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Venous thrombo-embolism associated with long distance air travel.

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A thesis submitted for the degree of

Doctor of Medicine

at the University of Auckland, Auckland

New Zealand

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Abstract

Background: The frequency and role of risk factors for venous thromboembolism related to air travel is uncertain. The objective of this thesis was to determine the frequency of this disorder in a group of long distance air travellers, the proportion of patients admitted to hospital with venous thromboembolism in whom recent air travel was documented, and to investigate the role of potential risk factors.

Methods: Phase 1 was a prospective study of individuals aged between 18 and 70 years, travelling for 4 hours or more by aircraft. D-dimer measurement was done before and after travel. Participants with a negative D-dimer (<500ng/L) before travel were included in the study. Those who became D-dimer positive (>500ng/L) or developed high clinical probability symptoms during the 3 months after travel were investigated with bilateral compression ultrasonography and CT pulmonary angiography. Suspected clinical and thrombophilic risk factors, and use of prophylactic measures were assessed. In Phase 2 a retrospective review of the medical records of patients with a primary or secondary discharge diagnosis of DVT or PE in four hospitals in New Zealand. From the medical records information was collected on demographic details, documentation of the presence of risk factors and results of radiological investigations.

Results: In Phase 1 1000 subjects were recruited, with 878 meeting inclusion criteria and completing the study. All participants travelled at least 10 hours, with a mean total duration of air travel of 39 hours (SD 12.5). There were 112 subjects with a raised D-dimer on their return. The risk factors associated with a raised D-dimer included increasing age, female sex, non-aisle seating position, obesity, thrombophilia and co-morbidity. Following radiological assessment the frequency of venous thromboembolism associated with travel was 1.4% (12/878), which included four cases of pulmonary embolism, five of deep venous thrombosis and three with superficial thrombophlebitis. Six patients with venous thromboembolism had pre-existing clinical risk factors, two had a recognised thrombophilic risk factor, three travelled exclusively in business class, seven used aspirin and four wore compression stockings. In Phase 2, 60 of 576 (10.4%) patients with a confirmed VTE had documentation of recent air travel; in 31 of these 60 subjects no other risk factors were recorded. In those cases in whom details of the air travel had been recorded, it had been undertaken in the previous one week in 65.0%, and in 43.3% the air travel was of at least 10 hours duration.

Interpretation: These findings suggest an association between multiple long distance air flights and venous thromboembolism, even in individuals at low to moderate risk. The role of traditional risk factors and prophylactic measures in air travel-related venous
thromboembolism needs further investigation. Long distance air travel is an important risk factor for venous thromboembolism requiring hospital admission and represents a significant public health problem in New Zealand.

Word Count: 462

Keywords: Air Travel, Venous Thromboembolism, Travellers Thrombosis, NZATT
Preface

This research was undertaken at two academic centres in New Zealand during the period of my advanced training in Respiratory Medicine. It was funded by significant grants from the University of Otago and the Medical Research Institute of New Zealand, although much of the time and effort required for the study was kindly undertaken by colleagues, friends and family, without compensation. We all believed that we had a unique opportunity to establish New Zealand in the forefront of research into travellers thrombosis. However, this was an ambitious project from the outset, and I am grateful to many people for having been given the opportunity and support to undertake this work.

I am deeply indebted to my supervisor, Professor Richard Beasley, Director of the Medical Research Institute of New Zealand, who believed in my ability to perform the study from the outset. He introduced me to the field of venous thromboembolism and has inspired many of his students to pursue a career inclusive of medical research. His support, advice and guidance during this time was invaluable to my personal development and the success of this project.

I also grateful to my co-supervisor, Dr Margaret Wilsher, Head of the Department of Respiratory Medicine at Greenlane Hospital, who supported this project from the outset and allowed me to undertake this research during a busy clinical attachment.

I would also like to acknowledge the assistance of my co-workers also involved in the study. In particular, Research Nurse Raewyn Hopkins worked endless hours and sat with me for long periods at Auckland International Airport recruiting subjects. Without Raewyn’s dedication to the Auckland site, this study would not have been successful. Kimberley Thomson, a Medical Student at Wellington School of Medicine, gave up her summer holidays to work many unpaid hours taking blood and consenting subjects at Auckland Airport. I would also like to thank the team in Wellington, lead by Dr Sarah Hill at Wellington Hospital, with the assistance nurse Jo Ayling and the team at P3 Research under the guidance of Dr Shaun Holt, who worked hard to ensure the second site was also successful.

I am particularly indebted to Dr Mark Weatherall, Physician and Bio-statistician at Wellington School of Medicine, who worked endlessly on ensuring the data analysis was appropriate and complete, and was a constant source of encouragement and advice.
I would also like to acknowledge the assistance of Professor Peter Browitt and Dr Niel Van de Water of Haematology Research Unit at Auckland School of Medicine, who undertook the thrombophilia genetic analysis, and the haematology teams at North Shore Hospital and Wellington Hospital (led by Dr Errol Crutch) for establishing and conducting the VIDAS D-dimer measurements.

Recruitment for his study would not have been possible without the co-operation of Auckland International Airport Management Group with support from Dr David Powell, Medical Director from Air New Zealand. Their support and provision of access and facilities were imperative to the outcome of this study. The friendly and helpful manner of the staff of the Airport and the Airline Lounges ensured appropriate representation of all travellers within the study.

I would like to thank the subjects who enrolled in the NZATT study, without who this study would never have been possible. Many of these people were happily preparing themselves to travel on holidays, work trips or to visit friends and family, when they agreed to take part in the study. I was amazed that so many took the time to return for their follow-up, fill out their questionnaires and were so eager to contribute to the study. In particular, I would like to thank Dr John Mayhew, Doctor for the New Zealand All Black Rugby Team, for encouraging members of the team and management to participate in the study and thus enhance publicity for the study.

And finally, I would like to express my deepest thanks to my wife, Lucy, who not only supported me during the trials and tribulations of this research, but spent endless hours contacting subjects, completing three month follow-up questionnaires and collating data. Our marriage and our two children, Michael and Benjamin, are the joys of my life.
List of Original Articles

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<td>Venous Thromboembolism</td>
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<td>PE</td>
<td>Pulmonary Embolism</td>
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<td>DVT</td>
<td>Deep Vein Thrombosis</td>
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<td>SVT</td>
<td>Superficial Vein Thrombosis (Thromboplebitis)</td>
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<td>FVL</td>
<td>Factor V Leiden</td>
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<td>PGM</td>
<td>Prothrombin Gene Mutation</td>
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<tr>
<td>ACL</td>
<td>Antocardiolipin Antibodies</td>
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<tr>
<td>TFPI</td>
<td>Tissue Factor Pathway Inhibitor</td>
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<tr>
<td>TAFI</td>
<td>Thrombin-activatable Fibrinolysis Inhibitor</td>
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<tr>
<td>CRP</td>
<td>C Reactive Protein</td>
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<tr>
<td>FDP</td>
<td>Fibrinogen Degradation Product</td>
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<tr>
<td>HRT</td>
<td>Hormone Replacement Therapy</td>
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<tr>
<td>OCP</td>
<td>Oral Contraceptive Pill</td>
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<tr>
<td>LMWH</td>
<td>Low Molecular Weight Heparin</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-linked ImmunoSorbent Assay</td>
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<td>NPV</td>
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<td>CTPA</td>
<td>Computer Tomography Pulmonary Angiography</td>
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<td>NZATT</td>
<td>New Zealand Air Travellers Thrombosis Study</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<td>SIT</td>
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Chapter 1

Introduction

Venous thromboembolism (VTE) is a common condition which is associated with significant morbidity and mortality in sufferers. This potentially fatal process is notoriously difficult to diagnose due to a combination of frequently unrecognised symptoms and signs, lack of suspicion by the patient or the treating physician, and sometimes complicated diagnostic investigations. Whilst there has been progress in the understanding and treatment of venous thrombotic events, many individuals remain unaware that they are at risk of, or are experiencing, the potentially dangerous consequences of this disease process.

In 1868, the German vascular surgeon Virchow performed autopsy examinations on a series of patients who had died as a result of massive pulmonary embolism [1]. He was first to describe the association between lower limb deep venous thrombosis and subsequent embolism and obstruction of pulmonary vasculature. He also described the phenomenon of thrombus propagation, valvular disruption and subsequent chronic lower limb deep venous obstruction. Virchow suggested that three distinct processes were important in the development of thrombi:

- Venous stasis
- Vessel wall damage
- Increased blood viscosity (hypercoagubility).

Since that time, “Virchow’s triad” has since remained the cornerstone of the understanding of venous thrombus formation.

Over the last 60 years air travel has become the predominant means by which passengers undertake long distance travel, and it is estimated that over 1.5 billion people travel by this modality every year. With the exception of the now discontinued Concorde, there has been little change in the basic design of commercial aircraft since the widespread introduction of jet propulsion 40 years ago. As a result, the anticipated progressive reduction in flight times has not occurred, and in fact new technology has been utilised to develop ultra long distance sectors of up to 16 hours duration. During this period commercial influences have forced airlines to maximise carrying capacity by dramatically reducing the leg space available to individual passengers by altering seat width and pitch. These changes have resulted in more
prolonged periods of progressively more confined seated immobility, thus fulfilling at least one of components of Virchow’s triad.

It is therefore not surprising that soon after the introduction of commercial air travel, there were reports of passengers suffering lower limb thrombosis with and without pulmonary embolism. The first published description of VTE occurring as a result of travel, now referred to as “Travellers’ thrombosis” was made by John Homans in 1954 [2]. Homans described five cases of apparent “spontaneous” lower limb venous thrombosis following prolonged sitting, four of which occurred following long distance journeys (two by air). Subsequent to this report there have been multiple cases and small case series describing similar individuals, and there has been growing suspicion that long distance travel may be a significant risk factor for VTE.

However, Homans’ cases highlight much of the difficulty in not only diagnosing VTE in this circumstance, but also in establishing such a causal relationship.

His first case, a 54 year old physician who undertook multiple flights over a 3 day period, developed symptoms within 2 hours of return. In this case there is a clear relationship, both temporally and in the mind of the patient, between the exposure and onset of symptoms. This case not only demonstrates the risk may increase following multiple flights in rapid succession, but also the observation that symptoms occur frequently following the return flight as opposed to outgoing flights.

Unfortunately such cases are not always so clear cut, as is highlighted by cases 2,3 and 4. Each of these individuals appears to have not developed, or not noticed, significant symptoms until several days after their journeys. These cases highlight the more complex complications of VTE, such as post thrombotic syndrome, that may not have been immediately identified as being the result of the journey. Only two of the cases (case 2 and 3) had obvious underlying thrombophilic states, with one case being that of recurrent VTE in a 53 year old male and the other that of a 19 year old female who subsequently developed signs of connective tissue disease.

Homans relates these cases, and that of his 5th case of a man who developed VTE following prolonged sitting whilst at the theatre, to “dependency stasis” as described by Keith Simpson during the London Blitz in 1940 [3]. Simpson observed a dramatic increase in fatal
pulmonary embolism in individuals forced to sit for prolonged periods in air-raid shelters. Both Simpson and Homans recognized that thrombosis may develop rapidly in this circumstance and that “propagation and pulmonary embolism may immediately follow” [2]. They also recognised that the other components of Virchow’s Triad may have played a role in his cases, with injury to the venous endothelium as a result of leg crossing or venous compression, and/or thrombophilia contributing.

Both Homans and Simpson suggested that physicians should be aware of this somewhat unpredictable but serious complication of prolonged immobility, and that suitable prophylaxis should be considered for at risk individuals. Unfortunately, fifty years later, the potential strength of association and/or causation between the prolonged immobility of long distance travel and VTE remains poorly understood, with adequate recommendations regarding risk assessment and prophylaxis lacking.

The purpose of this thesis is to review the previously published literature suggesting an association between long distance air travel and venous thrombotic events and to present new data reporting the frequency, risk factors and clinical impact of travellers’ thrombosis. Whilst it is clear that this condition is not exclusive to air travel, and other forms of travel will be discussed, the primary focus will be on events that occur during, or soon after long journeys via commercial aircraft.

For the purpose of consistency, VTE is used throughout this report to refer to both deep venous thrombosis (DVT) and pulmonary embolism (PE), as it is widely accepted that these diagnoses represent the same pathological process in most circumstances. Where there may be factors differentiating these conditions, this will be highlighted.
Chapter 2

**Thrombus Formation- Pathophysiology**

In order to understand the means by which long distance air travel may contribute to VTE, and indeed how to investigate this relationship further, it is necessary to more thoroughly understand how the components of Virchow’s Triad contribute to thrombus formation. In 1898 Welch translated and elaborated upon Virchow’s descriptions to formulate the following underlying causes of thrombus formation:

1. **Vessel wall injury**- A primary lesion of the wall of the vein which involves particularly the endothelium and gives rise to both the inflammatory changes and intra-vascular thrombosis.
2. **Hypercoagulability**- Alteration in the physical properties or chemical constituents of the blood itself, which produces increased coagulability.
3. **Venous stasis**- A relative slowing or other abnormality of blood-flow with resultant adherence of platelets to the intimal coat, development of a mixed thrombus, and subsequent inflammatory reactions of the wall of the vein due to the presence of thrombus [4].

The processes involved in thrombus formation and lysis and the relative contribution of the components of Virchow’s triad will be discussed below.

2.1 **Thrombin generation and the coagulation cascade.**

In order to maintain haemostasis, the apparently opposing processes of thrombin formation and fibrinolysis are in constant balance. Under normal physiological conditions in an intact vessel, fibrinolytic and thrombin inhibitory factors predominant in order to maintain the normal fluidity of blood. Laminar flow dictates that platelets and the proteinaceous components of blood containing pro-coagulant factors are concentrated at the vessel wall, due to the axial concentration and deformable nature of red cells. The intact endothelial cell plays a key role on maintaining normal haemostasis, orientated itself in the direction of flow, and inhibiting the activation of the coagulation cascade [5]. The most important of these inhibitors are antithrombin (AT) and tissue factor pathway inhibitor (TFPI), the relative concentrations of which determine the “threshold” of thrombus initiation for an individual. However, in the event of injury to the endothelium and exposure of the underlying extracellular matrix and
phospholipid membranes, local activation of the procoagulant factors rapidly overcomes these inhibitors, with the eventual conversion of soluble monomer fibrinogen to a gel-like fibrin clot, and subsequent cessation of blood loss.

The mechanism by which this occurs is a complex series of serine proteinases combining with cofactors and membrane bound receptors which eventually results in the conversion of prothrombin to thrombin (factor II). Thrombin plays a central role, not only as the final proteolytic step of fibrin formation, but also in regulating the subsequent propagation and resolution of clotting. This is achieved by a combination of conformational changes in protein structure resulting in exposure of cleavage sites for other substrates, in addition to dynamic changes in the function of these proteins under the influence other factors.

Following vascular wall injury, the key initiating event in thrombin generation is the interaction between membrane bound tissue factor and plasma factor VIIa, stimulating the so called “extrinsic pathway”. The Factor VIIa-tissue factor complex, in the presence of exposed phospholipids and calcium, mediates the conversion of factor X to Xa. In addition, a small amount of thrombin is directly generated by this complex, which is thought to have an important role in the subsequent propagation phase by activating platelets, factor V and factor VIII. The production of VIIIa and subsequently factor IXa initiates the “intrinsic pathway”, which will further augment thrombus propagation once fibrin formation has begun.

Factor Xa combines with factor Va on the platelet surface membrane to catalyse the conversion of prothrombin to thrombin. The generation of factor Xa is therefore the initial rate limiting step to further activation of the cascade. It’s rate production is dependant on factor VIIIa and factor IXa further amplifying the activity of the factor VIIa-tissue factor complex (the so called “prothrombinase complex”), which is the principal defect observed in haemophilia A and haemophilia B.

The primary inhibitors of this process are AT and TFPI. AT effectively inactivates and cleaves most procoagulant serine proteases, both in their activated and uncomplexed states. In addition TFPI inhibits the factor VIIa-tissue factor complex, thus reducing the production of factor Xa (and factor IXa). However, at a site of significant vascular injury, the rate of factor Xa production rapidly exceeds the concentrations of these inhibitors, and the subsequent thrombin production further accelerates both the extrinsic and intrinsic pathways. Furthermore, platelets become incorporated within the expanding fibrin matrix, facilitating
accelerated activation of thrombin and transition from the initiation phase to the propagation phase.

The potential effect of factor Xa is highlighted in primate studies where, when combined with an exogenous phospholipid surface, high dose factor Xa is able to result in the rapid consumption of circulating fibrinogen and platelets to immeasurable levels within 1 minute [6].

Fibrinogen is a large soluble monomer which consists of two globular D domains and a central E domain, off which four short peptide chains protrude; two fibrinopeptide A (FPA) chains and two fibrinopeptide B chains (FPB). Thrombin cleaves both FPA and FPB from the molecule, which results in a conformational change in both the E and D domains, and linking of D domains between adjacent molecules. Further cleavage of FPA and FPB causes linear polymers to form in a half-staggered fibril arrangement, with progressive propagation and branching. A mesh-like gelatinous material forms which traps platelets and red cells, forming a typical clot [7].

As opposed to platelet rich thrombi which form within damaged arterial vessels, the thrombi that occur within the venous system tend to be composed predominantly of fibrin.[8, 9] The nature of this difference is poorly understood, although Frenzel et al have suggested that structural difference in vessel wall and pulsatile flow within an artery appears to play a significant role. It is apparent that endothelial cell function is shear stress dependant, with differential expression of vasoactive and platelet stimulating compounds, such as von Willebrand’s factor (vWF), ICAM-1, VCAM-1 thromboxane A2 and endothelin-1 in vessel exposed to high pressure.[10] It is also apparent that the risk factors associated with thrombosis formation differ significant between the arterial and venous systems [11, 12].

The role of inflammation in the aetiology of thrombus formation remains uncertain. Thrombin itself is capable of activating multiple inflammatory pathways. In patients presenting with acute VTE, the inflammatory cytokines IL-6, IL-8, TNF-α and MCP-1 are frequently elevated, in addition to C Reactive Protein, an acute phase reactant.[13, 14] Thrombosis can directly elicit an inflammatory response within the vein wall, resulting in neutrophil activation, expression of selectins and other inflammatory mediators. It is also clear that thrombosis is frequent in patients with auto-immune vasculitic conditions, where the vessel wall is the target of the immune response. However, the levels of markers such as CRP and
IL-6 have also been shown to remain elevated in patients with recurrent VTE, and it remains unclear as to whether represents a true risk factor of recurrence or a consequence of ongoing vessel injury [14].

2.2 Fibrinolysis

In the primate studies mentioned earlier, the impressive potential of the procoagulant system was equally matched by the response of the fibrinolytic system. Despite massive thrombosis and consumption of coagulant factors, administration of tissue plasminogen activator (tPA) rapidly halted and reversed this process, returning circulating platelets to normal levels within 2 minutes, with no ill effect to the animal concerned [6].

Despite it’s apparently central role in fibrin formation, the production of thrombin almost immediately initiates inactivation of the coagulation cascade. Thrombomodulin, an endothelial cell surface protein, binds thrombin and results in a conformational change such that thrombin no longer cleaves fibrinogen. Instead, a separate cleavage site is created for protein C, the active form of which (with it’s cofactor, Protein S) is able to directly inactivate factors Va and VIIIa.

Simultaneously, the formation of fibrin serves as a cofactor with endothelial derived tPA to initiate the conversion of plasminogen to active plasmin. Plasmin facilitates the digestion of fibrin polymers at cleavage sites between the D and E domains, creating soluble fibrinogen degradation products (FDPs) such as D-dimer [15].

Much in the same way that the fibrinolytic pathway is activated at the onset of thrombus formation, inhibitors of fibrinolysis are also rapidly activated. Interestingly, the thrombomodulin-thrombin complex also catalyses the activation of thrombin-activatable fibrinolysis inhibitor (TAFI) to an antifibrinolytic enzyme that reduces the cofactor nature of fibrin in activating plasmin. Plasmin itself, at high levels, will also activate TAFI, thus providing a mechanism by which both the procoagulant and fibrinolytic pathways can regulate fibrin formation and degradation. TAFIa is intrinsically unstable, and although no naturally occurring inhibitor has been found, levels reduce spontaneously following the resolution of thrombus formation.
Plasmin activity and generation is also regulated by two serine protease inhibitors; plasminogen-activator inhibitor (PAI-1) and antiplasmin. Endothelium derived PAI-1 inactivates tPA, whilst antiplasmin inhibits plasmin activity [7]. These inhibitors, in addition to TAFI, provide a means by which to down-regulate the fibrinolytic pathway and restore normal haemostasis and the thrombosis threshold.

2.3 Hypercoagulability

As mentioned earlier, it is clear that in order to maintain haemostasis a constant balance of procoagulant and fibrinolytic mechanisms is essential. For some time it has been evident that some individuals will develop significant thrombosis more readily, particularly in the presence of a family history of VTE. The term “thrombophilia” refers to any identifiable abnormality of the procoagulant or fibrinolytic pathway reduces the thrombosis threshold and increases the risk of VTE to an individual.

In the 1965 Egeberg described a series of individuals with a strong familial tendency to VTE who were found to have reduced functional levels of antithrombin. [16] Since that time, over 100 polymorphisms within the gene encoding this large glycoprotein have been ascertained. Both reduced protein production (type 1 defect) and reduced function at normal levels of production (type II defect) have been described. Whilst this remains a relatively rare cause of VTE (approximately 1:1000 cases of VTE), carriers antithrombin deficiency are of high relative risk of VTE due to the wide ranging inhibitory activity of the protein on factors XIa, Xa, IXa and thrombin, which is enhanced by endothelial bound heparin. All carriers are heterozygotes, as homozygote foetuses do not survive to birth. This abnormality remains the original benchmark of thrombophilic tendencies.

Later abnormalities of fibrinogen which render it resistant to fibrinolysis (dysfibrinogenaemia) and deficiencies of the vitamin K dependant protein C and it’s cofactor protein S were also established, with most defects being type 1 in nature.[17-20] Although these abnormalities significantly increase the risk of first and subsequent VTE, particularly in young individuals, their frequency remains rare. Their combined effect accounts for less than 10% of patients presenting with spontaneous VTE.

In 1993 Dahlbach et al described reduced affinity of activated Protein C to it’s target binding site on factor Va in a cohort of individuals presenting with VTE (so called activated protein C
resistance) [21]. Subsequent investigation isolated a guanine to adenine substitution mutation at nucleotide 1691 of the factor V gene which was present in 21% of unselected patients with VTE and 50% of those with a personal or family history of VTE.[22] Further international estimates have found that heterozygotes for this mutation, which is now known as factor V Leiden (FVL), are found in between two to six percent of populations of European descent, although it is rare in other racial groups. It confers an increase in the relative risk of first VTE of between three to six fold. Additional, this abnormality interacts in a multiplicative fashion with other risk factors, increasing the risk significantly in affected individuals. The frequency of homozygotic individuals is approximately 1:1000, with such individuals having an eighty fold relative risk of developing VTE [23].

