0.50, 2.47	0.10	0.41	0.80
6 - 12 hours	0.81	0.46, 1.44	- 0.21	0.29	0.47
> 12 hours	5.63	1.24, 25.61	1.73	0.77	0.02
Travel: Model 2					
≤3 hours	1.65	0.68, 4.03	0.53	0.46	0.27
3 - 6 hours	1.28	0.43, 3.78	0.25	0.55	0.66
6 - 12 hours	1.32	0.63, 2.76	0.28	0.38	0.46
> 12 hours	2.82	0.52, 15.24	1.45	0.86	0.23

Legend:
Model 1: Crude association
Model 2: Adjusted for sex, age, family history, Factor V Leiden, previous VTE, OCP, HRT, warfarin, immobility, trauma

4.3.3 Logistic regression analysis: plane travel and DVT (Table 4.12, 4.13)

Travel specifically by plane was subsequently analyzed both as a dichotomous (Table 4.12) and a categorical (Table 4.13) outcome variable, as per *a priori* decision.

The crude odds ratio for plane travel was 1.57, with the lower confidence interval limit below 1.0 (95%CI: 0.84, 2.95). Adjustment for possible confounders from bivariate analysis and substantive knowledge increased the point estimate to 2.16 (95%CI: 0.89, 5.27). The Hosmer-Lemeshow test for plane travel as a dichotomous outcome via the LACKFIT option in SAS in Model 5 provided a p-value of 0.42.

Plane travel was further divided into short, medium, long and prolonged travel, analogous to the analysis for travel as a whole (Table 4.13). Travel by plane of 12 hours or longer (compared to no travel) resulted in a positive association with case status (OR 8.22, 95%CI: 1.02, 66.05)(Model 1). The confidence intervals were very wide, as there were

very few observations of prolonged travel among subjects. Further, it was not possible to create a model including Prothrombin or Factor V Leiden as separate variables as the number of missing observations resulted in an unstable model. Therefore, a new variable henceforth referred to as "hereditary factor" was created. This variable was deemed positive if either the family history, Factor V Leiden mutation or Prothrombin mutations were positive. The substitution of this variable for the three preceding ones created a model with 52 missing observations, and did not significantly change the association seen in the crude analysis. However, the observed association between prolonged travel time and case status resulted in even wider confidence intervals and rendered the association non-significant (OR 7.10, 95%CI: 0.70, 72.35)(Model 2). The Hosmer-Lemeshow p-value for this model was 0.54.

TABLE 4.12: MULTIVARIATE ANALYSIS OF PLANE TRAVEL

Variable	Odds Ratio	95% CI Intervals	Parameter Estimate	Standard Error	P-value
Plane Travel: Model 1	1.57	0.84, 2.95	0.45	0.32	0.16
Plane Travel: Model 2	1.32	0.69, 2.53	0.27	0.33	0.41
Plane Travel: Model 3	1.38	0.68, 2.79	0.32	0.36	0.37
Plane Travel: Model 4	Unstable	(see text)			
Plane Travel: Model 5	2.16	0.89, 5.27	0.77	0.46	0.09

Legend:
Model 1: Crude association
Model 2: Adjusted for sex and age
Model 3: Adjusted for sex, age, education surgery, immobility, family history, warfarin
Model 4: Adjusted for sex, age, education surgery, immobility, family history, warfarin, cancer, FVL, PT mutation, previous VTE, OCP, HRT, trauma
Model 5: Adjusted for sex, age, immobility, family history, warfarin, FVL, previous VTE, OCP, HRT, trauma

TABLE 4.13: MULTIVARIATE ANALYSIS OF INCREASING DURATIONS OF PLANE TRAVEL

Variable	Odds Ratio	95% CI Intervals	Parameter Estimate	Standard Error	P-value
Plane travel : Model 1					
≤3 hours	1.36	0.30, 6.17	0.31	0.77	0.71
3 - 6 hours	2.57	0.50, 13.33	0.94	0.84	0.27
6 - 12 hours	0.84	0.34, 2.05	-0.17	0.46	0.65
> 12 hours	8.22	1.02, 66.05	2.11	1.06	0.05
Plane Travel: Model 2					
≤3 hours	1.28	0.29,5.92	0.25	0.78	0.87
3 - 6 hours	2.16	0.33, 14.03	0.77	0.96	0.46
6 - 12 hours	1.14	0.38, 2.81	0.04	0.51	0.91
> 12 hours	7.10	0.70, 72.35	1.96	1.19	0.105

Legend:
Model 1: Crude association
Model 2: Adjusted for sex, age, hereditary factors, previous VTE, OCP, HRT, warfarin, immobility, trauma

4.3.4 Logistic regression analysis: car travel and DVT (Table 4.14):

Over 90% of all travel was conducted by car and plane. Therefore, car travel was assessed in order to determine whether the positive association between travel and DVT was driven by car or plane travel.

The crude estimate of risk of car travel for DVT was 0.86 (95%CI 0.53, 1.39) (Model 1). Adjustment for confounding factors analogous to the analysis performed for plane travel resulted in an odds ratio of 1.00 (95%CI 0.54, 1.83)(Model 2). Even car travel of over 12 hours' duration resulted in an odds ratio of approximately 1 (OR 1.19, 95%CI 0.15, 9.64) (not shown in Table).

