Incidence of Deep Vein Thrombosis in the Lower Extremity

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A thesis submitted in partial fulfilment
of the requirements for the degree of Master of Philosophy

Faculty of Health and Medicine
Department of Surgery
The University of Sydney

2020
Statement of Authentication

This thesis is submitted to the University of Sydney in fulfilment of Master of Philosophy in Medicine degree. The work presented in this thesis is, to the best of my knowledge and belief, original except where acknowledged in the text. I hereby declare that I have not submitted this material, either in full or part, for a degree at this or any other institution.

Anna Sophia de Wet

Date: 01/02/2020
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I am eternally grateful to my Creator † for blessing me and providing me the opportunity to do this research.
Presentations and Publications arising from this Work

- PhD Presentation VTE 21 November 2018 at Sydney University: Venous Thromboembolism, Pathophysiology, Risk and Preventative Strategies.


Abstract

Venous thromboembolism (VTE) encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE).\textsuperscript{1,2} Factors such as venous stasis, vascular injury, hypercoagulability and major orthopaedic surgery such as hip/ knee replacement or hip fracture surgery increases the risk for thrombosis. Currently there is limited information on the incidence and risk of VTE following ankle fracture surgery and the economic impact on the use of prophylaxis for the prevention of VTE in these patients.

Chapter one of this thesis provides a comprehensive literature review highlighting the epidemiology, risk factors, prophylactic modalities used and complications in both medical and surgical patients for the prevention of VTE. Chapter two is a retrospective study that examines this area, in particular, practice patterns in VTE prevention both in-hospital and beyond hospitalisation following ankle fracture surgery. These results showed that most of these patients received low molecular weight heparin (LMWH) and that the overall in-hospital VTE incidence was 2.9\% (95\% CI: 1.3 - 4.4). There was a 1.5-fold increase risk of VTE at three months post hospitalisation (4.3\% (95\% CI: 2.3 -6.2), bleeding rates were low and there were no major complications. This led to a systematic literature review for chapter three evaluating the economic impact with use of pharmacological prophylaxis in major orthopaedic surgery for VTE prevention as well as complications and treatment costs. These results highlighted economic benefits with the use of LMWH compared to difference in healthcare systems.

The first two chapters emphasise the importance of immobility for the risk of thrombosis. This is discussed in chapter four together with a summary of the main findings, gaps and future directions. The need to explore the importance of immobility on DVT risk led to a protocol
development and ethics approval for the evaluation of the rates of DVT in diabetic foot ulcer patients with total contact casts.
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<td>ACCP</td>
<td>American College of Chest Physicians</td>
</tr>
<tr>
<td>ACP</td>
<td>American College of Physicians</td>
</tr>
<tr>
<td>AES</td>
<td>Anti-Embolic Stockings</td>
</tr>
<tr>
<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
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<tr>
<td>AIS</td>
<td>Abbreviated Injury Scale</td>
</tr>
<tr>
<td>AML</td>
<td>Acute Myeloid Leukaemia</td>
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<tr>
<td>AOFAS</td>
<td>American Orthopaedic Foot and Ankle Society</td>
</tr>
<tr>
<td>APC</td>
<td>Activated Protein C</td>
</tr>
<tr>
<td>aPL</td>
<td>Antiphospholipid antibodies</td>
</tr>
<tr>
<td>APS</td>
<td>Antiphospholipid syndrome</td>
</tr>
<tr>
<td>ASA Score</td>
<td>American Society of Anaesthesiology Score</td>
</tr>
<tr>
<td>AT</td>
<td>Antithrombin</td>
</tr>
<tr>
<td>ATIII</td>
<td>Antithrombin III</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BKR</td>
<td>Bilateral Knee Replacement</td>
</tr>
<tr>
<td>C</td>
<td>Carbon</td>
</tr>
<tr>
<td>CEC</td>
<td>Clinical Excellence Commission</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary Heart Disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CIED</td>
<td>Cardiovascular implantable electronic devices</td>
</tr>
<tr>
<td>CO₂</td>
<td>Carbon Dioxide</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>CrCl</td>
<td>Creatinine Clearance</td>
</tr>
<tr>
<td>CRNMB</td>
<td>Clinically Relevant non-major Bleeding</td>
</tr>
<tr>
<td>CTA</td>
<td>Computed Tomography Angiogram</td>
</tr>
<tr>
<td>CTPA</td>
<td>CT Scan of Chest for Pulmonary Embolism</td>
</tr>
<tr>
<td>CTEPH</td>
<td>Chronic Thromboembolic Pulmonary Hypertension</td>
</tr>
<tr>
<td>CVC</td>
<td>Central Venous Catheters</td>
</tr>
<tr>
<td>CVI</td>
<td>Chronic Venous insufficiency</td>
</tr>
<tr>
<td>CRT</td>
<td>Central Venous Related Thrombosis</td>
</tr>
<tr>
<td>DOACs</td>
<td>Direct Oral Anticoagulants</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep Vein Thrombosis</td>
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<tr>
<td>eGFR</td>
<td>Estimated Glomerular Filtration Rate</td>
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<tr>
<td>ENDORSE</td>
<td>Epidemiologic International Day for the Evaluation of Patients at Risk for VTE in the Acute Hospital Care Setting</td>
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<tr>
<td>ETCO₂</td>
<td>End Tidal Carbon Dioxide</td>
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<tr>
<td>FID</td>
<td>Foot Impulse Devices</td>
</tr>
<tr>
<td>FVL</td>
<td>Factor V Leiden</td>
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<tr>
<td>GATE</td>
<td>Genetic Attributes and Thrombosis Epidemiology</td>
</tr>
<tr>
<td>GCS</td>
<td>Graduate Compression Stockings</td>
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<tr>
<td>HDL</td>
<td>High Density Lipoprotein</td>
</tr>
<tr>
<td>HFS</td>
<td>Hip Fracture Surgery</td>
</tr>
<tr>
<td>HIT</td>
<td>Heparin Induced Thrombocytopenia</td>
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<td>HITIG</td>
<td>Heparin –induced Thrombocytopenia PF4 antibody IgG</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
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<tr>
<td>HREC</td>
<td>Human Research Ethics Committee</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>ICD-10AM</td>
<td>International Statistical Classification of Disease and Related Health Problems. 10th Revision Australian Modification</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IHPA</td>
<td>Independent Hospital Pricing Authority</td>
</tr>
<tr>
<td>IPC</td>
<td>Intermittent Pneumatic Compression</td>
</tr>
<tr>
<td>ISTH</td>
<td>International Society on Thrombosis and Haemostasis</td>
</tr>
<tr>
<td>ISTH-BAT</td>
<td>ISTH Bleeding Assessment Tool</td>
</tr>
<tr>
<td>INR</td>
<td>International Normalised Ratio</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile Range</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low Molecular Weight Heparin</td>
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<tr>
<td>LOS</td>
<td>Length of Stay</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>MOS</td>
<td>Major Orthopaedic Surgery</td>
</tr>
<tr>
<td>MVA</td>
<td>Motor Vehicle Accident</td>
</tr>
<tr>
<td>NNTB</td>
<td>Number Needed to Treat for Beneficial</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Human Medical Research Council</td>
</tr>
<tr>
<td>NICS</td>
<td>National Institute of Clinical Studies</td>
</tr>
<tr>
<td>NOACs</td>
<td>New Oral Anticoagulants</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drugs</td>
</tr>
<tr>
<td>NSW</td>
<td>New South Wales</td>
</tr>
<tr>
<td>O₂</td>
<td>Oxygen</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>ORIF</td>
<td>Open Reduction and Internal Fixation</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>P</td>
<td>The P-value represents the probability of the occurrence of a given event.</td>
</tr>
<tr>
<td>PACE</td>
<td>Pre-Arrest Criteria for Escalation</td>
</tr>
<tr>
<td>PAD</td>
<td>Peripheral Artery Disease</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary Embolism</td>
</tr>
<tr>
<td>PCO₂</td>
<td>Partial Pressure of Carbon Dioxide</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>Partial Pressure of Carbon Dioxide in arterial blood</td>
</tr>
<tr>
<td>PHT</td>
<td>Post Hormonal Therapy</td>
</tr>
<tr>
<td>PO₂</td>
<td>Partial Pressure of Oxygen</td>
</tr>
<tr>
<td>POP</td>
<td>Paris of Plaster</td>
</tr>
<tr>
<td>PPS</td>
<td>Padua Prediction Scores</td>
</tr>
<tr>
<td>PTS</td>
<td>Post–Thrombotic syndrome</td>
</tr>
<tr>
<td>PVR</td>
<td>Pulmonary Vascular Resistance</td>
</tr>
<tr>
<td>RAM</td>
<td>Risk Assessment Models</td>
</tr>
<tr>
<td>RCT</td>
<td>Random Controlled Trail</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>RV</td>
<td>Right Ventricular</td>
</tr>
<tr>
<td>SCI</td>
<td>Spinal Cord Injury</td>
</tr>
<tr>
<td>TCC</td>
<td>Total Contact Cast</td>
</tr>
<tr>
<td>TGs</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>TBI</td>
<td>Traumatic Brain Injury</td>
</tr>
<tr>
<td>iTBI</td>
<td>Isolated Traumatic Brain Injury</td>
</tr>
<tr>
<td>TFPI</td>
<td>Tissue Factor Pathways Inhibitor</td>
</tr>
<tr>
<td>THR</td>
<td>Total Hip Replacement</td>
</tr>
<tr>
<td>TKR</td>
<td>Total Knee Replacement</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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</tr>
<tr>
<td>UH</td>
<td>Unfractionated Heparin</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>VFP</td>
<td>Venous Foot Pump</td>
</tr>
<tr>
<td>VSL</td>
<td>Value of Statistical Life</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous Thromboembolism</td>
</tr>
<tr>
<td>vWF</td>
<td>von Willebrand Factor</td>
</tr>
<tr>
<td>VQ Scan</td>
<td>Ventilation Perfusion Scan</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>WSLHD</td>
<td>Western Sydney Local Health District</td>
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CHAPTER ONE: General Introduction

1.1 Venous Thrombosis Embolism (VTE)

Venous thromboembolism (VTE) encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE). A thrombus could be any solid mass that forms within a blood vessel, comprised of fibrin and platelets with some trapped white and red blood cells, or any intravascular material, amniotic fluid, tumour, fat or obstruction that leads to the occlusion of the deep veins of the legs, pelvis, or arms. An embolus migrates from its original location to occlude a distal vessel. The condition where an embolus clots the deep veins of the leg, groin, or arm, is called a DVT. A PE is when a DVT breaks loose and travels through the blood circulation to lodge itself in the pulmonary arterial circulation of the lung. PE is usually caused by a DVT that was formed in the deep veins of the legs. VTE (DVT and PE) is an often unrecognised and a major cause in mortality and morbidity of hospitalised patients. VTE also contributes to longer hospital stays and is a very common complication among hospital inpatients and outpatients. Some VTE events may be subclinical, whereas others present as symptomatic DVT or sudden PE or even as unexpected fatal PE.

DVT typically develops in the lower extremities. It originates in the cusps of the calf vein valves and particularly in the soleus sinusoids, and can be either symptomatic or asymptomatic. As venous valves are avascular, the endothelium is predisposed to hypoxia, especially in concurrence with the already reduced flow of oxygenated blood in the veins. To attract leukocytes, adhesion molecules get excreted by the endothelium. Leukocytes transfer tissue factor to the endothelium, they begin the coagulation cascade with activated factor VII via the extrinsic pathway. Asymptomatic DVT is estimated to be five to 20-fold more common than symptomatic DVT. Asymptomatic DVT is of uncertain clinical significance and it often resolves spontaneously.
Historically, Rudolph Virchow was the first person to associate the link of risk factors to the development of VTE. The three conditions, including venous stasis, vascular injury, and/or hypercoagulability are collectively called the Virchow triad. Prolonged immobility, bed confinement and trauma to lower limb normally cause venous stasis and abnormal blood flow, leading to a DVT. The delicate haemostatic balance can be altered by any of the three conditions and that can lead to the forming of thrombosis. The pathophysiology of DVT includes swelling of the affected limb. DVT also presents with various other signs and symptoms in the lower limb (see Table 1.1).

Table 1.1 Signs and Symptoms of DVT and PE

<table>
<thead>
<tr>
<th>Signs and Symptoms of VTE</th>
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<tbody>
<tr>
<td><strong>Deep Vein Thrombosis (DVT)</strong></td>
<td><strong>Pulmonary Embolism (PE)</strong></td>
</tr>
<tr>
<td>Pain or tenderness, often starting in the calf</td>
<td>Unexplained shortness of breath</td>
</tr>
<tr>
<td>Swelling of the calf</td>
<td>Rapid breathing</td>
</tr>
<tr>
<td>Swelling, including the ankle and foot</td>
<td>Chest pain (may be worse upon deep breath)</td>
</tr>
<tr>
<td>Redness or noticeable discoloration of skin</td>
<td>Rapid heart rate</td>
</tr>
<tr>
<td>Warmth of skin to touch</td>
<td>Light headedness or passing out</td>
</tr>
</tbody>
</table>
The aggregate amount of DVT that arises in the lower limb accounts for 96% of all DVTs and only 4% of DVTs arise in the upper limbs. Patients with below knee injuries have a 10 to 40% risk of asymptomatic DVT. Most distal calf DVTs are usually asymptomatic and are not considered to normally lead to a fatal PE. Over 80% of DVT’s that are diagnosed are located distally. Of those diagnosed DVT’s, approximately 10 to 20% will extend proximally and 1% to 5% advance into developing fatal PE. Approximately 20% of untreated asymptomatic calf DVT and 20% to 30% of untreated symptomatic calf DVT’s extend into the popliteal vein. When proximal propagation occurs, it is associated with a 40% to 50% risk of clinically evident PE.

Postoperative DVT usually starts in the calf or, less commonly at the site of the venous trauma (endothelial injury). In the absence of treatment, postoperative calf vein thrombosis propagates and becomes proximal to the knee within a week in about 30% of patients. Only 12% of symptomatic DVT involving the calf veins stay distal to the knee. Approximately 88% of symptomatic DVT propagate past the knee and involve the proximal veins. Appropriate antithrombotic measures can reduce this complication. Proximal DVT are normally symptomatic and are bound to embolise and cause a fatal PE. A proximal lower-extremity DVT is linked to an estimated 50% risk of PE if not treated. As much as 10% of proximal DVT’s embolise fatally or massively. It is important to consider that postoperative DVT of the lower limb is often asymptomatic, and that fatal PE is the first clinical manifestation of postoperative VTE in patients.

The diagnosis of DVT requires confirmatory laboratory tests, such as duplex ultrasound imaging or contrast phlebography (venography), because up to 50% of patients with DVT will be asymptomatic. Ultrasonic doppler and venographic techniques have shown DVT of the
lower limb to occur in half of all major lower limb orthopaedic operations performed without antithrombotic prophylaxis. DVT of the lower limb is also seen in a quarter of patients with acute myocardial infarction (MI), and more than half of patients with acute ischaemic stroke\(^3\). Ischaemic stroke is a rare but additional DVT complication, occurring when a paradoxical embolus enters the brain through a patent foramen ovale.\(^{17}\) Depending on the location of the clot, the ischaemic stroke may lead to permanent physical limitations, disability or death.

In the long term a DVT may lead to phlegmasia alba dolens (white swollen leg) or phlegmasia cerulean dolens (blue swollen leg), venous insufficiency and the post-thrombotic syndrome (PTS) with consequent venous ulcerations.\(^{17}\) Chronic venous insufficiency (CVI) and PTS develop in 20 to 50% of lower extremity DVT, irrespective of the initial site of thrombosis.\(^{18}\) After about 5 years, 28% of patients with previous symptomatic DVTs will have developed PTS.\(^9\) About a third of all VTE patients experience a recurrence within 10 years of the initial event, with the highest risk occurring in the first year, yet the patient remains at risk throughout their lives. One third to one half of lower extremity DVT patients will develop PTS and CVI, lifelong conditions characterised by pain, swelling, skin necrosis and ulcerations.\(^2\)

Patients have a 6-fold higher risk of developing PTS if they had ipsilateral recurrent venous thrombosis. PTS features clinically with limb pain, leg oedema, and other signs of venous insufficiency. The symptoms may be relieved with rest and leg elevation.\(^5\) Unresolved thrombi start retracting within days, whilst inflammatory cells infiltrate and remodel the thrombi. The vessel wall incorporates the residual clot and forms a layer of endothelial cells on top. This causes scarring of the blood vessel wall, but some blood flow then resumes, however it destroys the vein valves along the length of the clot. These haemodynamic changes to the vein are a major cause of PTS. Residual clots, venous scarring and venous reflux caused by valve
destruction are also factors that play a role in PTS. The skin of the lower calf half may present with pigmentation, induration and even ulceration. Ulceration typically occurs in the region of the medial malleolus. If venous hypertension obstructs arterial inflow, it can cause occlusion of the capillary system and thus venous gangrene may set in. To prevent this sequela, proper and adequate anticoagulation needs to be prescribed to prevent VTE recurrence. To improve venous return patients should also be prescribed graduated compression stockings (GCS).

PE’s pathophysiology comprises of a proximal DVT propagating past the knee, ascending up the inferior vena cava and then on to the right side of the heart and chest where it lodges in the pulmonary vasculature. Small emboli will lodge in the smaller peripheral vessels, triggering partial perfusion distally to the emboli. This could lead to bronchoconstriction and collapse of part of the lung (atelectasis). This produces low oxygen (hypoxemia) in the artery and leads to reduced carbon dioxide in the blood (hypocapnia).