Although the presence of FVL is associated with an increased risk of first episode of lower limb DVT, somewhat paradoxically the strength of association with pulmonary embolism is somewhat diminished [24, 25]. The most widely held hypothesis for this observation is that although the mutation increases the likelihood of local fibrin formation, the resulting clot is in someway more adherent to the vessel wall and less likely to embolise. Additionally, a study by Bjorgell et al in which patients in who lower limb DVT was confirmed by venography, carriers of FVL were less likely to have proximal ilio-femoral thrombus (2.8% vs 23.2%). Proximal thrombus distribution is more commonly associated with PE.[26] The odds ratio of proximal DVT within the FVL population was 0.5, as opposed to 5.3 for more distal events.

In 1996 Poort et al described VTE occurring in families as a result of increased functional levels of prothrombin. This association was traced to a mutation at nucleotide 20210 of the prothrombin gene (PGM), in the apparently untranslated 3’ region. Recent proteomic analysis suggested that the mutation increases glycosylation of prothrombin conferring greater stability to the protein [27]. The abnormality is present in two to three percent of European populations and confers a relative risk of two to three fold.

The observation of increased risk of VTE in association with connective tissue disease, particular systemic lupus erthyrocytosis (SLE), lead to the discovery of a procoagulant state which could be acquired [28]. The antiphospholipid antibody syndrome (APS), the primary determinants of which is Lupus Anticoagulant and IgG antibodies to the phospholipid cardiolipin, is associated with arterial, venous thrombosis and recurrent miscarriage [29]. It would appear that these antibodies interact with proteins on surface membranes or phospholipids-binding proteins which subsequently activates clotting factors such as vWF,
and increase platelet adhesion [30]. Although initially described in association with SLE, it is now recognised to exist as a primary phenomenon, or secondary to other connective tissue disease and malignancy. Venous thromboembolic events are reported in up to one third of patients with APS. In a meta-analysis performed by Galli et al, the presence of lupus anticoagulant and/or anticardiolipin antibodies was associated with a relative risk for first VTE of between five to sixteen fold [31]. The relative importance of these abnormalities remains controversial, as many studies have failed to separate venous the arterial thrombi. In addition, the association with anticardiolipin antibodies is dependant of the titre levels obtained, which may be transient. As a result, it is important to ensure that titres are repeated at least 6 weeks after initial assessment before the diagnosis of APS can be made in the context of a recent thrombosis.

TABLE 1. Estimates of prevalence and relative risk of VTE associated with thrombophilia in European populations

<table>
<thead>
<tr>
<th></th>
<th>Prevalence in general population (%)</th>
<th>Prevalence in VTE patients (%)</th>
<th>Prevalence in idiopathic VTE patients (%)</th>
<th>Overall relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin def</td>
<td>0.02</td>
<td>1.9</td>
<td>4.3</td>
<td>10 – 15</td>
</tr>
<tr>
<td>Protein C def</td>
<td>0.2 – 0.4</td>
<td>3.7</td>
<td>4.8</td>
<td>10</td>
</tr>
<tr>
<td>Protein S def</td>
<td>0.1 – 0.2</td>
<td>2.3</td>
<td>4.3</td>
<td>10</td>
</tr>
<tr>
<td>FVL</td>
<td>5</td>
<td>20</td>
<td>40 - 60</td>
<td>5 - 8</td>
</tr>
<tr>
<td>PGM</td>
<td>2</td>
<td>7</td>
<td>16</td>
<td>2 - 3</td>
</tr>
<tr>
<td>Homocysteinuria (&gt;20 μmol/L)</td>
<td>5</td>
<td>10</td>
<td>-</td>
<td>3 - 4</td>
</tr>
<tr>
<td>Factor VIII (&gt;150%)</td>
<td>11</td>
<td>25</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>1 – 5</td>
<td>10 - 20</td>
<td>30 - 55</td>
<td>5</td>
</tr>
</tbody>
</table>

Hyperhomocysteinuria is associated with both venous and arterial thrombosis. This may result from either acquired causes, such as B12 or folate deficiency, renal failure or hypothyroidism or inherited causes influencing homocysteine metabolism. The most marked form of the condition, associated with the rare homozygous cystathionine B-synthase deficiency, results in 50% of affected individuals presenting with arterial or venous thrombosis prior to the age of thirty [32]. However, the most common genetic cause is that of a C667T substitution mutation.
of the methyltetrahydrofolate reductase gene, which occurs in five to fifteen percent of European and South East Asian populations, is of questionable significance [23, 33]. The strength of this association and the absolute level of homocysteine necessary to increase VTE risk remains controversial, and is further influenced by the difficulty in obtaining consistent representative samples in affected individuals due to dietary variations.

Elevated levels of factor VIII, factor IX, vWF, non-O ABO blood group and more recently polymorphisms of the factor XIII, PAI-1 genes and TAFI have also been linked with increased risk of VTE [34-37]. The underlying nature of these abnormalities and the strength of their association with VTE events require wider evaluation.

The prevalence of these abnormalities within the New Zealand general population is unclear. In a study performed to determine the prevalence of thrombophilia in female subjects attending family planning clinics, 15.9 percent had at least one abnormality detected, although full testing was not performed in any of the subjects [38]. In this predominantly Pakeha population, 6.8 percent were found to have activated Protein C resistance, suggested a frequency of Factor V Leiden similar to that of other Caucasian populations. It would appear that the gene frequencies of the established thrombophilias in the Pakeha population is similar to that of their predominantly Northern European ancestors. The prevalence in non-Pakeha populations, particular Maori and Pacific Islanders, has not been investigated.

2.4 Vascular Injury

With the exceptions of lower limb orthopaedic surgical intervention and trauma, the importance of vessel wall injury in thrombus formation within the venous system remains unclear. Whilst pro-inflammatory cytokines, such as those that occur in the context of sepsis or vasculitis, may result in direct endothelial damage, it is postulated that such conditions are predominantly affected by the hypercoagulability component of Virchow’s triad. It is now recognised that many clotting factors, such as fibrinogen and factor VIII, are acute phase reactants and functional levels may increase significant during any inflammatory response. In addition, elevated levels of inflammatory markers such as CRP, MCP-1 and IL-6 may in themselves be involved in the pathogenesis of VTE [13].

The term “thrombophlebitis”, popularised in the 1930’s as a description of DVT events that were predominantly the result of vessel wall inflammation, and therefore less likely to
embolise, has largely been abandoned. It is now recognised that intra-luminal thrombosis is, in most circumstances, the initiating event clot propagation, with vein wall inflammation occurring as a sequelae of this process [39]. It is only in the circumstance of previous lower limb DVT, where damage to venous valve leaflets and reverse flow from incompetent valves may result in significant vascular wall injury without the influence of direct trauma. Incomplete thrombus resolution, permanent scarring of the venous wall and disruption of the valve leaflets is common following DVT and produces an environment in which future recurrent events may occur.

2.5 Venous stasis

In a low pressure system such as the conduit veins of the lower limbs, continuous laminar flow is an important component of maintaining haemostasis. On standing from a lying position, an 80 to 90mmHg gradient in exerted between the heart and the foot as a result of gravity [40]. Without an adequate pump forcing blood against this gradient, blood rapidly pools within reservoirs within the calf and foot. The superficial subcutaneous veins and perforating veins with the soleus, gastrocnemius, tibialis anterior and planter muscles dilate to accommodate this additional volume. The degree of pooling is dependant on the capacitance of the veins, which is largely determined by the elasticity of the surrounding tissue. As such, dilatation of these vessels and the volume of blood pooled, increases with age. Hydrostatic pressure increases within the capillary beds drained by these vessels, resulting in fluid shift and oedema surrounding muscle and subcutaneous tissue. Under normal circumstances, this will stimulate the individual to move, and specifically activate the calf pump.

The calf pump can be considered as two chambers, which functions in a similar manner to one side of the heart. Blood pooled within the superficial veins drains into the perforating intramuscular veins of the calf and foot. This forms a “pumping chamber” which is rapidly emptied into the valve deep veins of the popliteal and femoral veins after calf contraction (primarily as a result of soleus contraction). As a result of a series of valves within the deep veins, back flow is prevented and unidirectional flow toward the heart is maintained. During normal weight bearing, the stroke volume of the calf pump is between 30 to 60ml and the foot pump 20 to 30ml [41, 42]. The maximum emptying rate occurs during the beginning of muscle contraction, with flow ameliorating during sustained contraction. During muscular relaxation, the perforating veins are refilled passively [43].
Without the activation of the calf pump, flow rates and velocity within the proximal deep veins reduces significantly. In 1960 McLachlin et al demonstrated that in the absence of calf contraction, contrast injected in to the soleus plexus remained for prolonged periods within the valve sinuses [44]. In moving from the supine position to standing, venous flow within the femoral vein reduces by approximately one third, and is similar in the sitting position. However, during simple dorsiflexion of the foot venous low rates increase to 2.5 to 3 times that of the supine position [45]. This rate of emptying is significantly slower in legs with deep vein flux or venous incompetence,[42] but is further increased if simultaneous foot compression is applied [46]. Flow within the calf remains elevated for up to one hour flow calf contraction before returning to baseline levels [47].

The calf pump also plays a significant role in maintain muscular oxygenation. During prolonged periods of pooling of blood within the intramuscular veins, significant haemoglobin desaturation occurs. As a result of increased capillary hydrostatic pressure and fluid efflux, the residual intravascular haemoglobin concentration increases. The result of these changes is not only tissue hypoxia, but diminished flow within the vaso vasorum, vessel wall hypoxia and endothelial damage. Muscular contraction also mediates arterial flow, by local production of nitric oxide by intramuscular venules. This generates a reactive hyperaemia to the area and improves oxygen delivery to the affected tissue [41].

Therefore, during sustained periods of immobility, the combined effects of venous pooling, reduced flow, localised oedema, haemoconcentration and tissue/vessel hypoxia create the conditions necessary for thrombus activation.

The site of thrombus formation following prolonged immobility has long been the source of considerable debate. Anatomical studies performed during the 1920’s and 1930’s have suggested that lower limb thrombosis following prolonged bed rest occurs most commonly in two distinct areas [39, 48]. These areas, the first being junction of the posterior tibial vein with the popliteal vein, and second being the termination of the superficial femoral vein at it’s junction with the profunda femoris vein, and the long saphenous veins to form the common femoral vein at the level of the inguinal ligament.(see figure 1) Both of these sites represent areas in which multiple veins merge in to a single conduit vessel resulting turbulent flow.
In most circumstances calf vein thrombi develop at sites such as the valve cusps and sinuses between the ostia of the intramuscular veins of the soleus muscle, where they anastomose with the intermuscular posterior tibial and peroneal veins. Following thrombus formation, the clot may propagate from within the small, high-compliance veins of the soleus plexus into the peroneal or posterior tibial veins. These two veins anastomose to form the tibioperoneal trunk, which combines proximally with the somewhat distinct anterior tibial vein to form the popliteal vein. At the point at which the tibioperoneal trunk combines with the anterior tibial vein, fresh thrombus may then either completely occlude flow into the popliteal vein, or may become dislodged by oblique flow from conjoining veins, resulting in embolism.

The anatomy of the tibiopopliteal trunk can be quite variable, and the veins are easily compressible during the course deep to the gastrocnemius muscle, making external imaging difficult (see figure 2) [50-52].
FIGURE 2. Variations in the anatomy of the tibiopopliteal trunk (taken from ref. 49).

Thrombus within the femoral vein is most likely to result from local thrombus formation rather than extensive propagation from a calf vein thrombosis [39, 48]. These occur most commonly within the valve pockets or at the termination orifice of the venous tributaries entering the femoral vein. Thrombus propagation may extend both anterograde and posterograde from the site of formation. Complete propagation of popliteal vein thrombosis to the femoral vein is considered rare, and may actually represent retrograde propagation due to initial occlusion of the femoral vein itself.

Iliac vein thrombosis in isolation is rare and is commonly associated with a pelvic mass or malignancy. Although it is recognised that between 85 to 90 percent of PE result from thrombi with the lower limbs [39], emboli can also occur from upper limb vessels, particular when associated with structural abnormalities or foreign bodies. Central catheters, pacemaker wires and ventriculo-atrial shunts are all thrombogenic and may result in partial or complete occlusion of large central veins. Rarely, thrombi may also form within low flow confluences of cerebral veins, such as the sagittal sinus, the subclavian or mesenteric veins. However, these events usually occur only in the context of anatomic anomaly or thrombophilic predisposition.
Thrombosis occurring within the large superficial veins of the leg, primarily the short and great saphenous veins, have long been considered a relative benign event. Whilst more commonly associated with discomfort and erythema (hence more commonly referred to a thrombophlebitis), their potential for propagation or embolism has been poorly recognised. There is however substantial evidence suggesting that SVT are not always benign. Deep vein thrombosis may be associated with SVT in 6 to 53%, and thrombus propagation may occur in a contiguous and non-contiguous fashion [53]. The most common contiguous extensions are from the great saphenous vein into the common femoral vein within the femoral triangle, whilst thrombus may also extend from the short saphenous vein into the popliteal vein through the sapheno-popliteal junction. Similar associations to prothrombotic states seen in DVT and also observed SVT, although varicose veins and venous reflux are important risk factors for SVT [54].

2.6 Factors influencing pulmonary embolism

Predicting the likelihood of pulmonary embolism based on the nature and distribution of lower limb DVT (or SVT) has been difficult. As mentioned previously, the presence of thrombophilic factors and inflammation may have variable effects on the formation and stability of the developing thrombus [24, 25]. Whilst traditionally proximal thrombus has been considered more likely to embolise than distal of calf thrombus, the effect of intervention bias has been under-estimated. Recent studies using venography and magnetic resonance imaging suggest that clot volume and surface area may be more important predictors of PE than the proximal extent of DVT [55, 56].

Pulmonary embolism may also occur in association with SVT, particularly in the instance of extensive great saphenous vein thrombosis. Between 7.8 to 33 percent of saphenous vein thrombi situated above the knee may result in PE [57, 58]. It is unclear whether these events are as a result of thrombus detaching directly from the superficial vein, or as a result of turbulent flow as the thrombus enters the deep venous system.

Finally, thrombosis in situ within pulmonary arteries may occur in the context of vasculitis, pulmonary arterial hypertension or congenital heart disease [59, 60]. This is an uncommon occurrence, and represents a combination of venous stasis within dilated arteries and vascular wall injury as a result of arteriopathy.
Chapter 3

The incidence and risk factors for “classical” VTE

The true incidence and absolute risk associated with specific clinical factors contributing to VTE events is difficult to estimate. Given the delicate balance of prothrombotic and fibrinolytic factors, it is likely that sub-clinical thrombi occur frequently and may be of little significance. Equally, it is apparent that lower limb venous thrombi and pulmonary emboli may occur without noticeable symptoms or signs, and may be the forerunners to more significant events.

Most large population based studies have primarily reported the incidence of symptomatic events, whilst interventional studies assessing the role of prophylaxis have focused on asymptomatic thrombi demonstrated by imaging after exposure to known risk factor, such as surgery. In both circumstances it is acknowledged that these observations vary widely in their study populations and clinical relevance, and accordingly the attributable risk of causative factors has been difficult to determine.

3.1 Incidence of VTE in the general population

Several large population based health studies have included the reporting of symptomatic VTE, with incidence rates ranging between 2.3 and 18.0 events per 10,000 person years [61-64]. Whilst most have been conducted in relatively homogenous populations in Scandinavia, France and the USA, these studies have differed significantly in their primary focus, including types of VTE events (DVT vs PE, primary vs recurrent), presentation of their populations (inpatients vs outpatients, medical vs surgical) and confirmatory testing (self reported questionnaires vs thorough radiological and notes review). In the most thorough systematic review, published by Fowkes et al [65], the authors restricted their analysing to DVT events only and several assumptions were made regarding the raw incidence rates in their analyses. Despite these limitations, the authors estimate that newly diagnosed symptomatic DVT appears to occur in approximately 5 per 10,000 of the whole population per annum, of which 2 per 10000 are idiopathic.

Several studies, some of which were included within this analysis, report that the incidence of VTE has remained relative static over the last 20 to 30 years, despite an increasingly aging
population and increased exposure to high risk exposures such as surgery.\[66, 67\] Whilst developments in diagnostic investigations have improved during this time, it is suggested that the increased use of adequate prophylactic measures may have contributed. Few of the studies have included subjects in who VTE was only diagnosed at the time of autopsy and the incidence PE as a primary cause of death is thought to be under-estimated. Approximately one third on autopsies performed on hospitalised patients show evidence of VTE, although calf veins are not usually examined for the presence of thrombus \[67\]. In a study reported by Pheby et al of over 3700 autopsies, in six percent of cases PE was found to be the cause of death. However, in eighty percent of these events, PE was an incidental finding that had not been suspected prior to death \[68\]. This is consistent with another study by Sandler et al in which ten percent of deaths were attributable to PE. Of these, eighty three percent had evidence of co-existing DVT, although only nineteen percent have symptoms suggestive of this prior to death. This suggests that although DVT was obviously present, the first symptom associated with this in the majority of individuals was a fatal event.\[69\]

All studies have demonstrated a progressive increase in the incidence of all VTE events with increasing age. One of the largest studies, based on the Worcester Epidemiology Project, reported that pulmonary embolism, with or without accompanying DVT, appeared to account for an increasing proportion of the VTE events with age. Thus, age appears to be an important determinant not only of the likelihood of VTE but also the probability that embolisation will occur. VTE is uncommon in individuals under the age of 20 years, and usually occurs in the context of a familial tendency or thrombophilia combined with an additional risk factor, such as the oral contraceptive or trauma (estimated incidence 1 per 10,000 per year). There is a rapid increase in incidence during the fifth and sixth decades such that the incidence is approximately 1 per 100 per year at 70 years \[70\].

Very few population studies have reported travel or prolonged immobility as a risk factor for VTE events in non-hospitalised patients. Whilst it is possible that some of those events classified as “idiopathic” or “spontaneous” in these studies may have occurred in individuals with an undocumented history of recent travel, the estimate of 1 to 2 per 1000 of the general population per annum (approximately 0.1 to 0.2 per 1000 for any six week period) for all forms of VTE provides a useful comparator by which to absolute risk of travellers’ thrombosis can be assessed. However it is acknowledge that the age of the study population needs to be considered carefully when making such comparisons.
3.2 The risk factors associated with VTE

Thrombus formation occurs when factors influence components of Virchow’s Triad, favouring excessive prothrombotic activity which exceeds the thrombosis threshold for that individual. Such risk factors may be “intrinsic”, and thus provide a constant level of background thrombotic risk to the individual, or may be “triggering” factors which place the individual at increased risk transiently. Intrinsic factors may be “genetic” in nature (eg. gender or thrombophilia), or may be “acquired” (eg. Obesity, antiphospholipid antibodies or malignancy) [71].

### TABLE 2. Risk factors associated with venous thromboembolism

<table>
<thead>
<tr>
<th>Strongly associated</th>
<th>Previous VTE event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Major orthopaedic or abdominal surgery (&gt;45 minutes) within preceding 4 weeks</td>
</tr>
<tr>
<td></td>
<td>Active malignancy (particularly in the presence of chemotherapy use)</td>
</tr>
<tr>
<td></td>
<td>Strong Family History of VTE (one or more first degree relatives)</td>
</tr>
<tr>
<td></td>
<td>Pregnancy / Postpartum</td>
</tr>
<tr>
<td></td>
<td>Major trauma</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular events</td>
</tr>
<tr>
<td></td>
<td>Acute spinal cord trauma</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure or myocardial infarction</td>
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<tr>
<td></td>
<td>Severe Sepsis</td>
</tr>
<tr>
<td></td>
<td>Anti-phospholipid antibody syndrome</td>
</tr>
<tr>
<td>Moderately associated</td>
<td>Lower limb trauma</td>
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<tr>
<td></td>
<td>Heparin induced thrombocytopenia</td>
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<tr>
<td></td>
<td>Increasing Age (Age &gt;40 years)</td>
</tr>
<tr>
<td></td>
<td>Central venous access</td>
</tr>
<tr>
<td></td>
<td>Prolonged immobility (&gt;72 hours) due to medical illness</td>
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<tr>
<td></td>
<td>Lapascopic surgery</td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
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<tr>
<td></td>
<td>Oral contraceptive use</td>
</tr>
<tr>
<td></td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td></td>
<td>Inherited thrombophilia</td>
</tr>
<tr>
<td></td>
<td>Hyperhomocysteinuria</td>
</tr>
<tr>
<td>Weakly associated</td>
<td>Obesity (&gt; 20% ideal body weight)</td>
</tr>
<tr>
<td></td>
<td>Current smoking</td>
</tr>
<tr>
<td></td>
<td>Varicose veins</td>
</tr>
<tr>
<td></td>
<td>Recent minor surgery</td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>Blood group other than O (esp A)</td>
</tr>
</tbody>
</table>

The risk factors associated with VTE are outlined in table 2. Estimates of the strength of these associations and relative risk vary between study populations and designs. Whilst several
large prospective population studies have identified the demographic components of risk, more in depth analysis of factors such as genetic predisposition has only been possible by case control format or smaller intervention studies often performed in asymptomatic individuals [61, 72-74].

This hypothesis assumes that exposure to risk factors is additive, and that the probability of any two risk factors causing VTE is predictable. In actually fact, interaction between risk factors is complex, and may in some cases be multiplicative (such as the interaction between factor V Leiden carriers and oral contraceptive use). In practice it is difficult to precisely predict the circumstances in which a VTE event will occur, even when the absolute and relative risk associated with a particular exposure is known.

FIGURE 3. The dynamic nature of thrombosis risk (modified from [78])

Risk factor assessment models have been proposed by several authors in order to rationalise appropriate investigation and prophylaxis, predominantly in the context of surgery or trauma [79-82]. Individuals may be classified as low, moderate or high risk based on their identifiable risk factors, although many of these factors cannot be ascertained easily. Whilst age, gender and previous medical history are usually apparent, inherited influences such as genetic thrombophilia may not be known at the time of risk exposure. However, most algorithms focus attention on high risk individuals, who may are usually defined by the presence of factors such as previous VTE, recent surgery (particularly lower limb orthopaedic), significant trauma, active cancer or strong family history of VTE. The distinction between low and
moderate risk patients is sometimes less clear without more thorough and expensive evaluation.