TABLE 4.14: MULTIVARIATE ANALYSIS OF CAR TRAVEL

Variable	Odds Ratio	95% CI Intervals	Parameter Estimate	Standard Error	P-value
Car Travel: Model 1	0.86	0.53, 1.39	-0.15	0.24	0.54
Car Travel: Model 2	1.00	0.54, 1.83	-0.0043	0.31	0.82

Legend:
Model 1: Crude association
Model 2: Sex, age, family history, FVL, previous VTE, OCP, HRT, warfarin, immobility, trauma

Chapter 4: Tables

TABLE 4.15: DEMOGAPHIC DATA IN ALL CASES COMPARED TO THE JGH/HND SUBSET OF CASES

Variable	Cases N = 359	Cases (JGH/HND) N = 165
Age (years), mean +/- SD	55.8 +/-14.8	57.0 +/- 15.4
Sex (% male)	180/359 (50.1%)	90/165 (54.5%)
BMI, mean +/- SD	27.3 +/-5.4	26.6 +/- 5.3
Smoker (%yes)	66/359 (18.4%)	27/165 (16.4%)
Patient location (% outpatient)	242/359 (67.4%)	101/165 (61.2%)
Education		
None	2/359 (0.6%)	0/165 (0.0%)
Grade school	34/359 (9.5%)	19/165 (11.5%)
High school	123/359 (34.3%)	55/165 (33.3%)
Some university	120/359 (33.4%)	53/165 (32.1%)
University degree	80/359 (22.2%)	38/165 (23.0%)

TABLE 4.16: MEDICAL CONDITIONS IN ALL CASES COMPARED TO THE JGH/HND SUBSET OF CASES

Variable	Cases N= 359	Cases (JGH/HND) N= 165
Stroke	11/359 (3.1%)	7/165 (4.2%)
Heart failure	12/359 (3.3%)	7/165 (4.2%)
Hyperlipidemia	72/359 (20.0%)	38/165 (23%)
Diabetes	29/359 (8.1%)	20/165 (12.1%)
COPD	14/359 (3.9%)	8/165 (4.8%)

TABLE 4.17: DVT PRECIPITANTS IN ALL CASES COMPARED TO THE JGH/HND SUBSET OF CASES

Variable	Cases N = 359	Cases (JGH/HND) N=165
Cancer diagnosis	78/359 (21.7%)	46/165 (27.8%)
Presently active	45/359 (12.5%)	24/165 (14.5%)
Past Thrombosis	78/358 (21.8%)	38/165 (23.0%)
Immobility	79/358 (22.1%)	23/165 (13.9%)
Recent surgery	100/357 (28.0%)	51/164 (31.1%)
Pregnancy †	8/177 (4.5%)	6/75 (6.6%)
OCP †	25/179 (14.0%)	8/75 (10.7%)
HRT †	51/179 (28.5%)	17/75 (22.3%)
Recent trauma	62/358 (17.3%)	19/165 (11.5%)
Family history	105/311 (33.8%)	44/143 (30.8%)
Factor V Leiden		
Heterozygous	45/300 (15%)	21/127 (16.5%)
Homozygous	1/300 (0.3%)	0/127 (0%)
Prothrombin gene		
Heterozygous	16/301 (5.3%)	6/127 (4.7%)
Homozygous	0/301 (0%)	0/127 (0%)

Note: † Denominator = women

5. DISCUSSION

The purported association between venous thromboembolism (VTE) and travel, particularly air travel, has received extensive media coverage, and is a potentially important public health issue, given the large number of travellers across the globe annually. Epidemiological evidence to date remains conflicting, and studies have not consistently distinguished among different travel modalities or have been restricted to air travel, as presented in the literature review. Other studies have not examined the effect of increasing travel durations, and confounders have been rarely accounted for.

Our study, the RT-DVT study attempts to address some of the weaknesses of prior studies. It is the largest study to date that analyzes the relation between travel and DVT that has used multivariate analysis to adjust for confounding factors. In this chapter I will discuss the main results of the RT-DVT study as well as their implications.

Discussion of Main results

5.1 Simple analysis

Univariate analysis demonstrated that, consistent with previous studies, many previously known DVT risk factors were associated with DVT (case status). Compared with controls, cases were 1.7 times more likely to have had a previous VTE event, 2.7 times more likely to have been immobilized in the previous 30 days, 1.8 times more likely to have undergone surgery and 2.1 times more likely to have experienced recent trauma. Case females were 8.9 times more likely to be on OCP medication and 3.5 times more

likely to be receiving HRT. Other factors that were associated with DVT were a family history of VTE (OR = 2.5), heterozygous state for Factor V Leiden mutation (OR = 2.4) and the Prothrombin mutation (OR = 4.4). Homozygous Factor V Leiden mutation and double heterozygous mutations (Prothrombin mutation plus Factor V Leiden mutation) were more common among cases but this difference was non-significant, likely due to the small numbers of affected patients. There were no patients in either group that were homozygous for the Prothrombin mutation.