In a normal lung, oxygen, and carbon dioxide transfer efficiently across the lung. An acute PE blocks an artery (small or big) and then the PE impairs the competent transfer obstructed blood flow in the embolised arteries. A common gas exchange abnormality that occurs is a decreased arterial partial pressure of oxygen (pO₂) (hypoxemia) and an increase in the alveolar-arterial oxygen tension gradient. This abnormal gas exchange increases the total dead space in the lungs. An increase in dead space has a direct effect on end-tidal carbon dioxide pressure (EtCO₂) and on partial pressure of carbon dioxide (pCO₂). This causes mismatched ventilation and perfusion, with blood from congested pulmonary arteries redirected to other gas exchange units. Circulation of oxygen rich blood may be disturbed by the possibility of shunting venous blood into system, carrying no oxygen and thus too much pCO₂.
Ventilation and perfusion (V/Q) are well matched in normal lungs. The ratio of blood flow to the pulmonary capillaries and the ratio of ventilation to the gas exchange structures is circa 1.0. The perfusion ratio of ventilation falls to -1.0 when the transfer of carbon (C) is impaired due to the reduced relative blood flow (i.e. low V/Q units), which occurs as the alveolar ventilation to pulmonary capillaries is reduced. When the ratio of ventilation to perfusion falls to -1.0 the transfer of oxygen (O\textsubscript{2}) is also impaired.\textsuperscript{19} Once there is no ventilation to perfuse lung units, right-to-left shunting occurs. This also occurs when venous blood bypasses the lungs. Notwithstanding reduced or non-existent perfusion, total dead space increases because lung units continue to be ventilated in patients with acute PE. Total dead space in the lungs increases in acute PE, because lung units continue to ventilate despite reduced or absent perfusion.\textsuperscript{19} The efficient elimination of CO\textsubscript{2} is also impaired by this.\textsuperscript{19}

When any increase in arterial pCO\textsubscript{2} is sensed by the medullary chemoreceptors, the chemoreceptors will lower the arterial pCO\textsubscript{2} to normal and often below normal, by increasing the total minute ventilation. Due to of an increased total minute ventilation, lower than normal arterial pCO\textsubscript{2} and respiratory alkalosis will be present in most patients with PE. Thus, in patients with an acute PE, a massive embolism would present with hypercapnia and also a huge increase in both anatomic and physiological dead space. Ventilator muscles are unable to sustain the marked increase of minute ventilation needed to maintain normal partial pressure of carbon dioxide in arterial blood (paCO\textsubscript{2}), thus the alveolar volume of each tidal breath is severely reduced.\textsuperscript{19}

Large emboli cause mechanical obstruction of large central vessels, which leads to vasoconstriction. The outcome of this is high pulmonary resistance or hypertension which leads to right heart overload. If the obstruction of the emboli is substantial, blood flow to the left of
the heart is compromised and leads to shock and heart failure. Large untreated PE’s will trigger death, because acute pressure increases in the right ventricle (RV) will cause RV failure.\textsuperscript{19,21} Patients surviving massive PE’s have a 15% to 18% mortality rate within three months of the initial event.\textsuperscript{22}

A non-fatal PE may lead to chronic thromboembolic pulmonary hypertension (CTEPH).\textsuperscript{23} CTEPH was once considered as a rare condition, but what has become evident, conversely, is that the number of patients suffering from this condition has been obviously underestimated.\textsuperscript{23} It is now estimated that 3.8% of acute PE patients develop CTEPH within two years. This is an extremely high risk for patients who have a history of previous PE with an odds ratio (OR) of 19.0.\textsuperscript{22} Such patients present with deteriorating dyspnoea on exertion. Previous PE is a significant cause of severe pulmonary hypertension, and as such is closely associated with significant morbidity and mortality. The quality of life is greatly reduced in such patients.\textsuperscript{22} The pathophysiology of CTEPH is characterised by the massive flow resistance through the pulmonary arteries, caused initially from PE of the arterial vessels and thus subsequently vascular remodelling in small unobstructed vessels. The clinical course of CTEPH is characterised by increasing pulmonary vascular resistance (PVR). RV dysfunction and PVR will cause death in this condition if left untreated.\textsuperscript{23}

PE is a dramatic and life-threatening impediment following a DVT event. Consequently, the prevention, diagnosis, and treatment of DVT is of utmost importance, given that 90% of all PE events result from DVT. Of this 70% are caused by asymptomatic and 30% caused by symptomatic DVT.\textsuperscript{21} Symptomatic proximal lower limb DVT’s are of particular concern, as 50% of these become asymptomatic PE’s. If asymptomatic episodes are also included, it is estimated that 50-60% of DVT patients develop PE.\textsuperscript{23} A study by Martin et al. (2008) showed
that all clinical fatal PE or massive PE occur in the presence of proximal DVT. Results from Beckman et al. in 2010 showed that 10% to 30% of all patients suffered mortality within 30 days. The majority of deaths occurred among those with PE, as an estimated 20% to 25% of all PE cases presented as sudden death. Findings from Moser et al. in 1994 showed that VTE is one entity and that patients admitted with DVT should merit a lung scan as part of the initial evaluation to detect possible PE. Therefore, all patients presenting with DVT should be evaluated with ultrasound of the effected limb and computed tomography (CT) scan of chest for PE, called a computed tomography pulmonary angiogram (CTPA), to uncover any PE’s and all patients presenting with PE should be evaluated with both CTPA and ultrasound of the limbs to detect DVT. To date, CTPA scanning has become the preferred imaging modality for the detection of PE.

1.2 Epidemiology of VTE

There is no current national or worldwide surveillance for VTE, therefore accurate numbers for people affected by VTE are unavailable. A study by White et al. in 2003 performed in the USA claimed that the first-time incidence of VTE is around 100 per 100,000 people every year. The rates of VTE differ by gender, age and type of ethnicity. For example, for a younger population the VTE rate is estimated to be 1 in 100,000, and for older people over 80 years of age, it is 1 per 100 people. The rate of VTE is slightly higher in males than females, however females have a slightly increased incidence rate of VTE during their reproductive years. The estimated overall annual incidence of VTE in the United States is approximately 1 to 2 per 1,000 people and as many as 900,000 are affected by VTE. Currently it is estimated that between 60,000 to 100,000 individuals die each year in the United States as a result of DVT and/or PE.
Worldwide the World Health Organisation (WHO) estimated between 0.75 to 2.69 per 1,000 individuals per year are at risk of VTE. Younger people’s first-time incidence of VTE is less than 5 people per 100,000 however this rises exponentially to around 500 people per 100,000 for first-time incidence for those older than 80 years of age. A large study by Heit et al. across 30 years found the VTE overall incidence, including recurrent events, to be approximately 199.7 per 100,000 person-years. The incidence of DVT was three times higher than that of PE with a PE to DVT ratio of 1 to 3. This is similar to work by White et al. who also showed a PE to DVT ratio of 1 to 2. Two thirds of VTE patients manifest with DVT and one third with PE. Worldwide the reported yearly death toll of VTE is approximately 300,000 with most of these attributed to PE.

Ageno et al. calculated the cumulative probability of experiencing a first VTE event at different ages. The probability was 0.5% at age 50 years, 2.0% at age 60 years, 8.2% at age 75 years and 10.7% by 80 years of age. Cushman et al. found that the first-time rate of VTE incidence for people of 45 years of age and older was 192 per 100,000 person-years and that men had higher rates than women. This study showed that the rate in both sexes increased with age.

In Australia, it is estimated that VTE leads to the hospitalisation of over 30,000 people every year. VTE causes the death of an estimated 2,000 individuals per year. According to post mortem studies 10% of all hospital deaths in Australia are a direct result of PE. In 2008 in Australia, the estimated VTE cases were 14,716. Here, PE accounted for 8,253 or 56% and DVT for 6,462 or 44% of all VTE cases. In general, PE accounts for 5% to 10% of all hospital associated deaths worldwide and at least one-third of all PE’s have been shown to occur as sudden death. In Australia, a Perth community-based study of VTE by Ho et al. found an incidence of VTE of 0.83(95% CI: 0.69–0.97) per 1000 population per year. This figure was
similar to the incidence of 0.74 per 1000 predicted by the Australian Institute of Health and Welfare drawn from their hospital discharge data.\textsuperscript{32}

1.3 Rates of VTE

VTE is a well-known complication of patients admitted to hospital. All surgical and medical patients may be at risk of developing VTE, leading to increased rates of morbidity and mortality. The absolute risk of DVT in all hospitalised patients is listed in Table 1.2.\textsuperscript{33-35}

Table 1.2 Absolute Risk of DVT in Hospitalised Patients\textsuperscript{33,34}

<table>
<thead>
<tr>
<th>Group of patients</th>
<th>DVT Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical/Medical patients</td>
<td>10 - 26</td>
</tr>
<tr>
<td>Stroke</td>
<td>11-75</td>
</tr>
<tr>
<td>Major gynaecological surgery</td>
<td>15-40</td>
</tr>
<tr>
<td>Major urological surgery</td>
<td>15-40</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>15-40</td>
</tr>
<tr>
<td>General surgery</td>
<td>15-40</td>
</tr>
<tr>
<td>Critical patients</td>
<td>15-80</td>
</tr>
<tr>
<td>Arthroplasty of the hip or knee</td>
<td>40-60</td>
</tr>
<tr>
<td>Major trauma</td>
<td>40-80</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>60-80</td>
</tr>
</tbody>
</table>
For many years routine thromboprophylaxis has been the standard of care for major orthopaedic surgery (MOS)\textsuperscript{36}. Without VTE prophylaxis, the overall incidence of VTE in medical and general surgery hospitalised patients ranges between 10% to 26\%,\textsuperscript{13} compared to 40% to 85% following MOS\textsuperscript{13, 37, 37}. The prevalence of VTE events after different orthopaedic surgery without prophylaxis is shown in Table 1.3.

Table 1.3 Prevalence of VTE after MOS in the Absence of Prophylaxis \textsuperscript{35, 38, 39}

<table>
<thead>
<tr>
<th>Procedure</th>
<th>DVT Total (%)</th>
<th>DVT Proximal (%)</th>
<th>PE Total (%)</th>
<th>PE Fatal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower extremity</td>
<td>20</td>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Knee arthroplasty (TKA)</td>
<td>41 - 85</td>
<td>5 - 22</td>
<td>1.5 - 10</td>
<td>0.1 - 1.7</td>
</tr>
<tr>
<td>Hip arthroplasty (THA)</td>
<td>42 - 57</td>
<td>18 - 36</td>
<td>0.9 - 28</td>
<td>0.1 - 2.0</td>
</tr>
<tr>
<td>Hip fracture (HF)</td>
<td>46 - 60</td>
<td>23 - 30</td>
<td>3 - 11</td>
<td>2.5 - 7.5</td>
</tr>
<tr>
<td>Trauma</td>
<td>58</td>
<td>18</td>
<td>4.8</td>
<td>0.9</td>
</tr>
</tbody>
</table>

The rates of symptomatic VTE in MOS within three months ranges between 1.3\% to 10\%.\textsuperscript{36} Without prophylaxis VTE rates for other orthopaedic procedures such as surgery for ankle fracture is as high as 12.2\%.\textsuperscript{40}
1.4 Aetiology and Risk Factors

Aetiology of VTE is intricate and complex with a multitude of factors, including acquired risk factors (hypercoagulable) and or hereditary factors (thrombophilia).\textsuperscript{41} Acquired risk factors are more associated with an increased VTE risk than hereditary risk factors. It is well known that a variety of patient risk factors play a role in the development of VTE. Identified VTE risk factors are listed in Table 1.4. More research is needed as the presence of one risk factor does not always result in disease status or VTE event, yet multiple risk factors can lead to clot formation and increased risk of thrombosis.
Table 1.4: Identified Risk Factors for VTE

<table>
<thead>
<tr>
<th>Acquired Hypercoagulable</th>
<th>Transient Acquired</th>
<th>Hereditary factors: Thrombophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged over 75 (advanced age)</td>
<td>Previous history of a VTE</td>
<td>Factor V Leiden</td>
</tr>
<tr>
<td>Antiphospholipid Antibodies</td>
<td>Acute medical illness, Nephrotic syndrome, Myeloproliferative disorders, Paroxysmal nocturnal haemoglobinuria</td>
<td>Prothrombin G20210A mutation</td>
</tr>
<tr>
<td>Cancer</td>
<td>Surgery</td>
<td>Protein C deficiency</td>
</tr>
<tr>
<td>Chronic Disease</td>
<td>Any infections, inflammatory bowel disease</td>
<td>Protein S deficiency</td>
</tr>
<tr>
<td>Obesity</td>
<td>Pregnancy and the postpartum period</td>
<td>Activated protein C resistance</td>
</tr>
<tr>
<td>Gender</td>
<td>Oestrogen-containing oral contraception</td>
<td>Anti-thrombin deficiency</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Selective oestrogen receptor modulators</td>
<td>Sickle cell trait</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Bed confinement</td>
<td>Family history</td>
</tr>
<tr>
<td>Smoking</td>
<td>Prolonged immobility</td>
<td>Raised factor VIII levels</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Respiratory failure</td>
<td>Hyperhomocystinemia</td>
</tr>
<tr>
<td>High Cholesterol</td>
<td>Paresis</td>
<td>Hyperfibrinogenemia</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>Hormone Replacement Therapy (HRT)</td>
<td>Hypercoagulability</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Cancer treatment radiotherapy</td>
<td>Varicose veins</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease (COPD)</td>
<td>Cancer treatment chemotherapy</td>
<td>Elevated levels of plasma homocysteine</td>
</tr>
<tr>
<td>Sickle Cell Disease</td>
<td>Central venous catheterisation</td>
<td>Thrombocythemia</td>
</tr>
<tr>
<td>Spinal Cord Injury</td>
<td>Trauma</td>
<td>Polycythaemia rubra vera</td>
</tr>
<tr>
<td>Stroke with Impaired Mobility</td>
<td>Hospitalisation</td>
<td>Paroxysmal nocturnal haemoglobinuria</td>
</tr>
</tbody>
</table>
1.4.1 Age

Age is a strong risk factor and a major cause for both arterial and venous thrombosis. With increasing age, the risk of VTE has an exponential increase for both arterial and venous thrombotic events. Advanced age is characterised by stiffness and dilation of the arteries. This is mainly due to the degeneration of elastic fibres and an increase in calcium and collagen substance. Possible cumulative risk factors of advanced age include the decrease in regular exercise, increasing immobility that results in venous stasis and increasing systemic activation of blood coagulation. Plasma concentrations of some coagulation factors (factors V, VII, VIII, and IX, fibrinogen) increase progressively with age. Likewise, the von Willebrand factor (vWF), a key protein in platelet-vessel wall interactions, increases progressively with age.

Kannel et al. showed with the Framingham study that plasma levels of fibrinogen increased from a mean value of 280 mg/dL in individuals aged 47-54 years to more than 300 mg/dL in those aged 65-79 years, with an increase of 10 mg/dL for each decade of age. As early as 1997 Oger et al. already indicated that an age above 65 years showed an OR of 1.75. For people aged ≥ 70 years the incidence of VTE increased to between 2 and 7 per 1000. Patient risk for developing VTE increases exponentially with age and the severity of the disease. VTE in an older person is more extensive and more frequent. A thirty-year-old patient may display less symptoms for the same size PE than in an 88 year old patient, who might already be suffering from age related heart or lung conditions.

Prevention of VTE is essential in advanced age patients who are at risk of suffering a VTE event. Usually low molecular weight heparin (LMWH) is the choice of anticoagulant for the elderly. According to a study by Bizien et al. for every increase in age per year, the incidence of recurrent VTE increases by 3% (OR=1.03; 95% confidence interval(CI): 1.01-1.05), P<0.001. According to Montagnana et al. the incidence and prevalence of VTE was also
strongly age-related, increasing to nearly 90 fold from <15 to >80 years.\textsuperscript{49} The main triggering factors of VTE in old age is prolonged immobilisation, related to hospitalisation, trauma, surgery, multiple comorbidities and institutionalisation.

\subsection*{1.4.2 Obesity and Height}

Although obesity is a significant risk factor for VTE, the related mechanisms remain unclear. Several studies have shown that obesity is an autonomous and convincing risk factor of VTE. The Body Mass Index (BMI) is usually used as the primary exposure of interest to explore the association between obesity and VTE. BMI indicates the total body fat in adults, but it cannot be used to consider the distribution of adipose tissue in the body.\textsuperscript{50} Various measures of body size and the risk of VTE have been reported, however these results have been inconsistent across genders and various studies.

Similarly, in a large cohort of Danish people, the study found a statistically significant positive connection between VTE and waist circumference in men but not in women. In women only, hip circumference was positively associated with VTE.\textsuperscript{51} Glynn et al. found that a greater BMI was connected with a substantial increase in risk for both manifestations of VTE. Proportionately, higher BMI was more strongly linked with risk of VTE than of either Coronary Heart Disease (CHD) or stroke, and taller men had a significantly increased risk of VTE but a lower risk of CHD.\textsuperscript{52} However, obesity is a strong risk factor for fatal postoperative PE and a study by Stein et al. in 2011 showed that the prevalence of PE in hospitalised patients throughout the United States was higher in obese compared to non-obese patients. The authors found a higher prevalence in obese women, than obese men and the relative risk for PE when comparing obese to non-obese patients was greatest in teenagers and young adults. This relative
risk decreased until patients were older than seventy years of age. Thus the data indicated that obesity is a risk factor for VTE in both men and in women.

A study by Flinterman et al. found a relationship between height and an increased VTE risk. In specific, taller men were at an increased risk of VTE, however not women. For men, a steadily increasing risk of a first venous thrombosis event with higher body height was found, with an up to 3.8-fold increased risk (95% CI: 1.5–9.8) for the tallest men (> 200 cm) compared with subjects with a height of 165–170 cm. This association was less strong for women, with a 1.5-fold higher risk (95% CI: 0.7–3.4) for the tallest women (> 185 cm) compared with the same reference group. For men, a higher risk was also found for the shortest participants (< 155 cm) compared with subjects with a height of 165–170 cm, although numbers were small (OR 3.7; CI: 95 0.6–24.0). The largest risk was found for women of 181–190 cm who were not mobile (hazard ratio (HR) 3.1; CI: 95% 1.6–6.1) compared with mobile women of 161–170 cm. When the study was stratified on gender, they found an increase in risk for both tall men and women.

1.4.3 Gender

Results have shown that VTE risk for men is greater than for women for the first and any recurrent VTE event. This risk is similar between men and women for the first episode of VTE, however men seem to have a 1.5 to 2.5 fold higher risk of recurrent VTE events after anticoagulant treatment is ceased. For both genders with unprovoked VTE, who comprise about a half of all patients with VTE the five year risk of recurrence has been reported to be approximately 20-30%. If the risk is however truly 1.5 to 2.5 fold higher in men than in women, this may warrant consideration of indefinite which may be lifelong anticoagulation in men with unprovoked VTE.
Some studies report that gender is not an independent risk factor of VTE, while others conclude that female gender might be a protective variable.\textsuperscript{49} In 2010, researchers attempted to define the role of gender on the risk for recurrent VTE in all patients and in patients with VTE that was unprovoked or provoked (by non-hormonal factors). There were 2,554 patients with a first VTE episode involved in the analysis.\textsuperscript{64} At the one-year mark, the incidence rate of recurrent VTE was 5.3\% (95\% CI: 4.1-6.7) among women and 9.5\% (95\% CI, 7.9-11.4) among men. At three years, the recurrence rate was 9.1\% (95\% CI, 7.3-11.3) in women and 19.7\% (95\% CI, 16.5-23.4) in men. In the unprovoked cohort, men were more likely to experience recurrence than women (Hazard Ratio(HR)=2.2; 95\% CI, 1.7-2.8).\textsuperscript{64}

1.4.4 Ethnicity

There are genetic disparities and many different lifestyle traits between ethnic groups and the incidence of VTE varies widely. Explanations can include the pervasiveness of obesity, psychosocial stress and socioeconomic status. If a group are of a low standing economic status, it might influence their ability to access medical care. VTE risk has been shown to be higher among Caucasians and African Americans than among Hispanic persons and Asian-Pacific Islanders.\textsuperscript{30} A study by White et al. first identified a rather heterogeneous annual incidence of idiopathic VTE in persons older than 18 years among different ethnicities, gradually decreasing from 29 per 100,000 among African Americans, to 23 per 100,000 among Caucasians, 14 per 100,000 among Hispanics, and 6 per 100,000 among Asian-Pacific Islanders, respectively. A study by White et al. reported a standardised incidence of total VTE in African-Americans (135 events per 100,000 adults) nearly 34\% higher than in Caucasians.\textsuperscript{56} Among western countries with primarily European descent, VTE incidence has been reported to be approximately 100 per 100,000 populations.\textsuperscript{65} An investigation in the Taiwanese
population reported a VTE rate of 15.9 per 100,000 suggesting that the rate of VTE is lower amongst non-European populations.66

The exact reasons as to why other ethnic groups have lower VTE rates than Europeans (except Africans), are not amply understood or well explained yet. There are likely multiple reasons, with interfaces between environmental and genetic factors. The two most predominant thrombophilic defects include the factor V Leiden and prothrombin gene G20210A mutations which have incidences of 4.4%67 and 3.1% respectively68 in European populations, however these are rare amongst the Asian populations.67, 69, 70 Fibrinogen, factor VIIc and VIIIc, are known risk factors for VTE in European populations, but studies suggests that Japanese people have lower mean levels of fibrinogen, factor VIIc and VIIIc implicating lower risk of VTE in Japanese populations.71, 72

Multiple studies72-76 have suggested that the risk of VTE is lower in Asians than in Caucasians. A recent study 2019 by Tran and Klatsky showed that Asians had lower rates of VTE than both Caucasians and South Asians (descendants from India). They concluded that Chinese, Japanese, Filipinos and other Asian Americans, but not South Asians had substantially lower VTE risk than Caucasians73. According to Tran and Klatsky, the data indirectly support a genetic explanation. Although the incidence of VTE varies widely among diverse racial/ethnic cohorts, it appears globally highest in African decent, is intermediate in Caucasians and is lowest in Asians.49

1.4.5 Cancer

VTE is a common complication in patients with cancer and those requiring cancer treatment. VTE incidence ranges from 4% to 20% and is associated with considerable morbidity and
mortality. VTE is the second leading cause of death in these patients and is associated with elevated bleeding complications and a high risk of recurrent VTE. Anderson and Spencer (2003) found that the incidence of VTE increased two to three-fold in patients undergoing surgery for cancer disease, compared with those undergoing surgery for non-cancer. Cancer is commonly associated with other risk factors, but the direct effect of cancer remains unclear. Specific cancers such as cancers of the breast, brain, lung, pelvis, rectum, pancreas and gastrointestinal tract have a higher VTE incidence. Patients receiving chemotherapy have been shown to be at an increased risk of developing VTE.