3.3 Long term outcome following VTE: symptomatic vs asymptomatic events

Several long term follow-up studies have also been conducted in order to determine prognosis following an initial VTE event. Long term morbidity, as a result of post-thrombotic syndrome and/or recurrent events, is high despite initial therapy (30% risk of recurrence within 10 years). Independent risk factors include events that are idiopathic or related to neurological events, malignancy, increasing age, obesity and male gender. The risk of recurrence is greatest at six to twelve months following the discontinuation of anticoagulation, and never falls to zero.[83] Delay in the rate of resolution of DVT on serial imaging, and perhaps persistent elevation in plasma D-dimer levels, have also been associated with an increased risk of recurrence.[84]

The distribution of PE is clearly associated with survival. Short term mortality is high in patients presenting with large emboli within the central pulmonary arteries, particularly in the context of acute haemodynamic compromise. However, small peripheral pulmonary emboli are generally assumed to be of less clinical significance, and mortality during treatment for these events is rare. However, the risk of fatal VTE recurrence following discontinuation of anticoagulation appears to be higher in any individual who is diagnosed with PE when compared to isolated DVT, regardless of it’s size and distribution of the initial embolus.[85]

Seinturer et al conducted a long term follow-up study of 1913 patients with acute DVT, 760 of who had co-existing PE. The distribution of the DVT seen at the time of diagnosis was closely correlated with survival at two years; 80% with unilateral distal DVT versus 65% with bilateral proximal DVT. The risk of recurrence was also predicted in a similar fashion; 7.7% versus 13.2% respectively at two years.[86]

It is therefore clear that one of the major determinants of future VTE is that of the presence and distribution of a prior event. The strength of this association is such that other markers of risk of first VTE, such as thrombophilia, are not necessarily predictive of recurrent events. However, what is unclear is the extent to which the first symptomatic event is preceded by prior asymptomatic events.
Small pulmonary emboli may have little haemodynamic effect, and usually only cause symptoms such as pleuritic chest pain in the context of peripheral pulmonary infarction.
Several studies have demonstrated that silent pulmonary emboli occur frequently, particular but not exclusively in association with proximal DVT. In carefully conducted studies in which perfusion scans were performed in patients presenting with symptoms suggestive of isolated DVT, PE is present in between thirty to fifty percent, even in cases where the DVT was isolated to the calf or superficial veins.[87-92]

Similarly, significant lower limb DVT may only result in symptoms if phlebitis or complete obstruction to flow within the vessel occurs. It is estimated that in 50% of pulmonary emboli the initial lower limb DVT is asymptomatic.[93, 94] In a study performed by Emmerich et al, the investigators undertook lower limb ultrasound assessment in apparently asymptomatic carriers of Protein C deficiency, an abnormality strongly associated with DVT. [95] Seven percent of these individuals were found to have evidence of venous injury consistent with a previous thrombosis. The authors suggested that chronic venous abnormalities in “at-risk” individuals may be more frequent than previously appreciated.

Additionally, post-thrombotic syndrome and chronic venous insufficiency whish are significant causes of morbidity and disability, may occur following lower limb surgery even when the initial DVT was asymptomatic.[96, 97] Of more concern are the findings of a retrospective review of medical patients who had taken part in a prophylaxis study, where ninety day mortality was significantly higher in those individuals with asymptomatic DVT as opposed to controls. Mortality within this period for asymptomatic proximal DVT was 13.9 percent, 3.3 percent with distal DVT and 1.9 percent in controls. [98]

The future absolute risk for recurrent events posed by an asymptomatic VTE is difficult to quantify. It is apparent that any PE is associated with a significant risk of future events. It is also apparent that any lower limb DVT can be associated with increased risk of PE, post-thrombotic syndrome and mortality. There is a poor correlation between the size of thrombi and the nature and duration of symptoms.[99] It is therefore uncertain as to whether making the distinction between those VTE events that result in symptoms noted by the patient, and those that are apparently asymptomatic, is clinically relevant. In practice the detection of significant PE or DVT, whether incidentally or in relation to suggestive symptoms, usually results in similar treatment and outcome.

3.4 Seated Immobility and VTE- A new phenomenon?
In 1898 Smith et al conducted a thorough review of the available literature to determine historical references pertaining to DVT. Unlike most common illnesses known to man, Smith had noted that there were no descriptions of DVT or DVT-like events in the Bible. The term “Milk Fever” had been used during the middle ages to describe sudden postpartum maternal death not related to obstetric complications, the majority of which are now assumed to be on the basis of PE. However, after an extensive review, which included Greeks texts by Homer and Aristotle, the Koran and available ancient Egyptian works, Smith was unable to find any references to VTE events occurring outside pregnancy until 15th century Europe. Three descriptions in Christian writings of that time describe severe venous insufficiency and cellulitis, with one of the cases being that of a baker who spent prolonged periods kneeling. Whilst the link is tenuous, Smith correlated these findings with the widespread introduction of formal cushioned seating during this period. Prior to the 15th century, seating had been functional, uncomfortable and expensive and usually reserved for mealtimes only. He hypothesized that more prolonged periods of seating had resulted in the new phenomenon of lower limb venous thrombosis. This suggestion was subsequently all but forgotten until the observations noted by Simpson in 1940, but adds to the suggestion that prolonged seating may indeed provide a catalyst for thrombus formation.

A more modern phenomenon has been described in recent case reports where VTE was temporally related to prolonged seating during extended computer use [100, 101]. Subsequently, other reports have identified cases of individuals developing VTE occurring during other short periods of immobilised sitting, such as whilst watching a long film at the cinema [101, 102]. The term “Seated Immobility Thrombosis” (SIT) has therefore been suggested as an appropriate description for all forms of VTE occurring in apparently healthy individuals as a result of prolonged sitting.
Chapter 4

Travel as a potential risk factor for VTE

4.1 Initial Case Reports

Despite the growing popularity of commercial air travel and the initial descriptions by Homans in 1954, there were few published reports of a potential association between long distance travel and VTE for the next 20 years. In 1968 Beighton and Richards described one death from paradoxical embolism soon after air travel [103]. In 1973 Johnson discussed the phenomenon of ankle swelling and discomfort following coach and air travel, which he named “Traveller’s ankle”. He suggested that it was likely to be associated with calf vein thrombosis, and that brief exercises that encourage activation of the calf pump may reduce the incidence of ankle swelling and DVT in association with travel and other medical illness [104].

It was not until 1974 that the general population and media became alerted to the existence of travellers’ thrombosis. After having previously suffered a DVT in his left leg in 1965, the then US President Richard Nixon developed a further event whilst flying during a long diplomatic visit to Europe, the Middle East and the Soviet Union. Despite apparently adequate anticoagulation, he developed symptoms suggestive of post-phlebitic syndrome, venous reflux and pulmonary embolism which resulted in him being unable to attend the Watergate trials due to hospitalisation. Subsequent attempted surgical ligation of the iliac vein was complicated by excess blood loss necessitating intensive care therapy for several days [105].

Horsley et al reported all causes of hospital medical admission in holidaymakers travelling to the Cornwall in 1975. During the 6 months reviewed, seven tourists had developed VTE although the method and duration of transport is not stated. Interestingly, they also describe high numbers of younger men who had sustained a myocardial infarction soon after journeys of greater than 10 hours [106].

In 1977 Symington and Stack reported eight cases of PE occurring shortly after travel during a three year period of observation. This represented 4.4% of all patients presenting with PE to that centre during that period. The journeys undertaken were between 2 to 24 hours duration
(mean 10 hours) and were made by car (three), aircraft (three), rail alone (one) and rail/ship combined (one). All patients were over the age of 40 years, with the exception of one 30 year old male. All except two had underlying “venous disorders”, although the exact nature of these is not described. The time between the end of the journey and onset of symptoms varied between 2 to 96 hours (mean 56 hours) and only four had symptoms suggestive of concurrent DVT. The authors coined the term “Economy Class syndrome” although acknowledge that the condition was not restricted to air travel alone[107]. After publication of this series, North American authors soon rephrased the condition “Coach Class syndrome” to comply with local terminology.

Ledermann et al described a further three cases of acute pulmonary embolism occurring soon after disembarking from long distance flights to Heathrow Airport in 1983. All three cases had experienced minor symptoms of swelling or discomfort in their calves during the flights, but had discounted these symptoms. One patient died as a result of the PE, and post mortem examination found evidence of calf vein thrombosis only in association with an undiagnosed breast malignancy [108]. These cases, and that of Thomas et al, were the first to report acute PE in direct association with mobilisation immediately after a long distance journey [109].

In 1988, Cruikshank et al reaffirmed this description in a report of six further cases of PE all in association with air travel. Two of the cases were the authors, one of whom had travelled in business class. All except one describe a delay in significant symptoms with 2 to 10 days, although it is apparent from the reports that early minor symptoms, particularly in the legs, were ignored [110].

At the same time, Mercer et al published a review of 134 patients with confirmed VTE, sixty six who had a recent history of travel, thirty three by air. All air travel had been longer than four hours duration, and twelve of these cases had no other identifiable risk factors. The median time to presentation after the flight was four days, with 82 percent occurring within fifteen days of the journey [111].

Kesteven et al identified 86 patients with VTE who had undergone travel within the prior 28 days. A retrospective questionnaire examining travel habits, medical history and the characteristics of the flight was undertaken. Seventy two percent of respondents had a least one identifiable risk factor for VTE (excluding thrombophilia) prior to their flight. The majority (92 percent) of patients developed symptoms within 72 hours of the flight, and
events occurred more frequently following either the return flight or after an outgoing flight that was comprised of multiple sectors. The authors concluded that in the majority of patients with traveller’s thrombosis, pre-existing risk factors were identifiable, and that multiple sequential flights may increase this risk [112]. These authors subsequently performed a prospective study in which a questionnaire which included travel history, was completed by 1250 cases of VTE diagnosed over a two year period. Forty seven (3.8 percent) were found to have a history of long distance travel within the proceeding four weeks, 60 percent by air, 36 percent by road and 4 percent by rail. At least one risk factors was found in 94 percent of those included. An estimate of incidence was made based on the population size served by their institution, of one per 27,600. The majority of patients included in this study had undertaken short duration flight, with only a eight percent cases with a history of travel having undertaken journeys of nine hours or more [113].

Following these initial descriptions there appears to have been widespread acceptance in the medical community that long distance travel may indeed be a risk factor for VTE. History of recent travel was included on routine questioning of patients presenting with VTE, although the extent of the risk has remained poorly defined. However, due to lack of publicity to the travelling public and acknowledgement by the airline industry, widespread awareness of this as a potential danger of long distance air travel remained poor. The terminology used has also resulted in confusion regarding the clinical significance of the syndrome, as it has been apparent since the earliest reports that this condition was neither confined to economy class or air travel.

4.2 Case control studies

Ferrari et al compared the travel history of 160 patients with confirmed VTE presenting to their emergency department with a control population of age matched hospital inpatients. In this study the odds ratio of a history of recent travel of longer than 4 hours was 3.98 in the VTE group compared to controls. Means of travel included train (two cases), aircraft (nine cases) and car (twenty eight cases). No other obvious risk factors were identified, and the authors comment that these cases would have otherwise been classified as “idiopathic” [114].

Sanama et al conducted a outpatient based case control study in which 636 cases with VTE were compared to 636 matched control subjects presenting to their general practitioners with influenzal or rhinopharyngeal syndrome during the same time period. Of the case group, 12.6
percent had undertaken recent travel as compared to 6.3% of the controls (odds ratio 2.35). The authors did not further elucidate the mode of travel [71].

However in a study by Kraagenhagen et al of 988 outpatients presenting with suspected VTE, the authors found no evidence of increased risk associated with a recent history of travel in those in who VTE was subsequently confirmed [115]. In this study only a small minority of all participants had undertaken any form of travel, and most were less than 5 hour duration. However a subsequent pooled analysis, which include a further 170 subjects included in an extension study, and a similarly designed study of 989 patients with suspected PE, showed a significant increase in the odds ratio to 2.5 in those travellers who had undertaken journeys of 10 to 15 hours. It should be noted however, that the mean duration of travel in this pooled analysis was only seven hours and only six percent of study population had undertaken any form of recent travel [116].

When these three studies are combined, a history of recent travel was seen in 151 of 1273 VTE cases compared to 136 of 2266 control subjects (odds ratio 1.97). However, it must be noted that the mode and duration of travel was not expressed in all of these retrospective studies.

4.3 Mortality studies

The widespread media publicity surrounding the sudden death of Emma Christopherson, a 20 year old apparently healthy young woman who suffered a fatal PE on arrival at Heathrow Airport following a 20 hour flight from Australia, has shocked and alarmed the general travelling public. Whilst fatal pulmonary embolism is a rare complication of travellers’ thrombosis, her case has significantly raised public awareness and medico-legal interest in the condition.

The first published post mortem series by Sarvesvaran in 1985, showed that fatal PE in the terminal at Heathrow Airport was the cause of death in 11 of 61 (18 percent) arriving passengers versus 1 of 28 (four percent) of departing passengers during a three year period. Of the arriving passengers who died as a result of PE, 72 percent had no significant past medical history, and 81 percent were female. All, except one passenger, had flight times of more than 12 hours [117].
However, in a recent post mortem review of fourteen cases of death occurring soon after air travel to Sydney Airport, four had morphological features of established thrombus which predated the flight. In nine patients the thrombus appeared to have occurred recently, although it could not be confirmed that these events had formed during the period of flight. The authors suggest that at least some of these deaths may have occurred coincidentally, rather than as a direct consequence of the travel [118].

4.4 Airport based studies

Following the Sarvesvaran study and several subsequent reports of events occurring in flight or soon after disembarkment from an aircraft, Lapostolle et al reviewed documented occurrences of non-fatal pulmonary embolism requiring medical attention on arrival at Charles d’Gaulle Airport, France. The authors identified 56 passengers who presented with symptomatic PE during or immediately after travel from a total of 136 million passengers (0.41 cases per million). There was a significant increase in absolute risk in association with duration of travel, with the incidence of PE in those whom travelled more than 10,000 kilometres rising to 4.8 cases per million [119].

Two similar studies were subsequently reported from hospitals close to other International Airports. A survey of acute pulmonary emboli at hospitals referred from Madrid-Berajas Airport, Spain identified sixteen cases over a six year period, with an incidence of 0.39 cases per million travellers, which similarly rose to 1.65 cases per million on flights of 8 hours or longer [120]. In another survey conducted over a three year period of passengers arriving at Sydney Internal Airport, Australia, seventeen cases of acute PE immediately following flight were seen. All patients had travelled more than 9 hours, representing an incidence of 2.57 per million of all passengers having flown this distance [121].

Interpretation of these studies is limited somewhat by reporting bias, their retrospective design and the likelihood that many cases may not have reported symptoms within the immediate period after their flight. In this circumstance, these incidence estimates suggest that sudden severe pulmonary embolism is an uncommon event (between 0.4 to 4.8 per million), but can occur immediate after disembarking from the plane, and is in part related to the duration of travel undertaken.
4.5 Prospective studies

Scurr et al published the first study to prospectively investigate the incidence of asymptomatic lower limb thrombosis following travel of at least eight hours [122]. This study was conducted in the context of a randomised controlled trial of class I (20 to 30mmHg at the ankle) graduated compression stocking compared with no intervention in 200 subjects aged over 50 years. The incidence of calf DVT, as assessed by compression ultrasonography (CUS), was 10% in those who were not randomised to stocking use. Although there has since been considerable debate as to the clinical significance of isolated calf thrombi detected, and regarding the actual criteria used for the diagnosis of DVT in the study, the estimate of incidence in this population of moderate risk travellers was much greater than had been previously considered.

The LONFLIT1 study, published by Belcaro et al, compared the risk of DVT in 355 low-risk subjects undertaking flights of at least eight hours in economy seating, with that of a group 399 subjects defined as high-risk (previous DVT, coagulation disorder, limited mobility, neoplastic disease or varicose veins) [123]. Compression ultrasonography was undertaken before and immediately after flight (within 90 minutes). The mean duration of travel was 12.4 hours. There were no DVT events in the low risk group, whilst 19 high risk subjects had either DVT (four proximal, seven distal) or SVT (six). Eighteen of the 19 subjects with VTE (94.7%) had been sitting in a non-aisle seat during travel.

Since the initial LONFLIT study, several further intervention studies have been performed in subjects deemed to be of moderate to high risk based on aged (greater than 40 years), chronic lower limb oedema and/or varicose veins and co-morbidity [123-130]. In those studies where radiological DVT was the primary outcome, a total of 2158 passengers were included, 864 of which received no active intervention. The incidence of DVT from this combined population was 3.8%. Despite this large control population, there is poor reporting of potential risk factors associated with VTE, aside from the stated inclusion / exclusion criteria. Only two studies discussed seating position, with non-aisle seating being implicated in 85% of DVTs [123, 124], and one study discussing oral contraceptive use [130]. In addition, none of the studies report the presence of suggestive symptoms, and in only two studies was D-dimer assessment undertaken (all of which were negative). Questions have therefore been raised regarding diagnostic criteria used for establishing the diagnosis of DVT and the wider applicability of the data as it is presented.
4.6 Intervention studies

The study performed by Scurr et al included randomisation to Class I compression stockings [122]. This study showed a marked reduction in risk of DVT associated with the use of stockings, with no thrombi occurring in the stockings group compared to 10% of the no intervention group. However, three individuals reported the development superficial calf vein thrombosis, which were attributed to irritation of these vessels by the stockings.

A variety of prophylactic measures have been investigated in the LONFLIT studies. These studies have varied somewhat in the characteristics of the study population, with the LONFLIT2 and LONFLIT3 focusing on what was considered moderate to high risk travellers, and the subsequent studies focusing on patients with risk factors for microangiopathic oedema. The outcomes from these studies have been confined to limited lower limb CUS and oedema symptoms scores and the results are difficult to compare directly. A summary of the interventions and results are presented in table 3.

TABLE 3. The LONFLIT intervention studies

<table>
<thead>
<tr>
<th>Title</th>
<th>Study size</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Control group</th>
<th>Intervention group</th>
</tr>
</thead>
<tbody>
<tr>
<td>LONFLIT2 [123]</td>
<td>833</td>
<td>Stockings</td>
<td>DVT, SVT</td>
<td>4.5%</td>
<td>0.24%</td>
</tr>
<tr>
<td>LONFLIT3 [124]</td>
<td>249</td>
<td>LMWH</td>
<td>DVT, SVT</td>
<td>4.8%</td>
<td>LMWH: 0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirin</td>
<td></td>
<td></td>
<td>Aspirin: 3.6%</td>
</tr>
<tr>
<td>LONFLIT4- SSL</td>
<td>343</td>
<td>Flight socks</td>
<td>DVT, SVT</td>
<td>3.4%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(14-17mmHg)</td>
<td>OS</td>
<td>8.0</td>
<td>2.6</td>
</tr>
<tr>
<td>LONFLIT4- Venoruton [127]</td>
<td>139</td>
<td>Venoruton</td>
<td>OS</td>
<td>7.2</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1g bd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LONFLIT4- EcoTraS [126]</td>
<td>211</td>
<td>Stockings</td>
<td>DVT, SVT</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(12-18mmHg)</td>
<td>OS</td>
<td>6.4</td>
<td>2.2</td>
</tr>
<tr>
<td>LONFLIT4- Kendall [128]</td>
<td>276</td>
<td>Stockings</td>
<td>DVT, SVT</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(20-30mmHg)</td>
<td>OS</td>
<td>6.9</td>
<td>2.3</td>
</tr>
<tr>
<td>LONFLIT-FLITE</td>
<td>186</td>
<td>Pinokinase</td>
<td>DVT, SVT</td>
<td>7.6%</td>
<td>0%</td>
</tr>
<tr>
<td>[129]</td>
<td></td>
<td>150mg</td>
<td>OS</td>
<td>9.8</td>
<td>7.5</td>
</tr>
<tr>
<td>LONFLIT5 JAP</td>
<td>205</td>
<td>Flight socks</td>
<td>DVT, SVT</td>
<td>5.8%</td>
<td>0.97%</td>
</tr>
<tr>
<td>[130]</td>
<td></td>
<td>(14-17mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(OS = Oedema Score)
From these studies it would seem that all interventions investigated, which included stockings of various compression, diuretic therapy and antithrombotic agents, with the exception of aspirin, were effective in the prevention of asymptomatic DVT and oedema in association with air travel. However, the same caveats must be applied in the interpretation of these findings as described previously.

4.7 Patho-physiological Studies

Several authors have suggested that the cabin environment of air travel may contribute to the occurrence of traveller’s thrombosis. Modern aircraft are pressurised to a cabin pressure equal to 5,000 feet when at an actual altitude of 32,000 feet, and pressurised to 8,000 feet when the actual altitude is 42,000 feet. Normal oxygen tension drops from 20kPa at sea level, to approximate 16kPa during a flight at 32,000 feet and 12kPa at 42,000 feet (equivalent to a fractional concentration of approximately 15 percent). Towards the end of long haul flights, cabin carbon dioxide levels rise to between two and three percent, and cabin humidity falls to less than fifteen percent. Thus, although the prolonged immobility associated with the cramped seating conditions of a long distance flight is recognised as a major contributor, the somewhat unique combination of hypoxia, hypobaria, reduced humidity, changes in circadian rhythm, dehydration and stress has been suggested to play a role in promoting thrombogenesis. Therefore, several authors have tried to artificially recreate and isolate these components of the cabin environment and measure their effect on thrombotic activity.

In 1976, Carruthers et al investigated the physiological responses of sixteen passengers and crew following a twenty hour flight from Buenos Aires to London. Increases in noradrenalin and adrenalin urinary metabolites, plasma lipids, and a brief decrease in cortisol levels were noted following the flight. Subjects passed low volumes of concentrated urine during the flight suggesting low fluid intake and / or mild dehydration. Aside from an increased heart rate response to takeoff and landing, no significant cardiovascular changes were noted. The authors suggest that prolonged sympathetic autonomic activity occurs during air travel as a result of stress and “transmeridian dyschronism” (disruption of circadian rhythm) [131].

Landgraf et al undertook a study of twelve healthy subjects exposed to prolonged sitting (twelve hours) in a non-flying aircraft at normobaria and normoxia. Six subjects were allocated to an “exercise group” and advised to walk around the cabin for five minutes of every hour, whilst the “sitting group” were only allowed out of their chairs every three hours
to provide a urine specimen. After the initial testing was performed both during the day and night the groups were switched in a cross over design. Plasma viscosity was unaffected during the night studies, by was moderately elevated during the daytime studies. There were small changes in haematocrit and plasma albumin, although the clinical importance of these changes was unclear. Fluid intake was higher than urinary output in all subjects, although insensible losses were not measured. This corresponded with a mean increase in weight of approximately one kilogram, which was associated with an increase in lower limb volume. The change in leg volume was greater for those studies perform at night, and there was a trend towards less swelling in the exercise group, although this did not reach significance. The authors concluded that although there was evidence of fluid accumulation and mild swelling, the rheology was basically unaffected by the seating arrangements and reflected alterations which were in keeping with circadian rhythms. Short term periodic leg exercising did not appear to have an effect on leg swelling or rheology. The authors do have however acknowledge that the actual conditions of flight were not reproduced in the study [132].