Neither pregnancy nor cancer were associated with DVT in univariate analysis despite being well recognized risk factors for DVT. Both pregnancy and cancer can result in symptoms suggestive of DVT (eg leg edema) for reasons other that DVT. A possible explanation for the lack of association between these conditions and DVT in this study is that physicians may have a high index of suspicion for DVT in these patients and a low threshold for sending such patients for a painless, non-invasive test to rule out DVT.

Control subjects were significantly more likely to have a range of general medical conditions including stroke, heart failure, and diabetes as compared with cases. However, these medical conditions commonly result in leg symptoms including lower leg edema or leg tenderness, which could be mistaken for DVT, and were likely the reason for referral to the vascular laboratory similarly to pregnancy and cancer. However, since the reason for referral was not documented, this hypothesis cannot be substantiated.

Univariate analysis of travel, the main exposure variable, did not reveal an association between DVT and overall travel (OR: 1.15, 95%CI 0.78, 1.69), between DVT and car travel (OR: 0.86, 95%CI 0.53, 1.39) or between DVT and plane travel (OR: 1.57, 95%CI 0.84, 2.95). However, the point estimate of risk for airplane travel was higher than that for car travel, a difference which becomes even more apparent in the multivariate analysis. The clinical significance of this finding will be discussed in the multivariate analysis section below.

Univariate analysis of increasing travel durations did not show an association between DVT and travel until travel durations of more than 12 hours, which was moderate in strength and statistically significant (OR = 5.63, 95%CI: 1.24, 25.61). Analysis of increasing durations of airplane travel found an even higher point estimate of risk of DVT for plane travel durations of more than 12 hours (OR = 8.22, 95%CI: 1.02, 66.05). Plane travel of shorter than 12 hours' duration was not associated with DVT. Analysis of car travel did not reveal an association with DVT for any travel duration, including prolonged travel of more than 12 hours. Travel by other means (train, boat) was infrequent, and did not allow for analysis for different travel durations. These findings suggest a threshold effect, whereby airplane travel of durations shorter than 12 hours is associated with a constant mild risk of DVT, which increases substantially with air travel of longer than 12 hours. No such effect was seen for car travel. The positive association between overall travel and DVT for prolonged travel durations therefore predominantly reflects the effect of air travel. A threshold effect is in keeping with the understanding of VTE pathophysiology, with venous stasis and activation of coagulation factors leading to

DVT only after a certain time period of exposure to immobility and plane travel. A threshold effect for VTE and plane travel was also suggested by Lapostolle and colleagues(52) who also reported a jump in incidence of pulmonary embolus for plane travel from 0.11/million for travel of less than 6 hours to 4.77/million for travel of ≥12 hours' duration.

5.2 Multivariate analysis

In both univariate and logistic regression analysis, male sex was found to be an independent predictor of DVT (adjusted OR = 2.69, 95%CI: 1.75, 4.14). Although a significantly higher proportion of males than females had undergone recent surgery, this difference was accounted for in multivariate analysis, and therefore does not explain this finding. There are several possible explanations. Firstly, male sex has been previously described to be an independent risk factor for DVT, (73;74) hence there may be biological differences between males and females that affect risk for DVT. However, the apparent association in our study may have been due to differential referral patterns of males and females to the vascular laboratory. Women tend to present to medical attention more often than men for non-fatal conditions,(75) and may therefore be referred more often to the vascular laboratory during investigation. Also, women are consumers of OCP and HRT and undergo pregnancy – all clinical situations that increase DVT risk. This may result in greater physician vigilance and subsequent referral of women to the vascular laboratory. Consequently, if more women are evaluated for leg symptoms and possible DVT for any of the aforementioned reasons, a smaller proportion of those presenting with clinical symptoms will be ultimately diagnosed with DVT as compared to

males, rendering female sex a "protective" variable. Sex differences in referral patterns have been found in studies of similar design as the RT-DVT study, where the controls were also more likely to be females as compared to cases,(49;50) and thus emphasizes the importance of controlling for gender in multivariate analysis.

Multivariate analysis found that DVT was not significantly associated with overall travel (regardless of mode) after adjustment for confounders that were identified in bivariate analysis and on a substantive basis (OR = 1.44, 95%CI: 0.86, 2.40). While this result was non-significant with a narrow 95%CI interval, both the point estimate and the upper end of the confidence intervals are of a magnitude that would have clinical significance. If substantiated, an OR of approximately 1.5 would be a risk factor for DVT of comparable magnitude to taking HRT or the presence of the Prothrombin gene mutation.(76) This OR is considerably higher than in the study by Kraaijenhagen and colleagues which used a similar methodology and reported an unadjusted OR = 0.7 (95%CI: 0.3 – 1.4) for travel in the preceding 4 weeks.(49) However, the relative frequency of different travel durations among study subjects was not provided, which limits the comparability of the results of the two studies. Arya and colleagues studied the relationship between travel and DVT using a similar design to both the RT-DVT and the Kraaijenhagen studies.(50) Only univariate analysis was performed, and found no association between travel and DVT. The importance of performing multivariate analysis is emphasized by the results of the RT-DVT study, where univariate analysis demonstrated an OR point estimate similar to that found by Kraaijenhagen and Arya, which subsequently increased after adjustment for confounders in multivariate analysis. Lack of control for confounders may have biased

other studies towards the null if there were more protective factors present among travelers. For example, increasing age is known to be associated with a higher risk of VTE. In the RT-DVT study, younger study subjects were more likely to travel than older subjects, but are a priori less likely to develop a DVT. Therefore, failing to control for age may have biased previous studies towards the null.