Cancer patients are at a greater risk of bleeding than non-cancer patients due to chemotherapy induced thrombocytopenia and anti-angiogenic therapy. A strong risk factor that needs to be taken into consideration in cancer patients is the presence of active metastatic disease, which is a strong predictor of mortality. VTE however is the most significant predictor of increased mortality during the first year among all types and stages of cancer. VTE is also associated with early death in ambulatory patients with cancer. In 2000, Heit et al. reported independent risk factors for VTE malignant neoplasm with chemotherapy HR, 7.5; (95% CI: 4.29-13.22) or without chemotherapy HR, 3.2; (95% CI: 2.1-4.8). Oger et al. reported independent risk factors for VTE malignancy with OR 5.59. Prandoni and colleagues reported that patients with cancer and VTE were approximately four times more likely to develop recurrent thromboembolic complications and twice as likely to develop major bleeding during anticoagulant treatment than those without malignancy. Thromboprophylaxis with unfractionated heparin (UH) or LMWH has been clinically proven to reduce the risk for VTE and improve outcomes but continues to be under prescribed in cancer patients. Gastrointestinal, pancreatic and neurological cancers have the highest risk for VTE without prophylaxis.
1.4.6 Diabetes Mellitus

There are many chronic diseases and diabetes mellitus is a reported risk factor for VTE and PE. A meta-analysis study estimated a 1.4-fold increased risk of VTE for persons with diabetes.\textsuperscript{79} The same process that causes such arterial vascular disease among persons with diabetes has been suggested to cause VTE. A study by Heit et al. identified diabetes mellitus as a risk factor for VTE. Similar to previous studies, this study showed a slight attenuation of the apparent risk of VTE with diabetes after controlling for BMI, suggesting that at least some of association with diabetes is related to the higher prevalence of obesity among persons with diabetes.\textsuperscript{80}

1.4.7 Chronic Obstructive Pulmonary Disease

COPD patients are thought to be at an increased risk for VTE, because of immobilisation, heightened systemic inflammation, cigarette smoking and venous stasis. VTE remains under-diagnosed in this population, because the symptoms of VTE mimic the symptoms of a moderate to severe COPD exacerbation. A study in 2014 by Kim and colleagues, highlighted that clinicians should suspect VTE in patients who present with dyspnoea and should consider possibilities other than infection as causes of COPD exacerbation.\textsuperscript{81} Post-mortem studies in COPD have found PE in 28\% to 51\% of patients.\textsuperscript{81,82} Overall, the reported prevalence of VTE during COPD exacerbations ranges from 5\%-29\%. Major findings from a retrospective cross-sectional analysis by Kim et al. showed that smokers with severe airflow obstruction were more likely to have a history of VTE compared to non-smoking controls and smokers with no or mild airflow obstruction.\textsuperscript{81}

1.4.8 Sepsis

Sepsis is considered a risk factor for VTE, particularly when complicated by hypotension and shock.\textsuperscript{83} A study by Kaplan et al. was performed to prospectively determine the incidence
of VTE among these patients and to identify independent risk factors for VTE. This study was the first prospective, multicentre investigation to examine the VTE incidence, outcomes, and risk factors in patients admitted to the Intensive Care Unit (ICU) with severe sepsis and septic shock. They identified a high incidence of VTE (37.2%) in patients with sepsis despite the use of universal, guideline-recommended thromboprophylaxis. The majority of patients (88%) had clinically significant VTE (symptomatic PE, proximal DVT, or symptomatic distal DVT) that influenced clinical management. It was also associated with a significantly longer ICU length of stay and the authors identified that critically ill patients with sepsis have a markedly higher incidence of VTE compared with published reports in patients in the ICU primarily without sepsis. Mortality was higher in patients with acute VTE however this did not reach statistical significance.84

1.4.9 Antiphospholipid Syndrome

Antiphospholipid syndrome (APS), or sticky blood, is an acquired autoimmune disorder characterised by vascular thrombosis. In severe conditions such as pregnancy morbidity, there is evidence of antiphospholipid antibodies (aPL). Patients with aPL are at an elevated risk of VTE events. APS is accepted as an acquired prothrombotic condition and is seen as an acquired thrombophilia which is predisposed to VTE. Healthy patients with these antibodies (lupus anticoagulant) presented with VTE rates of 6% to 8%.85 The overall prevalence of anticardiolipin antibodies and lupus anticoagulants in the general population has not been fully determined and estimation rates of 1%-5% have been assessed.7 People with comorbidities such as cancer, severe atherosclerosis, leg ulcer, chronic and/or acute infection and the elderly have higher rates.86 In a case control analytic study by Ginsberg, in which participants with anticardiolipin antibodies, tittered above the 95th percentile, showed a 5.3-fold increased risk of developing DVT or PE over a 5-year period.87 Previous VTE, lupus anticoagulant, and
elevation of the IgG idiotype anticardiolipin antibodies have all been implicated as factors that increase the risk of thrombosis.

Currently there is no cure for APS, however anticoagulant treatment may reduce the risk VTE events. These patients should be managed by preventing VTE in at risk patients (primary prevention) whereas secondary prevention is to prevent recurrent VTE and complications in patients with a chronic of thrombosis. Clinical studies evaluated antithrombotic options for the prevention and treatment of VTE in patients with aPL with recent interest in the direct oral anticoagulants (DOACs), given their increasing use and convenience in the general population. In general, secondary prevention of VTE with long-term anticoagulation is recommended in patients with APS, however in those patients where bleeding complications are an issue, evaluation of thrombotic risk can assist in determining whether ongoing anticoagulation is warranted.

1.4.10 Hormone Therapies and Pregnancy
In the late 1960’s oral oestrogen contraceptive became popular and easily available. There was an alarming rate of VTE in young, healthy women taking contraceptives. A study by Lidegaard concluded that the rate of VTE was 1 and 3 per 10,000 years. Pregnancy increased that risk by five times, low-dose third-generation oral contraceptives by four times, and low-dose second-generation oral contraceptives three fold. There have been concerns regarding the role of HRT in the development of VTE. The oestrogen dose in HRT is generally 20% to 25% of the levels in modern contraceptives. The VTE risk for women on HRT are 2 to 4 fold more than that of women not on HRT. An investigation in 2006 by Ageno and colleagues found that the relative risk (RR) of VTE was 2.1 among postmenopausal HRT users and was highest, 3.5
during the first year of use. Like women receiving oestrogens for contraception or menopause, men receiving oestrogen therapy for prostate cancer are also at increased risk for VTE.90

1.4.11 Genetics and Thrombophilia

VTE is a multi-causal disorder which has some genetic risk factors or hereditary factors also known as thrombophilia to consider.91 Thrombophilia is usually divided into two sections, acquired and inherited and these risk factors interact.91 In addition to acquired risk factors, a variety of inherited traits contribute to the overall risk of VTE in a patient.7,92 Over the last few decades, variants of several genes have been linked and identified as VTE risk factors and are part of the inherited thrombophilia. These are known as “thrombophilic disorders,” “thrombophilias” or “hypercoagulable syndromes”. Genetic makeup plays an important etiologic role, because a personal or a family history of VTE is a risk factor which is closely linked to a VTE events.93

For example, patients who have had a previous episode of DVT, are at twice the risk of a new DVT, compared with patients without a previous history of a DVT.17 An ipsilateral DVT also increases the risk for recurrent DVT.94,95 Genetic factors play a role in the development of VTE, however these genetic risk factors are less common in the general population and the prevalence varies from 1% to 5%.2 In their heterozygous states, it implies a three to ten-fold increased probability for the development of a VTE event. Patients with one of these mutations do not necessarily always lead to the development of VTE, however it is estimated that up to 35% of first time VTE patients will have at least one of the genetic risk factors.2,3

Patients with the Factor V Leiden (FVL) mutation with a leg injury increases the risk of VTE by up to 50-fold.41,96 Oral contraceptives confer a two to three-fold increase in risk. In the
presence of both risk factors, (oral contraceptives and FVL), the RR is increased by 34-fold. Oral contraceptives induce activated protein C resistance, making the biochemical defect associated with FVL worse and therefore the RR increasing the risk for VTE.

Antithrombin (AT) III deficiency was first noted in 1965. In 1980s Protein C and protein S deficiencies were identified and other causes of inherited thrombophilia were recognised. In 1993, Dahlback et al. discovered activated protein C (APC) resistance. In 1996, Poort et al. discovered the prothrombin G20210A mutation. The prothrombin 20210A and the APC resistance are more prevalent and monogenic than previously described thrombophilias such as protein C, S and AT deficiencies. There may well be some more unknown genetic or acquired risk factors involved in the developing of VTE, because in up to 50% of VTE cases there is no idiopathic/acquired risk factor, and in 10-20% of patients there is no genetic or acquired risk factors identified. Thus, in half of all VTE patients no specific predisposing risk factors can be identified at the time of presentation.

1.4.12 Dyslipidaemia

Dyslipidaemia is a clinical condition with an abnormal elevation of plasma cholesterol, triglycerides (TGs), or both, or a low, high density lipoprotein (HDL) cholesterol level that contributes to the development of atherosclerosis. Lipids and lipoproteins modulate the expression and/or function of thrombotic, fibrinolytic and rheological factors. There is a relatively high prevalence of dyslipidaemia in the population and it has been associated with an increased thrombotic risk. Most dyslipidaemias are hyperlipidaemias (raised levels or elevation of lipids in the blood), especially in developed countries. Hyperlipidaemias are habitually due to lifestyle and diet. A study in 2014 by Garcia et al. confirmed the association between dyslipidaemia and VTE. Results from this study presented a risk of thrombosis nearly
four times higher in individuals with this disease. Furthermore, alterations in the lipid profile were related to a higher prevalence of thrombotic complications, recurrence and PTS.27, 103, 104

1.4.13 Immobilisation and Hospitalisation

Immobility is the strongest risk factor for developing VTE. As early as 1957 a study by Gibbs and colleagues found at autopsy a VTE incidence of 15% in deceased patients, who were on bed rest for at least one week before death. The incidence rose to 80% in deceased patients who were on bed rest for longer than a week period. Anderson et al. suggests that prolonged bed rest or immobility alone does not provide adequate reason for prescribing prophylactic anticoagulant therapy, they suggest that prolonged immobility in combination with risk factors may increase the likelihood of a VTE event.7

Immobility during long flights may increase the risk of developing a thrombotic event. A study by Symington and Stack suggested that air travel is a risk factor, after their study showed eight patients out of 182 developing PE soon after air travel in the coach class of the airplane.105 The term “Economy Class” syndrome was coined by Cruickshank et al. who described three thrombosis cases after long-haul air flights.106 A study by Ferrari et al. found that any means of travel (car, train, bus or plane) can cause VTE after finding DVT in individuals after long bus and car journeys. They suggested a more suitable term, “traveller’s thrombosis”.107 A history of recent travel is a risk factor for VTE disease. Post travel VTE can also occur after short journeys in patients with no risk factors or concomitant disease. People on long air flights are at risk from DVT and PE, even if they are relatively young and without a previous history of cardiovascular disease. Stasis of the lower limbs due to immobility, exacerbated by cramped conditions in economy class and dehydration due to excessive alcohol intake, are most probably the main causes.106
It is clear that multiple factors together can cause travellers thrombosis. Factors such as immobility, stasis, dehydration, hypobaric hypoxia, prolonged sitting in small cramped positions effect all passengers and then there are also those factors that are specific to individual passengers such as age, acquired or inherited hypercoagulability, varicose veins and obesity. Other factors also play a role such as length of flight, problems with peripheral circulation and heart problems. Therefore it is clear that air travel itself acts as an additional risk factor for people with pre-existing risk factors for DVT. The number of passengers traveling over long distance by air increases each year. Studies showed that up to 20% of patients presenting with VTE have undertaken recent air travel.

Any patient is at risk of VTE if they are unable to mobilise. This includes all patient with chronic disease, trauma, spinal cord injury, cancer and patients requiring a period of immobilisation postoperatively. Patients in ICU or high care after trauma or surgery are at risk of developing a VTE event due to immobilisation. Pregnant and post-partum (after giving birth) patients, are also at risk of not mobilising fast enough. Normally patients of childbearing age are relatively young and mobilise quickly after birth. It is important for them to keep moving and walking. Among pregnant women, the highest risk period for VTE and PE specifically is the post-partum period. These women are especially at risk for PE if they do not mobilise fast enough after giving birth. Approximately 40% and 60% of all acute PE cases reported to occur postpartum. Heit et al. concluded that during the last 20 weeks of pregnancy the incidence of VTE can be high, predominantly among the oldest and the youngest mothers. Consequently, the period of hospitalisation or immobilisation provides a unique environment for VTE prevention and intervention.
VTE is a common complication during and after hospitalisation for acute medical illness or surgery. As early as 1992 Clagett et al. summarised and made recommendations for VTE prophylaxis for all patients, medical and surgical. Their evidence based consensus guidelines for VTE prophylaxis have been available to use, but despite the availability of these and other guidelines, VTE prophylaxis remains underused.\textsuperscript{111,112} Five studies showed a rate between 13.3\% to 64\% in the overall use of VTE prophylaxis.\textsuperscript{111-115} These studies had large variability in their VTE rates which was probably due to the assessment of limited predefined study populations (surgery and orthopaedic). A study by Otero and colleagues showed a large variability of prophylaxis rates between 27\% to 70\% across different hospitals in Spain.\textsuperscript{111} Many studies tried to assess VTE prophylaxis compliance in hospitals in different countries but data remained inadequate.\textsuperscript{111, 113-115}

A multinational cross-sectional survey which enrolled over 68,183 patients in 358 hospitals across 32 countries, including Australia called the ENDORSE (Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting) study was performed in 2008. This survey assessed the prevalence of VTE risk in the acute hospital care setting and determined the proportion of at risk patients who receive effective prophylaxis.\textsuperscript{116} The study included 30,827 (45\%) surgical and 37,356 (55\%) medical patients. All enrolled patients were VTE risk assessed as per American College of Chest Physicians (ACCP) evidence based guidelines. Of these patients, 35, 329 (51.8\%; 95\% CI 51.4-52.2) patients were deemed to be at risk for VTE. This consisted of 19, 842 (64.4\%) surgical and 15, 487 (41.5\%) medical patients. Findings showed that 58.5\% of at-risk surgical patients received appropriate prophylaxis as per ACCP recommended guidelines compared to 39.5\% of at-risk medical patients. The ENDORSE study revealed that, worldwide, more than half of all hospitalised patients are at risk for VTE, and that surgical patients seem to be at a higher
risk than medical patients. They also indicated that only half of at risk patients received an ACCP recommended method of prophylaxis (ranging between 2% to 84%) with poor use in the medical group.\textsuperscript{116}

Furthermore, findings reflected limited differences between countries regarding the proportion of patients at risk for VTE, but there were definite differences in the use of the ACCP recommended guidelines regarding the type of prophylaxis used between countries.\textsuperscript{117, 118} Factors, such as the availability of VTE guidelines, education resources, reimbursement, physician awareness and national health-care resources may have contributed to these findings. The ENDORSE study highlighted the importance of VTE prevention and the global need to increase awareness on the use of hospital wide strategies to ensure that those patients at risk receive appropriate prophylactic strategies.\textsuperscript{113, 119}

\textbf{1.4.14 Outpatient Setting}

It has been estimated that as many as half of outpatient VTE occurrences may be directly linked to a prior hospitalisation for up to three months post-discharge.\textsuperscript{120} In 2007 a study by Spencer et al., found that almost three quarters (73.7\%) of patients diagnosed as having VTE presented from the outpatient setting. However, on closer scrutiny, roughly half of these patients had been hospitalised or had undergone surgery in the antecedent three months. While reducing the risk of VTE in hospitalised patients is important, findings from this study reinforce that decreasing the occurrence of VTE events beyond hospital discharge may have a greater influence on the overall VTE burden.\textsuperscript{120}
1.4.15 Trauma and Surgery

Trauma of the veins and venous stasis in the lower limb may cause VTE. When a patient is not mobile, due to trauma or surgery, the immobility causes venous stasis that may lead to VTE. Damage to the intima or the endothelial layer of the blood vessel, may be intrinsic or secondary to external trauma. Damage can be due to an accidental injury or surgical insult. Damage to the endothelial wall of a vessel alters the dynamics of blood flow.

There are some anticoagulant mechanisms, or coagulation pathway inhibitors, that exist in the blood system to prevent unintentional initiation of the clotting process. They are AT III, APC, tissue factor pathways inhibitor (TFPI) and thrombomodulin protein S. They hinder flow reactions, reducing the rate of thrombin production and ultimately clot formation. During surgery or just after trauma occurs, the levels of circulating AT III are decreased.\(^{121}\)

Biochemical imbalance between circulating factors can cause a hypercoagulable state. Circulating tissue activating factor increases and circulating plasma anti-thrombin and fibrinolysins decreases the risk of thrombosis. Venous stasis may take place when something slows or barricades the flow of venous blood. Damage to the endothelial wall of a vessel alters the dynamics of blood flow. This causes an increase in viscosity and results in the formation of micro-thrombi.\(^{122}\) Early thrombus interaction with the endothelium stimulates local cytokine production and facilitates leukocyte adhesion to the endothelium. Both these stimulate venous thrombosis. Micro-thrombi are normally washed away, but because of the stasis, the thrombus keep growing and propagates. Thrombus propagation occurs depending on the relative balance between activated coagulation and thrombolysis. Chronic venous insufficiency develops due to decreased vein wall contractility and vein valve dysfunction. The rise in ambulatory venous
pressure causes a variety of clinical symptoms of varicose veins, lower extremity oedema, and venous ulceration.\textsuperscript{122}

In 2000, Heit et al. reported trauma as an independent risk factor for VTE with an OR of 12.7; (95\% CI 4.1-39.7).\textsuperscript{77} Transient conditions such as trauma, surgery and immobility are associated with an increased risk of venous thrombosis. The baseline incidence of DVT associated with major trauma is up to 58\% without prophylaxis. PE occurs in 2\% of these individuals and major trauma is the third leading cause of death among hospitalised patients who survive the first 24 hours after trauma.\textsuperscript{123}

The RR of VTE associated with previous minor injury has been reported to be approximately 3.1 (95\% CI 2.5-3.8) in a large, population-based, case-control study.\textsuperscript{96} Minor injuries in other parts of the body were not associated with VTE, however minor injuries in a leg were strongly associated with VTE (OR 5.1; 95\% CI 3.9-6.7).\textsuperscript{96} A study by Oger et al. evaluated the potential association between DVT and acquired circumstances suspected as risk factors for VTE. In their study cohort of outpatients with a clinically suspected DVT an OR of 1.69 in high risk circumstances of any type of surgery or leg trauma within the past three months was noted.\textsuperscript{46}

In 2010, a consecutive cohort of major trauma patients, admitted between 1994 and 2002, were assessed by Ho and colleagues.\textsuperscript{124} In this study, fatal PE accounted for 11.9\% of all deaths despite unfractionated heparin prophylaxis being used in 44\% of these patients. Results showed that fatal PE occurred in patients who were older (mean age 51 versus 37 years, P=0.01), with more co-morbidities (Charlson’s co-morbidity index 1.1 versus 0.2, P=0.01), had a larger BMI (31.8 kg/m\textsuperscript{2} versus 24.5 kg/m\textsuperscript{2}, P=0.01), and less severe head and systemic injuries when compared with those who died of other causes. Site of injuries were not significantly related to
the risk of fatal PE, however fatal PE occurred much later than deaths from other causes (median 18 days versus 2 days, P=0.01), and the estimated attributable mortality of PE was 49% (95% CI: 36–62%).