Bendz et al performed two studies investigating the effect of simulated flight on the thrombotic system. In the first study, twenty healthy male volunteers were rapidly exposed to a hypobaric hypoxic environment equivalent to an ascent to 2400 metres (7900 feet) at which they remained for eight hours. General activity and fluid intake was not restricted, except for vigorous physical exercise which was not possible due to space constraints. During the study oxygen saturations in the subjects were reduced from 98 percent to 93 percent. Markers of thrombus activation were significantly increased, including concentrations of prothrombin fragments 1 and 2 (2.5 fold), thrombin-antithrombin complex (8.2 fold) and factor VIIa activity (17 percent), where the inhibitory activity of TFPI was decreased by 10 percent. Levels of plasma D-dimer remained unchanged. The authors concluded that the changes indicated activation of the prothrombotic system which might relate to a direct effect of hypobaric hypoxia on endothelial cells, or perhaps due to neuroendocrine responses e of activation of coagulation [133, 134].

In a subsequent study performed by these authors, the same procedure was performed in twelve healthy volunteers, but prior to exposure all participants were administered low molecular weight heparin (LMWH) at a prophylactic dose. Although a similar reduction in resting oxygen saturations was noted, there was no evidence of an increase in activation markers from baseline, except for a small increase in levels of TFPI which was comparable to responses seen after heparin administration in normobaric environments. Thus the authors
concluded that LMWH prevents activation of coagulation in hypobaric environments such as air travel.

However, in a study by Crosby et al, these findings were refuted. The authors undertook a study of eight healthy volunteers who were randomly exposed to normobaric hypoxic conditions and normobaric normoxic conditions for 8 hours. The hypoxia corresponded to an altitude of 3,600 metres. There were no significant differences in the changes in the levels of prothrombin fragments F1+2, factor VIIa, thrombin-antithrombin complex or D-dimer between the groups. The authors questioned the control values obtained by Bendz et al and concluded that there was no evidence of significant activation of the clotting system after eight hours of hypoxic exposure in their study population [135].

4.8 Other forms of travel

Several reports have described cases of VTE occurring after long distance travel by car, bus, truck and train. Many of the case series discussed previously included such events [112, 113, 116, 136-139]. The term “Highway thrombosis” has been used to describe patients presenting after long distance car journeys, or in truck drivers performing long distance haulage. This highlights the possibility of recall bias favouring the reporting of air travel, given that it is undertaken infrequently by most people, and the recent publicity regarding it’s potential hazards. At present the frequency of VTE after travel by means other than by flight has not been adequately scrutinised.

4.9 Summary

In 2000 the Scientific Committee of the House of Lords of the United Kingdom commissioned a report entitled “Air Travel and Health”, which focused on the available literature regarding VTE following air travel. The conclusion of this review was that there is growing evidence of an independent association between long distance air travel (and perhaps other forms of travel) and VTE. It would appear from the case control studies conducted to date, that the relative risk associated with air travel is between two to four and increases with age and duration of travel. Although, as with other forms of VTE, intrinsic risk factors are likely to play a key role in establishing background risk prior to travel, the absolute risk and the role of factors unique to air travel was unclear [140].
The most concerning (and headline grabbing) manifestation of the condition, that of fatal pulmonary embolism immediately following travel, is rare. However, given the large number of people exposed to this risk factor every year (currently estimated at 1.5 billion travellers per year), it is likely that travellers’ thrombosis is a significant cause of morbidity in the general population. A clearer understanding of the epidemiology of this condition is urgently required.
Chapter 5

The investigation of suspected VTE

The symptoms associated with VTE are variable and non-specific. As mentioned previously, relatively large DVT or PE can be occur without overt clinical signs. Similarly, symptoms of significant PE such as chest pain, breathlessness and haemodynamic compromise may occur with other conditions and may be misdiagnosed. It is therefore necessary to combine good clinical assessment of history, risk factors and physical signs, with laboratory and radiological investigations in order to confirm or refute the diagnosis of VTE in a patient presenting with suggestive symptoms. As a results, attempts have been made to develop algorithms for the investigation of such patients in order to establish the presence of thrombosis without subjecting the patient to unnecessary investigation [141]. An example of such an algorithm, developed by the author for use at Wellington Hospital, is presented in appendix 1. These algorithms are based on the use of Bayesian theorem to determine the probability of VTE based on the stepwise assessment of clinical history and subsequent investigations with known specificity and sensitivity.

In general these algorithms make several assumptions regarding the nature of VTE:

1. PE and DVT are manifestations of the same underlying condition
2. Most PE occur as a result of preceding lower limb DVT, which may be symptomatic or asymptomatic
3. PE is more commonly associated with proximal rather than distal DVT
4. Identifiable risk factors are present and interpretable at the time of presentation
5. There is only one cause for the patients presentation and more than one diagnosis for the patients symptoms is unlikely

Whilst for the majority of otherwise healthy individuals presenting to outpatient or emergency departments with suggestive symptoms these assumptions are acceptable, it is apparent that the use of set algorithms is limited in other circumstances. In addition, these management algorithms must be tailored to allow for the availability of investigations, both during normal working hours and after hours, within the hospital they are being applied. Therefore, it is necessary for each of these components common to the majority of diagnostic algorithms to be explored.
5.1 Clinical Pre-test probability

The clinical presentation of VTE is varied and often mis-interpreted. Given the potential consequences of failing to diagnosis such an event, most clinicians have adopted an approach of thorough investigation whenever the suspicion of VTE is raised. With experience, such an empirical approach to assessing the probability of VTE based on clinical information can be effective [142]. However, standardised prediction models based on combining clinical criteria and immediately available investigations have been developed for both DVT and PE.

In the case of PE, two prospectively validated clinical scores have been developed. The “Wells score” utilises components of the presentation, past medical history and the presence of symptoms suggestive of DVT [143]. The overall score is somewhat dependant on a clinical assessment of whether “an alternative diagnosis is more likely than that of PE”, thus introducing some subjectivity to the assessment. On the basis of the final score achieved, patients are classified as low (10 percent), moderate (21 percent), or high (76 percent) probability of PE [144]. The score has been validated in both outpatients and inpatients, and is usually combined with simultaneous assessment of the bedside D-dimer test, SimpliRED (see below). Further refinement of this assessment allows classification of probability as “PE likely” versus “PE unlikely” which improves the negative predictive value of this score further when combined with a negative SimpliRED Test [143, 145].

The “Geneva score” relies more heavily on physiological variables such as gas exchange and heart rate and radiological changes on plain film chest radiograph interpretation. This score has been established and validated in outpatient populations only, and is not applicable to inpatients. The score again establishes low (10 percent), intermediate (38 percent), or high (81 percent) pre-test probability of PE, but can be applied in isolation, regardless of D-dimer assessment. In both cases, further radiological evaluation is recommended for all patients designated to have a high pre-test probability [146].

When comparison has been made between the Geneva score, the Wells score for PE, and the Wells score for DVT, with empirical assessment of risk by an experienced clinical, there is little difference in outcome [142, 147, 148]. These scoring systems serve as a means by which to standardise the assessment of patients with suspected VTE, particularly for junior medical staff, but in themselves show poor sensitivity and specificity. However, the reliance of the Geneva score on arterial blood gas analysis has limited it’s utility in some institutions [149].
5.2 D-dimer assay (IV)

D-dimer is a fibrinogen degradation product formed as a result of fibrin digestion by plasmin. As such, release of this fibrin fragment constitutes evidence of the almost immediate activation of the fibrinolytic system in response to thrombus formation. Initially utilised as a marker of diffuse thrombotic activity in such conditions as disseminated intravascular thrombosis, it has been adapted as an indicator of more localised thrombus formation, such as DVT. An increase in the circulating plasma level of D-dimer constitutes evidence of increased thrombotic activity, although it is non-specific to any particular location within the vasculature. It’s most useful application in the context of VTE is in “ruling out” significant thrombus formation in a patient presenting with suggestive symptoms. The absence of significant elevation in D-dimer is highly suggestive that baseline thrombus formation has not increased (high sensitivity). However, an elevation in D-dimer level can occur in many circumstances, such as acute infection, cardiac failure and atherosclerotic disease, and is therefore not specific to VTE alone (low specificity) [150, 151]. Thus, the true value of assessing D-dimer is it’s ability to exclude VTE in a patient presenting with suggestive symptoms [152].

Measurement is possible utilising monoclonal antibodies directed at various epitopes on the D-dimer molecule. The specificity of these antibodies not only varies in their affinity to components of D-dimer, but also to whether they bind to D domains yet to be cleaved from insoluble fibrin or soluble fibrinogen monomers. As a result, the receiver operator characteristics and reference ranges vary significantly between assays. However, the most striking differences relate to the mechanism of detection of the antibody complexes.

Initial assays used two monoclonal antibodies directed at complementary D-dimer epitopes and were measured using highly specific Enzyme-linked ImmunoSorbent Assays (ELISA). Whilst these assays performed well, they are technically demanding, required prolonged preparation time and the results were not instantly available. Several subsequent techniques where developed in order to overcome these constraints:

- Manual latex agglutination tests (semi-quantitative)
- Enzyme-linked fluorescent assay (ELFA)
- Membrane-based immunoassays
- Whole blood agglutination tests
- Automated latex-enhanced light-scattering immunoassays [152]
Over twenty different assays are currently available, all varying in sensitivity, specificity and, more importantly, clinical validation. Most quantitative assays report their results as fibrinogen equivalent units (FEU) utilising a cut-off value (usually the upper limit if the 95th percentile of the normal range), above which the test is considered “positive”. However, few assays have undergone extensive reference range testing in the general population. In some circumstance a lower cut-off value has been modified in order to increase the apparent sensitivity of the assay, resulting in poor specificity and a high false positive rate. Therefore, thorough clinical validation has become the most important determinant of the reliability of D-dimer assessment.

When using such a test as a screening tool, it is necessary to consider the population in whom it has been, and is to be, employed. Whilst many of the assays mentioned above will generate a reliable test with high sensitivity, most have not undergone thorough evaluation in large long term outcome studies. The four most extensively studied assays are:

1) SimpliRED (Agen Biomedical)- This is a whole blood agglutination assay which uses bivalent antibodies against D-dimer antigen and red blood cells. In the presence of sufficient D-dimer antigen the red blood cells agglutinate to give a visual positive or negative result within minutes. When used in isolation in a study involving 1177 patients with a prevalence of PE of 17 percent, the sensitivity of this assay was 85 percent with a specificity of 68 percent, resulting in a negative predictive value (NPV) of 85 percent. This suggests that despite it’s easy of use and rapid result, the test performs poorly as a screening tool. However, when combined with a low clinical probability score, the NPV increases to 97 percent [153]. Therefore, in most studies, the SimpliRED assay has been used in conjunction with the Well’s score to safely rule out PE in low probability patients. In the cohort studied, it was projected that this would have resulted in avoidance of unnecessary further radiological evaluation in 44 percent of patients presenting with suspected VTE. The results were similar in a subsequent study in patients presenting with suspected DVT (sensitivity 82 percent, specificity 85 percent and NPV of 100 percent in low risk patients) [154]. Criticism of this assay has focused on it’s reliance on the Well’s clinical probability scoring system, which as mentioned previously, is in itself open to interpretation.

2) MDA D-dimer (Organon Tehnika)- The MDA D-dimer, a quantitative automated latex micro particle assay, was initially studied retrospectively in 595 patients presenting
with suspected VTE, and subsequently validated prospectively in a management study involving 556 patients [155, 156]. In both studies, the assay showed high sensitivity and moderate specificity (96 percent and 45 percent respectively), with a NPV of 98 percent across all patients. The NPV remained high (98 percent) when both low and moderate risk individuals were considered. This assay has the advantage that it can be rapidly performed (within 30 minutes) and can be processed through an automated analyser available in many laboratories. The cut-off value used for this assay is 500 mcg FEU/L.

3) IL-Test (Instrumentation Laboratory)- This is another quantitative automated latex micro particle assay with a processing time of less than 35 minutes [157]. It has been evaluated in comparison to the SimpliRED assay in a management study of DVT involving 1075 patients. The authors do not state the proportions of each assay used, but in the context of low clinical probability and a negative result, anticoagulation was with-held without imaging. Of the 882 subjects who fulfilled this criteria, the risk of subsequent proximal DVT in the next three months was one percent [158]. In a parallel study, 566 subjects to randomised to assessment by IL Test D-dimer, or conventional imaging with compression ultrasonography. The subsequent risk of DVT occurring within the following 3 months was similar between the two groups (0.4 percent versus 1.4 percent), with the use of D-dimer significantly reducing the need for imaging [145]. However, the cut-off value used for this test (usually 200 mcg FEU/L) has been questioned, with a subsequent study of 512 subjects with VTE suggesting that a cut-off value of 237 mcg FEU/L may significantly improve the specificity of the test when used in isolation in both low and moderate probability patients [159].

4) VIDAS D-D ELISA (bioMerieux)- The VIDAS D-dimer assay is a bivalent antibody ELISA based technique which has been modified to incorporate fluorescent activation of the antibody complex (ELFA). This results in a quantitative assay that can be processed and read rapidly (within 35 minutes), but retains the high sensitivity of the conventional ELISA assays (r =0.91), with good reproducibility (less than five percent variability) [160]. Of all of the quantitative assays, the VIDAS D-dimer has undergone the most extensive clinical evaluation, having been used in more than 1400 patients with suspected PE and 1200 patients with suspected DVT. It has an established population reference range, with the lower and upper limit of the 95th percentile
occurring between 68 and 494 mcg FEU/L. However, as is probably the case with all assays, D-dimer levels rise with age and may be consistently above 500 mcg FEU/L in otherwise healthy individuals over the age of seventy years. Despite this, the cut-off value used in most studies has been 500 mcg FEU/L, although increasing the cut-off to 1000 mcg FEU/L has been suggested in more elderly patients. At this level, the sensitivity of the assay is between 94 to 100 percent for both PE and DVT, with a NPV between 98 to 100 percent in most studies, in all clinical probability categories [141, 157, 161-166]. The specificity of this assay varies between 35 to 42 percent, and false positive results remain common [165, 166]. Extensive cost-benefit analysis has also been performed using this assay, showing that a strategy based on the VIDAS D-dimer assay and clinical probability is more cost-effective that any other strategy [167, 168]. It has also been assessed in other forms of vascular disease and has been shown to be a predictor for stroke and recurrent myocardial infarction in patients with peripheral vascular [169, 170]. Thus, levels are elevated in also subjects with systemic atherosclerotic disease, in addition to renal disease, where reduced clearance of D-dimer and intra-renal thrombotic activity have been implicated [171, 172].

Of all the methods for assessing D-dimer, the VIDAS system has become the “gold standard” due to it’s extensive use in clinical management studies in both PE and DVT, reliability, cost effectiveness, and rapid analysis time. However, caution still exists in using this assay to rule out VTE in patients deemed to be at high risk of VTE, with all management studies having elected to fully image this population regardless of the D-dimer result.

5.3 Contrast Venography

Ascending contrast venography has served as the “gold standard test” for lower limb VTE [173, 174], although it’s clinical utility has diminished since the widespread adoption of compression ultrasonography (CUS). It continues to be used in pharmacological clinical trials, particularly following surgical prophylaxis, but only selected centres continue to perform this procedure on a routine basis. Criteria for the diagnosis of acute DVT include: a contrast filling defect intra-luminally, abrupt termination of the column of contrast material, and / or repeated non-filling of a segment of a deep vein [175]. Although venography is an invasive technique which is associated with appreciable mortality, this approach generally yields reliable information as to the location and extent of thrombus throughout the affected limb [176].
5.4 Plethysmography

A number of plethysmographic methods can be used to detect acute DVT, including impedance plethysmography (IPG), air-cuff plethysmography, strain-gauge plethysmography and phleborheography [174, 177-179]. These methods are based on assessing changes in blood volume in different compartments of the legs, usually following compression. An acute DVT occludes the major veins of the leg, thus reducing venous compliance and increasing venous outflow resistance. IPG has been demonstrated to have moderate sensitivity (83 to 88 percent) in the diagnosis of flow limiting proximal DVT, but poor sensitivity (63 to 71 percent) for distal and non-occlusive events when compared to venography [178, 179].

5.5 Compression ultrasonography

Compression ultrasonography (CUS) of the lower limb venous system involves combining the use of B-mode imaging, Doppler flow detection and colour mapping and the compressible characteristics of patent veins to establish the presence of thrombus by a non-invasive method. When compared with contrast venography for the detection of proximal DVT, the sensitivity of CUS approaches 100%, without the associated complications of venography [180-182]. In comparison to IPG, CUS has superior sensitivity (77 percent versus 90 percent) and specificity (91 percent versus 98 percent) [183]. The initial studies of CUS undertook extensive imaging of the lower limb deep venous system, but these demonstrated that the sensitivity for distal and isolated calf vein thrombi was moderate and varied widely (55 percent to 91 percent) [184]. Following observations by Cogo et al regarding the distribution of thrombi in 562 subjects who underwent venography, and the recognised limitations of scanning the calf veins, simplified CUS protocols were developed which limited scanning to the superficial femoral and popliteal veins only [182, 185]. This significantly reduced scanning time and complexity and reduced inter-observer variability, particularly in the context of anatomical variation of the calf veins. However, this approach has reinforced the perception that thrombi detected in other veins within the lower limb are of less clinical significance.

During a CUS examination, the presence of thrombus is confirmed by direct visualisation of the clot material, loss of normal compressibility of the vein and / or reduced flow on augmentation manoeuvres such as deep inspiration. When combined with clinical probability
scoring and D-dimer assessment, this technique yields a NPV of greater 99 percent in moderate risk populations [186]. However, serial imaging, performed seven days apart, is necessary in high risk populations even if the first scan is negative. Some authors have also advocated that the same approach should be taken in the event of thrombosis involving the short or great saphenous vein [53].

Complete colour duplex ultrasonography (CCUS) of all venous segments has once again been suggested by several experienced centres. Utilising recent advances in scanning technology, it is possible to more accurately determine the anatomy and flow characteristics of the calf veins. These examinations take considerably more time and require experienced ultrasonographers, but in a study of 1646 patients presenting with suspected DVT, where the technical failure rate of a single CCUS was one percent, only 0.3 percent of 1023 patients with negative scans developed DVT within the subsequent three months [184].

Due to the high incidence of asymptomatic proximal DVT in patients with PE (23 percent to 82 percent) [93], CUS has been performed as a means by which to establish a diagnosis in patients with symptoms suggestive of PE [187, 188]. In many hospitals CUS is more easily obtained that other imaging modalities, and this approach has obtained widespread acceptance. However, the sensitivity of CUS in this context is poor, with at least third of patients with a negative limited scan subsequently being found to have PE on lung imaging [189].

5.6 Other investigations for lower limb thrombosis

In the $^{125}$I-fibrinogen uptake test surface radioactivity is measured after injection of radio-labelled fibrinogen, which is rapidly incorporated into evolving clot. This method has been used extensively for detecting postoperative DVT, but has demonstrated large variations in sensitivity between studies (14 to 59 percent) for distal and isolated calf thrombi, particular when asymptomatic or in the context of previous events [190]. This technique is now rarely performed.

Magnetic resonance direct thrombus imaging (MRDTI) utilise the magnetic properties of iron within haemoglobin and methaemoglobin. Red cells trapped within thrombi not only fail to demonstrate normal flow characteristics but in the process of degrading release methaemoglobin which has a strong paramagnetic signal. Using T1-weighted images it is
possible to further improve signal and image quality by maximising the contrast between blood and clot, thus producing a positive image of the thrombus without the use of contrast [191]. MRDTI can be used to calculate the volume and surface area of a clot, which has been shown to correlate with D-dimer levels [192]. In addition MRDTI may be useful for determining the age and presence of recurrent clot, due to the fact that the methaemoglobin effect resolves as an acute thrombus dissipates [56]. However, this technique is still undergoing evaluation, and its use as a routine investigation remains limited due to the cost of the procedure when compared to other non-invasive investigations such as CUS.

5.7 Pulmonary Angiography

Direct pulmonary angiography, performed as cine images or utilising digital subtraction angiography techniques [193], has been the cornerstone of the investigation of suspected PE since the 1960’s. The technique involves sequential positioning a catheter into the left and right main pulmonary arteries and selectively injecting contrast, obtaining imaging throughout the arterial and venous phases of flow. When correctly performed, vessel and flow defects can be visualised to the sub-segmental level with demonstration of the resulting peripheral perfusion defects[194-196]. However, experience with this modality is diminishing due to the invasive nature and perceived risk associated with the procedure. Although in the context of modern contrast media and imaging adverse events are uncommon [194], direct pulmonary angiography is rarely performed in most centres.

5.8 Isotope Ventilation Perfusion Scanning

“V/Q scanning” involves the comparison of radio-labelled albumin perfusion scanning with Xenon ventilation scanning to determine areas of perfusion mismatch. Following a protocol developed for the PIOPED study, scans are most commonly reported as normal, low, intermediate or high probability based the presence and distribution of unmatched perfusion defects [197, 198]. Although this test has high sensitivity, its interpretation is dependant on the presence of near normal ventilation, and it performs poorly when any form of parenchymal lung disease if present. Whilst normal scans and low probability scans in the context of low clinical suspicion can accurately exclude PE, the frequency of such a finding is uncommon [199, 200]. Similarly, a high probability scan, which has high specificity for PE and is usually accepted as diagnostic, is also rare [200]. In recent studies utilising V/Q
scanning, the diagnosis of PE was adequately confirmed or excluded in as few as 11 percent of tests performed [201].

At present isotope scanning may be considered as an initial investigation of suspected PE providing that a chest radiograph is normal, there is no evidence of concurrent cardiopulmonary disease, it is combined with an assessment of clinical probability and further investigations are performed in the event of a non-diagnostic test [202].

5.9 CT Pulmonary Angiography

Technological advances in contrast enhanced helical CT pulmonary angiography has revolutionised the investigation of suspected PE. Single detector scanners, followed recently by multi-detector scanners, have allowed fast and convenient scanning of the pulmonary arteries to the segmental and now sub-segmental level, with high sensitivity and specificity. This scanning modality also provides full imaging of the thorax and allows for the determination of alternative diagnosis that may explain the presenting symptoms of the patient. Whilst reliant on appropriate timing of the scan in relation to contrast injection and the requirement for the patient to perform an adequate breath-hold, diagnostic images can be obtained in greater than 90% of scans.