The case-control study by Samama and colleagues did find a significant association between "long haul" travel and DVT (OR 2.35, 95%CI: 1.45, 3.80).(51) However, the authors did not provide the time period used to define "recent" travel, nor did they provide details on what duration of travel was considered "long haul". Also, only univariate analysis was performed, which also found that OCP, a known DVT risk factor, was protective for DVT putting into question the validity of the results. Ferrari and colleagues also found a significant association between DVT and travel in the preceding 4 weeks (OR = 3.98, 95%CI: 1.9, 8.4).(47) The authors did not state whether interviewers were blind to the study hypothesis. The analysis was not adjusted for confounding factors, and the control population were hospitalized controls, who a priori are less likely to travel. Overall, the trend towards a positive association between travel and DVT found in the RT-DVT study is consistent with these positive observational studies, albeit that the RT-DVT study found a lower degree of risk perhaps due to adjustment for confounders.

Multivariate analysis of increasing travel duration (regardless of mode) in our study gave comparable results to the univariate analysis. As with univariate analysis, travel durations

of greater than 12 hours' duration were associated with a considerably higher point estimate of risk than shorter travel durations, although the 95% CI did not reach statistical significance (OR = 2.92, 95%CI: 0.54, 15.73), which was most likely the result of the inclusion of multiple variables in the model (i.e. reduced power) and a lower than expected number of travelers rather than being indicative of absence of risk.

As discussed in the literature review, travel modality must also be taken into consideration in determining the risk of DVT associated with travel, since ground and air transportation differ in ways that could result in different risks of DVT. Although both ground and air travel can lead to venous stasis due to prolonged immobility, only airplane travelers are subjected to hypobaric conditions that have been found to activate factors of coagulation,(41) and dehydration from dry cabin air and alcohol consumption may increase blood viscosity. In our study, travel was analyzed separately for plane and car travel. Travel by other means (boat, train) occurred too infrequently to be analyzed individually. Plane travel was associated with DVT (adjusted OR 2.16, 95%CI: 0.89, 5.27). However, this result was not statistically significant, possibly as a result of an inadequate number of plane travelers (i.e. inadequate power), or a low ratio of long duration to short duration travelers. However, our result suggests that had this been a larger study, travel by plane of any duration would likely have been shown to be a mild independent risk factor for DVT.

Analysis of increasing durations of plane travel revealed that plane travel of ≥12 hours was associated with DVT (adjusted OR 7.10; 95%CI: 0.70, 72.35). This association was

apparent on the scatter plot diagram (Figure 2), which showed that no control patients traveled by plane for more than 15 hours. The low numbers of subjects with plane travel of this duration did not permit a more precise estimate of risk. However, the point estimate is comparable to the univariate analysis (OR = 8.22, 95%CI: 1.02, 66.05). Therefore we conclude that plane travel of ≥ 12 hours duration is most probably a moderate independent risk factor for DVT. Clinical situations with ORs for DVT of similar magnitude include cancer or pregnancy. Patients with cancer or pregnancy in situations of further heightened risk such as surgery or immobility are often prescribed thromboprophylaxis such as compression stockings or heparin therapy. Even though the multivariate analysis result is non-significant, this implies that plane travel of more than 12 hours' duration could warrant consideration of thromboprophylaxis, notably in those with concomitant VTE risk factors. It would have been of interest to determine the habits of study subjects while on the plane (eg. sleeping versus frequent walking), but this was not established. The various methods of thromboprophylaxis that could be considered include non-invasive means (e.g. calf exercises and fluids), non-pharmaceutical devices (e.g. elastic stockings) and medications (e.g. heparin).

Results of the analysis of car travel differed from plane travel. Adjusted analysis did not demonstrate any association between DVT and car travel (OR = 1.00, 95%CI: 0.54, 1.83). This was also true when the analysis was restricted to car travel of more than 12 hours' duration (OR 1.19, 95%CI 0.15, 9.64). However, it is unknown whether the reported travel time represented uninterrupted travel time, or whether subjects included stops for gas or food in their estimation of travel time. This would involve walking,

reducing the exposure to continuous venous stasis and immobility, and may explain the absence of risk seen with car travel. There are no other studies that have examined increasing durations of car travel for comparison.

There was no effect modification found in any of the above-mentioned analyses of combined travel, plane travel and car travel. Variables tested as potential effect modifiers for the travel/DVT association included OCP, HRT, thrombophilia, cancer, previous VTE and a family history of VTE. This result contrasts with a recent case control study which demonstrated by stratified analysis that OCP was an effect modifier for the association between travel and DVT (unadjusted OR 13.9, 95%CI: 1.7, 117.5).(63) However, this study by Martinelli and colleagues was limited by probable selection and recall bias given their study design where case subjects were patients presenting to a tertiary thrombosis clinic specifically for thrombophilia testing while control subjects were their friends or partners. The RT-DVT study is the second study of travel and DVT that has analyzed Factor V Leiden and Prothrombin mutations among study subjects. Martinelli and colleagues also examined these mutations among study subjects in their study of travel and DVT.(63) However, interpretation of this study's results are limited because of the significant possibility of selection bias given their study design, as outlined above.