Specific types of surgery carry a higher risk of VTE. Combination of a patient’s individual predisposing risk factors and the risk factors from specific type of surgery (Table1.2 and Table 1.3) may lead to VTE events. Recent surgery, malignancy, especially during chemotherapy, are the burliest risk factors of VTE for all patients. Immobilisation and surgery are intertwined as risk factors for VTE. All patients are at increased risk after surgery, especially if a period of immobilisation follows on from the procedure. A study by Heit et al. reported independent risk factors for VTE, including surgery (OR, 21.7; 95% CI: 9.4-49.9) and trauma (OR,12.7; 95%CI,4.1-39.7).

As early as 1997 Oger et al found five impartial variables that were considerably connected with the occurrence of DVT; in a multivariate analysis, 64.7% of patients were correctly classified. The OR for having DVT in the presence of these underlying conditions were correspondingly: 1.75 for age over 65 years, 1.68 for prior history of VTE, 1.69 for high risk circumstances (leg trauma or any type of surgery within the past 3 months), 5.59 for malignancy, and 2.56 for varicose veins. The risk also increases depending on the type of surgery or procedure. The risk of VTE is higher after major orthopaedic surgery than general surgery. Major orthopaedic surgery such as total hip replacement (THR), total knee replacement (TKR) and hip fracture surgery (HFS) is a major risk factor for VTE. Without prophylaxis the rates of DVT range from 40% to 60% post major orthopaedic surgery. Surgery from a laparotomic approach is associated with a risk 15% to 60% of thrombosis, but the risk from laparoscopic and arthroscopic surgery is less defined. Without prophylaxis the
overall rates of DVT for minor orthopaedic surgery such as knee arthroscopy patients for therapeutic and diagnostic purposes is 9.9% and the risk for proximal DVT is 2.1%. Incidence for DVT without prophylaxis on ankle fractures can be as high as 12.2%, however there is limited research in this area.

1.4.16 Medical Illness

Medical patients are at moderate to high risk of VTE, with some studies reflecting comparable VTE rates to patients requiring major general surgery. Acutely ill medical patients include those with chronic diseases such as cancer, cardiac diseases, infectious diseases, inflammatory bowel diseases, respiratory diseases and rheumatologic diseases. These are all medical conditions that are associated with a high risk of VTE. It is estimated that 10% to 30% of medical patients may develop DVT and or PE.

A study by Schmidt et al. in 2011 indicated that respiratory tract, urinary tract, skin and abdominal infections, as well as sepsis diagnosed in hospital or treated in the community were related to an almost equal to twofold increased VTE risk. This association was strongest within the first two weeks after infection onset, gradually diminishing thereafter. Inflammatory bowel disease patients such as extra-intestinal manifestation of ulcerative colitis and Crohn’s disease also have an increased risk of thrombosis. Studies in Sweden and UK confirmed an association between a large number of immune-mediated disorders and VTE.

1.4.17 Brain or Spinal Injury with Paresis or Paralyses

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality in the trauma population. In patients with TBI, risk factors for DVT include immobility, lower extremity fracture, paralysis, and disruption in coagulation and fibrinolysis.
A study by Van Gent in 2014 hypothesised that an increased severity of brain injury in patients with isolated TBI is associated with an increased incidence of VTE. The significant variables in their study were all measures of TBI severity: head Abbreviated Injury Scale (AIS) score, operative decompression, ventriculostomy, and ventilator days. Timing of pharmacological prophylaxis was the same for all the groups. This suggested that severity of injury was the major risk of VTE in this population. After using conditional regression, the authors found that increasing severity of TBI was associated with VTE after adjusting for relevant covariates noted that the severity of TBI was significantly correlated with the incidence of VTE in isolated TBI patients. The investigators suggested that VTE surveillance protocols may be warranted in these high-risk patients, as early detection of VTE could guide subsequent therapy.\textsuperscript{131}

DVT is also a well-known complication of an acute spinal cord injury (SCI). The incidence of VTE in acute SCI patients in medical reports are extremely variable and are reported to range between 9\% to 90\%.\textsuperscript{132} The overall incidence of DVT within three months of paralytic SCI is 38\%, and that of ensuing PE is approximately 5\%.\textsuperscript{133} Heit et al. indicated a risk of VTE for neurological disease with extremity paresis OR, 3.0; (95\% CI: 1.3-7.4).\textsuperscript{125} The initial two weeks post SCI seems to be the period of greatest risk for VTE. Within the first three months, 88\% of DVT cases are seen and after this, the incidence of fatal PE is rare.\textsuperscript{7,133}

A study by Jones et al. surveyed patients from the third to the twelfth month after trauma for DVT found an incidence of 12\%.\textsuperscript{134} Milewska et al. had similar results of 8\% in their study.\textsuperscript{133} DVT after SCI may be clinically asymptomatic and without prophylaxis the incidence of DVT among patients with SCI ranges from 47\% to 100\%. With prophylaxis the incidence of DVT among patients with SCI ranges from 5.3\% to 64\%.\textsuperscript{133-139} This study confirmed that DVT does occur past the third month and usually up to sixth months.\textsuperscript{133}
1.4.18 Central Venous Catheter

The VTE risk in cancer patients is 4 to 5-fold higher than the general population and occurs in up to 20% of cases. A study by Siragusa et al. in 2012 investigated VTE in cancer patients receiving intensive chemotherapy through central venous catheters (CVC) and the efficacy of antithrombotic prophylaxis. Central venous related thrombosis (CRT) represents a well-known complication in patients with acute myeloid leukaemia (AML) receiving intensive chemotherapy. The result of their retrospective study, proposed that the occurrence of CVC exit site infections and neutropenic sepsis following chemotherapy significantly increased the risk of CRT in AML, independently from the use of LMWH prophylaxis. Oger et al. noted an OR of 5.6; (95% CI: 1.6-19.6) for a VTE event in inpatients with CVCs.

1.4.19 Myocardial Infarction and Pacemaker

Although MI is linked with VTE, MI itself has not clearly been established as an independent risk factor, as common risk factors for MI are also risk factors for VTE, such as age, bed rest, immobility and venous stasis. Heart patients admitted to hospital with acute MI have the similar VTE risk as that of moderate risk general surgical patients (approximately 20% overall and 2% symptomatic). Patients with respiratory or congestive heart failure are similarly at risk of VTE events and complications.

With an aging population and an improving technology, pacemakers or cardiovascular implantable electronic devices (CIEDs) are more widely used due to the high safety of the implantation and their effectiveness in treating cardiac arrhythmias. A study by Noheria et al. found that despite the high incidence of lead-related thrombi in patients with CIEDs, the risk of symptomatic PE and associated mortality is possibly no different than that in the general population. PE among these patients is usually explained by other risk factors and rarely must
be attributed to the CIED leads.\textsuperscript{143} It is possible that embolism of trans-venous CIED lead-related thrombus is uncommon. This study concluded that though lead-related thrombus is commonly seen in patients with trans-venous CIED leads, clinical PE occurs with a low incidence. It is possible that embolism of lead thrombus is uncommon or emboli are too small to cause consequential pulmonary infarction.\textsuperscript{143}

1.4.20 Varicose Veins

Varicose veins are common but rarely associated with serious health risks. Varicose veins as a risk factor is debatable. There is only a very small number of studies regarding varicose veins. DVT, PE and peripheral artery disease (PAD) are also vascular diseases but associated with serious systemic effects. Little is known about the association between varicose veins and the incidence of other vascular diseases including DVT, PE, and PAD. Heit et al. found varicose veins to be a risk factor for VTE and that this risk declines with age: OR 4.2 at 45 years, OR 1.9 at 60 years and OR 0.9 at 75 years.\textsuperscript{144} Oger et al. showed that the risk for VTE has an OR 2.56 for varicose veins.\textsuperscript{46} A study by Chang and colleagues in 2018, investigated whether varicose veins were associated with an increased risk of DVT, PE, or PAD.\textsuperscript{145} Their results showed that among adults diagnosed with varicose veins, there was a significantly increased risk of incident DVT; the findings for PE and PAD were less clear due to the potential for confounding. Overall, varicose veins are a weak risk factor for VTE.\textsuperscript{7} Whether the association between varicose veins and DVT is causal or represents a common set of risk factors requires further research.\textsuperscript{145}

1.4.21 Previous History of VTE

The presence of a residual thrombus after a first episode of DVT is an independent risk factor for recurrence.\textsuperscript{76} Patients are 40 times more likely to develop a recurrent event after a first episode of VTE, compared to previously unaffected individuals.\textsuperscript{11} Previous VTE is the most
important risk factor for recurrence of DVT or PE (OR 15.5; 95% CI 6.77–35.99). The risk is higher in patients with previous idiopathic VTE than in those with secondary VTE.\textsuperscript{146} The risk of a recurrent VTE event varies over time, being higher during the first 6-12 months after the manifestation event.\textsuperscript{147} In a study by Prandoni et al, involving 355 patients, the incidence of recurrent VTE was 8.6% at six months and 17.5% after two years. After eight years, the rate of VTE recurrence was as high as 30.3%.\textsuperscript{148}

Moreover, recurrent DVT or PE was associated with an increased risk of PTS and chronic CTEPH.\textsuperscript{95} It is crucial to prevent any secondary VTE events in order to reduce the burden of VTE disease. A conceivable method by which a residual thrombus increases the risk of a recurrent VTE event, is impaired venous outflow at the site of the residual thrombus, resulting in blood stasis and clot formation. However, some patients develop recurrent thrombosis in the initially unaffected leg and others develop isolated PE, thus the method may not necessarily work in all cases. Other methods must be implicated and be explored. Residual thrombosis is perhaps a marker for a more generalised procoagulant diathesis. Indeed, elevated plasma D-dimer levels after withdrawal of oral anticoagulation (a marker of hypercoagulability) are an independent risk factor for recurrent venous thrombosis.\textsuperscript{95, 149}

\textbf{1.4.22 Smoking}

Studies have shown that smoking increases the risk for arterial thrombosis, but evidence that it increases the risk for VTE was conflicting. In 2013, a study by Chen et al. did a meta-analysis, involving approximately four million participants and more than 35,000 patients with VTE from 32 observational studies. They establish that for smokers the risk of VTE is slightly increased compared with non-smokers. When studies were adjusted for conventional cardiovascular risk factors, the risk for VTE was higher, especially for BMI. For current
smokers, the risk of VTE was higher than for former smokers. Their study results also found a dose-response relationship for daily smoking and pack-years smoked.\textsuperscript{150}

1.4.23 Homocysteine

Homocysteine is a common amino acid in blood. It is acquired mostly from eating meat. Elevated homocysteine has been linked to early development of heart disease and as a risk factor for VTE.\textsuperscript{151} It is associated with low levels of vitamins B6, B12, and folate, as well as renal disease. Elevated homocysteine levels can be reduced with vitamin B supplementation.\textsuperscript{93, 152} However, specific VTE risk attributable to hyperhomocysteinemia is unidentified. Epidemiologic studies identified mild to moderate homocysteinemia, as an independent risk factor for VTE. The Leiden Thrombophilia Study showed 10\% of patients with first DVT had homocysteine levels above the 95th percentile (adjusted OR for VTE 2.5, compared with healthy matched controls).\textsuperscript{153} A meta-analysis of 10 case-control studies showed the same odds ratio.\textsuperscript{154} Patients with elevated homocysteine are also at an elevated risk for recurrent VTE.\textsuperscript{7}

1.5 Critically Ill Patients

Critically ill patients admitted to ICU frequently develop VTE events as complications.\textsuperscript{155, 156} Extended periods of immobilisation, surgery, mechanical ventilation and vascular injury are high risk factors for developing VTE in critically ill and ICU patients. Previous DVT history, including PTS and/or varicose veins, are also considered high risk factors.\textsuperscript{157} Severe sepsis and acute inflammatory bowel disease are some conditions renowned for having a high risk for DVT.\textsuperscript{157}

Patients in ICU that are not managed with thromboprophylaxis have up to 81\% risk of developing a VTE event. Furthermore, despite the use of thromboprophylaxis, 44\% of patients
can still develop some form of VTE. It is reported that approximately 12% of ICU patients with documented DVT (despite receiving prophylaxis) still progress to PE. The standard of care in ICU includes the use of thromboprophylactic measures to reduce the rates of VTE events.\textsuperscript{155, 156} Better and improved perioperative care, early mobilisation and more extended use of prophylaxis has reduced the risk of VTE in surgical patients. Nevertheless, the risk for VTE remains high because of more extensive operative procedures, greater medical comorbidities and the more advanced age of patients. The risk of VTE may also be higher in the presence of multiple risk factors.

1.6 Prophylaxis

1.6.1 Mechanical and Pharmacological Prophylaxis

The methods to prevent VTE are universally known as “prophylaxis”. VTE prevention methods consist of mechanical and or pharmacological prophylaxis. Mechanical methods of prophylaxis include graduated compression stockings (GCS) for ambulant patients or anti-embolic stockings (AES) for immobile patients,\textsuperscript{158} intermittent pneumatic calf compression (IPC) devices and venous foot pumps (VFP) or foot impulse devices (FID).\textsuperscript{158}

Over the years, GCS have long been recognised to be very effective as prophylaxis against DVT and have been the main mechanical prophylaxis used. GCS are available as thigh or knee length. Theoretically, thigh length stockings have a potential advantage over knee length stockings because the thigh length distributes the mechanical compression effect over a greater portion of the lower limb. This potential advantage is inconclusive. Disadvantage of thigh length stockings is the difficulty applying them to the leg. If it is incorrectly applied, it may lead to more pronounced tourniquet effect over the upper thigh or allowed to ruck after application. This tourniquet effect can cause skin damage or reduced venous outflow,
potentially increasing the risk, or leading to the formation of a DVT. Knee length stockings can also roll down to the ankle, but because the pressure gradient is not reversed, there is less change of tourniquet effect. The pressure remains the greatest at the ankle level, and because the calf is relative wide compared the ankle, the pressure in the stocking is not an issue. The knee length seems to be preferred by patients, because it is more comfortable than thigh length. A study by Sajid et al. compared the use of thigh to the knee length stockings. In hospitalised patients, there was little evidence of difference between knee and thigh length stockings. On the basis of that analysis, there was a 6% risk of developing DVT if subjects were using knee length stockings, while that risk decreased to 4% if the patient used thigh length stockings.

Situations where compression stockings may be contraindicated includes morbidly obese patients where the correct fitting for the patient cannot be obtained. Others include patients with lower leg inflammatory conditions, or severe peripheral arterial disease, diabetic patients with diabetic neuropathy due to decreased sensation and discomfort if there is a problem with the fitting. Patients with severe oedema of the legs or unusual leg deformity should also not receive stockings. Those with cardiac failure or that are allergic to the material of the stocking, should also avoid GCS. Complications of GCS can include bunching of the stockings due to incorrect fitting causing leg ulceration and pressure injuries. Patients also need to be given over socks with anti-slipping soles to prevent, slipping and falling on mobilisation.

The most up to date 2018 Cochrane review of the original study performed by Sachdeva A et al. in 2010 revealed high quality evidence is available regarding effectiveness of GCS apropos reducing the risk of DVT in hospitalised patients (general or orthopaedic surgery) with or without other methods of background thromboprophylaxis, where clinically applicable. Some average-quality evidence is available that claims GCS reduces the risk of proximal DVT.
Furthermore, some low-quality evidence suggest that GCS may reduce the risk of PE. However, clearly there is still a paucity of evidence to evaluate the effectiveness of GCS in diminishing the risk of PE and DVT in medical patients.\textsuperscript{160}

IPC, which encompasses a pneumatic pump that inflates a leg garment or sleeve is a useful tool against VTE. The sleeves may be short or knee length, wrapping around just the lower leg, or long, thigh length wrap around the whole leg. The pump alternately inflates and deflates the leg garment with intermittent cycles of air, thus enhancing venous return in the leg. It is estimated that IPC reduces the risk of DVT by 60\% relative risk 0.40, 95\% CI 0.29-0.56, \( P<0.001 \).\textsuperscript{161}

An important study by Dennis et al. 2013 on stroke patients, called the CLOTS Trials, was an international multicentre trial (parallel group design, with central randomisation) on 2,518 immobile stroke patients. These patients were allocated to either thigh-length GCS or not in the CLOT 1 trial. For the second trial (CLOT 2), there were 3,014 patients enrolled with patients receiving either thigh-length or below-knee GCSs. This study measured vital status, Oxford Handicap Scale, and quality of life (EQ5D-3 L) at six months. The results showed that in both trials (CLOT 1 and 2) allocation to thigh-length GCS was associated with a very slight, but non-significant, increased hazard of death in the first six months. The HR was 1.087; 95\% CI: 0.913–1.295 for CLOT 1 and 1.037; 95\% CI: 0.892–1.205 for CLOT 2. There were no statistically significant differences in VTE events, Oxford Handicap Scale, or EQ5D-3 L between the treatment groups in CLOTS Trials 1 or 2. The authors concluded that even though the study was underpowered to detect clinically important effects on long-term outcomes, the results of these studies effectively excluded a \( >10\% \) relative reduction in the hazard of death.
within six months associated with the use of thigh-length stockings. No other long-term benefits were apparent.\textsuperscript{162}

Another study by the same lead author, Dennis et al.2015 called “Clots in legs or stockings after stroke (CLOTS) 3 trial,” on patients with strokes, found that the primary outcome (DVT in popliteal or femoral veins) occurred in 122 (8.5%) of 1,438 patients allocated to IPC and 174 (12.1%) of 1438 patients allocated to no IPC, giving an absolute reduction in risk of 3.6% (95% CI:1.4% to 5.8) and a RR reduction of 0.69 (95% CI: 0.55 to 0.86). After excluding 323 patients who died prior to any primary outcome and 41 who had no screening doppler ultrasound, the primary outcome occurred in 122 of 1267 IPC participants compared with 174 of 1245 no-IPC participants, giving an adjusted OR of 0.65 (95% CI:0.51 to 0.84; \( p = 0.001 \)). Secondary outcomes (death, any DVTs, symptomatic DVTs, pulmonary emboli, skin breaks on the legs, falls with injury or fractures) in IPC compared with no-IPC participants were: death in the treatment period in 156 (10.8%) versus 189 (13.1%) (\( P = 0.058 \)); skin breaks in 44 (3.1%) versus 20 (1.4%) (\( P = 0.002 \)); and falls with injury in 33 (2.3%) versus 24 (1.7%) (\( p = 0.221 \)). Among patients treated with IPC, there was a statistically significant improvement in survival to six months (HR 0.86, 95% CI 0.73 to 0.99; \( P = 0.042 \)), but no improvement in disability. The authors concluded that IPC was an effective and inexpensive method of reducing the risk of DVT and improving survival in immobile stroke patients.\textsuperscript{163}

A recent systematic meta-analysis by Zhang et al. concluded that the use of IPC in stroke patients significantly reduces the risk of DVT. They identified seven randomised controlled trials that included 3,551 stroke patients. Overall findings showed that IPC significantly reduced the incidence of DVT in stroke patients (risk ratio [RR] = 0.50; 95% confidence interval [CI 0.27, 0.94]). At the same time, IPC increased IPC-related adverse events (RR =
Though IPC was associated with a significant increase in survival by 4.5 days during six months of follow-up (148–152 days; 95% CI [–0.2, 9.1]), there was a mean gain of only 0.9 days (26.7–27.6 days; 95% CI [2.1, 3.9]) in quality-adjusted survival during the six-month follow-up. It also significantly improves the survival rates of these stroke patients, who are immobile after stroke, but it did not significantly improve quality of life for survival.

A study by Roderick et al. showed that GCS and IPC reduced the risk of DVT and PE in a wide range of surgical patients. IPC has mainly been used in surgical patients during and immediately after operations. A systematic review identified 22 randomised controlled trials (RCTs) of IPC, which included a total of 2779 patients. Use of IPC was associated with a 64% reduction in the odds of DVT (P < 0.00001). Their review concluded that a priority for future research was trials of ‘prevention of VTE with mechanical methods among high-risk medical patients (such as those with stroke)’.  