Initial studies performed at non-specialist centres with single detector scanners suggested the sensitivity of CTPA was as low as 78 percent. However, imaging performed using multi-slice scanners at experienced centres which is interpreted in the context of clinical probability and D-dimer, can reliably exclude significant PE. In a large multi-centre study in which patients were investigated with both CTPA and ultrasound, those with negative tests and low or intermediate pre-test probability were not anticoagulated. In the following three months only 0.2 percent of individuals were found to develop PE [203]. This approach has been confirmed in a larger subsequent study of 965 patients, were those with a negative D-dimer, CTPA +/- CUS had a incidence of subsequent PE of only one percent at three months [204]. However, recent data suggest that CTPA should be interpreted with caution in more elderly patients (greater than 73 years), as there is a higher false negative rate in these individuals [205].

CT scanning also offers the opportunity to extend the scan to image the pelvis and lower limbs for DVT. This so called CT venography requires no more contrast administration, but does significantly increase radiation exposure [206]. This technique compares favourably with
CUS in imaging the femoral veins and has the advantage of demonstrating the iliac veins. However, as with CUS, interpretation of the calf veins is limited [207, 208].

5.10 Magnetic Resonance Imaging

Preliminary studies suggest that MRI angiography of the pulmonary arteries may provide an alternative non-invasive means by which to investigate PE without the need for exposure to ionising radiation. Studies comparing MRI with single detector CTPA show similar sensitivity and specificity for imaging up to the level of sub-segmental vessels [209]. However, the technique is expensive, more time consuming, not widely available and does not offer the opportunity to image the lung parenchyma in detail. Newer, rapid scanning techniques are currently under development [210].

5.11 Summary

In most circumstances, no one test or investigation can be used to conclusively diagnose or exclude VTE. A combined and systematic approach involving assessment of clinical probability, D-dimer measurement and appropriate imaging is necessary, and must be tailored to local experience and test availability. Even in patients in whom VTE is confirmed on initially test, further imaging may be necessary in order to accurately determine clot burden, extent of involvement and risk of recurrence. An example of such an approached developed by the author for use at Wellington Hospital is presented in Appendix 1.
Chapter 6

The New Zealand Air Travellers Thrombosis Study-
Rationale and Study Design

6.1 Study Aims
To determine the frequency of VTE in a population of low to moderate risk air travellers.

6.2 Study Design and Outcomes
Prospective cohort study

Primary Outcome
1. The incidence of radiographically confirmed VTE (PE, DVT or SVT)

Secondary Outcomes
1. Analysis of the risk factors associated with VTE following air travel
2. Analysis of factors associated with change in D-dimer following air travel

6.3 Subjects
One of the primary objectives of the study was to include individuals who were representative of the general New Zealand travelling population. It was decided to be as inclusive as possible to allow adequate recruitment and to maximise the relevance and applicability of the outcomes of the study. However, it was acknowledged that there was sufficient evidence from previously published literature to suggest that intervention should be considered for individuals undertaking long distance travel who were at high risk of VTE. Therefore, potential subjects who were deemed to be at high risk of VTE were excluded from the study and were advised to seek medical advice prior to travel. This was established by use of a pre-flight questionnaire which was developed to provide subject demographics and to clarify some of their intrinsic risk factors (see appendix 2).

Although there had been case reports of VTE occurring following short duration flights, it was apparent that the risk increased with longer duration flights [116, 119]. On this basis, it was decided to only recruit subjects who were undertaking outgoing flight of which at least one sector was more than four hours duration. This requirement did restrict recruitment somewhat, as the majority of trans-Tasman passengers were excluded.
The upper limit of age was set due to the recognised increase in plasma d-Dimer levels over the age of 70 years. Inclusion of these subjects would have significantly increased the false positive rate of the test, and unnecessarily recruited inappropriate subjects within the study.

An arbitrary return time of six weeks from departure was set due to the logistical and time constraints of the study. Longer periods of time would also have increased the incidence of spontaneous VTE unrelated to the travel occurring.

The inclusion criteria were therefore as follows:
1). Age between 16 years and 70 years
2). Flight duration longer than 4 hours
3). Returning within 6 weeks of departure

The exclusion criteria were:
1). Previous VTE
2). Pregnancy
3). Recent major surgical intervention within the preceding 6 weeks
4). Recent lower limb trauma within the preceding 6 weeks
5). Receiving long term anticoagulation

Ethical approval for the study was obtained from the Auckland and Wellington Regional Ethics committees. In addition, consent was obtained from the Auckland Ethics committee to obtain blood for thrombophilia (including genetic) analysis. All subjects provided written informed consent to participate in the study. The study was conducted according to the Helsinki Declaration and all participating staff complied with Good Clinical Practice Guidelines.

6.4 Recruitment strategies

It was recognised that in order to recruit a significant number of appropriate individuals, widespread media advertisement and varied recruitment strategies would be required. Methods included:
1). Local and national newspaper, radio and television interview
2). Local travel agent advertisement
3). Corporate travellers advertisement
4). Celebrity endorsement (and media coverage)
5). Direct approach at departure airport

Potential subjects who contacted the investigators prior to their travel were invited to attend one of the study centres to complete consent and initial enrolment. Despite the adequate initial media coverage and recruitment, it soon became apparent that additional methods would be required in order to optimise subject participation. The management of Auckland International Airport Limited were approached and, with the endorsement of the major airline carriers, permission was obtained for study investigators to approach subjects within the departure area of the airport. A small study centre, including an appropriate equipped first aid room, was established at a high pedestrian volume site within the main departure gate of the airport. In addition permission was obtained to enter the Business lounges of two major airline carriers in order to invite a broad range of long distance travellers to participate. The airport study centre was staffed during periods of high flow of long distance travellers, particularly during the weekends.

Further publicity and recruitment occurred after members of the New Zealand All Blacks Rugby team and management volunteered to take part in to the study. Permission was obtained from the team doctor and management to approach these subjects, which was motivated by one of the players having incurred a lower limb DVT during a recent tour to South America. This strategy proved an effective means by which to improve awareness of the study following the down turn in long distance air travel and media interest that occurred following the events in the United States on September 11th, 2001.

Subjects were reimbursed for any costs incurred as a result of travelling to and from the investigating centre (a $10 petrol voucher). No other reimbursement or incentive was offered to any individual invited to participate.

6.5 Screening protocol

In order to screen the required sample size of 1000 subjects is was necessary to utilise a tool which was quick and easy to perform, cost effective and minimised the need for unnecessary radiological investigations, whilst maintaining high sensitivity for VTE. It was evident for the reasons outlined previously, that VIDAS D-dimer measurement could potentially fulfil these
criteria, providing the samples were taken promptly following travel. Serial samples taken before and then after travel would provide evidence of thrombin activation following exposure to the risk factor.

It was also acknowledged that VTE events may have occurred following the initial outgoing flight which could have been undertaken up to 6 weeks prior to return. All subjects were advised to seek medical attention whilst overseas if any concerning symptoms occurred. It was therefore necessary to undertake a thorough clinical history and examination (including calf circumference measurement) of all individuals returning for travel and to assign a clinical probability of VTE, utilising the Well’s scoring systems (see post-flight questionnaire, appendix 3). Regardless of the D-dimer result, all subjects with a high clinical probability would also be referred for imaging.

VIDAS DD ELISA D-dimer assays (bioMerieux, Paris, France) were established and validated at the two central study laboratories (Haematology laboratories, North Shore Hospital, Auckland and Wellington Hospital, Wellington). The analysers were calibrated as per manufacturer instructions. All D-dimer samples were taken via fresh antecubital vein punctures utilising the Vacutainer™ system to minimise clotting activation. Samples were stored upright for no more than two hours before be centrifuged and separated and either analysed immediately or stored at negative 30 degrees Celsius. Due to travel insurance requirements, samples taken prior to outgoing flights were stored until the day of their return and then defrosted and batched processed. Subsequent samples were couriered and processed immediately by the laboratory. All samples were destroyed following analysis. A positive result for this assay was defined as a level greater 500 ng/mL (500 mg FEU/L). The study investigators were notified of any positive results within twenty four hours (usually sooner).

Although previous data had suggested that most events occurred within 72 hours of travel, patients may also present with new onset of symptoms up to four weeks after travel. It was deemed necessary to perform a repeat D-dimer measurement at least two weeks after returning. Subjects were given instructions, request forms and sample bottles to take to their local community laboratory for this testing. These samples where separated, frozen and subsequently transported to the central laboratory for analysis. Those subjects who had not undertaken repeat testing within 3 weeks of return were contacted by telephone by the study investigators and reminded to do so.
Subjects were contacted by telephone at least three months after their return from travel. A brief questionnaire was completed regarding further travel and any symptoms suggestive of VTE (appendix 4).

The screening protocol was therefore as follows:

**Pre-flight:**
- Within one week of departure: Screening questionnaire, D-dimer measurement

**Post-flight:**
- Within 72 hours of return: Clinical review, questionnaire and examination, Assign clinical probability score, D-dimer measurement, Thrombophilia screen
- After two weeks: D-dimer measurement, Clinical review if new suggestive symptoms
- After three months: Telephone questionnaire

6.6. *In-flight questionnaire.*

All subjects were provided with a Flight Diary at the time of recruitment. This diary included details of their subject number and contact details of the investigators. The subjects were instructed to complete the flight log and questionnaire after each individual flight / sector undertaken (see appendix 5). Subjects were instructed to return the flight diary at the time of their post flight visit to the investigating centre. The investigators made no attempt to influence the subject's use of prophylactic measures or behaviour during flight.

All questionnaires were co-developed, tested and validated on ten independent subjects for clarity and reproducibility by Dr Kristen Wickens, Public Health Consultant at Wellington Hospital.
6.7 Thrombophilia assessment

Thrombophilia testing was undertaken in those subjects who participated at the Auckland centre. On return from travel, an additional 30 millilitres of blood was obtained, frozen and stored at -30 degrees for subsequent analysis. This included functional antithrombin assessment (abnormal less than eighty percent activity), anticardiolipin IgM and IgG antibodies titre (abnormal if greater than 20IU per millilitre) and PCR based DNA analysis for factor V Leiden and prothrombin gene mutation. All assays were undertaken by TELARC accredited laboratories. If initially abnormal, antithrombin and anticardiolipin antibody assessments were repeated after at least six weeks for confirmation.

Subjects with confirmed VTE underwent more extensive testing of thrombophilic risk factors which included protein C, protein S, homocysteine and factor VIII levels.

6.8 Imaging

During the three month follow-up period, all subjects with a positive D-dimer or high clinical probability score were investigated with radiological examinations. This included bilateral lower limb CUS (ATL 3500, Philips Electronics), and helical single slice CTPA (GE Prospeed SX Advantage, General Electric or Picker PQ5000). The CUS involved a bilateral examination of all major deep and superficial veins in the calf and thigh, with augmentation, with the subject in the supine position (approximate scanning time, 45 minutes). Confirmed deep venous thrombosis and superficial venous thrombosis were defined as the presence of visible thrombus at least partially obstructing colour Doppler flow despite augmentation, or lack of compressibility within one of the vessels in the deep venous system and short or great saphenous vein respectively. Confirmed pulmonary embolism was defined as a filling defect in a segmental vessel or more proximal vessel on at least three contiguous slices, after the administration of 150mL of non-ionic intravenous contrast. Ventilation/perfusion (V/Q) scanning was offered to those individuals unwilling to have a CTPA performed, with a high probability scan confirming the presence of pulmonary embolism.

Senior ultrasonographers and specialist chest radiologists performed and interpreted all imaging, and they were blinded to the clinical history, D-dimer level or presence of symptoms wherever possible. All CTPA series were reviewed on the computer consoles locally, and
then films were sent to the participating radiologist at the other investigating centre for review.

6.9 Statistical Analysis

Frequency of VTE following travel
Simple summary statistics were presented for the continuous variables. For categorical variables the proportion in each category were presented. For the purpose of this analysis, a collective group of “co-morbid conditions” was defined which included: systemic hypertension requiring therapy, cardiovascular disease, cerebro-vascular disease, chronic lung disease, diabetes, connective tissue disease, varicose veins, obesity (BMI >30 kg.m\(^2\)) and chronic antidepressant or sedative use. The incidence of VTE was expressed as an absolute percentage with 95 percent confidence intervals.

The projected sample size was calculated by making the assumption that the background population prevalence of DVT and PE is 1 per 1000 per year, or 0.15 per 1000 during any 6 week period. Assuming an alpha value of 0.05, in order to confirm an incidence of VTE of one percent during the travel period with a power of 0.8, a sample size of 817 subjects was required (Kelsey method). It was projected that approximately ten percent of subjects would be excluded on the basis of positive D-dimer prior to travel, and that there would be a dropout rate of five to ten percent. Therefore the study would require recruitment of approximately 1000 subjects in order to achieve sufficient statistical power to determine the primary outcome.

Baseline D-dimer assessment.
Plasma D-dimer levels had a skewed distribution and statistical assumptions of normality were not met for analysis of univariate associations by simple correlation and t tests. For univariate associations non-parametric tests, rank correlation and the Mann-Whitney test, were used. It was also found that a logarithm transformation meant that statistical assumptions for normality were met and so in the multivariate analysis, the logarithm of the plasma D-dimer level was the dependent variable, and linear regression was used to find independent predictors, with categorical variables assigned dummy values of one or zero. With this method of analysis the beta coefficient relating the explanatory variable to the response variable (the plasma D-dimer level), had a multiplicative interpretation. The potential explanatory variables examined were age, sex, family history of clotting disorder,
thrombophilia, co-morbidity, body mass index, and hormone use. Males were treated as not using hormones for the purposes of the model selection. A backwards selection process with a ‘P value’ for leaving a variable in the model of 0.1 was used, however forwards and stepwise procedures resulted in the same model being selected.

Change in D-dimer following travel.
Logistic regression analysis was used to model the probability of a subject being "D-dimer positive" versus "D-dimer negative" with reference to demographic and other subject-related variables. Both univariate and multivariate analyses were undertaken. The potential explanatory variables examined were age, sex, family history of clotting disorder, thrombophilia, co-morbidity, body mass index, and hormone use. Males were again treated as not using hormones for the purposes of the model selection. Co-morbid conditions were defined in the same method as above. Class of travel was assessed only for flights returning to New Zealand of 10 hours duration or more. A backwards selection process with a ‘P value’ for leaving a variable in the model of 0.1 was used, however forwards and stepwise procedures resulted in the same model being selected.

SAS Version 8.2 (SAS Institute, Cary, NC 2001) was used for all analyses.
Chapter 7

NZATT Study Results (II, III)

7.1 Study Population and Characteristics

Of the 1000 subjects who were recruited 83 were subsequently excluded due to an elevated D-dimer prior to travel. When compared to the study subjects, these individuals tended to be older (mean age 59.3 years vs 49.0 years), female (66.3 percent vs 50.5 percent), and have more co-morbidity (43.8 percent vs 21.4 percent). Thirty nine subjects failed to undertake follow-up on return. One of these subjects had an episode of collapse during their journey and was extensively investigated for possible VTE. These investigations were negative and the subjects subsequently declined further involvement.

The characteristics of the 878 subjects who completed the study as defined by D-dimer status are shown in Table 4.

### TABLE 4. Risk factors and in-flight characteristics of subjects

<table>
<thead>
<tr>
<th>Continuous variables</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.0 (11.8)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>25.8 (4.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categorical variables</th>
<th>Percentage (number with information available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin use</td>
<td>23.1 (878)</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>36.3 (878)</td>
</tr>
<tr>
<td>Economy class travel</td>
<td>72.8 (878)</td>
</tr>
<tr>
<td>Family history of VTE</td>
<td>11.0 (873)</td>
</tr>
<tr>
<td>Female</td>
<td>50.6 (878)</td>
</tr>
<tr>
<td>Hormone use in females</td>
<td>28.3 (444)</td>
</tr>
<tr>
<td>Symptoms of DVT</td>
<td>32.8 (878)</td>
</tr>
<tr>
<td>Symptoms of PE</td>
<td>10.3 (877)</td>
</tr>
<tr>
<td>Stocking use</td>
<td>13.9 (878)</td>
</tr>
<tr>
<td>Thrombophilic risk factor</td>
<td>8.4 (627)</td>
</tr>
</tbody>
</table>
All 878 subjects had repeat D-dimer measurements performed within 72 hours and again two weeks after their return to New Zealand.

The mean period of time overseas was 22.3 (range 1 to 67) days with 37 subjects returning after the designated six week period. The mean duration of air travel was 39.4 (range 10 to 81) hours with a mean duration of return air travel of 18.1 (range 4.5 to 37) hours. The longest single sector returning to New Zealand is approximately 14 hours and as a result, return travel longer than this requires at least two flights. There was an increased use of compression stockings with increasing duration of travel with 12/123 (9.8 percent) and 134/752 (17.8 percent) of subjects wearing stockings during air travel of a total duration of ≤24 and >24 hours respectively. The odds ratio for compression stocking use for air travel >24 hours compared to ≤24 hours was 2.00 (95 percent CI, 1.07 to 3.74, p<0.03).

All 106 subjects who met the criteria for radiological evaluation underwent investigation. In addition to bilateral compression ultrasonography, 103 subjects underwent CTPA while three subjects underwent V/Q scanning due to concerns regarding administration of contrast. In one subject in who the clinical probability was considered high, the CTPA was non-diagnostic. This subject proceeded to undergo direct pulmonary angiography before PE was excluded. Figure 4 summarises the manner in which these subjects were investigated.

One subject developed calf swelling and discomfort after their outgoing flight. This subject underwent CUS whilst overseas, which was reported as negative. This subject’s symptoms had settled prior to returning to New Zealand, and subsequent D-dimer measurements were within the normal range.

Ethical approval for assessment of thrombophilia states was obtained from the Auckland, but not the Wellington Regional Ethics Committee. As a result, specimens for thrombophilia assessment were only obtained from 676 subjects who attended the Auckland centre.
FIGURE 4: Algorithm for investigated subjects

Pre-flight assessment
Questionnaire
D-dimer measurement
(n=1000)

Positive

Withdrawn
n=83

Inflight Questionnaire
(n=917)

Failed to return for follow-up
n=39

Return Assessments
including Questionnaire
Clinical probability score
D-dimer measurements
Thrombophilia screen
(n=878)

D-dimer positive and/or high clinical probability

Investigations
Bilateral Lower Limb CUS
1,2Helical CTPA (n=106)

Positive
VTE Positive
(n=12)

Negative
VTE Negative
(n=94)

D-dimer negative and low/moderate clinical probability

No Imaging
(n=772)

Footnote:
1Three subjects underwent V/Q scanning instead of CTPA
2One subject with an inconclusive CTPA with high pre-test probability also underwent Pulmonary Angiography
7.2 Incidence of venous thromboembolism

The incidence of radiologically confirmed VTE was 1.4 percent (12/878, 95 percent CI 0.7-2.1). These VTE events included five cases of pulmonary embolism (one of whom had a co-existing lower limb proximal deep vein thrombosis), three cases of lower limb proximal deep vein thrombosis (one of whom had bilateral thrombus), one case of calf deep vein thrombosis and three cases of lower limb superficial venous thrombophlebitis (all short saphenous vein thrombosis). Table 5 demonstrates the nature of the VTE events and background characteristics of these subjects.

All 12 subjects had a positive plasma D-dimer measurement (>500 ng/L) with or without symptoms on their return. In 11 subjects, the D-dimer was positive at the time of the initial review; one subject had a negative D-dimer at initial review but had a positive D-dimer on repeat testing at Day 14. At the time of initial assessment, 9 (75 percent) subjects reported at least one symptom suggestive of possible VTE, with 6 (50 percent) subjects being classified as moderate or high clinical probability on the basis of the standardised scoring system used.

Of the 12 subjects with confirmed VTE, there were 2 (17 percent) who had travelled exclusively in business class during all of their long distance flights. Four (33 percent) subjects had been using aspirin alone; three (25 percent) both took aspirin and wore stockings; and one (8 percent) subject used stockings alone as prophylaxis. Six (50 percent) subjects had pre-existing risk factors that could have been identified prior to travel, and two had a recognised thrombophilic risk factor.

There was no difference in the duration of travel between subjects who experienced a VTE (mean (SD) 37.5 (10.7) hours) compared with those who did not (mean (SD) 39.4 (12.5) hours). The incidence of VTE in subjects with a total duration of travel ≤24 hours was 2/126 (1.59 percent) compared with 10/752 (1.33 percent) in those with travel >24 hours (p=0.82).