5.3 Strengths and Limitations

The RT-DVT study had strengths and limitations, which I will discuss in terms of their contributions to internal validity, external validity and precision of the study.

Internal validity

Internal validity of a case control study depends on the influence of a number of biases on the study's results. The potential roles of selection bias, recall bias, differential misclassification and non-differential misclassification in the RT-DVT study are discussed below.

5.3.1 Selection bias:

This study was neither a randomized-controlled nor a population-based study. As such, selection bias may have influenced the results of this study. All patients were referred to the vascular laboratory for the same indication (i.e. clinically suspected DVT), had the same objective testing for DVT and underwent the same structured interview by personnel blind to the study hypothesis. However, for logistical reasons explained in the Methods chapter, the recruitment of cases and controls was performed in a non-concurrent manner, separated by almost one calendar year. If there had been any new public information during the intervening year highlighting the possible association between travel and VTE, this could have altered physician index of suspicion and referral patterns to the vascular laboratory such that a different population of controls might have been recruited concurrently as opposed to non-concurrently. Selection bias resulting from non-concurrent control recruitment would result in a bias towards the null. However, the high profile case which brought air travel and VTE to the public's attention and the publication of the positive observational studies on the association between travel and DVT occurred several months prior to the recruitment of any patient included in this

study.(3) Therefore, non-concurrent recruitment of controls was unlikely to have led to selection bias.

Media attention on the possible association between travel and DVT may have influenced the referral pattern of patients to the vascular laboratory on yet another level. It is possible that due to mass media reports, people who traveled and subsequently experienced leg symptoms were more likely to report to a physician specifically because of concerns about DVT. In addition, physicians who obtained a history of travel in a patient with leg symptoms may have been more likely to refer that patient to a vascular laboratory. Since the exact reasons for referral of individual patients to the vascular laboratory were unknown, the possibility of referral bias could not be examined. The presence of referral bias would result in a bias towards the null. However, Statistics Canada data support the amount of travel reported by the control study subjects in the RT-DVT study as reflective of the general Canadian population. According to Statistics Canada, there were 211.1 million person-travels of distances greater than 80km (one way) in 2003,(77) which meant approximately 7 trips/person/year in Canada. These figures support the frequency of travel reported by the RT-DVT study subjects.

Also, the recruitment of control subjects occurred at only two of the seven hospitals that recruited case patients. It is possible that the control subjects recruited at these two sites were not representative of control subjects had they been recruited from all seven centers. However, as presented in the results section, the subset of case subjects recruited from the JGH/HND sites were comparable to the entire group of case patients. Therefore, it is

likely that the control subjects recruited at the two sites were also representative of control subjects had they been recruited at all seven sites.

Lastly, patients were a mix of inpatients and outpatients (majority), distributed similarly among cases and controls. A previously mentioned limitation of the Ferrari study (47) was their exclusive use of inpatients for control selection. While there were some inpatients in the RT-DVT study, given their presence among both cases and controls, this is not likely to have caused any selection bias.

5.3.2 Misclassification bias

Great efforts were made to ensure correct classification as a case or as a control. The referring physicians and vascular laboratory technicians were blind to the research hypothesis, allowing for objective testing. Doppler ultrasound above the knee has an estimated sensitivity and specificity of over 95%. Therefore, out of 359 controls it is possible that up to 18 people did, in fact, have a DVT despite having a negative index examination (i.e. false negative test). The sensitivity and specificity for the detection of below knee DVT is unknown. Therefore, additional patients with below knee DVT may have been misclassified as controls. However, patients with a high clinical index of suspicion for DVT with a negative test undergo repeat ultrasonography after one weeks' time. Subjects with re-assigned diagnosis (i.e. now positive for DVT) would have been captured and eliminated as control subjects by the research assistants, who were on site during the entire duration of control recruitment. There is a small possibility that controls later presented to other institutions where they were subsequently diagnosed with a VTE,

or worse yet died of a fatal thromboembolic event without presenting to hospital. These misclassified controls would not have been captured with the methodology used in this trial. However, most patients return to a given institution, and the risk of fatal VTE in the absence of a detectable DVT is low. Therefore, misclassification of controls was unlikely. Similarly, it was possible that up to 18 case subjects did not have a DVT despite having a positive ultrasound (i.e. false positive test). However, a diagnosis of DVT is often made by combining results of ancillary tests including D-dimer assay and V/Q scanning, which increases the specificity of the tests for DVT above that of Doppler ultrasonography alone. Therefore, misclassification of cases was also unlikely.

5.3.3 DNA sampling

DNA extraction for testing of Factor V Leiden mutation and prothrombin gene mutation differed between cases and controls. The cases were tested through whole blood sample analysis while controls were tested through buccal swab sampling. This resulted in a lower yield of cells though buccal swab sampling, as has been previously described. (65;66) Therefore, fewer DNA test results available among controls with reduced power during multivariate analysis. However, the reliability and precision of both tests (presence or absence of a given mutation) are felt to be equivalent. (66)

5.3.4 Recall bias

Information regarding travel exposure, medical history and DVT risk factors was obtained from subjects by standardized interview. Therefore, prevention of differential recall bias (i.e. cases being more likely to report recent travel than controls) was crucial.