The use of IPC devices for VTE prophylaxis is comparable to GCS recommendations in that they should be used during the immobility stage until the stage of full ambulation of the patient. There are a variety of IPC devices available, but little evidence is available to differentiate between them. Newer IPC devices are designed with reduced size and weight, aimed at the patients’ comfort. Thus, patient compliance and acceptance of IPC as preventative measure has improved. Choosing an IPC device comes down to ease and comfort of use, obtainability, patient compliance and expenditure of the device. IPC should be used according to IPC guidelines.
IPC can exacerbate lower limb ischaemic disease and should not be used in limbs with critical ischemia.\textsuperscript{165} IPC is contraindicated in patients with peripheral arterial disease or arterial ulcers and also in acute lower limb DVT. IPC is not recommended in patients with severe leg oedema due to heart failure, severe peripheral vascular disease or open wounds/ ulcers on the legs in the area where the sleeves would be applied. Caution should be applied in patients who are confused and attempting to mobilise. IPC can be used instead of stockings if patient has heel ulcer, as long as the sleeve does not touch the ulcer.

VF\'s are increasingly being used, especially when access to the lower limb is restricted. VFP\’s require higher compression pressures to produce similar changes in the femoral vein flow velocity as IPC. VFP\’s used in combination with GCS are more effective for DVT and PE prevention than GCS alone.\textsuperscript{166} Due to the availability of GCS and their effectiveness, GCS should be combined with pharmacological prophylaxis in high-risk patients whenever possible. In moderate risk patients when pharmacological prophylaxis is contraindicated, IPC can be used as an alternative.\textsuperscript{165}

A study in 2002 by Warwick et al. compared VFP to LMWH as prophylaxis in patients after a unilateral TKA. The group of 229 patients were randomly divided to either receive LMWH or to use the VFP. Patients all received an ascending Venography test for VTE, between the sixth and eight-day postoperative. In the VFP group, the prevalence of venographic DVT was 58\% (57/99) and in the LMWH group it was 54\% (48/89), which was not statistically significant. In the VFP group there were four cases of proximal thrombi and two fatal PE cases. There were no fatalities in the LMWH group. The VFP had fewer haemorrhagic complications and soft-tissue effects than the LMWH group. Warwick et al. conclude that neither method provided superior prophylaxis.\textsuperscript{167}
A study by Sakai et al investigated the effects of a VFP on the incidence of DVT after TKA in patients given edoxaban. Half the study group received only edoxaban and the other half received edoxaban plus the use of VFP. The incidence of DVT up to day 28 post operation was 31% and 17.7% in patients with and without the VFP respectively. The study showed that the VFP did not have any additional benefit over the edoxaban prophylaxis in patients undergoing TKA.\textsuperscript{168}

There are some instances where a VFP is contraindicated, such as in the case of severe arteriosclerosis or other ischemic vascular diseases.\textsuperscript{169} Severe congestive cardiac failure or any condition where an increase of fluid to the heart may be detrimental and known or suspected acute DVT, thrombophlebitis or PE, are contraindications for VFP. Patients that are prone to bleeding or taking blood thinners should be careful about the use of VFP. Cancerous tumours, poor somatosensory receptor on feet planar surface, arterial insufficiency or trauma of the lower foot should contra indicate the use of VFP.

Both mechanical and pharmacological methods are effective VTE prophylaxis especially if used in permutation, they have synergistic effects.\textsuperscript{161} The primary goal of administering thromboprophylaxis is to prevent VTE events and to achieve optimal health.\textsuperscript{157} In a hospital environment, especially with high risk patients, the use of combination of mechanical and pharmacological modalities should be used as together they are very effective VTE prophylaxis.

Pharmacological prophylaxis consists mainly of UH, LMWH, new oral anticoagulants (such as rivaroxaban, dabigatran etexilate, and apixaban), pentasaccharide fondaparinux, aspirin or
Testroote et al. found an incidence of VTE ranging from 4.3% to 40% in patients who had a leg injury that had been immobilised in a plaster cast or a brace for at least one week and who received no prophylaxis, or placebo. This number of VTE events were significantly lower in patients who received daily subcutaneous injections of LMWH.

LMWH may include enoxaparin, dalteparin or fragmin, etc. Enoxaparin is available as prepacked syringes with 20mg or 40mg. Prepacked syringes of 60mg, 80mg, 100mg, 120mg and 150mg are available as graduated syringes. The usual LMWH dose depends on the patient’s condition and other factors, such as their weight and their related risk as per the risk assessment tool. Under normal conditions of use LMWH does not modify global clotting tests and therefore there is no need to perform these tests in order to monitor therapy as in the case of warfarin, where international normalized ratio (INR) needs testing. If any special symptom or circumstance renders the use of pharmacological prophylaxis inadvisable (usually because of perceived risk or harm to the patient such as an increased risk of bleeding), mechanical prophylaxis should be prescribed if feasible.

1.6.2 Use of Prophylaxis

In the United Kingdom (UK), guidelines for VTE prophylaxis, were developed in 2007, by The National Institute for Health and Clinical Excellence (NICE), to reduce VTE risk in surgical inpatients and others. An updated version of the NICE guidelines was published in 2013 and called the “NICE guideline: management of venous thromboembolic disease and the role of thrombophilia testing”.

Likewise, the National Institute of Clinical Studies (NICS) in Australia has identified the prevention of VTE in hospitals as a priority in improving patient safety, by improved use and
documentation of appropriate prophylaxis in patients with VTE risks. They also promote the awareness of VTE and to make sure all Australian hospitals have VTE prophylaxis policies in place.

Currently there are many guidelines available for the prevention of VTE. Most of the states in Australia have their own guidelines. NSW has their VTE prevention policy and when patients are risk assessed, they are generally classified in three risk categories: high risk, moderate risk and lower risk.\textsuperscript{157} Lower risk patients normally do not require prophylaxis.

The Australian government formed the Australian Commission on Safety and Quality in Health Care also have their own “Venous Thromboembolism Prevention Clinical Care Standard guideline”.\textsuperscript{157} International guidelines are also available from sources such as American Society of Haematology, American College of Physicians (APC), European Association Urology, United Kingdom (NICE) and many more. It is recommended that all hospitals have their own VTE protocol in place in cooperation with their government legislation.

1.6.2.1 Introduction to Risk Assessment

The best way to determine if a patient needs prophylaxis is to assess the patient for VTE risk factors. Anderson et al. reviewed the VTE risk factors and categorised these into weak, moderate and strong factors based on their odds ratios. According to Anderson and colleagues the following low risk factors are associated with a lower OR (<2) for development of VTE:

- Bed rest for three days
- Immobility due to sitting (e.g. prolonged car or air travel)
- Increasing age
- Laparoscopic surgery (e.g. cholecystectomy)
These low risk factors individually are normally not sufficient to justify antithrombotic prophylaxis. However, the combination of two or more low risk or moderate factors may create a cumulative risk for VTE and therefore justify prophylaxis. Kind and amount of risk factors have important implications for what type and duration of prophylactic treatment is suitable.

**Fig 1.1 Cumulative Risk of DVT Increases with the Number of Risk Factors.**

The proportion of patients with clinically suspected DVT in whom the diagnosis was confirmed by objective testing increases with the number of risk factors. (Data adapted from Wheeler et al. Arch Surg. 1982; 117:1206–1209.3)
Some of these low risk factors includes bed-rest of more than three days, increasing age, obesity, and pregnancy/ante-partum laparoscopy surgery. Immobility due to prolonged illness care or due to sitting during air travel and varicose veins are weak risk factors with an OR of 1 to 2. Previous history of VTE and thrombophilia are a moderate risk factors. Similarly factors such as HRT, oral contraceptive therapy, malignancy, chemotherapy, the use of central venous lines, congestive heart failure, respiratory failure, paralytic stroke, pregnancy/post-partum and arthroscopic knee surgery all have an OR between 2 to 9 classifying them as moderate risk factors. However, strong risk factors have an OR of >10. This category includes major trauma, spinal cord injuries, major general surgery, knee replacement and also hip or leg fracture and hip replacement surgery.

1.6.2.2 High Risk Patients

The New South Wales (NSW) Department of Health has a VTE policy in place and the Centre of Excellent Commission (CEC) has developed a NSW VTE Risk Assessment Tool for state-wide use. The tool was developed to classify patients and procedures into three risk categories, namely high, moderate and lower risk (See Table 1. 5).

37
Table 1.5 Clinical Criteria for Calculations of Prediction Scores

<table>
<thead>
<tr>
<th>Risk Predictors</th>
<th>Yes</th>
<th>No</th>
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<tr>
<td>Active Cancer?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Venous Thromboembolism (VTE)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced Mobility?</td>
<td></td>
<td></td>
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<tr>
<td>Known thrombophilia?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent (≤1 month) Trauma and/or Surgery?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elderly Age (≥70 years)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart and/or Respiratory Failure?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Myocardial Infarction or Ischemic Stroke?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Infection and/or Rheumatologic Disorder?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI ≥30)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing Hormonal Treatment?</td>
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Procedures such as THR, TKR, or HFS and patients with multiple major trauma injuries are categorised as high risk. Other procedures such as abdominal or pelvic surgery for cancer and spinal cord injury with paresis are also classified as high risk. All high-risk patients should be prescribed pharmacological and/or mechanical prophylaxis unless contraindicated. Pharmacological methods under this category include:

- Enoxaparin 40 mg subcutaneous once daily
- Enoxaparin 20 mg subcutaneous once daily if Creatinine Clearance (CrCl) < 30 mL/min (or use heparin 5,000 units subcutaneous 8-12 hourly)§
- Dalteparin 5,000 units subcutaneous once daily
Alternative pharmacological agents that may be used in these patients include, dabigatran, rivaroxaban, apixaban or fondaparinux for THR and TKR surgery. Whereas, fondaparinux, or aspirin in combination with LMWH for hip fracture surgery. In some cases, these agents may be contraindicated or require dose adjustments depending on the degree of renal impairment; calculate CrCl.\(^{37}\)

In THR and TKR surgery, LMWH is preferred over UH. For high risk patients, the combination of both pharmacological and mechanical prophylaxis is advised. If pharmacological prophylaxis is contraindicated then one or more mechanical methods need to be selected such as GCS, IPC, FID unless contraindicated. In all cases, patients need to be educated on the risk factors for VTE, the symptoms and preventative measures, to increase patients’ compliance and to mobilise the patients as early as possible.

For medical patients (which includes those that have suffered an acute stroke, that are critically ill, that have been diagnosed with cancer and the acutely ill patients), the recommendations are for pharmacological prophylaxis such as LMWH or UH if there is no increased risk of bleeding and/or the use of mechanical prophylaxis if there are no contraindications.

**1.6.2.3 Moderate Risk Patients**

According to NSW VTE Risk Assessment Tool\(^{37}\), moderate risk patients are those patients who are not in either the lower or higher risk group. For these patients only one pharmacological option needs to be selected from the VTE Risk Assessment Tool\(^{37}\). As mentioned earlier, all patients should be educated on VTE risk and mobilised as early as possible. In cases of renal impairment or extreme body weight (high or low) dose adjustment may be required as per evidence-based guidelines.
1.6.2.4 Lower Risk Patients

The NSW VTE risk tool specifies that ambulatory patients without VTE risk factors, non-surgical ambulatory patient with VTE risk factors, but expected length of stay $\leq$ 2 days and minor surgery in patients without risk factors and operating time less than 30 minutes, are considered as lower risk patients and do not require prophylaxis. These patients require early mobilisation and patient education on VTE, which may include information leaflets regarding VTE risk as well as the signs and symptoms they may experience.

1.6.2.5 Duration of prophylaxis

Duration of pharmacological prophylaxis for major orthopaedic surgery varies. For THR or hip fracture surgery, the duration should be between 28 to 35 days postoperatively. For TKR, continue prophylaxis for up to 14 days. For patients with lower limb immobilisation due to injury, prophylaxis should be continued until a patient’s mobility returns to normal (or baseline). The duration of pharmacological prophylaxis is for up to 28 to 35 days for high risk surgical patients requiring abdominal or pelvic surgery for cancer.

For medical patients the duration of prophylaxis is determined by the duration of therapy and the length of thrombosis risk. Currently, the recommendations are to continue prophylaxis until the patient is no longer at increased risk of VTE in this group. For example, until their acute medical condition is stable, and mobility returns to baseline or until hospital discharge. Early mobilisation is advised for patients at low risk of VTE.

1.6.2.6 VTE Risk Reassessment

Under all circumstances, patients should be reassessed when clinical conditions change or at regular intervals no greater than seven days. All staff need to confirm the appropriate peri-
operative prescription of both pharmacological and mechanical prophylaxis where indicated and this should be clearly documented in the patient notes. Regular review of VTE risk should be performed during the patient care episode, particularly as clinical conditions change or if there is a transfer of care and in all cases, prophylaxis should be monitored and adjusted accordingly.

As mentioned previously, pharmacological prophylaxis should not be prescribed if there are contraindications against it however, mechanical prophylaxis should be applied as an alternative if there are no contraindications to its use. Active major bleed, a recent bleed within the last 48 hours, bleeding risk, inherited or acquired bleeding disorder (haemophilia) are some contraindications to pharmacological prophylaxis. Others include heparin induced thrombocytopenia (HIT) with the use of either LMWH or UH. The use of LMWH when the patient is having a planned lumbar puncture increases the risk of spinal epidural haematomas. To minimise this risk, careful planning of the timing of pharmacological prophylaxis administration with respect to the timing of the catheter or needle insertion and the removal of the catheter or needle must be considered. Another important aspect to consider with the use of pharmacological prophylaxis is a patient’s renal function. Those patients with renal impairment need careful clinical observation with the use of pharmacological prophylaxis. LMWH should not be used in patients with acute renal failure, end stage renal disease or patients that are dialysis dependent. If there is any doubt about the correctness of the estimated glomerular filtration rate (eGFR), then UH should be considered and used in these patients. Specialist advice should be sought for obese patients with renal impairment. If their renal function is less than 15 or medically it is not advisable for a particular patient, then no pharmacological prophylaxis must be administered. See Table 1.6 for prophylaxis dose adjustments for renal impaired patients.
Table 1.6 Heparin–based VTE Prophylaxis Dose Adjustments for Renal Impairment

<table>
<thead>
<tr>
<th>Renal function (mL/min)</th>
<th>UFH</th>
<th>LMWH</th>
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</thead>
<tbody>
<tr>
<td>30-50</td>
<td>No adjustment required</td>
<td>No adjustment required</td>
</tr>
<tr>
<td>15-29</td>
<td>No adjustment required</td>
<td>Enoxaparin- reduce dose to 20mg subcutaneous injection daily Dalteparin: No adjustment required</td>
</tr>
<tr>
<td>Less than 15</td>
<td>No adjustment required</td>
<td>Do Not Use LMWH</td>
</tr>
</tbody>
</table>

If any special symptom or circumstance renders the use of pharmacological prophylaxis inadvisable (usually because of perceived risk or harm to the patient such as an increased risk of bleeding), mechanical prophylaxis should be prescribed if feasible. Early mobilisation and education also apply to all patients.

The Australia and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism convened in 2008 to formulate a national strategy to promote the optimal use of VTE prophylaxis. Initiatives of the Working Party included the development of simple, user-friendly VTE prevention guidelines that will assist doctors to identify and treat at-risk patients. Adoption of clinical guidelines by hospitals can lead to increased levels of appropriate prescribing of VTE prophylaxis. However, the risk of thromboembolic events continues after hospital discharge, and far less research has been conducted into the use of VTE prophylaxis in the community. There is an increasing trend for at-risk medical patients (e.g. patients with chronic lung disease or cardiac failure) to be managed in the community, especially through hospital-in-the-home and early discharge programs. With increasingly short hospital stays for
both surgical and medical patients, it is important that community-based doctors are aware of the importance of VTE risk assessment and the continuation or commencement of VTE prophylaxis for their patients.

Most hospital inpatients are at risk of DVT and the associated complications of PE and PTS.\textsuperscript{171} In the past, several surveys have shown that evidence-based guidelines for proper prophylaxis of VTE are not always followed despite extensive research reflecting benefits.\textsuperscript{172-174} Therefore, all patients being admitted into hospital and an emergency department, should receive a VTE risk assessment for the possible development of a VTE event. Patients may have low risk factors present, which on their own may not warrant prophylaxis, but if two or more low risk factors are present, combined, their risk increases the likelihood of developing VTE, thus a combination of more than one low risk factor, warrants prophylaxis.

In NSW, the Clinical Excellence Commission (CEC) was established in 2004 to ensure and promote and support improved clinical care, safety and quality across the NSW public health system, and to meet functions specified by the Minister for Health. The CEC is a board-governed statutory health corporation established under the \textit{Health Services Act 1997}. Since its development, the CEC has gained local, national and international recognition for their work improving clinical care. They address many areas such as deteriorating patients, end of life care, falls prevention, infection control and many more. They also work extensively on VTE prevention. The CEC’s central and distinct role is the monitoring of processes and performances, to provide assurance of clinical quality and safety improvement at a system-wide level in NSW health system. The CEC played a significant role in the NSW’s VTE Prevention Policy which included and was responsible of the provision of tools and resources to implement the NSW VTE Policy state-wide and for maintaining it.
Unlike NSW, not all states or territories have VTE policies in place. Classifying patients into broad generalised risk classifications would be a great start, but a well-designed risk assessment tool is ideal to identify the total and specific VTE risk for each individual patient. Some of the predisposing risk factors on their own, are not adequate to warrant the use of prophylaxis. However, individual risk factors, or combinations thereof, are important VTE risk factors and together have allusions for prophylaxis treatment. A clinical review by William Cayley in 2007 found that the absolute risk of DVT to be between 40% to 60% for patients having knee or hip surgery and up to 80% for patients with major trauma. Among general medical patients the risk for a VTE event is 10% to 26% (see Table 1.3). Thus up to 50% of certain categories of hospitalised patients could develop DVT without any prophylaxis.

Consequently, it is essential that the overall risk factors for each patient are carefully assessed. Hence, patients with positive risk profiles should be appropriately consulted with to determine suitable prophylaxis pre- and post-surgical and follow up evaluations. Across the world, a range of Risk Assessment Models (RAMs) or tools were developed for in hospital (postoperatively) patients to determine the risk that each patient may have for the development of a VTE event. Caprini and colleagues have championed the concept of a weighted risk stratification tool for VTE events since the early 1990’s. His “2005 Caprini RAM” is the most widely used and most validated risk prediction model for postoperative patients in the United States of America. Across the world different assessment tools are in use. “Padua Prediction Scores” PPS (Italy) are also well known and are used as a risk assessment tool (See Table 1.7).
Table 1.7 Classification of Degree of VTE Risk as per NSW VTE Risk Assessment Tool

<table>
<thead>
<tr>
<th>Degree of Risk</th>
<th>Risk Factors</th>
</tr>
</thead>
</table>
| **High Risk** | - Total hip replacement, total knee replacement, or hip fracture surgery  
- Abdominal or pelvic surgery for cancer  
- Multiple major trauma  
- Acute spinal cord injury with paresis |
| **Moderate Risk** | - Patients who are not in either the lower- or higher-risk group |
| **Lower Risk** | - Ambulatory patient without VTE risk factors  
- Non-surgical ambulatory patient with VTE risk factors but expected length of stay ≤ 2 days  
- Minor surgery* in patient without VTE risk factors  
- Same day surgery or operating time <30 minutes |

Clinical practice guidelines endorse the use of risk prediction tools, such as PPS. PPS is used to classify the risk of VTE of patients and can be applied to hospital patients who have the potential risk of VTE. The PPS is calculated based on 11 clinical criteria that are weighed and summed to a score that stratifies patients as either high or low risk for VTE occurrence. PPS uses a four-point scoring system where the risk of VTE is defined as low risk when total score is less than four and defined as high risk if the total score is greater than or equal to four. When using PPS, a clinician can use an online calculator for computation but must input a response for each individual clinical criterion. The manual PPS is seen as the gold standard of risk prediction tools.\(^{176}\)

In England, the “Wells score” was developed in 1997 as a clinical prediction tool for DVT and in 1998 was further developed to include PE. In 2003 the original Wells score was updated and is currently part of England’s NICE clinical guidelines.\(^{177}\) In 2016, Kocialkowski and
colleagues, developed a VTE risk assessment tool to help decide whether patients are at high risk for VTE.\textsuperscript{178} Recent guidelines in the United Kingdom have therefore recommended thromboprophylaxis for all patients immobilised in plaster that have one or more further risk factors. To standardise their thromboprophylaxis process, they developed their own RAM or assessment tool. Patients are scored on a variety of risk factors and if judged to be at sufficiently high risk they are prescribed LMWH. Regular audits of the process have shown that good compliance can be achieved. In addition to this a root-cause analysis demonstrated three cases of VTE since the introduction of the tool. This suggests that the assessment can accurately differentiate patients considered to be at high risk.