In total 845 (96 percent) subjects were contacted three months after return from travel. No further VTE events were identified during this period, although eight subjects underwent review and radiological imaging for suggestive symptoms. The subsequent investigations performed in these subjects did not yield any further VTE events.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Event</th>
<th>D-dimer pre-flight ng/L</th>
<th>D-dimer post-flight ng/L</th>
<th>Clinical score</th>
<th>Class of travel</th>
<th>Travel Period (days)</th>
<th>Duration of travel (h)</th>
<th>Prophylactic use</th>
<th>Pre-existing risk factors</th>
<th>Thrombophilic risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>62yo female</td>
<td>Proximal DVT</td>
<td>297</td>
<td>541</td>
<td>Low</td>
<td>Economy</td>
<td>46</td>
<td>40</td>
<td>Stockings</td>
<td>HRT</td>
<td>Negative</td>
</tr>
<tr>
<td>40yo male</td>
<td>Distal DVT</td>
<td>222</td>
<td>1049</td>
<td>Mod.</td>
<td>Economy</td>
<td>9</td>
<td>34</td>
<td>Nil</td>
<td>Nil</td>
<td>Negative</td>
</tr>
<tr>
<td>50yo female</td>
<td>Segmental PE</td>
<td>290</td>
<td>644</td>
<td>Mod.</td>
<td>Economy</td>
<td>42</td>
<td>58</td>
<td>Nil</td>
<td>Nil</td>
<td>Negative</td>
</tr>
<tr>
<td>66yo male</td>
<td>Short saphenous SVT</td>
<td>385</td>
<td>557</td>
<td>Low</td>
<td>Economy</td>
<td>41</td>
<td>26</td>
<td>Aspirin</td>
<td>Nil</td>
<td>Negative</td>
</tr>
<tr>
<td>68yo male</td>
<td>Short saphenous SVT</td>
<td>424</td>
<td>541</td>
<td>Low</td>
<td>Economy</td>
<td>24</td>
<td>24</td>
<td>Aspirin</td>
<td>Nil</td>
<td>Negative</td>
</tr>
<tr>
<td>56yo female</td>
<td>Segmental PE</td>
<td>338</td>
<td>631</td>
<td>Low</td>
<td>Business</td>
<td>40</td>
<td>35</td>
<td>Nil</td>
<td>Crohn’s disease</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>64yo female</td>
<td>Proximal DVT/Segmental PE</td>
<td>453</td>
<td>1322</td>
<td>High</td>
<td>Economy</td>
<td>28</td>
<td>38</td>
<td>Stockings</td>
<td>HRT</td>
<td>Elevated Factor VIII levels</td>
</tr>
<tr>
<td>54yo female</td>
<td>Short saphenous SVT</td>
<td>467</td>
<td>906</td>
<td>Mod.</td>
<td>Economy</td>
<td>16</td>
<td>21</td>
<td>Aspirin</td>
<td>Nil</td>
<td>Negative</td>
</tr>
<tr>
<td>32yo female</td>
<td>Bilateral proximal DVT</td>
<td>411</td>
<td>616</td>
<td>Mod.</td>
<td>Economy</td>
<td>34</td>
<td>45</td>
<td>Stockings</td>
<td>OCP</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>54yo female</td>
<td>Segmental PE</td>
<td>250</td>
<td>1265</td>
<td>Mod.</td>
<td>Economy</td>
<td>32</td>
<td>51</td>
<td>Aspirin</td>
<td>HRT</td>
<td>Negative</td>
</tr>
<tr>
<td>63yo male</td>
<td>Segmental PE</td>
<td>371</td>
<td>1256</td>
<td>Low</td>
<td>Economy</td>
<td>19</td>
<td>38</td>
<td>Aspirin</td>
<td>Previous CVA</td>
<td>Negative</td>
</tr>
<tr>
<td>63yo male</td>
<td>Distal DVT</td>
<td>483</td>
<td>1965</td>
<td>Low</td>
<td>Business</td>
<td>15</td>
<td>42</td>
<td>Aspirin</td>
<td>Prothrombin gene mutation</td>
<td>Negative</td>
</tr>
</tbody>
</table>
7.3 Pre travel baseline D-dimer measurement

All 1000 subjects who were recruited in the study completed the pre-flight risk factor questionnaire and had blood taken for baseline plasma D-dimer analysis. However, in seven subjects the blood samples had haemolysed prior to analysis and as a result the D-dimer measurement could not be reliably undertaken in these individuals. The characteristics of this population are shown in Table 6.

TABLE 6: Characteristics of all subjects in who pre-flight D-dimer was obtained

<table>
<thead>
<tr>
<th>Continuous variables</th>
<th>N with data</th>
<th>Mean (SD)</th>
<th>Median (Interquartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer (ng/ml)</td>
<td>993</td>
<td>288.4 (235.4)</td>
<td>243 (175 to 345)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1000</td>
<td>49.7 (12.0)</td>
<td>51.8 (41.3 to 58.7)</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>986</td>
<td>25.9 (4.6)</td>
<td>25.3 (22.8 to 28.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categorical variables</th>
<th>N with characteristic</th>
<th>N with data</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>514</td>
<td>1000</td>
<td>51.4</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>376</td>
<td>1000</td>
<td>37.6</td>
</tr>
<tr>
<td>Family history of VTE</td>
<td>111</td>
<td>1000</td>
<td>11.1</td>
</tr>
<tr>
<td>Hormone use in females</td>
<td>150</td>
<td>514</td>
<td>29.2</td>
</tr>
<tr>
<td>Thrombophilic state</td>
<td></td>
<td></td>
<td>8.6</td>
</tr>
<tr>
<td>- FVL heterozygote</td>
<td>58</td>
<td>676</td>
<td>3.7</td>
</tr>
<tr>
<td>- PGM heterozygote</td>
<td>25</td>
<td>674</td>
<td>2.1</td>
</tr>
<tr>
<td>- Combined FVL/PGM</td>
<td>14</td>
<td>673</td>
<td>0.1</td>
</tr>
<tr>
<td>- Antithrombin deficient</td>
<td>1</td>
<td>673</td>
<td>0.7</td>
</tr>
<tr>
<td>- ACL antibodies</td>
<td>10</td>
<td>676</td>
<td>1.4</td>
</tr>
</tbody>
</table>
On univariate analysis of the entire population, higher plasma D-dimer levels were associated with increasing age, body mass index (BMI), female sex, the presence of a co-morbid condition, or thrombophilia states. This analysis in Table 7 is presented in terms of the untransformed data. A similar univariate analysis, not shown, using the logarithm of the plasma D-dimer levels gave similar results.

**TABLE 7: Univariate association between D-dimer (ng/ml) and possible predictors**

<table>
<thead>
<tr>
<th>Categorical Variable</th>
<th>Present Median (IQR) N</th>
<th>Absent Median (IQR) N</th>
<th>Difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>275.5 (195.5 to 374) N=510</td>
<td>208.0 (157.0 to 297.0) N=483</td>
<td>55.0 (40 to 69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>275 (200 to 386.5) N=372</td>
<td>223 (160 to 316) N=621</td>
<td>−52 (−67 to −37)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family history of VTE</td>
<td>235.0 (171 to 341) N=111</td>
<td>244.0 (175 to 345) N=882</td>
<td>−1.0 (−24.0 to 24.0)</td>
<td>0.89</td>
</tr>
<tr>
<td>Hormone use (in females)</td>
<td>271.5 (212.3 to 378.3) N=148</td>
<td>278.0 (190.8 to 374.0) N=362</td>
<td>−13.0 (−37.0 to 12.0)</td>
<td>0.31</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>288.0 (199.8 to 409.0) N=58</td>
<td>245.5 (175.3 to 338.8) N=616</td>
<td>40 (8.0 to 73.0)</td>
<td>0.015</td>
</tr>
<tr>
<td>Continuous variables</td>
<td>Rank correlation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.514</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>0.134</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Using the logarithm transformed plasma D-dimer level, increasing age, larger BMI, the use of hormone therapy (OCP or HRT), the presence of a thrombophilia state, co-morbidity and female sex, significantly predicted a higher baseline D-dimer level (Table 8). For example, for each 10 years of age, the predicted D-dimer would increase by a factor of 1.2. The R-squared for this model was 33 percent and regression assumptions appeared to be met.
TABLE 8: Multivariate association between parameter value and the logarithm of D-dimer level

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter value</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.018</td>
<td>0.015 to 0.021</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.017</td>
<td>0.010 to 0.024</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.21</td>
<td>0.14 to 0.27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>0.095</td>
<td>0.002 to 0.19</td>
<td>0.046</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>0.076</td>
<td>0.010 to 0.42</td>
<td>0.026</td>
</tr>
<tr>
<td>Thrombophilia state</td>
<td>0.12</td>
<td>0.006 to 0.230</td>
<td>0.039</td>
</tr>
</tbody>
</table>

7.4 Change in D-dimer after travel

All twelve subjects who had confirmed VTE had a positive D-dimer following travel. In addition, there were 94 subjects (10.9 percent, 95 percent CI, 8.8 to 12.9) who had a positive plasma D-dimer result on return from travel, but in whom there was no radiological evidence of VTE (D-dimer positive, VTE negative). Therefore, 106 subjects had a change in D-dimer following air travel such that their result fell outside the 95th confidence intervals of the normal range (a “positive D-dimer”).

Univariate analysis of the factors associated with a positive D-dimer following travel are outlined in table 9. Of the pre-existing intrinsic risk factors, age greater than 50 years, female gender, hormone use, obesity (BMI greater than 30), height less than 165cm and the presence of thrombophilia were associated with increased risk of raised D-dimer following travel. Of the transient risk factors associated with travel, only non-aisle seating was associated with increased risk. Somewhat concerning was the finding that symptoms suggestive of possible pulmonary embolism were strongly associated with raised D-dimer.
**TABLE 9. Univariate analysis of factors associated with raised D-dimer following travel**

<table>
<thead>
<tr>
<th>Variable</th>
<th>D-dimer &lt;500 (Percent)</th>
<th>D-dimer &gt;500 (Percent)</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 50yrs</td>
<td>50.0</td>
<td>73.6</td>
<td>1.47</td>
<td>1.29 to 1.68</td>
</tr>
<tr>
<td>Female gender</td>
<td>48.2</td>
<td>67.9</td>
<td>1.41</td>
<td>1.21 to 1.64</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>35.0</td>
<td>46.2</td>
<td>1.32</td>
<td>1.05 to 1.66</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30)</td>
<td>21.2</td>
<td>13.6</td>
<td>1.55</td>
<td>1.03 to 2.34</td>
</tr>
<tr>
<td>Height &lt; 165cm</td>
<td>20.6</td>
<td>35.8</td>
<td>1.74</td>
<td>1.30 to 2.33</td>
</tr>
<tr>
<td>Height &gt; 180cm</td>
<td>18.9</td>
<td>11.3</td>
<td>0.60</td>
<td>0.35 to 1.04</td>
</tr>
<tr>
<td>Family history of VTE</td>
<td>11.0</td>
<td>15.1</td>
<td>1.37</td>
<td>0.84 to 2.25</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- FVL</td>
<td>7.5</td>
<td>13.5</td>
<td>1.80</td>
<td>1.00 to 3.24</td>
</tr>
<tr>
<td>- PGM</td>
<td>3.0</td>
<td>7.3</td>
<td>2.42</td>
<td>1.03 to 5.74</td>
</tr>
<tr>
<td>Hormone use (females)</td>
<td>13.2</td>
<td>24.5</td>
<td>1.85</td>
<td>1.27 to 2.71</td>
</tr>
<tr>
<td>Economy Class</td>
<td>72.7</td>
<td>73.6</td>
<td>1.01</td>
<td>0.90 to 1.14</td>
</tr>
<tr>
<td>Non-aisle seat</td>
<td>38.6</td>
<td>53.8</td>
<td>1.39</td>
<td>1.14 to 1.70</td>
</tr>
<tr>
<td>Alcohol in flight</td>
<td>33.8</td>
<td>27.4</td>
<td>0.81</td>
<td>0.58 to 1.12</td>
</tr>
<tr>
<td>Regular fluid intake</td>
<td>95.5</td>
<td>93.4</td>
<td>0.98</td>
<td>0.93 to 1.03</td>
</tr>
<tr>
<td>Regular exercise</td>
<td>79.8</td>
<td>80.2</td>
<td>1.01</td>
<td>0.91 to 1.11</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>22.2</td>
<td>30.2</td>
<td>1.36</td>
<td>0.99 to 1.87</td>
</tr>
<tr>
<td>Stocking use</td>
<td>13.1</td>
<td>19.8</td>
<td>1.51</td>
<td>0.99 to 2.31</td>
</tr>
<tr>
<td>PE Symptoms</td>
<td>8.8</td>
<td>20.8</td>
<td>2.36</td>
<td>1.52 to 3.64</td>
</tr>
<tr>
<td>DVT Symptoms</td>
<td>32.0</td>
<td>38.7</td>
<td>1.21</td>
<td>0.93 to 1.57</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>26.6</td>
<td>31.1</td>
<td>1.17</td>
<td>0.86 to 1.59</td>
</tr>
</tbody>
</table>

On multivariate analysis, those in the D-dimer positive, VTE negative group were significantly more likely than the D-dimer negative subjects to have a thrombophilic risk factor and be older, obese or female (Table 10). In addition, they were more likely to have
been seated in a non-aisle seat during their return journey, and have experienced symptoms suggestive of possible pulmonary embolism. Of these individuals, 7.8 percent were assessed to be of at moderate or high clinical probability of VTE, versus 3.0 percent in the D-dimer negative group.

Variables of interest which were not recorded more commonly in the D-dimer positive group included duration of travel, economy class travel, aspirin or stocking use. Factors such as height less than 165cm and hormone use were difficult to separate from female gender in this analysis.

**TABLE 10: Multivariate analysis of factors associated with raised D-dimer following travel**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age (per decade)</td>
<td>1.87</td>
<td>1.50 to 2.35</td>
</tr>
<tr>
<td>Symptoms suggestive of PE</td>
<td>2.27</td>
<td>1.44 to 3.56</td>
</tr>
<tr>
<td>Non-aisle</td>
<td>1.76</td>
<td>1.20 to 2.57</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30)</td>
<td>1.53</td>
<td>1.14 to 2.23</td>
</tr>
<tr>
<td>Thrombophilic risk factor</td>
<td>1.84</td>
<td>1.07 to 3.16</td>
</tr>
<tr>
<td>Female gender</td>
<td>2.20</td>
<td>1.45 to 3.34</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>1.43</td>
<td>0.98 to 2.10</td>
</tr>
</tbody>
</table>

**7.5 In-flight Behaviour**

In-flight questionnaires were completed fully by all of the 878 subjects included in the analysis of their return flights. Eighty percent reported that they walked around or performed stretching exercises regularly during the course of their journey. Most subjects (96 percent) reported that they drank fluid frequently during the journey (at least 200 millilitres every two hours). Thirty three percent drank alcohol and fourteen percent used sedatives during the course of their return travel, with the mean number of hours slept 4.2 hours per flight.
Fourteen percent reported the use of stockings during their return journey, and 23 percent self-administered aspirin prior to embarking on the plane. One subject who took aspirin reported minor epistaxis during the flight, and ten subjects reported increased bruising tendency over the following days. Most subjects were unaware of the dose of aspirin taken and it is not possible to report this. Five subjects reported significant discomfort from the use of stockings, which resulted in two subjects abandoning them during the flight. It was not possible to ascertain the type, manufacturer or compression characteristics of stockings used by most of these individuals.

There was a positive correlation between travel duration and prophylactic use. For aspirin, the correlation coefficient with the duration of the return flight was 0.13 (p<0.001), and for stockings the correlation coefficient was 0.11 (p=0.002). Many subjects used both forms of prophylaxis, with the correlation coefficient being 0.19 (p< 0.001). Subjects who used stockings were more likely to be older (correlation coefficient 0.15, p<0.001)

Anecdotally, several subjects reported that the recent publicity regarding the potential risks of travel had not only prompted their enrolment in the study, but had prompted them to change their in-flight behaviour. This was apparent from the use of prophylactic methods observed above. The extent to which this has influence the results of this study is unclear.
Chapter 8

NZATT Study Discussion

8.1 Incidence of VTE following air travel

In this large prospective study we have identified an incidence of VTE of 1.4% in low to moderate risk travellers who had undergone multiple long distance air flights. These findings indicate that VTE is a significant potential health hazard for many long distance air travellers, including those without recognised risk factors.

We considered it important to investigate subjects thoroughly for pulmonary embolism as well as deep venous thrombosis and superficial venous thrombosis, which has not been undertaken previously. Whilst deep venous thrombosis and pulmonary embolism are considered different manifestations of the same disease process, it is apparent that pulmonary embolism may occur without radiological evidence of an associated deep venous thrombosis [188, 211], and that some differences in thrombophilic risk profile may be present in those individuals with isolated deep venous thrombosis [24]. We included cases of short and long saphenous vein thrombosis due to their clinical significance being similar to that of isolated calf deep venous thrombosis in terms of the risk of extension into the proximal deep venous system and associated pulmonary embolism [53, 58].

In terms of diagnostic imaging, we used helical CTPA and bilateral lower limb complete CUS, which represent the most widely recommended radiological methods for the investigation of VTE due to their availability and high sensitivity and specificity [184, 202, 212]. We acknowledge the reduced sensitivity of ultrasonography in identifying distal DVT and of single slice helical CTPA sub-segmental PE. As a result, the true incidence of below VTE in our cohort may have been underestimated.

Because of the multiple long distance air flights undertaken by the participants and the inability to perform these investigations following their outward air travel, it was not possible to determine the specific flight during which the VTE arose. When the mean period of time overseas of 22 days is considered, it is conceivable that there may have been minor VTE events that occurred during the outward flights that had completely resolved prior to the return trip to New Zealand. This represented an unavoidable feature of the study design, but
as previous investigators have suggested that most VTE events occur following multiple or return journeys [113], this probably does not affect the public health significance of the results.

Another factor which may have reduced the frequency of VTE noted in this study was the uncontrolled use of prophylactic measures, particularly exercise and compression stockings. Stockings, which have been reported previously to significantly reduce the incidence of deep venous thrombosis associated with long distance travel [122, 123, 126, 130], were used in approximately one in seven subjects included in this study, with increasingly frequent use as duration of travel and age increased.

A further consideration is the background frequency of VTE in this group of travellers. Due to the absence of a control group, it was not possible to determine the relative risk of VTE that is attributable to long distance travel. Furthermore, we were unable to report the absolute incidence of “symptomatic” VTE, as our diagnostic criteria was based on radiological imaging. However, 50 percent of the subjects who sustained a VTE where classified as moderate to high clinical probability, and 75 percent reported symptoms suggestive of possible VTE versus 39 percent in the remainder of the study population. It is therefore possible that the early intervention undertaken by the investigators may have prevented more overt symptoms becoming apparent. Despite the use of validated scoring systems, this highlights the poor positive and negative predictive value of clinical symptoms and signs for both PE and DVT, and further diminishes the clinical relevance of distinguishing between symptomatic and asymptomatic VTE events.

Thus, the frequency of VTE of 1.4% found in this study should be considered to represent a conservative estimate of the frequency of radiologically confirmed VTE in low to moderate risk long distance air travellers. This estimate relates to multiple flights, involving a long total duration of travel, with the majority of subjects travelling at least ten hours, with a mean duration of total air travel of 39 hours within a 6 week period. As a result, the findings are not necessarily applicable to all air travellers, particular those undertaking single flights of a shorter duration.

Our findings contrast with those of Scurr et al, who reported a 10% incidence of DVT in long distance air travellers [122]. However, only a few of the subjects in that study had a positive D-dimer level despite ultrasonic evidence of deep venous thrombosis [10]. Although this may
reflect a difference in the sensitivity of the assay used when compared to the VIDAS system, this observation raises concerns regarding the validity and clinical significance of the isolated calf deep venous thrombosis demonstrated on limited CUS in their study. However, our findings are similar to those of Belcaro et al, who reported 0% and 4.9% incidence of deep venous thrombosis in low and high risk individuals respectively [123].

Despite the small number of participants that developed VTE, these findings question the previous assumption that the majority of individuals who suffer a VTE event have pre-existing risk factors that are identifiable prior to travel [112, 213, 214]. We studied subjects at only mild to moderate risk of VTE and excluded subjects with recognised major risk factors. Whilst some cases had relevant co-morbid conditions or were taking hormone therapy, many of these individuals did not possess any pre-identifiable risk factors, and only a few had a recognised thrombophilic risk factor.

The long duration of travel undertaken by the study participants, the greater use of prophylactic measures with increasing duration of travel, and the small number of subjects experiencing a VTE limited the ability of our study to investigate the relationship between VTE and duration of travel. However, the study from Charles de Gaulle Airport has reported that the risk of pulmonary embolism increases with progressively greater distances travelled [119]. In that study the risk of pulmonary embolism significantly increased with flights longer than six hours, with the risk increasing a further three-fold after 12 hours. This suggests that long distance air travel itself is an independent risk factor for VTE with the duration of travel being an important determinant of outcome.

Finally, we were able to describe a proportional level of risk in travellers of all classes. As a result our findings support the WHO recommendation that the term "economy class syndrome" should be avoided, with the phenomenon renamed "air travel-related "venous thromboembolism (ATVT)" or be incorporated into the unifying diagnosis of “seated immobility thrombosis (SIT)”.

8.2 Baseline D-dimer measurement

One of the novel methodological features of this study was the use of serial VIDAS D-dimer assessment as the primary screening tool of a possible VTE event. The well validated, high sensitivity and high negative predictive value of the VIDAS D-dimer assay enabled us to
restrict our radiological investigations to those with evidence of thrombotic activity [143, 144, 164, 215, 216]. This assay also provided a convenient means by which to retest individuals within the four week period after their travel [111, 112]. We excluded individuals in whom the D-dimer was elevated prior to travel, thus increasing the specificity of this assay when measured in a serial fashion.

However, in performing D-dimer specimens at baseline on all potential participants we were in fact obtaining a somewhat random representation of basal thrombotic activity within our study population. Whilst we acknowledge that this may not have been representative of the general population, the results of this analysis suggest that the basal level of plasma D-dimer in adults with no recent stimulus for thrombosis is related to the presence of known risk factors for VTE. Increasing age, hormone use, increased BMI, history of comorbid conditions and thrombophilia states, which are well recognised risk factors for idiopathic VTE, were all positively correlated with D-dimer levels. Previous evidence has suggested that the risk factors for VTE are multiplicative rather than additive. We also observed a similar relationship between such risk factors and the presence a positive D-dimer results [76].

Previous literature has suggested that in patients with a confirmed VTE who have completed an appropriate course of anticoagulation, a persistently elevated plasma D-dimer is associated with increased risk of recurrent thrombosis [217, 218]. This association occurs in the absence of demonstrable persisting thrombus, suggesting that the plasma D-dimer is an independent marker of risk of recurrence in these individuals. The analysis of this study has identified a comparable relationship between plasma D-dimer with known VTE risk factors in otherwise healthy subjects.

As a result, random plasma D-dimer measurements may have a role in assessing prothrombotic risk in otherwise healthy individuals, in much the same way that C-reactive protein has been used as a marker of coronary artery disease risk. Possible applications would include the assessment of baseline risk in patient groups such as women commencing oral contraceptive therapy or family members of patients with confirmed VTE.

Another issue raised by these results is in the interpretation of so called “false positive” D-dimer measurements in patients presenting to Emergency Departments with suspected VTE. In the presence of a high level without any obvious explanation, consideration may need to be
given to more thoroughly evaluating thrombotic risk, or the presence of other causes of vasculopathic processes.

Intriguingly female gender, independent of hormone use, was associated with higher plasma D-dimer measurements. This contrasts with the recent observation that males are more likely to experience recurrent VTE compared with females [219]. The explanation for these contrasting findings will need further study, in particular the relationship between D-dimer and menstrual status.

In conclusion, increased plasma D-dimer levels are associated with recognised risk factors for VTE such as age, female gender, hormone use, obesity, co-morbidity and thrombophilia states. Whether D-dimer measurements may provide a means to stratify an individual’s risk of VTE or other vascular disease will require further study.

8.3 Change in Plasma D-dimer following flight

In this study a significant rise in D-dimer, and hence thrombus activation, following the return flight was observed in 106 subjects. It would appear that the rise noted is related thrombus formation secondary to the exposure to travel, rather than any other obvious factor. One concern was that inflammatory conditions, such as upper respiratory tract infection, would increase the frequency of false positive results [220, 221]. This does not appear to have been the case, as the relative risk of symptoms suggestive of respiratory tract infection were similar in both the D-dimer positive and D-dimer negative groups. Furthermore, one subject returned from holiday with extensive cellulitis following an abrasion to his upper limb. Despite this, the D-dimer result was negative.