This was addressed by blinding both the study subjects and research assistants to the research hypothesis. Furthermore, all subjects had been sent to the vascular laboratory because of a clinical suspicion of DVT, and therefore cases and controls had equal opportunity to reflect on possible contributing factors. Questions regarding medical history were asked using the same questionnaire for all patients. Therefore, despite being aware of their clinical status (presence or absence of DVT) at the time of the interview, there was unlikely to be significant differential recall between cases and controls.

Potential for non-differential recall bias among study patients was also addressed. This refers to the possibility of poorer recall for distant events than for more recent events, or for less severe illness (e.g. hypertension) than more severe illness (e.g. cancer). Recall for travel within the preceding four weeks was felt to be reliable given the short duration between exposure and presentation to the vascular laboratory. The validity of assessing the potential confounders in this study by interview (e.g. cancer, OCP, HRT, etc) has been reported to be acceptable and largely accurate in other studies.(67-69) With the exception of specific events occurring in the few weeks preceding presentation (including trauma, surgery and immobility), most exposures had to be recalled only in a binary (yes/no) fashion, without requiring the subject to report a time frame. Therefore, non-differential recall bias is unlikely to have a significant impact on results of this study.

5.3.5 Disease latency

Travel, the main exposure of interest, had to have taken place within four weeks prior to presentation to the vascular laboratory. This latency period was selected in accordance

with our understanding of pathophysiology of VTE, and was the same as that used in similar studies of travel and DVT. However, if this latency period was too long, the calculated effect of travel on DVT may have been diluted resulting in a bias towards the null.

5.3.6 Confounding bias

Multiple logistic regression analysis was used to control for potential confounding variables. These included results of genetic studies for Factor V Leiden and Prothrombin gene mutations. However, residual unmeasured or undetected confounding may still have occurred.

5.3.7 External validity

Evaluation of the external validity of this study is important for assessing the generalizability of the results outside of our study population. Although external validity was not formally assessed, the RT-DVT study results are likely to be generalizable because of the following factors:

The study included patients across a wide age range and both genders were well represented. Exclusions to study entry were few, and were chosen primarily to ensure data accuracy (e.g. exclusion of patients with dementia). The study recruited subjects from several centers including a community-based hospital, thereby broadening the range of subjects eligible for study entry.

Another factor that suggests that our results are likely to be generalizable is that known risk factors for DVT were shown to be risk factors in our population with similar magnitudes of relative risk as those found in population-based studies. Therefore, the results of this study could likely be generalized to a large spectrum of adult people.

5.3.8 Precision

This was a fairly large study, which allowed more precise estimates of risk compared with a number of other previously published studies. Only Lapostolle's population-based study (52) and Samama's case control study (51) had larger numbers of subjects, but neither controlled for confounding factors. The large number of patients we studied allowed for the testing of a number of confounding variables in multivariate analysis. Unfortunately, there were fewer travelers overall than were originally anticipated, which decreased the anticipated power of the study, and may be the reason that the confidence intervals crossed unity. Although the point estimate of risk and the upper bounds of the confidence intervals both for travel as a whole and for plane travel were of a magnitude that would be considered clinically significant, more precise estimate of risk would have been preferable.

5.5 Conclusion

The RT-DVT study conducted for this thesis examined the association between travel modality, travel duration and DVT, taking into account genetic data and a number of confounding factors. Our results suggest that plane travel overall is a mild risk factor for DVT, while plane travel of more than 12 hours' duration is likely to be an independent

moderate risk factor for DVT. Our results also showed that shorter durations of plane travel were not associated with DVT, suggesting a threshold effect. Furthermore, our results indicate that travel by car is not associated with DVT for any travel duration.

Strengths of this study include the large number of study subjects, assessment of exposures and outcomes by research assistants blind to the study hypothesis, control for clinical and genetic confounders and separate analysis by travel modality and increasing travel duration. Potential study limitations include the non-concurrent recruitment of control subjects, and inadequate power to calculate more precise estimates of risk for increasing travel durations.

Despite the lack of statistical power to conclusively demonstrate an independent association between plane travel of more than 12 hours' duration and DVT, these results are in accordance with those of a large population based study.(52) Together these studies suggest that physicians should consider recommending thromboprophylaxis for patients with additional VTE risk factors who are embarking on prolonged airplane flights. The safety and effectiveness of this approach should be evaluated in future clinical trials. Further research should focus on which travelers are at particularly increased risk of thrombosis, to study the effect of walking, fluid intake and stretching exercises during flight as well as the cumulative effect of travel.