They concluded that a RAM for lower limb immobilisation can be used successfully to target high risk individuals with thromboprophylaxis. This process ensures that all patients are correctly risk assessed and that low risk patients are not over exposed to the risks of LMWH therapy.\textsuperscript{178} A variety of RAMs have been compiled by different countries. Some organisations such as the “The Global World Thrombosis Day Movement” has a RAM that is available online, which is freely available to everyone to be used as a guideline for risk assessment.\textsuperscript{179} In Australia, the “Thrombosis and Haemostasis Society of Australia and New Zealand” developed updated VTE prophylaxis guidelines, which are available in full at \url{https://www.thanz.org.au/resources/thanz-guidelines} since 2019.\textsuperscript{180}

Nevertheless, these pharmacological prophylactic measures all carry an associated risk of bleeding and in some cases, such as after major trauma, pharmacological prophylaxis may be precluded. Conversely, Testroote et al. stated complications of major bleeding events were extremely rare (0.3\%) and there were no reports of HIT. The use of pharmacological prophylaxis such as LMWH reduces the incidence of VTE events when immobilisation of the
lower leg is required. High risk patients should receive both mechanical (GCS and VFP) and pharmacological prophylaxis (such as LMWH or UH) to reduce their relative risk of VTE. When pharmacological prophylaxis cannot be used, mechanical prophylaxis may then become crucial to prevent any VTE events.

In Australia the NSW Department of Health has a VTE policy in place, including their own adult VTE risk assessment tool that was developed for use in all NSW hospitals (Table 1.8). The ultimate purpose of this policy is to ensure routine VTE risk assessment is undertaken on all adult patients admitted and discharged from public hospitals, and that patients that are identified as at risk of developing VTE receive appropriate pharmacological and/or mechanical prophylaxis.

There are five mandatory requirements in the NSW VTE policy: This states that all adult patients admitted to a NSW public hospital, must have a VTE risk assessment within the first 24 hours and regularly as indicated. This includes, all adult patients that have significantly reduced mobility as a result of acute illness or injury, getting discharged from the Emergency Department, must be VTE risk assessed and if appropriate prophylaxis with mechanical and/or pharmacological should be prescribed. In addition, the policy also states that all pregnant and postpartum women must undergo a VTE risk assessment. Those patients at risk for the development of a VTE event must receive appropriate thromboprophylactic methods according to the risk category identified unless there is contraindication for prophylaxis. All NSW public health organisations must have processes in place to comply with the actions summarised in the VTE Prevention Framework. This framework states that a VTE risk assessment must be completed for all admitted adult patients and other patients identified to be at risk. Decision
support tools should be made available to guide prescription of prophylaxis appropriate for the patients’ risk level.

After the initial risk assessment, the patients’ risk of bleeding should be reassessed regularly as clinically appropriate, at a minimum every seven days, as stipulated by the NSW Health Department policy and Risk assessment tool. A guideline summary called the “New guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand for the diagnosis and management of venous thromboembolism”, led by Associate Professor Huyen Tran (Head of the Haemostasis and Thrombosis Unit at Alfred Health and Monash University in Melbourne) was published in 2019 for the management of thrombosis. These VTE guidelines are available online in full at https://www.thanz.org.au/resources/thanz-guidelines.

1.7 VTE Complications

VTE is estimated to be the second most common medical complication, second most common cause of excess length of hospital stay (LOS), and the third most common cause of excess mortality. More than half of cases are caused by hospitalisation, of which 24% are attributable to surgery. Furthermore other complication such as PE, recurrent DVT, PTS, CTEPH, bleeding and heparin induced thrombocytopenia (HIT) may also be experienced by patients and form part of the patient’s morbidity. Its incidence and economic burden are expected to increase as the population ages.

1.7.1 DVT, PE, and Recurrence

A study in 2017 by Asim and colleagues investigated the development of recurrent DVT after the first VTE event. Findings of this study showed that advanced age, obesity, smoking,
diabetes mellitus, and dyslipidaemia were the most frequent comorbidities associated with the pathogenesis of single as well as recurrent VTE. They also observed that diabetes, obesity, and dyslipidaemia were associated with recurrent DVT. Previous studies have shown that a history of previous VTE is a very strong independent risk factor for VTE recurrence in medical patients.

Studies have shown that during the 21 months following a VTE event in a hospital, one in four patients had additional VTE related events that required hospitalisation (secondary VTE events). Studies have shown that between 7% to 14% of all patients with VTE event, will acquire another VTE event within one year. These figures rise to about 30% after approximately 10 years. Work by Mohr et al. and White and colleagues established that recurrent VTE in high risk surgical patients occurs most regularly in the first three months after the initial event. Readmissions for VTE within 30 days of original hospital discharge is a source for concern with regards to patient care at those institutions. The initial VTE seems to be interrelated to the recurrent VTE episode. After an initial DVT, 86% of recurrent VTE present as DVT and likewise after an initial PE, 66% of recurrent VTE present as PE. Recurrent VTE also include other long term complications such as PTS and postmenopausal hormone therapy (PHT), which also play a role in the staggering economic cost of VTE. Some high risk VTE patients may require ongoing long-term pharmacological prophylaxis to prevent recurrent VTE. The additional risk here is of bleeding with the use of pharmacological prophylaxis. Beusing et al. compiled a table of the rates of recurrent VTE and major bleeding events with long term anticoagulation using guidelines from ACCP evidence based clinical practical guidelines (see Table 1.8).
Table 1.8 Recurrent VTE rates and Major Bleeding Events with Long-Term Anticoagulants.

<table>
<thead>
<tr>
<th>Outcomes After 5y of Treatment</th>
<th>Low Risk of Bleeding</th>
<th>Intermediate Risk of Bleeding</th>
<th>High Risk of Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>First VTE provoked by surgery</td>
<td>Recurrent VTE reduction %</td>
<td>2.6 (2.2–2.9) (0.1 fatal)</td>
<td>2.6 (2.2–2.9) (0.1 fatal)</td>
</tr>
<tr>
<td></td>
<td>Major bleeding increase %</td>
<td>2.4 (0–8.7) (0.3 fatal)</td>
<td>4.9 (0.1–17.3) (0.5 fatal)</td>
</tr>
<tr>
<td>First VTE provoked by a nonsurgical factor/first unprovoked distal DVT</td>
<td>Recurrent VTE reduction %</td>
<td>13.2 (11.3–14.2) (0.5 fatal)</td>
<td>13.2 (11.3–14.2) (0.5 fatal)</td>
</tr>
<tr>
<td></td>
<td>Major bleeding increase %</td>
<td>2.4 (0–8.7) (0.3 fatal)</td>
<td>4.9 (0.1–17.3) (0.5 fatal)</td>
</tr>
<tr>
<td>First unprovoked proximal DVT or PE</td>
<td>Recurrent VTE reduction %</td>
<td>26.4 (22.5–28.5) (1 fatal)</td>
<td>26.4 (22.5–28.5) (1 fatal)</td>
</tr>
<tr>
<td></td>
<td>Major bleeding increase</td>
<td>2.4 (0–8.7) (0.3 fatal)</td>
<td>4.9 (0.1–17.3) (0.5 fatal)</td>
</tr>
</tbody>
</table>

1.7.2 Post Thrombotic Syndrome (PTS)

Morbidity from VTE survivors can be considerable. After the initial DVT, patients are prone to persistent oedema (swelling) of the leg, and pain, due to damaged vein valves, that lead to venous hypertension. Following that, other symptoms such as purpura (bleeding into the skin), pruritus (itchiness), tingling, cramping, increased skin pigmentation, eczematoid (eczema-like) dermatitis and cellulitis (bacterial infection just below the skin) may also present as part of the complications. These symptoms result from the impaired return of blood through the veins of the lower leg to the heart and are known as PTS. Within a year or two of the initial DVT, 25% to 60% of patients develop PTS.¹⁸⁴

The most important factor causing this is initial poor-quality anticoagulant therapy. Approximately one-third to one-half of all DVT patients will develop PTS. In some severe instances, PTS can lead to lipodermatosclerosis and intractable venous skin ulcers may form. Together with impaired mobility, PTS may prevent patients leading active normal lives. Due of its chronic nature PTS is a cause of substantial morbidity. Once a patient has had a DVT event, the patient is prone to recurrent VTE events. Once diagnosed with acute recurrent VTE events, patients may be treated with anticoagulants for life. Newer oral anticoagulants such as rivaroxaban and apixaban do not have the drawbacks of Vitamin K antagonists and hold promise for more effective treatment of DVT, possibly resulting in a reduction in the incidence of PTS.¹⁸⁴ These patients with PTS may suffer considerable mental anguish for life. When hospitalisation is prolonged due to DVT and PE complications after surgery or medical illness, in addition to the mortality risk, the healthcare costs are amplified.¹⁰
1.7.3 Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

CTEPH is a relatively common and serious complication of PE. It refers to high blood pressure in the lungs arteries, caused by previous PE (blood clots and related scarring). A study performed in 2004 by Pengo et al found that CTEPH affects approximately 4% of patients within two years after first episode of symptomatic PE, with no subsequent increase in incidence. The authors concluded that CTEPH appears to be a surprisingly frequent serious complication of PE. Future diagnostic and therapeutic strategies for PE should strive to minimise its incidence. The incidence of CTEPH is difficult to assess and historically has been underestimated. Although autopsy studies indicate that CTEPH incidence to be 0.1-0.5%, recent prospective epidemiologic data indicate an incidence of approximately 4% after acute PE. Physicians need to be more aware of long-term risk of CTEPH associated with PE, even in post PE patients who show no clinical obvious symptoms (e.g. exertional dyspnoea). Analysis of the time course of changes in pulmonary artery pressure versus right ventricular function could aid early identification of persistent pulmonary hypertension and right heart dysfunction in monitoring for possible CTEPH.

Pulmonary artery pressure >50mm Hg has been suggested as predictive of greater risk of persistent pulmonary hypertension. Risk factors for CTEPH includes ventriculo-arterial shunts and infected pacemakers (OR 76.40, 95%CI: 7.67-10,351), splenectomy (OR 17.87, 95%CI: 1.56-2,438), previous VTE (OR 4.52, 95%CI: 2.35-9.12), recurrent VTE (OR 14.49, 95%CI: 5.40-43.08) blood groups other than O (2.09, 95%CI: 1.12-3.94). Lupus anticoagulant/antiphospholipid antibodies (OR 4.2, 95%, CI: 1.56-12.21) were more than often associated with CTEPH. Thyroid replacement therapy (OR 6.10, 95%CI: 2.73-15.05) and a history of malignancy (OR 3.76, 95% CI: 1.47-10.43) emerged as novel CTEPH risk factors. CTEPH is a relatively common and serious complication of PE and is associated with
considerable morbidity and mortality. It is notoriously underdiagnosed and its true prevalence remains unknown. In a prospective, long-term follow-up study of 314 consecutive patients who presented with an initial acute PE, the cumulative incidence of symptomatic CTEPH was 1% at 6 months, 3.1% at 1 year, and 3.8% at 2 years.\(^{185}\)

### 1.7.4 Heparin Induced Thrombocytopenia (HIT)

Heparin Induced Thrombocytopenia (HIT) is an adverse drug reaction presenting as a prothrombotic disorder related to antibody mediated platelet activation. It is a paradoxical immune reaction resulting in thrombin generation in vivo, which leads to a hypercoagulable state and the potential to initiate venous or arterial thrombosis. It is a severe impediment of heparin therapy, facilitated by the immune system and consequently it has devastating thromboembolic outcomes.\(^{186}\) HIT can cause thrombosis, due to the activation of high and low affinity antibody receptors. These antibody receptors exist in a subset of 20% of platelets and then form by HIT PF4 antibody IgG (HITIG) immune complex formation.\(^{186}\) This complex induces endothelial injury leading to tissue factor and also activates monocytes. All of this leads to thrombin production and coagulation. After platelets aggregate, they are removed by the reticuloendothelial system. The increase platelet consumption leading to thrombocytopenia.\(^{186}\) There are a number of factors thought to cause the incidence of HIT.

For example, the type of heparin and the preparation of the heparin (UFH or LMWH). There is a perception that LMWH has replaced UH due to superiority, but evidence to that effect is scarce, nothing to support the superiority of LMWH compared with UH.\(^{187}\) High-quality evidence about HIT from randomised controlled trials (RCTs) is sparse. A Cochrane review in 2017 by Junqueira and colleagues could only find three studies to include in their review of the incidence of HIT in UH and LMWH. In this update, they included three trials involving 1398
postoperative participants. The minimum age of the participants was 49 years and participants were divided into minor and major general surgical procedures. Findings from the pooled analysis showed a significant reduction in the risk of HIT with LMWH compared with UH (RR 0.23, 95% CI 0.07 to 0.73); reflecting low-quality evidence. The number needed to treat for an additional beneficial outcome was 59. The risk of HIT was consistently reduced comparing participants undergoing major surgical procedures exposed to LMWH or UH (RR 0.22, 95% CI 0.06 to 0.75); low-quality evidence. The occurrence of HIT complicated by VTE was significantly lower in participants receiving LMWH compared with UH (RR 0.22, 95% CI 0.06 to 0.84); low-quality evidence. The number needed to treat for additional benefit was 75 and arterial thrombosis occurred in only one participant who received UH. There were no amputations or deaths documented and although limited evidence is available, it appears that HIT induced by both types of heparins is common in people undergoing major surgical procedures (incidence greater than 1% and less than 10%).187

If a patients’ platelet counts falls below the normal laboratory range, or if it falls by 50% and the patient develops a skin allergy or new thrombosis (within days 4 to 14 of start of heparin administration), HIT should be suspected and a clinical assessment should be made. If the diagnosis is HIT, heparin should be stopped. These skin lesions normally occur at the sites of the subcutaneous injections. The skin lesions differ in appearance, from skin necrosis to plaques or indurated erythematous nodules. Platelet count typically begins to fall five to ten days after starting heparin. Patients who have received heparin in the previous three months, and are receiving heparin now again, who develop HIT, may have a rapid onset, because of pre-existing antibodies. Normally HIT onset can occur up to ten days after first heparin dose, but it is rare after 15 days. The platelet count drops by >50% and the platelet count is about 55X10⁹/L.188 Platelets <15 x 10⁹ per L is considered severe, but it rarely occurs. Patients with
HIT develop skin lesions at the injections site, whilst still receiving subcutaneous injections. Associated thrombosis is found in 50% of patients with HIT. Patients presenting without thrombosis (isolated HIT), have a high risk of recurrent thrombosis if the heparin is not stopped. Alternative pharmacological prophylaxis should be started at full dose unless there are significant contraindications for the pharmacological prophylaxis.

In 2006 the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology has produced a concise practical guideline to highlight the key issues in the management of HIT for the practicing physician in the UK. A platelet count should be done on all patients the day they start treatment. For patients who have been exposed to heparin in the last 100 days, a baseline platelet count and a platelet count 24 h after starting heparin should be obtained. All patients receiving UH should have platelet counts done every alternate day. Alternate day platelet counts should be done from day 4 to 14 for all patients receiving UH. Platelet counts should be performed every 2 to 4 days from days 4 to 14 for medical and surgical patients receiving LMWH. It is similar for obstetric patients however they are at low risk for HIT.

The NSW VTE prevention policy states that based on evidence, for patients with heparin sensitivity or diagnosed as having heparin-induced thrombocytopenia (HIT), the heparin and heparin-like agents should generally be avoided. A heparinoid (e.g. danaparoid) can be used as a substitute. A Haematologist should be consulted for further advice when managing a patient with heparin sensitivity or HITs.
1.7.5 Bleeding

Risk of bleeding after surgery is always there when anticoagulation is used as prophylaxis against VTE. Bleeding is usually defined in terms of major bleed in surgical and major bleed in non-surgical patients, minor bleeding and minor clinically relevant non-major bleeding (CRNMB).

Major bleeds are those that are life threatening, causing chronic problems, consume massive healthcare resources and or fatal bleeding that result in death. According to the International Society on Thrombosis and Haemostasis (ISTH) a major bleed in non-surgical patients is defined as a symptomatic presentation with fatal bleeding and or bleeding into an organ or critical area, such as intra-spinal, intraocular, intracranial, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome. It includes bleeding leading to a drop in haemoglobin level of 20 g L⁻¹ (1.24 mmol L⁻¹) or more, or leading to transfusion of two or more units of whole blood, or red cells or bleeding leading to death.¹⁹⁰,¹⁹¹

The ISTH defines a major bleed in surgical patients as fatal bleeding and or bleeding that is symptomatic and occurs in a critical area or organ, such as intracranial, intra-spinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon.¹⁹² Extra-surgical site bleeding causing a fall in haemoglobin level 20 g L⁻¹ (1.24 mmol L⁻¹) or more, or leading to transfusion of two or more units of whole blood or red cells, with temporal association within 24 to 48 hours to the bleeding. Furthermore, a surgical site bleeding that requires a second intervention (open, arthroscopic, endovascular) or a haemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilisation or delayed wound healing, resulting in prolonged hospitalisation or a deep wound infection, and/or surgical site bleeding that is unexpected and
prolonged and/or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associate fall in haemoglobin level of at least 20 g L\(^{-1}\) (1.24 mmol L\(^{-1}\)) or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24 h to the bleeding. The period for collection of these data is from start of surgery until five half-lives after the last dose of the drug with the longest half-life and with the longest treatment period (in case of unequal active treatment durations). The population is those who have received at least one dose of the study drug.\(^{192}\)

The definition of a CRNMB by ISTH is as follows, any sign or symptom of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria:

- requiring medical intervention from a healthcare professional
- leading to hospitalisation or an increased level of care and/or
- prompting a face to face evaluation, not a telephone call or/and an electronic communication\(^{192}\)

Thus acute or sub-acute clinically overt bleeding that did not satisfy criteria for major bleeding and led to hospital admission (bleeding, physician-guided medical/surgical treatment, or a change in antithrombotic therapy (including study drugs) for bleeding) is defined as a minor CRNMB.\(^{193}\) All non-major bleeds are considered minor bleeds.