On univariate analysis, the intrinsic risk factors associated with this change in D-dimer were increasing age, female gender, hormone therapy use, height less than 165cm, obesity and the presence of comorbidity and thrombophilia. The association with female gender is somewhat surprising, given that DVT appears to occur more commonly in men [219]. It was difficult to separate this from factors such as hormone therapy use and height, which in themselves have been suggested to play a role. Of the possible transient risk factors associated with air travel, only non-aisle seating was associated with the risk of raised D-dimer. This further suggests that the primary aetiological factor responsible for this condition is that of prolonged immobility, rather than any other factor unique to air travel.
Until now the assumption has been that taller travellers are at greater risk of VTE during travel, due to the reduced seat pitch and cramped conditions of economy class. These data suggest the contrary, with the risk of thrombus activation being greater in shorter individuals, and the confirmation that the condition is not restricted to any particular class of travel. Shorter passengers have reduced tibial length, and require a more acute angle at the knee to place their feet on the ground. In addition, they may be more likely to experience compression on the popliteal fossa from the front corner of their seat. Such flexion of the popliteal vein has been suggested to cause rippling of the vein wall, predisposing to turbulent flow and possibly thrombus formation [139]. It is therefore postulated that seat design and height may play a more important role than seat pitch. Unfortunately due to the wide variation in seat design within the aircraft in which the subjects travelled, it was not possible to analyse this hypothesis further in this study.

The lack of association with duration of flight is intriguing and contrary to other published data. There are several possible explanations for this. The mean during of flight during the return travel for this population was 19 hours, with 87 percent of subjects travelling in excess of 10 hours. The maximum duration for a single sector of a long distance flight to New Zealand is 13 hours, at which time passengers usually disembark the aircraft to transit to connecting flights. Thus, the maximum period of prolonged immobility is fixed at 13 hours.

In addition, subjects included in the study were not restricted in their use of prophylactic measures such as aspirin, stockings or exercise. It would appear that subjects who were undertaking longer distance travel were more likely to undertake these measures. The univariate analysis suggested a trend towards an increased odds ratio of positive D-dimer in these prophylaxis users, which suggests a tendency towards thrombus activation despite aspirin or stocking use.

It is concerning that there was a strong relationship between raised D-dimer and those symptoms described by the subjects that were suggestive of possible PE. Given the limitations of the scanning modality used (single slice CTPA), it is possible that more subjects with a positive D-dimer may have experienced small sub-segmental PE than were reported. Whilst the clinical significance of sub-segmental PE is contentious, it is reassuring that no further events were reported at the time of three month follow-up.
In summary, it would appear that evidence of thrombus activation following air travel, in the form of rise in D-dimer, is associated with the interaction of pre-existing established risk factors, and factors that influence the duration and degree of seated immobility. Serial D-dimer measurement performed well as a screening modality for VTE in this condition, and avoided the need to unnecessary imaging in 88 percent of participants in the study.

8.4 In-flight behaviour

Extensive data regarding the behaviour of passengers during travel was collected for all included subjects. It is difficult to ascertain the affect that participation in the study had on the behaviour of these subjects. The high reported frequency of leg exercises and fluid intake may have been influenced by this bias, and it is not possible to analyse these affects of these interventions. However, one third of passengers consumed alcohol during their return flights, and this does not appear to have influenced either evidence of thrombus formation or sleep duration.

The data did not attempt to analyse the effect of departure time and changes in time zones and circadian rhythm on the risk of thrombosis. Given the complexity of the travel undertaken by the participants, with multiple legs of varying duration, this was not considered possible.

The observation that 14 percent of the participants wore compression stockings and 23 percent took aspirin suggests that the study group might not have been representative of the general travelling public. Furthermore, because subjects were not randomly assigned to different prophylactic measures recommended for VTE and those taking prophylactic measures were likely to be at higher risk (either in association with the presence of co-morbid conditions, age or longer flight duration), it was not possible to assess their efficacy in this study. However their efficacy is questioned by our findings as several individuals developed VTE despite aspirin use, an observation that has recently also been reported in the LONFLIT3 study [124]. Furthermore, although graduated compression stockings have been demonstrated to reduce the risk of developing VTE with long distance travel [122, 123, 126, 130], four of the participants in this study developed proximal thigh DVT despite below knee compression stocking use.

Despite an extensive examination of in-flight behaviour, we were unable to establish the role for other suggested prophylactic measures such as regular hydration, physical exercise, time
zone change and avoidance of sedatives or alcohol, due to the wide variability in use and the difficulty in obtaining accurate data on these factors in our study population. At the present time there is little data support the use of these measures despite their recommendation by several experts.
Chapter 9

Recent Air Travel as a risk factor for patients hospitalised with VTE (I)

9.1 Study Aim
To establish the frequency of air travel as a potential risk factor in patients admitted to four teaching hospitals in New Zealand.

9.2 Study Design and Outcomes
Retrospective case review

Primary:
- The presence of reported risk factors associated with a VTE event, with particular reference to travel

Secondary:
- To determine the nature of the travel undertaken and its relationship to the onset of symptoms of VTE

9.3 Study Protocol
A review of the medical records of patients discharged with a diagnosis of deep vein thrombosis (DVT) or pulmonary embolism (PE) was undertaken. Records were identified from Wellington and Kenepuru Hospitals in Wellington and Green Lane and Auckland Hospitals in Auckland between 1997 and 2001.

Inclusion Criteria
1. Primary or secondary discharge diagnosis of DVT or PE
2. Radiographic of VTE confirmation by one of the following:
   - positive compression Doppler ultrasound,
   - positive contrast venography,
   - high or intermediate probability V/Q scan
   - positive helical CT with pulmonary angiography,
   - contrast pulmonary angiography
   - findings from post mortem
Exclusion Criteria:

1. Diagnosis of DVT or PE was not confirmed by the above radiological criteria
2. An alternative diagnosis such as superficial thrombophlebitis was present
3. Case represented a repeat admission for the same VTE event, occurring within four months of the index admission.

While these strict criteria will have resulted in some subjects being excluded who had experienced a VTE, they did ensure that subjects were not included in whom the diagnosis of VTE was not firmly established. Subjects with confirmed superficial thrombophlebitis were excluded due to poor reporting of such events.

From the medical records information was collected on demographic details, documentation of the presence of risk factors and results of radiological investigations. In terms of the documentation of the details of recent travel (within 28 days of admission), this included type of travel (road, train or air) and duration (if available). The criteria used for the duration of flights was as follows: not stated, less than 2 hours, 2 to 4 hours, 4 to 10 hours, 10 to 20 hours and greater than 20 hours.

The requirement for the hospital admission to occur within 28 days of the air travel was based on the observation that at least a third of subjects with air travel-related VTE present with symptoms more than a week after their travel. Thrombophilia tests were not routinely undertaken in the patients included in the study and for this reason could not be included in the analysis.

The data was entered independently by two investigators, with any differences resolved by subsequent review. Ethical approval was obtained from the Wellington and Auckland Ethics Committees.

9.4 Statistical Analysis

Simple tabulations of examined variables were performed. The data is presented as the absolute number and percentage of the relevant population. All available notes were reviewed during the study period.
9.5 Results

There were 645 case records identified from the hospital computerised databases. From these case records, 69 cases were excluded as the subjects either did not have a radiologically confirmed DVT or PE, or the case represented a repeat admission for the same VTE event. As a result there were 576 case records identified in which the subjects met the inclusion criteria. The median (range) age was 63 (11 to 94) years, and 53.7 percent were women. There was a radiological confirmation of DVT and PE in 266 (46.2 percent), and 383 (66.5 percent) of subjects respectively, with both DVT and PE in 73 (12.7 percent) of subjects. Recent air travel was documented in 60 (10.4 percent) of the 576 subjects (Table 11).

<table>
<thead>
<tr>
<th>Risk Factors:</th>
<th>Number of subjects/Number with information recorded (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Previous VTE</td>
<td>152/576 (26.4)</td>
</tr>
<tr>
<td>• Family history VTE</td>
<td>76/576 (13.2)</td>
</tr>
<tr>
<td>• Malignancy</td>
<td>116/576 (20.1)</td>
</tr>
<tr>
<td>• OCP use</td>
<td>36/309 (11.7)</td>
</tr>
<tr>
<td>• HRT use</td>
<td>35/309 (11.3)</td>
</tr>
<tr>
<td>• Trauma within prior 4 weeks</td>
<td>61/576 (10.6)</td>
</tr>
<tr>
<td>• Air Travel within prior 4 weeks</td>
<td>60/576 (10.4)</td>
</tr>
<tr>
<td>• Surgery within prior 4 weeks</td>
<td>58/576 (10.0)</td>
</tr>
<tr>
<td>• Recent road travel ‡</td>
<td>27/576 (4.7)</td>
</tr>
<tr>
<td>• Pregnancy</td>
<td>3/309 (1.0)</td>
</tr>
<tr>
<td>• Recent train travel</td>
<td>3/576 (0.5)</td>
</tr>
</tbody>
</table>

The median age of these subjects was 59.5 (range 26 to 87) years and 48.3 percent were women. There was a radiological confirmation of DVT and PE in 27 (45 percent) and 40 (66.7 percent) of subjects respectively, with both DVT and PE in 7 (11.7 percent) of subjects. In those cases in who details of the air travel were recorded, it had been undertaken within the previous one week in 65 percent. The median duration between air travel and hospital admission was 4.5 (2 to 21) days. In 43.3 percent of cases, the air travel was of at least 10 hours duration (Table 12).
TABLE 12: Number of subjects with VTE in relation to duration of air travel

<table>
<thead>
<tr>
<th>Duration of flights</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not recorded</td>
<td>7 (11.7)</td>
</tr>
<tr>
<td>&lt;2 hours</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>2 to 4 hours</td>
<td>16 (26.7)</td>
</tr>
<tr>
<td>4 to 10 hours</td>
<td>6 (10.0)</td>
</tr>
<tr>
<td>10 to 20 hours</td>
<td>12 (20.0)</td>
</tr>
<tr>
<td>&gt;20 hours</td>
<td>14 (23.3)</td>
</tr>
</tbody>
</table>

In 31 of the 60 subjects with a history of recent air travel no other risk factors were recorded (Table 13). In addition to a past medical or family history of VTE, malignancy, recent surgery or trauma represented other commonly documented risk factors. The proportion of patients in whom air travel was documented was similar to that for recent surgery (10.4 percent vs 10.0 percent respectively). The proportion of patients in whom road and train travel was documented in the medical records was 4.7 percent and 0.5 percent respectively.

TABLE 13: The proportion of VTE subjects in whom specific risk factors were documented

<table>
<thead>
<tr>
<th>Risk Factors:</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>12/60 (20.0)</td>
</tr>
<tr>
<td>Family history VTE</td>
<td>6/60 (10.0)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>3/60 (5.0)</td>
</tr>
<tr>
<td>OCP or HRT use</td>
<td>8/29 (27.6)</td>
</tr>
<tr>
<td>Trauma within prior 4 weeks</td>
<td>6/60 (10.0)</td>
</tr>
<tr>
<td>Surgery within prior 4 weeks</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
9.6 Discussion

These results indicate that long distance air travel is an important risk factor for VTE requiring hospital admission in New Zealand. The frequency of documented recent air travel of about 10% most likely represents an underestimate of the true figure due to the probable incomplete ascertainment of this aspect of the history in a proportion of the medical records. This is likely to have occurred from the lack of systematic documentation of travel as part of the medical history by some of the doctors, due to their lack of awareness or acceptance of the link between air travel and VTE, as well as inadequate or incomplete elucidation of the history of the presenting complaint in the case records. Late presentations after travel may also have resulted in the lack of recognition of the temporal association, and in addition events which led to admission more than four weeks after their return from travel did not meet the criteria for a travel-related event.

It is intriguing to compare the 10% incidence of travel related VTE noted in this study with that reported from other countries [71, 111, 114, 115, 214, 222, 223]. In hospital-based studies in Hawaii, recent air travel has been documented in 17 to 25% of patients admitted with VTE [111, 214, 223]. In contrast, studies from mainland Europe have reported air travel in <6% of VTE cases admitted to hospital [114, 116]. The most likely explanation for this difference is that in geographically isolated island populations (the closest countries to New Zealand are Australia and Fiji, both over 3 hours away by air travel; Hawaii is over 3 hours by air from mainland USA), long distance air travel is considerably more common compared with mainland Europe. To some extent this is supported by the observation that even in Nice, with the second largest airport in France, travel-associated VTE was three times more common by car than with air travel [114], which contrasts with our New Zealand findings in which air travel was twice as common than documented car travel in patients admitted to hospital with a VTE.

Our observation that the majority (56%) but not all of the subjects had a duration of travel greater than 10 hours is consistent with the study from Charles de Gaulle Airport which reported that the risk of pulmonary embolism increases with progressively greater distances travelled [119]. In that study the risk of PE increased exponentially with increasing duration of travel with a three-fold increase for travel greater than 12 hours compared with 6 to 12 hours. Likewise, in the meta-analysis of three Dutch studies, ten Wolde reported a greater than two-fold risk of VTE associated with travel over 10 hours duration, compared with travel
of lesser duration [116]. In a case series from the United Kingdom, the majority of cases involved flights ≥9 hours which presumably represented only a small minority of the flights undertaken in this population [112]. In addition, this study reported that the risk of VTE was increased with return flights compared with outward flights, and with multiple flights. While these observations are intuitively obvious, they do serve to indicate that the duration of air travel is an important factor contributing to the risk of VTE.

One of the implications from these observations is that caution is required in interpreting studies of the role of travel in the development of VTE from countries in which long distance air travel is relatively uncommon. This is illustrated in the meta-analysis of the association between travel and the risk of symptomatic VTE from the Netherlands [116]. In the three case-control studies included in the meta-analysis only 7% of all subjects had travelled over 3 hours (including air, car, bus, train and boat travel), with only 1.5% having travelled over 10 hours.

We reported the duration between the air flight and the presentation to hospital, rather than the onset of symptoms. This approach was followed as the initial symptoms are often not recognised by the patient and may be variably reported to the admitting doctor. We observed that just over one-third of subjects presented more than one week after their return flights is also consistent with a previous study from Hawaii in which one third of subjects with a VTE developed symptoms more than one week after their travel [111]. Similarly, a recent study from Australia has shown that there is a 2.6-fold increased risk of hospital admission with VTE in the second week after a single international flight, relative to a non-flyer of the same age [224]. These findings suggest that those studies that do not have follow-up for prolonged periods after the return flight may underestimate the incidence of VTE associated with air travel. It also suggests that awareness is required of the development of symptoms suggestive of DVT or PE in those following long distance air travel, and that one to four weeks afterwards does not rule out travel as a relevant risk factor, contributing to the determination of the clinical probability of the VTE event.

These findings are consistent with the observations from the NZATT study in that most individuals who suffer a VTE following air travel do not have a pre-existing risk factor that is identifiable prior to travel. Similarly, other studies have observed that this form VTE may occur in previously fit individuals who would not be considered to be at risk of VTE many of whom are young. This has implications in terms of preventive strategies in which low cost-
effective measures undertaken by the general travelling population would be recommended, rather than a focused approach just on high risk individuals.

We conclude that long distance air travel is an important risk factor for VTE requiring hospital admission and represents a significant public health problem in New Zealand.
Chapter 10

Subsequent Studies

Since the time period in which NZATT study was undertaken, several further studies have been completed. These studies are summarised below:

The BEST study, conducted by Jacobsen et al, recruited 898 passengers undertaking travel from London Heathrow Airport to Johannesburg International Airport, a flight of eleven hours duration [225]. All subjects with an identifiable predisposition to VTE were excluded. The intention of the study was to perform D-dimer measurement (IL-Test D-dimer assay) before and immediately after flight in combination with CUS to determine the incidence of DVT. Specimens were also obtained to undertake thrombophilia assessment. Unfortunately, 353 of the 844 pre-flight D-dimer specimens obtained became “activated” during transportation, and complete analysis was not possible. Despite this, in seven percent of the passengers with paired samples, the D-dimer was elevated following the flight. Regression analysis showed significant associations with the presence of FVL, aspirin use and hormone replacement therapy in women. There was no difference noted with class of travel or any other investigated risk factor such as smoking, fluid intake, alcohol or sedative use. Four hundred and thirty four subjects (48 percent) underwent CUS, with no subjects showing conclusive evidence of DVT. This represented only 51 percent of those subjects with an elevated D-dimer following flight.

Published at the same time as the NZATT study was a similar study by Schwartz et al in which 964 subjects were evaluated by means of complete CUS before and after a flight of at least 8 hours [226]. The group undertook extensive scanning of the deep veins of the lower limbs, and detected 27 subjects had evidence of new thrombosis (2.8 percent). The majority of these thrombotic events occurred within the calf muscle veins (20 subjects, 2.1 percent), with only seven subjects (0.7 percent) showing extension in to the deep venous system. The mean duration of travel in the VTE population was 10.5 hours. Eight nine percent of the VTE events were asymptomatic. Pulmonary embolism was diagnosed in one passenger with DVT on the basis of suggestive symptoms. The study also included a age and sex matched population of 1213 control subjects, and found the overall odds ratio of VTE associated with air travel to be 2.83, and with DVT of 4.4. The study did not include formal assessment for PE in the absence of symptoms, and only 11 subjects (41 percent) had an increase in D-dimer
(assay no stated) in association with these events. The cohort was followed for four weeks following travel, with no further events noted.

Also published in the same journal was a study by Martinelli et al, who conducted a case control study of 210 subjects with VTE compared to 210 healthy age and gender matched controls (friends or partners of the cases) [227]. Air travel within the prior three months was reported in 31 cases (15 percent) and 16 controls (8 percent), with an odds ratio of 2.1. In patients using the oral contraceptive who had travelled, the odds ratio was 13.9, and in those with a thrombophilia the odd ratio was 16.1. The authors concluded that on it’s own, air travel was a mild risk factor for VTE, but had a multiplicative interaction with oral contraceptive use and the presence of a thrombophilia.

The MEGA study, a large epidemiological study of symptomatic VTE, has been expanded to include a questionnaire enquiring regarding recent travel. In this case control study, cases were matched with their spouses as controls. Of the 1710 cases included, 217 (12.7 percent) had travelled for four or more hours within the preceding eight weeks. The odds ratio for all travel was 2.9, which increased to 13 in those cases with FVL, ten for those taller than 1.90m and greater than twenty for OCP users. The risks were similar for all modes of travel, except for height less than 1.60 metres, which was associated with an odds ratio of 21 in air travel [228].

The United Kingdom Department of Health commissioned a survey of 1500 passengers about to embark upon a long distance air journey. The primary focus was to examine the intended use of prophylactic measures, with particular reference to aspirin. In this study it was found that 20 percent of long distance travellers took aspirin prior to or during air travel. The use of aspirin was related to the presence of associated risk factors, and was greatest in women aged greater than 55 years who flew infrequently (less than four times in the prior two years). The majority of subjects took aspirin within the three hours prior to flying (89 percent). Nineteen percent intended to take aspirin during the flight, 77% of whom would continue taking a dose every four hours. Nineteen percent also reported that they would undertake further dosing after the flight, 36 percent of whom intended to take the dose at least twelve hours after the flight. The majority of these subjects felt that they were following recommended guidelines, or advice from their Doctor, family or friends [229].
Boccalon et al undertook coagulation testing in thirty healthy male volunteers following an eleven hour in economy class from Toulouse to the Reunion Islands and then back to Paris. Subjects behaviour was not restricted during the flights. There were no statistical differences noted in aPTT, factor VIII, t-PA, D-dimer, fibrinogen, weight or haematocrit. However, an increase in leg circumference by nearly 1cm bilaterally was noted. In this study the levels of factor VIIa, prothrombin fragment F1+2 and thrombin-antithrombin complex actually fell following the flights. The authors concluded that there was no evidence of coagulation activation in their subjects, although further study of “at risk” subjects was necessary [230].

The majority of the subsequent research performed has been under the guidance of the World Health Organisation Research Initiative into the Global Health Risks of Travel (WRIGHT) Project. Phase one of this project, which has been funded by a grant from the United Kingdom Department for Transport and the European Union, has attempted to further investigate the risk of VTE following air travel by three primary means:

1. Epidemiological studies
2. Clinical and physiopathological studies
3. Physiopathological and coagulation studies

Preliminary data from studies of the first two components of this outline are available in abstract and personal communication format.

In the first epidemiological study three multinational corporations were asked to distribute a questionnaire regarding flying habits and VTE events to their employees. A total of 9953 employees received questionnaires with 45 percent responding. Twenty nine VTE events had occurred in relation to 59438 long haul flights (greater than four hours), with an incidence of one per 5944 flights and a relative risk of VTE of 3.45. The relative risk rose to 4.2 if the employee had been exposed to multiple flights within a four week period [231].

A further questionnaire was sent to 3657 current or ex-members of the Dutch Airline Pilot Association, a group heavily exposed to long distance air travel. The response rate in the individuals, the majority of which were male (96 percent), was 68 percent. However, the response rate in ex-members was only 33 percent. The incidence of VTE in this population was 0.3 per 1000 per year. The authors concluded that the risk of VTE was lower in Dutch airline pilots than in the general population, but under-reporting could not be excluded [232].
The “WRIGHT Volunteers Study” prospectively evaluated markers of thrombin activation before and after an eight hour flight in 71 healthy volunteers aged 18 to 40 years. Amongst these individuals were 26 asymptomatic carriers of FVL, and 30 women who were taking an OCP, half of which were FVL carriers. The results of the assessments in flight were compared with two control situations, one being activities of daily living and the other during an “eight hour movie marathon”. There were no differences in factor VIIa, factor VIIc, factor VIIIc, von Willebrand factor antigen, endogenous thrombin potential or activated protein C sensitivity ratio with any of the exposures. However, measurements of the thrombin-antithrombin complex and prothrombin fragments F1+2 showed more marked increases following flight, particularly in eight female individuals. The authors suggested thrombin generation can occur in some individuals after an eight hour flight than could be explained by immobilisation alone. The abstract does not discuss seating position or any exercise restraints undertaken during the exposures [233].