9. Immobilization (last 3 months): NO☐ YES ☐ ⇨ If yes, No of days ☐☐

10.Travel (in the last month): NO ☐ YES ☐

⇨ f yes: Car ☐ Train☐ Plane ☐

Other ☐ Specify _____

No. Hours longest trip total Hours ☐☐

11. Pregnancy in last year: NO☐ YES ☐

⇨ If yes, currently pregnant? NO ☐ YES ☐

⇨ If yes, weeks gestation: ☐☐ weeks

⇨ If no, date delivered/miscarried/aborted:

☐☐ ☐☐ ☐☐☐☐

D D M M Y Y Y Y

12. Current smoker: NO ☐ YES ☐ If yes, average number of cigarettes per day:

☐ < 1 ☐ 1 – 5 ☐ 5 – 14 ☐ 15 – 24 ☐ 25 – 35 ☐ 36 – 44 ☐ 45 +

13. Prior history of VTE:

Has the patient ever had a venous thromboembolism: ☐ NO ☐ YES

If yes, total number of: ☐☐ DVT ☐☐ PE

Prior DVT # 1⇨ Side: ☐ Right ☐ Left

Site: Proximal leg ☐ Distal leg☐ Other ☐ Specify _____

Year: ☐☐☐☐ Duration of anticoagulation: ☐☐ months

Prior DVT # 2⇨ Side: ☐ Right ☐ Left

Site: Proximal leg☐ Distal leg☐ Other ☐ Specify _____

Year: ☐☐☐☐ Duration of anticoagulation: ☐☐ months

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CERTIFICATION OF ETHICAL ACCEPTABILITY FOR RESEARCH INVOLVING HUMAN SUBJECTS

The Faculty of Medicine Institutional Review Board consisting of:

NEIL MACDONALD, MD	ARTHUR CANDIB, MED
LAWRENCE HUTCHISON, MD	CELESTE JOHNSTON, DED
WILSON MILLER, PHD, MD	ROBERTA PALMOUR, PHD

MARGARET SWAINE, BA

has examined the research project **A03-M29-03A** entitled **"A Case Control Study Examining Travel as a Potential Independent Risk Factor for Deep Venous Thrombosis: A Sub-Study to the Venous Thrombosis Outcomes Study (VETO)"**

as proposed by: Susan Kahn (Applicant) to _____ (Granting Agency, if any)

and consider the experimental procedures to be acceptable on ethical grounds for research involving human subjects.

May 6, 2003
Date

Chair, IRB

Dean of Faculty

Institutional Review Board Assurance Number: FWA 00004545

APPENDIX 2

Sir Mortimer B Davis
Jewish General Hospital
Department of Medicine and
Clinical Epidemiology

A Case-Control Study Examining Risk Factors for the Development of Deep Venous Thrombosis
(VETO substudy)

CONSENT FORM

Dr. L. Opatrny, Dr. S. Shapiro and Dr. S.R. Kahn

General Description and purpose of the study

We invite you to participate in a research study that will examine the presence of any risk factors for deep vein thrombosis (phlebitis) that you may have. The purpose of the study is to see the presence of risk factors in people *with* versus people *without* thrombosis in people presenting for a venous ultrasound.

Procedures

We will administer a short questionnaire asking about aspects of your medical history, some of which have already been asked by the physician who sent you to undergo testing. This will take approximately 15 minutes of your time. You are free to refuse answering any questions that you feel are inappropriate.

In addition, a cotton swab from your cheek to measure 2 abnormalities associated with blood clotting will be done. Results of these tests can be made available to you or your physician on your request. The cells will be used for the purposes of this study only, after which it will be stored for 5 years under the responsibility of Dr. S. Kahn, after which it will be destroyed.

Risks and Benefits

This study will not interfere whatsoever in your treatment, and there are minimal risks to you if you agree to participate. While you may not derive any direct benefits from the study, your participation will lead to a greater understanding of this serious disease, and so may help future patients with a similar condition. The cotton cheek swab is a painless procedure.

Confidentiality

All information you provide to us including your name will be kept confidential. In order to ensure confidentiality, you will be assigned a study number. All forms and computer entry will be referred to by this number. All study documents will be stored in a locked cabinet.

Voluntary consent and the right to withdraw

Your participation in this study is voluntary. Your refusal to participate will involve no penalty or compromise to your medical care which you would otherwise have. You may discontinue participation at any time.

Information

If you have any questions, you may contact either Dr. L. Opatrny (406-3547) or Dr. S.R. Kahn (340-8222 at #4667). If you have any questions about your rights as a study participant, you can contact your hospital's patient representative, Ms. Liane Brown (340-8333 at #5833). You will be given a copy of your consent form to keep.

Understanding

"I have read and clearly understood all the information provided. I have been given the opportunity to ask questions, and all questions have been answered to my satisfaction. I agree to participate in this study.

YES ☐ NO ☐

"I consent to a cotton swab of my cheek to measure two blood abnormalities associated with blood clotting, after which it will be stored for a period of 5 years. I understand that my consent would be obtained for any use of this sample."

YES ☐ NO ☐

Participant:

Name	Signature	Date

Investigator or delegate:

Name	Signature	Date

APPENDIX 3

DVT Risk Factor Study
Assessment Control Report Form

CENTER: STUDY ID:	PATIENT INITIALS
DATE OF ASSESSMENT:	

Section A. Demographic information

1. Gender: Male ☐ Female ☐

2. Date of birth: ☐☐ ☐☐ ☐☐☐☐ (D D M M Y Y Y Y) Age: ☐☐☐ years

3. Height: ☐☐☐ cm ☐ ft ☐☐ in

4. Weight: ☐☐☐ ⇨ lbs ☐ kg ☐

5. Current Hospital Status: Outpatient ☐ Inpatient ☐

6. Education:
   - No schooling ☐
   - Grade (primary) school only ☐
   - High School only ☐
   - Some college/university ☐
   - University graduate ☐