Newer anticoagulant agents are associated with lower risk of bleeding. A 2011 meta-analysis, the ADVANCED 1 and 2 trials were large random Phase III clinical trials that evaluated apixaban compared to enoxaparin following patients who had TKR for 10 to 14 days. Study
findings indicated that apixaban is associated with lower rate of haemorrhages than enoxaparin (OR:0.55; 95%CI:0.32-0.96).\textsuperscript{194}

A meta-analysis on patients after TKR or THR after two periods, 90 days and five years, by Gomez-Cerezo et al in 2012, compared incidence of bleeding between apixaban and dabigatran. Their study found that the bleeding risk was lower with apixaban (RR:0.81; 95% CI:0.48-1.31), compared to dabigatran (RR:1.00; 95% CI:0.44-2.49).\textsuperscript{195} A study by Nieto et al. showed the lowest clinically relevant bleeding risk with apixaban than the direct oral anticoagulants (RR:0.81; 95% CI : 0.64-1.01).\textsuperscript{196}

The ISTH has developed a bleeding assessment tool (ISTH-BAT) that is a diagnostic method used to assist in the diagnosis of patients with suspected inherited bleeding disorders. This tool includes data on the frequency and severity of symptoms. A normal range for this score, merging data from previous bleeding scores, published in 2014: the cut-off was set at $\geq 4$ in males, $\geq 6$ in females, and $\geq 3$ in children.\textsuperscript{197} Refer to table 1.11 for the ISTH bleeding score.
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>0 Score</th>
<th>1 Score</th>
<th>2 Score</th>
<th>3 Score</th>
<th>4 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>No/trivial</td>
<td>&gt;5 year or more than 10 minutes</td>
<td>Consultation only</td>
<td>Packing or cauterization or antifibrinolytic</td>
<td>Blood transfusion or replacement therapy (use of haemostatic blood components and rFVIIa) or desmopressin</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>No/trivial</td>
<td>For bruises 5 or more (&gt;1 cm) in exposed areas</td>
<td>Consultation only</td>
<td>Extensive</td>
<td>Spontaneous hematoma requiring blood transfusion</td>
</tr>
<tr>
<td>Minor wounds</td>
<td>No/trivial</td>
<td>&gt;5 year or more than 10 minutes</td>
<td>Consultation only</td>
<td>Surgical haemostasis</td>
<td>Blood transfusion, replacement therapy, or desmopressin</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>No/trivial</td>
<td>Present</td>
<td>Consultation only</td>
<td>Surgical haemostasis or antifibrinolytic</td>
<td>Blood transfusion, replacement therapy or desmopressin</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>No/trivial</td>
<td>Present (not associated with ulcer, portal hypertension, haemorrhoids, angiodysplasia)</td>
<td>Consultation only</td>
<td>Surgical haemostasis, antifibrinolytic</td>
<td>Blood transfusion, replacement therapy or desmopressin</td>
</tr>
<tr>
<td>Haematuria</td>
<td>No/trivial</td>
<td>Present (macroscopic)</td>
<td>Consultation only</td>
<td>Surgical haemostasis, iron therapy</td>
<td>Blood transfusion, replacement therapy or desmopressin</td>
</tr>
<tr>
<td>Tooth extraction</td>
<td>No/trivial or none done</td>
<td>Reported in ≤25% of all procedures, no intervention</td>
<td>Reported in &gt;25% of all procedures, no intervention</td>
<td>Re-suturing or packing</td>
<td>Blood transfusion, replacement therapy or desmopressin</td>
</tr>
<tr>
<td>Surgery</td>
<td>No/trivial or none done</td>
<td>Reported in ≤25% of all procedures, no intervention</td>
<td>Reported in &gt;25% of all procedures, no intervention</td>
<td>Surgical haemostasis or antifibrinolytic</td>
<td>Blood transfusion, replacement therapy or desmopressin</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>No/trivial</td>
<td>Consultation only or Changing pads more frequently than every 2 hours or Clot and flooding or PBAC score &gt;100</td>
<td>Time off work/school &gt;2/year or Requiring combined treatment with antifibrinolytics and hormonal therapy or Present since menarche and &gt; 12 months</td>
<td>Requiring blood transfusion, replacement therapy, desmopressin or requiring exam under anaesthesia and/or use of uterine balloon/package to tamponade the uterus</td>
<td>Acute menorrhagia requiring hospital admission and emergency treatment or Requiring blood transfusion, Replacement therapy, Desmopressin or Requiring dilatation &amp; curettage or endometrial ablation or hysterectomy</td>
</tr>
<tr>
<td>Post-partum haemorrhage</td>
<td>No/trivial or no deliveries</td>
<td>Consultation only or Use of syntocin or Lochia &gt; 6 weeks</td>
<td>Iron therapy or Antifibrinolytics</td>
<td>Requiring blood transfusion, replacement therapy, desmopressin or requiring exam under anaesthesia and/or use of uterine balloon/package to tamponade the uterus</td>
<td>Any procedure requiring critical care or surgical intervention (e.g. hysterectomy, internal iliac artery legation, uterine artery embolization, uterine brace sutures)</td>
</tr>
<tr>
<td>Muscle hematomas</td>
<td>Never</td>
<td>Post trauma, no therapy</td>
<td>Spontaneous, no therapy</td>
<td>Spontaneous or traumatic, requiring desmopressin or replacement therapy</td>
<td>Spontaneous or traumatic, requiring surgical intervention or blood transfusion</td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>Never</td>
<td>Post trauma, no therapy</td>
<td>Spontaneous, no therapy</td>
<td>Spontaneous or traumatic, requiring desmopressin or replacement therapy</td>
<td>Spontaneous or traumatic, requiring surgical intervention or blood transfusion</td>
</tr>
<tr>
<td>CNS bleeding</td>
<td>Never</td>
<td>—</td>
<td>—</td>
<td>Subdural, any intervention</td>
<td>Intracerebral, any intervention</td>
</tr>
<tr>
<td>Other bleedings</td>
<td>No/trivial</td>
<td>Present</td>
<td>Consultation only</td>
<td>Surgical haemostasis, antifibrinolytic</td>
<td>Blood transfusion or replacement therapy or desmopressin</td>
</tr>
</tbody>
</table>

**Table 1.9** ISTH Bleeding score
1.7.6 Institutionalisation Aged Care, Hospitalisation and Outpatient Setting

With an increased ageing population, aged care facilities are becoming more available and are growing in popularity. Retirement villages or nursing home residences are very popular, where older people can live independently and as they grow older and weaker and need more care. They can move into units in the same retirement village with more care facilities and eventually into high care where they receive constant care as patients. This concept of institutionalised aged care helps to relieve the burden on already very full hospitals. However, some these patients may need to go to hospital from time to time if they get sick, or need operations which the high care cannot facilitate. A study by Heit et al. claimed more than half (59%) of VTE cases are accounted for by institutionalisation (current/recent hospitalisation/nursing home residence), 25% are caused by recognised risk factors and the rest are idiopathic.

1.7.7 VTE Related Deaths

Worldwide the yearly death toll of VTE is approximately 300,000 and are mostly attributed to PE. These estimates are expected to increase as the population ages, because VTE disproportionately affects older patients. In the general population and in the hospital setting, the incidence of VTE is rising. This might be due to the increase in the population at risk, the average age of the population is getting older and live longer and more and newer surgical procedures are available, which could also increase the risk of VTE. Additional to this is also the under use of prophylaxis and inadequate identification of at high risk population.

The Australian Institute of Health and Welfare (AIHW) data indicates that 7% of all deaths in Australian hospitals are due to VTE, thus VTE are a major cause of hospital death and furthermore some autopsy studies suggest the percentage may be as high as 10%. A study by Sandler et al. showed that death from PE is a frequent complication in hospitalised patients and
that retrospective analysis is likely to underestimate the problem and even the finding that 10% of patients undergoing autopsy died of PE may itself be a serious under estimation of the true incidence. Similarly, a systematic Cochrane review in 2014 by Testroote et al estimated up to 10% of hospital related deaths are due to PE. Consequently 10% of hospital related deaths can be prevented as VTE is the most preventable cause of all hospital deaths. Ollendorf et al. reported a mortality rate of 1.02% among those with no VTE, rising to 2.51% in those with DVT alone, and 19.49% in those with PE. In patients who had finished a course of anticoagulant therapy for a first episode of symptomatic VTE, the risk for fatal PE was reported to be 0.19 to 0.49 events per 100 person-years.

1.8 Conclusion

To surmise, hospitalisation after trauma, any surgery (especially orthopaedic surgery), immobility, previous history of VTE, pregnancy, and cancer are all well known risk factors that increase the likelihood of VTE and the development of the complications associated with VTE. A combination of one or more of these risk factors increase the risk of acquiring a VTE event. Patients should be VTE risk assessed and prescribed appropriated prophylaxis to suit their individual needs to prevent any VTE events.

The aim of this thesis was to assess the incidence of VTE in ankle fractures, risk factors for thrombosis, the use of prophylaxis for prevention and to assess the economic impact in the orthopaedic setting.
CHAPTER TWO: VTE in Orthopaedics and Ankle Fractures

2.1. Abstract

2.1.1 Introduction

Without prophylaxis, VTE rates consisting of DVT or PE are as high as 12.2% following an ankle fracture. Immobilisation, surgery and the use of plaster casts in these patients increase the risk of thrombosis.

2.1.2 Aims

To evaluate the use of prophylactic modalities and the rates of VTE (in-hospital and beyond hospitalisation) in patients following ankle fractures over a five-year period.

2.1.3 Methods

A retrospective study on 421 patients with ankle fractures (2010-2015) occurred at Westmead Hospital. Information such as demographic details, VTE risk factors, body mass index (BMI), use of pharmacological prophylaxis such as LMWH or UH and/or mechanical prophylaxis, operative details, hospital length of stay (LOS) and complications such as bleeding, DVT, fatal and non-fatal PE (in-hospital and up to one-year post discharge) was collected.

2.1.4 Results

Male to female ratio was 1:1.8. Median age for males was 41.5 years (interquartile range, IQR: 26.5 - 57.3) and 55 years (IQR: 44.0 - 67.8) for females. Overall median BMI was 29.6 kg/m² (IQR: 25.5-34.3) and hospital LOS was 7 days (IQR: 3.0 – 16.0). The most common mechanism of injury was falls (81.3%) followed by motor vehicle accidents (MVA) (12.0%). In total, 8.7% of patients had malignancy, 10.7% experienced a previous trauma injury and 2.6% had a history of thrombosis. Overall, 84.7% of patients underwent ORIF and with a 62%
usage of tourniquets. Of these patients, 72% received casts postoperatively. In total, 68% of patients received mechanical prophylaxis and 94.7% received pharmacological prophylaxis postoperatively (UH 18.0% and LMWH 76.7%). The overall in-hospital VTE incidence was 2.9% (95% CI: 1.3 - 4.4); this included 1.4% (95% CI: 0.3 - 2.5) for non-fatal PE, 0.2% (95% CI: 0.04 - 1.3) for fatal PE, 0.9% (95% CI: 0.4 – 2.4) for DVT and 0.2% (95% CI: 0.04 -1.3) for patients that developed both DVT and non-fatal PE. At three months post hospitalisation, our VTE rate was 4.3% (95% CI: 2.3 - 6.2) and the 30-day mortality was at 0.9% (95% CI: 0.4 – 2.4).

2.1.5 Conclusion

Our in-hospital VTE rates were kept relatively low with the use of appropriate prophylaxis. Given the 1.5-fold increase in the VTE rate beyond hospitalisation, consideration should be given to extended prophylaxis beyond hospital discharge based on risk factors such as decreased mobility, type of surgery performed and underlying thrombosis risk factors.

2.2. Introduction

Most VTE events are preventable with adequate prophylaxis. A recent multicentre retrospective cohort study of NSW hospitals over an eight-year period, explored the VTE incidence rates and their variations among elective surgical patients in acute hospitals. These elective surgeries included six major surgical procedures including coronary-artery bypass graft, abdominal aortic aneurysm (AAA) repair, THR, TKR, cholecystectomy and other surgical procedures. Findings from this large cohort study revealed the VTE incidence rate to be 2 of 1000 post elective surgery with a VTE-associated mortality to be 8%. The adjusted incidence of VTE increased significantly over the study period (30%), with no change in
mortality. This number is double the figure for VTE in the USA.\textsuperscript{37, 204} Current data suggests that VTE prophylaxis is grossly under used in Australia and some overseas hospitals.

An abundant amount of research has been done, predominantly on VTE events after hip or knee replacement surgery or hip fracture surgery. These procedures are considered to be major orthopaedic surgeries and these patients are particularly at high risk for the development of a VTE event. The incidence of PE in major orthopaedic surgery in the absence of prophylaxis is around 8.6\%.\textsuperscript{205} The VTE incident of THR and TKR surgery can be as much as 30\%-60\% without pharmacological prophylaxis.\textsuperscript{206} Routine prophylaxis is the standard care for these patients.\textsuperscript{39} Currently there is a paucity of research on VTE after lower leg trauma and for ankle fractures, most orthopaedic surgeons do not deem prophylaxis necessary or perceive the risk of VTE to be not that high following surgery to warrant prophylaxis necessary and cost effective.

It is well known that hospitalisation is a key risk factor for the development of VTE. Patients’ immobility, due to bed rest, plaster cast or after the postoperative period following surgery after trauma, increases the risk of thrombosis. Patients with these conditions carry a higher risk of VTE development than the population at large.\textsuperscript{30} The potential risk of VTE may be increased after foot or ankle surgery and lower limb injury, because the incidence of VTE of the distal lower limbs are poorly understood. This is at least partly due to the wide range of procedures and injuries encountered in this area of the body. There are a multitude of different procedures and surgeries, all with varying levels of complexity that are performed on the lower extremities. The aftercare protocols vary from immediate weight bearing or total non-weight bearing for a certain time period.\textsuperscript{207} Thus most orthopaedic surgeons perceive of low risk of VTE after foot and ankle surgery.
Studies have evaluated the effect of ankle joint immobilisation on venous blood in the lower limb.\textsuperscript{208} Results of these studies have demonstrated that ambulating non-weight bearing is not associated with significant increases in venous blood flow above resting levels. To stop chemical prophylaxis once patients are ambulating irrespective of weight-bearing status is therefore not justified. In contrast, both partial and full weight bearing resulted in a significant increase in venous flow compared with resting levels, irrespective of whether the ankle joint was immobilised. However venous blood flow remained significantly lower with partial weight-bearing (50\%) compared with full weight-bearing.\textsuperscript{209} When comparing venous blood flow among full weight-bearing exercises, a significant reduction with the ankle joint in equinus compared with no ankle joint immobilisation was observed. These results demonstrate that venous blood flow return to normal levels when the subjects were permitted to fully weight bear in below knee casts or walking boots, provided the ankle was not in equinus. It was also noted that both active and passive ankle plantar flexion also increase the venous return from the lower limb.\textsuperscript{209, 210} However, utilising these techniques is not possible when the joint is immobilised using a cast or pneumatic boot.\textsuperscript{208}

In 2014, a study using a calf muscle pump in the presence of a plaster cast was examined, demonstrating that a simple strategy of toe and ankle exercises maintain venous return despite below-knee cast immobilisation. The study recommended that all patients with below-knee casts are given a program of exercises that can be comfortably performed with the cast; this could provide a useful, inexpensive, and safe thromboprophylactic strategy acting at the site of greatest risk and targeting a major cause of VTE.\textsuperscript{211}

Unfortunately, for lower limb injuries or surgery distal from the knee, mechanical compression is not always viable. Adding compression to anticoagulation decreased the risk of DVT by 49\%
(risk ratio RR 0.51, 95% CI 0.36 to 0.73) while adding anticoagulation to compression decreased the risk of DVT by 44% (RR 0.56, 0.45 to 0.69) and increased the risk of bleeding (RR 1.74, 1.29 to 2.34). As such combined compression and anticoagulation appears more effective at preventing postoperative DVT than either modality alone. However, adding anticoagulant to GCS increases the risk of bleeding, and the evidence that GCS and anticoagulation together reduces VTE risk, is of low quality.\textsuperscript{212}

A multicentre study on 2733 patients following foot and ankle surgery evaluated patients for pre-operative risk factors and postoperative thromboembolic events. The use of postoperative VTE prophylaxis, if any, was determined by the surgeon and info regarding medication and dose and duration was not included in the study. Incidence of DVT was 0.22% and non-fatal PE 0.15%. No fatal PE was reported; however, the authors reported the frequency of fatal PE after foot and ankle surgery appears to be less than 0.04%. They concluded that routine prophylaxis for VTE prevention after foot and ankle surgery was not warranted. Their study found the only statistically significant relationships with VTE were the postoperative regimens of cast immobilisation and non-weight bearing. The percentage of patients from their study that developed VTE was 0.5%. All of the VTE patients had been non-weight bearing and immobilised.\textsuperscript{213}

In 2002 Solis and Saxby also investigated the incidence of VTE after foot and ankle surgery.\textsuperscript{214} They studied 201 patients, none of whom received DVT prophylaxis. Deep calf clots were found in 3.5% via duplex ultrasound on first postoperative visit. None of these showed progression upon follow up ultrasound and none extended proximal to the calf. These authors also concluded risk of DVT is low after foot and ankle surgery.\textsuperscript{214} A study by Calder et al 2016 showed that isolated foot and ankle surgery has a lower incidence of clinically apparent VTE
when compared to general lower limb procedures. They stated that this rate is not significantly reduced using LMWH. The incidence of VTE following Achilles tendon rupture is high whether treated surgically or conservatively. With the exception of those with Achilles tendon rupture, they felt that routine use of chemical VTE prophylaxis is not justified in those undergoing isolated foot and ankle surgery. They concluded that patient-specific risk factors for VTE should be used to assess patients individually.

In contrast with the above studies, a literature review in 2008 by Martin and Hardy demonstrated an increased risk for VTE after immobilisation after leg injury, thus confirming that immobilisation of the lower leg is a significant risk factor for the development of VTE.  

Of 253 outpatients with lower limb injuries who were immobilised in a plaster cast formed part of a prospective study by Kujath et al. In 1993, thrombosis was more common in patients with fractures than in those with ligamentous and other soft tissue injuries. They concluded that LMWH is recommended for all patients with injury of the lower limb being immobilised by a plaster cast, irrespective of age.

A randomised prospective study in 1995 by Kock et al. was performed to study the effect of LMWH on the incidence of DVT on a group of 339 patients with minor injuries immobilised in a plaster cast. The prophylaxis group of patients received daily injections of 32mg LMWH and the control group received no prophylaxis; none of the LMWH group developed DVT events whereas 4.3% of the control group did. The mean duration of immobilisation in control group was 18.8 days and DVTs were found after 11.4 days. No side effects of the LMWH were observed. They concluded that LMWH administered once daily is effective in reducing the risk of DVT in outpatients with plaster cast immobilisation.
A study in 2002 by Lassen et al. on patients that were in a plaster cast or brace for at least five
weeks after leg fracture or Achilles tendon rupture revealed that DVT occurred in 19% of the
placebo group and 9% of patients receiving Reviparin.\textsuperscript{217} Two patients in the placebo group
developed PE. There were no differences in the adverse events between the groups. This study
concluded that DVT is common in patients with prolonged immobilisation after leg injury.\textsuperscript{217}

In 2002 Jorgensen et al. investigated the incidence of DVT in 205 patients (immobilised in a
plaster cast) and the efficiency of LMWH as prophylaxis.\textsuperscript{218} They concluded that DVT after
plaster casting is a problem; the incidence of DVT was almost 20% in the young untreated
population. They also concluded that the prophylaxis regiment was not sufficient to prevent
DVT.\textsuperscript{218} In 2002 Wang et al. noted that DVT often develops weeks after surgical patients have
been discharged, and that the danger of DVT or PE persists up to five or six weeks following
surgery.\textsuperscript{219} This study concluded that the use of extended prophylaxis postoperatively in the
outpatient setting may also be beneficial for ankle surgery patients who presents with additional
VTE risk factors.\textsuperscript{219}

In a Cochrane systematic review, Testroote et al. found that the risk of VTE events were from
4.3% to 40% in patients with lower limb injury who had immobilisation in a plaster cast or a
brace for at least one week and whom received no prophylaxis. Overall they found a significant
reduction in the incidence of VTE events with the use of LMWH with an odds ratio of 0.5.\textsuperscript{10}
In their study, the control group (n=740) received no prophylaxis or placebo and the
prophylaxis group (n=750) received LMWH once daily. The incidence of thromboembolic
events in the control group ranged from 4.3% to 40% and from 0% to 37%. In the prophylaxis
group event rates ranging from 0% to 37%; (odds ratio (OR) 0.49; 95% CI: 0.3-0.7) with
minimal evidence of heterogeneity with an I-squared ($I^2$) of 20%, $P = 0.29$. Comparable results were seen in the following subcategories: operated patients, conservatively treated patients, patients with fractures, patients with soft-tissue injuries, patients with proximal thrombosis, patients with distal thrombosis and patients with below-knee casts. Patients who had a leg injury that had been immobilised in a plaster cast or brace, (regardless of whether they were operated on, or whether the injury was a fracture or soft tissue damage) had significantly reduced occurrence of DVT (proximal and distal) events, when treated with LMWH. There was no difference in PE events with LMWH.\(^\text{10}\) Importantly, LMWH was administered daily during the entire period of immobilisation. This suggests all patients who have had a lower leg fracture or injury (which involves immobilisation in a brace or a plaster cast for a prolonged period) should receive LMWH for the entire period of immobilisation to prevent a VTE event.