Jones et al have undertaken studies of the effects of hypobaric hypoxia exposure. Seventy three subjects (49 young healthy individuals, 12 OCP users and 12 subjects older than 50 years) were seated in a hypobaric chamber and exposed for eight hours to either normobaric normoxia or hypobaric hypoxia (equivalent to an altitude of 8,000 feet). Subjects were exposed to both conditions in a randomised fashion within a two week period. Extensive testing for markers of prothrombotic and fibrinolytic activity are undertaken. Similarly to previous studies, there were no significant differences noted between the exposures in the young, healthy group. Minor differences in sE-selectin, platelet responsiveness to ADP and leucocyte count were noted in the older group and the oral contraceptive users, although the clinical significance of these changes is uncertain. The authors concluded that there were no significant alterations in haemostatic parameters associated with mild hypobaric hypoxia exposure [234].

In a subgroup of thirty one subjects, thromboelastography and red blood cell count was also performed following the exposures. Thromboelastography is an in-vitro technique that provides a rapid assessment of whole blood haemostasis in a simulated condition of reduced blood flow. Change in shear elasticity enable the determination of clot kinetics, the growth, strength and stability of formed clot. Somewhat paradoxically in this study, clot formation rate and clot firmness increased during normobaric normoxic exposure and decreased in hypobaric hypoxic exposure. There was a small, but statistically significant rise in red blood
cell count during hypobaric hypoxia. The authors concluded that the rate of thrombus formation actually decreased during exposure to the simulated cabin environment [235].
Chapter 11

Summary and Conclusions

The results of NZATT study reinforce the results of previous studies in establishing an association between long distance air travel and VTE. The flights to and from New Zealand undertaken by this low to moderate risk population in this study represent the extreme of exposure to this risk factor, and the incidence of 1.4 percent derived is representative of the maximal risk to the general travelling public. Whilst the absolute risk established by this study, and the relative risk demonstrated by other studies, is apparently low, the heterogeneity and size of the population exposed to this risk factor of a daily basis implies that air travel is a significant independent risk factor for VTE. Although fatal events immediately following travel are very rare [119-121], these highlight the potential for serious long term adverse effects and morbidity as the result of any form of VTE.

The studies performed subsequent to the NZATT study are consistent with its results, and those of earlier studies, regarding the incidence and relative risk of VTE associated with travel. The reported incidence of asymptomatic DVT by Schwartz et al of 0.7 percent is in keeping with the NZATT study, as is incidence of rise in plasma D-dimer reported in the BEST study [225, 236]. The results of the study by Schwartz et al, the WRIGHT Epidemiological Study and the MEGA study confirm the earlier reports by Ferrari et al and ten Wolde et al that suggested that air travel is associated with a two to four fold risk of VTE, particularly in individuals with other underlying risk factors [114, 116, 231, 236].

It is clear the VTE can occur in any individual exposed to this risk factor, regardless of their class of travel. The previous descriptions of “Economy Class Syndrome” or “Coach Class Thrombosis” are misleading, give false reassurance to first and business class passengers, and should therefore be abandoned.

The results of pathophysiological studies performed during exposure to features unique to the aircraft cabin environment suggest that minor changes in haemostatic pathways may be present in some individuals, but play a questionable role in VTE formation [132, 133, 234, 235]. The role of other factors such as transmeridian dyschronism, seat design and in flight behaviour are also unclear. The overriding cause of this phenomenon appears to be the prolonged seated immobility associated with this form of travel. The association with duration
of travel noted by earlier studies, and the relationship with seating position noted in the NZATT study support this [112, 119]. It is clearly evident that VTE can occur in association with other forms of travel, and that the only feature that may differentiate air travel is the duration of exposure to restricted seating. These data strongly supports the suggested use of the term “Seated Immobility Thrombosis” (SIT) to describe this condition as a whole [102].

The data from the NZATT study, the study of patients hospitalised with VTE and subsequently the WRIGHT Volunteers Study are in agreement with the findings in previous studies that travel may be the only identifiable risk factor in patients presenting with symptomatic VTE. Until recently, a history of recent travel has not been routine sought in patients presenting with such events, and it is likely that many such patients will have been labelled as having had an idiopathic event. This has lead to an underestimate of the role of travel and may also have resulted in patients being exposed to more prolonged period of anticoagulation than are necessary.

It is apparent from data from both the NZATT study and that of the UK Department of Health study that many individuals are undertaking prophylactic measures despite the lack of evidence to support their use. Travellers with underlying risk factors for VTE, such as previous VTE, thrombophilia, co-morbidity and hormone use, should consider travel as an additional transient exposure that will further increase their risk of thrombus formation. In “high risk” patients, the provision of prophylactic measures as used to prevent other forms of VTE should be considered on an individual basis.

However, at the present time there is insufficient data to determine more broad evidence based guidelines regarding prophylaxis. Unfortunately the NZATT study was unable to determine the effect of the measures undertaken by the participants. However, it was apparent that several individuals developed evidence of increased thrombotic activity and confirmed VTE despite the use of stockings and / or aspirin. The previous studies conducted by Scurr et al and Belcaro et al showing benefit from stockings and other agents have been criticised methodologically for the clinical significance of the VTE events occurring in the control populations [122, 124, 126, 128, 129]. It is the central focus of the forthcoming WRIGHT-II intervention study to undertake a large randomised controlled trial to establish the role of prophylactic measures, an initiative which should be strongly supported.
This data obtained from the present studies are unique in several areas. This appears to be the first example of the use of serial D-dimer as a screening tool before and after exposure to a transient risk factor for VTE. This provided a reliable, easy and highly sensitive means by which to limit the exposure to imaging and radiation to a minority of subjects included in the study (12.6 percent). This has also resulted in several interesting conclusions regarding the nature of D-dimer in the general population, and its use a screening tool for patients with suspected VTE. In the absence of acute risk factor exposure, the background level of D-dimer present in an individual reflects a marker of basal prothrombotic activity. This in turn is dependant on the intrinsic risk factors, both genetic and acquired, which are present at that time. Therefore, in the absence of another acute factor affecting D-dimer, individuals with an elevated D-dimer level should be considered to be at greater risk for future VTE. This presumption does require further study, and in particular needs to be adjusted for age. However, this has significant potential implications on the current interpretation of D-dimer in patients presented with suspected VTE, where a negative result is useful for excluding VTE, but a positive result is generally discarded.

The co-operation obtained from the Auckland International Airport and the Airlines it services was also unique to this study. In general it has not been in the commercial interests of these organisations to support research that may highlight potential hazards associated with air travel. Several previous authors have reported that attempts to conduct similar studies in other countries have been unsuccessful due to lack of such co-operation. It should be considered a major success of this study that such support was obtained. Since the time of this study most international carriers have introduced warnings and advice to passengers regarding the risk of VTE during and following air travel.
11.1 Conclusions

1. The incidence of VTE in a population of low to moderate risk travellers undertaking long distance air travel from New Zealand was 1.4 percent. Seventy five percent of cases identified were associated with suggestive symptoms and identifiable risk factors were present in only 58 percent. Air travel is associated with a two to four fold increase in relative risk of VTE.

2. It is unclear whether any environmental conditions specific to air travel, other than prolonged restricted seated immobility, contribute significantly to the risk of VTE. The association with travel in economy class is a misnomer, as is the perception that this condition is unique to air travel.

3. Serial D-dimer measurement provides an effective means by which to screen individuals exposed to a transient risk factor for VTE, such as air travel. Baseline D-dimer levels are related to the presence of underlying risk factors. Following exposure to air travel, D-dimer levels rose in 12.6 percent of subjects and was associated with increasing age, female gender, presence of thrombophilia, non aisle seating position and symptoms suggestive of pulmonary embolism.

4. Use of prophylactic measures during long distance air travel is common despite the lack of evidence based efficacy. Urgent studies are required in order to determine the most effective prophylactic strategies.

5. Travel is a common, often overlooked, risk factor for VTE in New Zealand. It is likely that in the past this has resulted in the over-utilisation of long term anticoagulation in some patients with confirmed VTE, and the under-utilisation of prophylactic measures in high risk individuals.
12. References.


92


137. Lee, T.H., Ask the doctor. One of my neighbors took a long bus trip and then had to be hospitalized for a blood clot. I will be flying to Asia soon. Should I be concerned about this hazard? Harv Heart Lett, 1999. 10(4): p. 8.


228. Cannegieter, S.C., et al., *Travel-related venous thrombosis: Results from a large population-based case control study (MEGA Study).* Personal communication.


APPENDIX 1:

**Suspected Venous Thrombo-embolism Algorithm**

**Suspected Massive PE (Emergency)**
- Acute clinical RHF or
- Acute RBBB on ECG or
- SBP <90 or
- FiO2 > 0.40 required to keep pO2 > 60

**Arragne ICU admission**
Consider Thrombolysis (refer to protocol)
Consider the following investigations
- Echo - thrombolyse if signif. RV dysfunction
- Troponin T
- CT Pulmonary Angiogram if stable

---

**Clinical Suspicion of DVT/PE**

- Onset of symptoms within last 7 days

**D-dimer Assay**

- Positive
  - High clinical probability
    - Suspected DVT
      - Lower Limb Compression U/S
        - Positive
          - Anticoagulate Refer to DVT Clinic
        - Negative
          - Low clinical probability
            - Book repeat U/S within 7 days or consider Venography / MRDTI
          - Moderate – High clinical probability
            - No further investigation
    - Suspected PE
      - CT Pulmonary Angiogram
        - Normal
          - Low - Moderate clinical probability
        - Non-diagnostic
          - Low clinical probability
          - Moderate – High clinical probability
            - Bilateral Lower Limb U/S
              - Negative
                - Low - Moderate clinical probability
              - Positive
                - High clinical probability
                  - Consider Pulmonary Angiography, V/Q Scan or empirical treatment
        - Positive
          - Anticoagulate Refer to DVT +/− Chest Clinic
    - Low - Moderate clinical probability
      - No further investigation

- Negative
  - Low - Mod clinical probability
  - No further investigation

**Notes:**
- Based on highly sensitive D-dimer assay
- Causes of false positive to consider:
  - Chest infection, menstruation
  - Malignancy, recent trauma/surgery
  - Inc age (esp>70), renal impairment
  - Should not be used as substitute for thorough clinical history and examination.

---

**References:**
- Lorut et al. AJRCCM 2000;162: 1413-1418

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1. V/Q scan may be considered instead of CTPA if:
   1. Contra-indication to IV contrast eg allergy, creat >150
   2. The Chest Xray is normal
APPENDIX 2:

Pre-flight Questionnaire

ID:_________

I would like to ask you some questions about your health, as well as measuring and weighing you, and possibly checking for varicose veins. You may refuse to take part in any of these procedures, including refusing to answer any of the questions.

1. Respondent’s name: ___________________ __________________
   FIRST NAME   LAST NAME

2. Date of birth:_______________

3. Record sex:
   Male   Female

4. Do you regularly take any medication?
   Yes   No   → Go to Q7a if female or Q9 if male

5. Do you take aspirin (Dispirin, Cartia or Solprin) daily?
   Yes   No   → Go to Q7a if female or Q9 if male

6. What (other) medications are you currently taking regularly?

<table>
<thead>
<tr>
<th>Name of medication</th>
<th>Dose (mg)</th>
<th>Times each day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
IF MALE GO TO QUESTION 9a.

IF FEMALE AND HRT OR BIRTH CONTROL NOT MENTIONED ABOVE ASK;

7a. Are you on …..

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone replacement therapy?</td>
<td>7b. Which one(s)?_________________________</td>
</tr>
<tr>
<td>Birth control medication?</td>
<td>7c. Which one?__________________________</td>
</tr>
</tbody>
</table>

ASK ALL FEMALES

8a. Have you ever had a miscarriage?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>8b. How many times have you miscarried?</td>
<td></td>
</tr>
</tbody>
</table>

ALL RESPONDENTS

9. Have you had any of the following health problems?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease e.g. angina or heart attack</td>
<td></td>
</tr>
<tr>
<td>Stroke or mini stroke</td>
<td></td>
</tr>
<tr>
<td>Poor circulation to the legs</td>
<td></td>
</tr>
<tr>
<td>Chronic lung disease e.g. emphysema</td>
<td></td>
</tr>
</tbody>
</table>

10a. Are you aware of any relatives who have had a clot in their leg or lung?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>10b. What relationship are/were they to you? Tick all that apply.</td>
<td></td>
</tr>
<tr>
<td>Sister</td>
<td></td>
</tr>
<tr>
<td>Brother</td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td></td>
</tr>
<tr>
<td>Daughter</td>
<td></td>
</tr>
<tr>
<td>Son</td>
<td></td>
</tr>
<tr>
<td>Other (please describe)</td>
<td></td>
</tr>
<tr>
<td>___________________________</td>
<td>___________________________</td>
</tr>
</tbody>
</table>
11a. Are you aware of any advice about how to prevent clots during flying?

   [ ] Yes  [ ] No

11b. What was the advice?

[ ] Yes  [ ] No

12a. Which of these best describes your smoking habits? READ OUT.

   [ ] I smoke every day
   [ ] I smoke but not every day
   [ ] I used to smoke
   [ ] I have never smoked

12b. How long ago did you give up? [ ] Yrs

13a. In the last 4 weeks have you travelled in a train, car or plane for 4 hours or more at one time?

   [ ] Yes  [ ] No

13b. How many different trips of more than 4 hours have you made?

13c. How many weeks ago was the most recent trip?

14a. Between now and when you leave New Zealand, do you plan to travel in a train, car or plane for 4 hours or more at one time?

   [ ] Yes  [ ] No

14b. How many different trips of more than 4 hours did you make?

14c. How long before leaving NZ was the most recent trip? [ ] weeks

15a. In the last 4 weeks have you knocked or injured your leg?

   [ ] Yes  [ ] No

15b. Can you describe what happened please?

16a. In the last 4 weeks have you spent more than a day in bed due to illness or injury?

   [ ] Yes  [ ] No

16b. FOR EACH SPELL IN BED ASK What was the reason?

16c. FOR EACH SPELL IN BED ASK. How many days were you in bed for?
17a. Do you have varicose veins, that is veins on your legs that are raised and lumpy? **IF THE RESPONDENT ANSWERS YES THEN ASK TO CHECK THEM.**

Yes [ ]  
No [ ]  
Don’t know [ ]

17b. At what age were you first aware of them (in years)?

**18. Name of respondent’s GP:** ____________________________

 **Practice:** ____________________________

 **Address:** ____________________________

**19. Record date of departure from New Zealand** __________/________/________

**20. Record date of return to New Zealand** __________/________/________

 **Flight Number (if known):** ________________

**21. Make an appointment for 1st return visit.** __________/________/________

 **Time:** ________________

**22. Contact Phone number on return:** _(____)_______________

 **Field worker initials:** ________________

 **Today’s date:** __________/________/________

**23. Measure height and weight:**

 **Height:** ________________  
feet  inches  metres  cms

 **Weight:** ________________  
stones  lbs  kgs

**24. Make a copy of the respondent’s itinerary if available.**

**Thank you for your help with this study**
APPENDIX 3a:

Post flight health questionnaire I

Your name: ___________________________ Id: __________

First name           Last name

1a. Since leaving New Zealand did you develop any of the following symptoms during or after flying?

1b. FOR EACH SYMPTOM NOTICED ASK (EXCEPT COLDS AND CHEST INFECTIONS): Have you noticed having this [SYMPTOM] at any time before this trip away?

<table>
<thead>
<tr>
<th>Q 1a</th>
<th>Q 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Swelling of the calves or thighs

Ache or pain in the legs
Redness of the legs
Hardness of the legs
Shortness of breath
Chest pain or discomfort
Coughing up blood
Cold or chest infection

1c. Have you taken antibiotics for this infection?
Yes No

IF NO SYMPTOMS NOTICED THEN GO TO QUESTION 3A

2a. Did it first occur during that flight or after that flight?

2b. How long after the flight did you first notice the symptom?

<table>
<thead>
<tr>
<th>Swelling of the calves or thighs</th>
<th>Q 2a From:</th>
<th>To:</th>
<th>2b. During or after flight?</th>
<th>2c How long after? Record hours/days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ache or pain in the legs</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Redness of the legs</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hardness of the legs</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Shortness of breath</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain or discomfort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughing up blood</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cold or chest infection</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
3a. Other than medication that you take regularly, did you take any medication within 2 days of landing at any port? Include aspirin or other pain-killers, sleeping pills and any other medication that you do not take regularly.

No  [ ]  Go to question 4a

Yes  [ ]  Complete table below

3b. After which flights did you take this medication?

<table>
<thead>
<tr>
<th>From: (name city)</th>
<th>To: (name city)</th>
<th>What medication did you take?</th>
<th>How many tablets did you take?</th>
<th>Dose (mg)/per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

4a. Other than the flights that you have answered questions about already, while you were away did you travel in a plane, car or train for 4 hours or more on one trip?

Yes  [ ]

4b. How many different trips of 4 hours or more did you make?

No  [ ]

5a. While you were away did you knock or injure your leg at all?

Yes  [ ]  5b. Can you describe what happened please?

No  [ ]

6. How many days ago did you arrive back in New Zealand?  [ ] Hrs/Days

7. Which ethnic group do you belong to? You may give more than one group.

NZ European/Pakeha  [ ]

Maori  [ ]

Pacific Island group  [ ]

Other  [ ]  Specify:_____________________________

Thank you for your participation. Please have the final blood test performed in 10 to 14 days time.
APPENDIX 3b:
Post flight clinical assessment

(Complete for study participants reporting any symptoms as listed in Questions 1 & 2, with the exception of ‘Cold or chest infection’).

Your name: __________________________  __________________________  ID: __________

Preflight d-dimer: ________________  Preflight Creatinine: ________________

Pulse: ________  Blood pressure: ________/_______  Respiratory rate: ________

Chest exam:

Leg examination:  

(R)  Calf Circumference: _____  _____

(L)  (10cm below tibial tuberosity)

Evidence of possible alternative diagnosis?

WELLS SCORE

<table>
<thead>
<tr>
<th>Suspected DVT</th>
<th>Points</th>
<th>Suspected PE</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immobility in previous 4 weeks</td>
<td>1.0</td>
<td>Immobility in previous 4 weeks</td>
<td>1.0</td>
</tr>
<tr>
<td>Localised tenderness along the distribution of the deep venous system</td>
<td>1.0</td>
<td>Clinical symptoms/signs of DVT (minimum of swelling + pain on palpation)</td>
<td>3.0</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1.0</td>
<td>Haemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Asymmetrical calf swelling &gt; 3cm</td>
<td>1.0</td>
<td>Heart rate &gt; 100</td>
<td>1.0</td>
</tr>
<tr>
<td>Asymmetrical pitting oedema</td>
<td>1.0</td>
<td>Alternative diagnosis less likely than PE</td>
<td>3.0</td>
</tr>
<tr>
<td>Collateral superficial veins (non-varicose)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative diagnosis more likely than DVT</td>
<td>-2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>TOTAL</td>
<td></td>
</tr>
</tbody>
</table>

Clinical probability of DVT:

- low-moderate (10-21%)  □  1 - 2
- high (76%)             □  > 2

Clinical probability of PE:

- low (2%)               □  < 2
- moderate (19%)         □  2 - 6
- high (50%)             □  > 6

Low-moderate probability:  await D-dimer result
High probability:         arrange further investigations (USS or CTPA)
APPENDIX 4:
Post flight health questionnaire II

Your name: ___________________    ___________________  ID: ____________

First name  Last name  Time since return

1a. Since returning to New Zealand have you developed any of the following symptoms?

1b. FOR EACH SYMPTOM NOTICED ASK (EXCEPT COLDS AND CHEST INFECTIONS): Have you noticed having this [SYMPTOM] at any time before this trip away?

<table>
<thead>
<tr>
<th>Q 1a</th>
<th>Q 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Swelling of the calves or thighs</td>
<td>Ache or pain in the legs</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1c. Did you have any other tests done as a result?

Yes  No

Result

IF NO SYMPTOMS NOTICED THEN GO TO QUESTION 3

2  How long after the flight home did you first notice the symptom?

Swelling of the calves or thighs  Ache or pain in the legs  Redness of the legs  Hardness of the legs  Shortness of breath  Chest pain or discomfort  Coughing up blood

Days

Did you consult a Doctor regarding any of these?

Yes  No

Result

3. Have you been on any other journeys for longer than 4 hours since your last visit?

Number
APPENDIX 5: In-flight Questionnaire

Your name: ___________________________ ID: ________________________

FIRST NAME LAST NAME

1. Flight between _______________________ and ________________________

2. Do you take aspirin on a daily basis?
   £ No ⇐ Go to question 4
   £ Yes

3. Did you remember to take your aspirin on the day of this flight?
   £ No
   £ Yes ⇐ Complete table below

4. Other than medication that you take regularly, did you take any medication up to 3 days before this leg of your flight? Include aspirin or other painkillers, sleeping pills and any other medication that you do not take regularly.
   £ No ⇐ Go to question 5
   £ Yes ⇐ Complete table below

<table>
<thead>
<tr>
<th>How long before flying did you take it (days/hours)?</th>
<th>What medication did you take?</th>
<th>How many tablets did you take?</th>
<th>Dose (mg) per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Other than medication that you take regularly, did you take any medication during this leg of your flight? Include aspirin or other painkillers, sleeping pills and any other medication that you do not take regularly.
   £ No ⇐ Go to question 6 on the back of this page
   £ Yes ⇐ Complete table below

<table>
<thead>
<tr>
<th>What medication did you take?</th>
<th>How many tablets did you take?</th>
<th>Dose (mg) per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. Did you get up and walk down the aisle during this flight?
   £ No
   £ Yes ⇐ Approximately how many times? __________

7. Did you carry out any stretching exercises of your legs while seated?
   £ No
   £ Yes ⇐ Regularly
   £ Yes ⇐ Occasionally

8. How many glasses or cups of each of these did you drink…….

<table>
<thead>
<tr>
<th>Within 2 hours of boarding?</th>
<th>On board this flight?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tea / Coffee cups</td>
<td>cups</td>
</tr>
<tr>
<td>Coca Cola / Pepsi glasses</td>
<td>glasses</td>
</tr>
<tr>
<td>Other non-alcoholic e.g. water, juice glasses</td>
<td>glasses</td>
</tr>
<tr>
<td>*Alcohol glasses</td>
<td>glasses</td>
</tr>
</tbody>
</table>

*Please count ½ pint of beer or one small glass of wine or spirits as 1 glass.

9. Did you sleep at all during this leg of your flight?
   £ No
   £ Yes ⇐ For approximately how long? __________ Hours

10. Did you lie down flat, or sit in an aisle, middle or window seat (most of the time)?
    £ Lie down
    £ Aisle
    £ Middle
    £ Window

11. Was this: a seat behind a bulkhead (a partition separating compartments)?
    £ No
    £ Yes

12. Was this seat in an emergency row?
    £ No
    £ Yes

13. Was there a free seat beside you (most of the time)?
    £ No
    £ Yes

14. Were you wearing surgical stockings on this flight?
    £ No
    £ Yes