7. Employment: Which term best describes main job?
   - Not currently employed ☐
   - Executive, managerial or professional ☐
   - Technical, sales or clerical ☐
   - Service occupation ☐
   - Farming, forestry, fishing ☐
   - Precision, productions, craft or repair ☐
   - Operator, fabricator or laborer ☐
   - Other_____ ☐

   If not currently employed:
   - retired ☐
   - student ☐
   - homemaker ☐
   - laidoff/unemployed ☐

Rating of physical demands of job: ☐ Low ☐ Medium ☐ High

Average number daytime hours spent standing: |_|_|

Average number daytime hours spent sitting: |_|_|

Section B. Medical History

8. Comorbid conditions:

Hypertension	☐ NO ☐ YES
Diabetes mellitus	☐ NO ☐ YES
High cholesterol	☐ NO ☐ YES
Asthma	☐ NO ☐ YES
COPD	☐ NO ☐ YES
Angina/ myocardial infarction	☐ NO ☐ YES
Stroke	☐ NO ☐ YES
Congestive heart failure	☐ NO ☐ YES
Cancer	☐ NO ☐ YES

⇨ If yes, specify: year diagnosed: |_|_|_|_|

Site: _____

Active at present: NO ☐ YES ☐

Musculoskeletal problem affecting hip or leg (eg. Fracture, prior surgery, arthritis) NO ☐ YES ☐
⇨ If yes: Right ☐ Left ☐
Specify: _____

Other active conditions ☐ NO ☐ YES
⇨ If yes, specify: _____

Surgery (last 3 months) ☐ NO ☐ YES
⇨ If yes, specify surgery: _____

Trauma (last 3 months) ☐ NO ☐ YES
⇨ If yes, specify site: _____

Does the patient have leg swelling?

NO ☐ YES ☐ ⇨ If yes, duration: |_|_| Days ☐ Months ☐ Years ☐

⇨ If yes, leg(s) affected Right ☐ Left ☐ Both ☐

9. Immobilization (last 3 months): NO ☐ YES ☐ ⇨ If yes, No of days ☐☐

10. Travel (in the last month): NO ☐ YES ☐

⇨ f yes: Car ☐ Train ☐ Plane ☐

Other ☐ Specify _____

No. Hours longest trip total Hours ☐☐

11. Pregnancy in last year: NO ☐ YES ☐

⇨ If yes, currently pregnant? NO ☐ YES ☐

⇨ If yes, weeks gestation: ☐☐ weeks

⇨ If no, date delivered/miscarried/aborted:

☐☐ D D ☐☐ M M ☐☐☐☐ Y Y Y Y

12. Current smoker: NO ☐ YES ☐ If yes, average number of cigarettes per day:

☐ < 1 ☐ 1 – 5 ☐ 5 – 14 ☐ 15 – 24 ☐ 25 – 35 ☐ 36 – 44 ☐ 45 +

13. Prior history of VTE:

Has the patient ever had a venous thromboembolism: ☐ NO ☐ YES

If yes, total number of: ☐☐ DVT ☐☐ PE

Prior DVT # 1⇨ Side: ☐ Right ☐ Left

Site: Proximal leg ☐ Distal leg ☐ Other ☐ Specify _____

Year: ☐☐☐☐ Duration of anticoagulation: ☐☐ months

Prior DVT # 2⇨ Side: ☐ Right ☐ Left

Site: Proximal leg ☐ Distal leg ☐ Other ☐ Specify _____

Year: | | | | | Duration of anticoagulation: | | | months

Prior PE # 1 ⇨ Side: ☐ Right lung ☐ Left lung ☐ Not known
Year: |_|_|_|_| Duration of anticoagulation: |_|_| months

Prior PE # 2 ⇨ Side: ☐ Right lung ☐ Left lung ☐ Not known
Year: |_|_|_|_| Duration of anticoagulation: |_|_| months

Section C. Medication History

14. Has the patient taken any of the following medications in the 30 days prior to the current Doppler examination?

Hormone replacement therapy	NO☐ YES☐	If yes, specify drug:	_____
Oral contraceptives	NO☐ YES☐	If yes, specify drug:	_____
Antiestrogen or antiandrogen	NO☐ YES☐	If yes, specify drug:	_____
Aspirin	NO☐ YES☐	If yes, specify indication:	_____
Warfarin	NO☐ YES☐	If yes, specify indication:	_____
Heparin	NO☐ YES☐	If yes, specify indication:	_____
Non-steroidal anti-inflamatory drugs (NSAIDS)	NO☐ YES☐	If yes, specify drug:	_____
Antiplatelet agent (eg. Clopidogrel, dipyridamole)	NO☐ YES☐	If yes, specify drug:	_____
Lipid lowering drugs ('statin' type)	NO☐ YES☐	If yes, specify drug:	_____

Section D. Family History

15. How many relatives were EVER diagnosed with DVT or PE?

Parents ☐ Siblings☐ Children☐ Don't know ☐

Are there any relatives with more than one event ?

Parents ☐ Siblings☐ Children☐ Don't know ☐

Section E.

16. Day of this examination to rule out deep venous thrombosis

|_|_| |_|_| |_|_|_|_|
D D M M Y Y Y Y