It is important to note that major adverse events such as haematoma, acute bleeding, allergy and thrombocytopenia were rare. Only a few adverse events were reported, the majority of which were bleeding events leading to the discontinuation of LMWH administration; two patients in the treatment group and one in the placebo group had to discontinue the LMWH due to major bleeding events. In the treatment group, minor bleeding events were reported in up to 8% of cases. The complications of major bleeding events were extremely rare (0.3%) and no reports of heparin induced thrombocytopenia (HIT). A study by Testroote et al. determined that LMWH should be considered in adult patients with immobilisation of the lower leg to prevent occurrence of VTE events. This should be available to all patients, not only in above-knee casts, but those with below-knee casts as well.\(^\text{10}\) They also suggested that LMWH can safely be used for this indication. Based on their results, they concluded that use of LMWH in outpatients significantly reduces VTE events when immobilisation of the lower leg was required.\(^\text{10}\)
A Swedish study by Milbrink and Bergqvist, based on a large cohort of 15,000 Swedish patients that had orthopaedic operations over a three year period, were followed for up to four months. The results showed that the incidence of VTE in the classical high-risk groups of hip fracture surgery, THR and TKR was low at 0.6%, while the PE incidence in the hip fracture group was at 0.27%, with two cases of fatal PE occurring at 72 and 109 days following surgery. Patients with ankle fractures had a higher incidence of VTE. The majority of clinical VTE events, occurred after discharge from hospital. The investigators concluded that when using routine thromboprophylaxis with LMWH in orthopaedic surgery, the rate of symptomatic VTE is low.

A recent Cochrane updated review of LMWH for prevention of VTE in patients with lower-limb immobilisation by Zee et al in 2017, was conducted to review previous studies according to methods and quality. It implicated that the evidence was of moderate quality and showed that the use of LMWH in outpatients reduced the number of VTE events when a plaster cast or brace was required, when compared with no prophylaxis or placebo. Low-quality evidence showed no clear differences in PE between the LMWH and control groups, but less symptomatic VTE events in the LMWH group. The quality of evidence was downgraded due to risk of bias and imprecision of results. Results showed that the incidence rate of DVT events ranges from 0% to 10%, which indicates a high rate of morbidity in the population. Further research was advised to develop treatment options that are less immobilising. They also suggest investigating further uses of other drugs and DOACs.

Although it remains a controversial topic as to whether VTE prevention measures are effective or effectively employed in the clinical setting, it appears that VTE is a real risk in certain patients with immobilisation, not withstanding, only a small number of studies have been done.
on below the knee lower limb prophylaxis. In patients with full plaster casts it is difficult to use mechanical prophylaxis, so it is therefore necessary to provide other anticoagulation alternatives and antiplatelet drugs. Overall, it appears that pharmacological and mechanical prophylaxis play an important role in the prevention of VTE, not only in major orthopaedic surgeries, but also in lower limb immobilisation.\textsuperscript{10}

Given the scarcity of literature on lower limb prophylaxis, the American Orthopaedic Foot and Ankle Society (AOFAS) currently have no uniform guidelines for or against routine VTE prophylaxis for patients undergoing foot and ankle surgery. Similarly, both in 2004 and 2012 the American College of Chest Physicians (ACCP) Antithrombotic Guidelines also suggest no prophylaxis for orthopaedic patients with lower limb immobilisation, due to surgery or trauma.\textsuperscript{10, 207} Certain cases may warrant no pharmacological prophylaxis. When pharmacological prophylaxis is contraindicated, mechanical prophylaxis may then become crucial as VTE prophylaxis.\textsuperscript{173} Thus the current trend in America is not to provide any prophylaxis unless there are clear VTE risk factors. The ACCP recommendations of hip and knee prophylaxis have not been adopted for foot and ankle surgery. Even though this group of orthopaedic patients have a low incidence of DVT there are still patients who develop PE.

However, in England, The National Institute for Health and Clinical Excellence (NICE) in April 2007 recommended that all orthopaedic inpatients be offered a LMWH for the duration of their stay in hospital.\textsuperscript{222} They acknowledged the lack of orthopaedic specific data, (relating to ankle and foot) regarding the incidence of VTE for the use of widespread use of LMWH as prophylaxis. Nevertheless, if mobility is significantly reduced following surgery or, if casting/moonboot is used, NICE still recommends pharmacological prophylaxis for the duration of immobilisation. They also recommend that any surgery of the lower limb that lasted
longer than an hour (this includes anaesthetic time), patients that are older than 60 and also all obese patients and other comorbidities should be offered pharmacological prophylaxis. They recommended that centred on these benchmarks, most patients undergoing foot and ankle surgery should be offered pharmacological prophylaxis, such as LMWH. In 2018, the updated NICE guideline still recommends LMWH and has not formed an opinion about the newer DOACs. The NICE committee commented that “despite this burden of ill-health for VTE, no randomised studies comparing modern anticoagulants that are available in oral preparations (perhaps more suitable for outpatient treatments) with established treatments such as LMWH or fondaparinux were identified in the evidence review.” The committee were unable to make a recommendation to consider oral anticoagulants for this patient group given this lack of evidence.223

This research further examined the factors surrounding VTE and prophylaxis in lower limb immobilisation, ankle fractures with or without surgery, and casts, in order to obtain a more complete and relevant understanding, allowing for the development of more effective model to prevent, diagnose and treat VTE in the future.

2.3. Objectives and Aims

The overall objective of this study was to evaluate the incidence of VTE and risk of bleeding complications with the use of pharmacological prophylaxis in patients admitted to Westmead Hospital with ankle fractures.

The specific aims for this project were to:

- Evaluate the thrombotic risk factors that may increase the risk of VTE.
- Evaluate thromboprophylactic usage (both mechanical and pharmacological) in these patients.
- Assess the incidence of VTE in-hospital and up to three months beyond hospitalisation (any readmission during that period).

2.4 Methodology

2.4.1 Design and Setting

A retrospective, non-interventional cohort study was conducted at Westmead Hospital in the Western Sydney Local Health District (WSLHD). This district in the State of New South Wales, (NSW) is the second most populated and one of the fastest growing areas with the populations expected to increase by 48% by 2036. Westmead Hospital is classified as a level one major trauma service (MTS) in Australia, servicing Western Sydney and the western parts of the state. An MTS provides the full spectrum of care for major and moderately injured patients, from initial resuscitation through to rehabilitation and discharge. Westmead Hospital provides emergency, trauma and critical care 24 hours a day, seven days a week. Westmead Hospital’s trauma service admits around 1600 patients every year, with about one third of these patients being moderately to severely injured. Westmead hospital’s emergency department treats 192, 122 emergency patients yearly. The hospital has 975 beds for in-patients and receives 181, 446 admissions per year.

According to the Centre for Road Safety, every year since 2008 there have been between 6,000 and 7,000 serious injuries from road accidents in NSW. At Westmead, road incidents account for one third of all cases coming through the doors and about 40% of all trauma admissions are due to falls. At least a third of these trauma patients have multiple injuries.
2.4.2 Duration and Sample Size

A total of 421 patients were included in the study over a five-year period from the 1st of January 2010 to the 31st December 2015. Of these patients, a computer-generated random sample of 150 patients were selected to collect data on prophylaxis used, and bleeding complications only. VTE events that occurred in and out of hospital up to one-year post hospitalisation were collected on all patients.

2.4.3 Inclusion Criteria

Patients were included in the study if they had the following criteria:

- Being $\geq 18$ years of age
- Presented with a unilateral or bilateral ankle fracture with or without multiple trauma
- Required surgery or not
- Admitted to Westmead Hospital between 1st January 2010 to the 31st December 2015.

2.4.4 Exclusion Criteria

Patients were excluded from this study if they:

- Were $< 18$ years of age
- Had no fractures of the ankle
- Were admitted with only soft tissue injury
- Admitted before the 1st of January 2010 or after the 31st of December 2015
2.5 Coding

2.5.1 Coding Information

The ICD-10-AM codes were scrutinised for selecting our eligible patients. ICD-10-AM entails a tabular list of diseases and accompanying index and is the International Statistical Classification of Diseases and Related Health Problems. It is the tenth Revision and is modified (Australian Modification- AM) for Australia. ICD-10-AM was created in 1998 by the National Centre for Classification in Health and used since then. It was developed and modified in collaboration from clinicians and clinical coders to ensure that the classification is current and appropriate for Australian clinical practice.

The World Health Organization (WHO) created ICD-10 and ICD-10-AM is a derivative version of it. ICD-10-AM employs an alphanumeric coding system for diseases and external causes of injury. ICD-10-AM is structured by body system and aetiology. ICD-10-AM encompasses three, four- and five-character categories and is regularly updated, including any updates of ICD-10 as well (see Table 2.1).

There were 421 patients that were eligible for the study and of those, 150 patients were randomly selected to take part in the study for the type of prophylaxis received. The medical record number of each patient identified the record for review. Those patients were de-identified and were given a number for the study purpose. Data was collected on a proforma and did not contain the medical record number or any other potential identifiable information.
Table 2.1 ICD-10-AM Codes for ankle fractures

<table>
<thead>
<tr>
<th>ICD-10-AM Codes collected for ankle fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S8281</strong> Bimalleolar fracture, ankle</td>
</tr>
<tr>
<td><strong>S8282</strong> Trimalleolar fracture ankle</td>
</tr>
<tr>
<td><strong>M8407</strong> Malunion of fracture, ankle and foot</td>
</tr>
<tr>
<td><strong>M8417</strong> Non-union of fracture[pseudarthrosis], ankle and foot</td>
</tr>
<tr>
<td><strong>M8427</strong> Delayed union of fracture, ankle and foot</td>
</tr>
<tr>
<td><strong>M8437</strong> Stress fracture, not elsewhere classified, ankle and foot</td>
</tr>
</tbody>
</table>

2.6 Data Collection

2.6.1 Demographic and VTE Risk Factors

Data was extracted from hard copies of patient medical files which were retrieved from the Department of medical records. Any electronic data were accessed from the hospital electronic system called Cerner. All patients with ankle fractures were identified from the Department of Surgery Orthopaedic Database and from medical records using the relevant ICD 10-AM codes (Table 2.1). A proforma was developed (Appendix A) to include information such as patient age, gender, hospital length of stay (LOS), VTE risk factors, body mass index (BMI), smoking status, use of contraceptives, hormone replacement therapy (HRT) and any hereditary factors (Protein C, S, factor V Leiden). See Table 1.2 Risk factors. Other comorbidities included smoking status, injury type, previous surgery in the last three months, diabetes mellitus, ulcers, were also recorded for analysis. It was also recorded if any prophylaxis were given (before or after) and if any incidence of DVT occurred.
2.6.2 Surgical Details

Surgery required as a result of ankle fracture was recorded. This included operation details such as the date of surgery, operative duration, use of tourniquet (including start and end time), type of surgery such as open reduction and internal fixation (ORIF) and site of surgery and duration of surgery. The duration of anaesthesia was also recorded. The American Society of Anaesthesiologists (ASA) classification system was also collected. This is a global score that assesses the physical status of each patient before surgery.226 Refer to Table 2.2 for a description of the ASA scoring system. The immobilisation period and the use of postoperative plaster cast or moonboot was also documented.

Table 2.2: ASA Scoring System for Anaesthetics227

<table>
<thead>
<tr>
<th>ASA Score</th>
<th>Description of Patient’s Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA I</td>
<td>A normal Healthy patient</td>
</tr>
<tr>
<td>ASA II</td>
<td>A patient with mild systemic disease for example: mild diabetes.</td>
</tr>
<tr>
<td>ASA III</td>
<td>A patient with severe systemic disease.</td>
</tr>
<tr>
<td>ASA IV</td>
<td>A patient with severe systemic disease that is a constant threat to life.</td>
</tr>
<tr>
<td>ASA V</td>
<td>A moribund patient who is not expected to survive.</td>
</tr>
<tr>
<td>ASA VI</td>
<td>A declared brain –dead patient whose organs are being removed for donor purposes</td>
</tr>
</tbody>
</table>

2.6.3 Type of Prophylaxis

Prophylaxis comprised both mechanical and pharmacological prophylaxis. Mechanical prophylaxis included GCS, VFP and/ or IPC devices. Pharmacological prophylaxis included anticoagulants such as LMWH as anticoagulants, such as enoxaparin (Sanofi Aventis). The usual dose depended on the patient’s condition and other factors, such as their weight. UH at either 2500IU or 5000IU twice or three times daily or LMWH dose of 20mg or 40mg
administered subcutaneously daily either pre- or postoperatively. Clinicians can also prescribe extended duration of prophylaxis on an outpatient basis.

2.6.4 Complications, VTE Events and Hospital Readmissions

Any postoperative complications such as surgical site infection, MI and bleeding complications were noted. The term CRNMB has recently been incorporated into VTE disease clinical trials to define a bleeding event that is not a major bleed as defined by the International Society on Thrombosis and Haemostasis (ISTH) or a non-clinical consequential minor bleeding event. ISTH defines major bleeding in non-surgical patients as having a symptomatic presentation:

1. Fatal bleeding, and/or
2. Bleeding in a critical area or organ, such as intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
3. Bleeding causing a fall in haemoglobin-level of 20 g L\(^{-1}\) (1.24 mmol L\(^{-1}\)) or more or leads to transfusion of two or more units of whole blood or red cells.

Thus major bleeding was well-defined as clinically evident, with a clear source of bleeding that was overt. Any thromboembolic events such as DVT-proximal or distal, non-fatal or fatal PE (in-hospital and up to one-year post discharge), was recorded. Results for suspected symptomatic VTE tests such as imaging, duplex ultrasound, D-Dimer, CT scan of chest for pulmonary embolism (CTPA) or VQ Scan (ventilation perfusion), during hospital stay in the study population were also collected and documented. All VTE events were recorded for the whole period, including during hospital admission, at three months post discharge and up to one-year post hospitalisation. Hospital readmission rates were recorded at three months and up.
to one-year post discharge. The 30-day mortality rate and cause of death was recorded from the patient medical records and death certificates.

2.7 Ethics

The study was approved by the local hospital research and development department (Ethics Committee) and ethical approval of the study protocol (Appendix B) was obtained from the Human Research Ethics Committee of Sydney University on the 26 September 2016 (Approval number: 4888).

Each proforma had a de-identified code (1-150) attached to the patient’s medical record number and kept under lock and key in a locked room and locked cabinet as per Westmead Hospital’s security procedures protocol. Computer data files were password protected, with tracking features and firewalls as per Information Technology Services Department Protocol. Access was only available to the investigators for this study. The size, retrospective nature, age and volume of information make it very difficult to track all individuals to obtain consent and risk of introducing bias into the study will be high. No information used was detrimental to the patient or the treating surgeon, as all data were de-identified and anonymity was maintained. Data collection forms will be kept for a minimum of seven years after the completion of the study. Thereafter the forms will be shredded by the investigators. Publications of results will be in terms of de-identified data presented epidemiologically in terms of trends per year.

2.8 Statistical Analysis

The incidence of VTE was the primary outcome measure of our analysis. Categorical variables were compared by using the Chi squared test or Fisher’s exact test for a sample size of less
than five. Continuous variables were compared by using the Student t test. Probability values were of considered statistically significant if P < 0.05. All analyses were performed using IBM SPSS Statistics version 24. Nonparametric continuous data was analysed using the Mann Whitney Test. All tests performed were two tailed.

2.9 Results

2.9.1 Patient Demographics
Male to female ratio was 1:1.8. Median age for males was 41.5 years (interquartile range, IQR 26.5-57.3) and 55 years for females (IQR: 44-67.8). (P<0.0001 (95%CI 2.67 to 3.05). Overall median BMI was 29.6 kg/m$^2$ (IQR: 25.5-32.8) and hospital LOS was 7 days (IQR: 3.0 -16.0).

2.9.2 VTE Risk Factors and Comorbidities
In total, 10% of patients previously had malignancy, 15% experienced a previous trauma injury and 2.6% had a past history of thrombosis. Only three patients (2%) had previous DVT and one patient had a previous history of PE (0.66%). Diabetic conditions accounted for 17.3% of the patients. Four patients (2.7%) had leg ulcers. Only one patient used NSAID. Heart disease history within the group showed 33 females (22%) and 14 males (9.3%). Previous trauma was experienced by 10% of patients, 44 (29.3%) had previous surgery (more than 3 months previously). There were 34 (22.7%) current smokers, 13 (8.7%) ex-smokers, total of 29 (19.3%) patients never smoked. Smoking status of 74 (49.3%) were not available. No patients had a DVT and PE simultaneous, or had any of the thrombophilia. Please see Table 2.3 for associated Medical conditions.
Table 2.3 Associated Medical Conditions

<table>
<thead>
<tr>
<th>Medical Conditions</th>
<th>Number (n)</th>
<th>Percentage (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous PE</td>
<td>1</td>
<td>0.7</td>
<td>0.2 to 1.8</td>
</tr>
<tr>
<td>Previous DVT</td>
<td>3</td>
<td>2</td>
<td>2.2 to 3.8</td>
</tr>
<tr>
<td>Ulcer</td>
<td>4</td>
<td>2.7</td>
<td>3.2 to 4.8</td>
</tr>
<tr>
<td>Malignancy</td>
<td>15</td>
<td>10</td>
<td>14.2 to 15.8</td>
</tr>
<tr>
<td>Diabetic</td>
<td>26</td>
<td>17.3</td>
<td>25.2 to 26.8</td>
</tr>
<tr>
<td>Previous Surgery</td>
<td>44</td>
<td>29.3</td>
<td>43.2 to 44.8</td>
</tr>
<tr>
<td>Cardiac Disease</td>
<td>47</td>
<td>31.3</td>
<td>46.2 to 47.8</td>
</tr>
</tbody>
</table>

2.9.3 Mechanism and Type of Injury

In this study, the most common mechanism of injury was falls (81.3%). This was followed by motor vehicle accidents (9.3%), pedestrians (6.7%) and then motorbike accidents (2%). The least common injury type was bicycle accidents (0.7%). See Figure 2.1. For a detailed data breakdown of mechanism of injury and gender and age, refer to Table 2.4.
Table 2.4 Mechanism of Injury with Gender and Age

<table>
<thead>
<tr>
<th>Mechanism of Injury</th>
<th>Gender</th>
<th>18-30 N (%)</th>
<th>31-40 N (%)</th>
<th>40-60 N (%)</th>
<th>61-80 N (%)</th>
<th>&gt;80 N (%)</th>
<th>M/F Total N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls</td>
<td>Males</td>
<td>9 (6)</td>
<td>13 (8.7)</td>
<td>13 (8.6)</td>
<td>6 (20.7)</td>
<td>2 (1.3)</td>
<td>39 (25.9)</td>
<td>122 (81.4)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>10 (6.7)</td>
<td>31 (20.7)</td>
<td>25 (16.7)</td>
<td>4 (2.7)</td>
<td>83 (55.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVA</td>
<td>Males</td>
<td>2 (1.3)</td>
<td>2 (1.3)</td>
<td>4 (2.7)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>6 (3.9)</td>
<td>14 (9.3)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1.3)</td>
<td>8 (5.4)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Pedestrians</td>
<td>Males</td>
<td>2 (1.3)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td>2 (1.3)</td>
<td>5 (3.3)</td>
<td>10 (6.6)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (3.3)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>MBA</td>
<td>Males</td>
<td>2 (1.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cyclists</td>
<td>Males</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
2.9.4 Injury Type

There were broadly seven injury types in the study group. Ankle non-specific fractures were 38.7% and bimalleolar fractures were 30.6%. The third most common type of fractures were trimalleolar fractures at 19.3%. Patients with multiple other trauma fractures and ankle fractures accounted for 6.7%. Only five (3.3%) patients had bilateral ankle fractures and one (0.7%) presented with dislocation fracture. Another patient presented with a closed fracture (0.7%). Refer to Table 2.5 for a more detailed breakdown of fracture type and gender.
<table>
<thead>
<tr>
<th>Injury Type</th>
<th>Gender</th>
<th>18-30 N (%)</th>
<th>31-40 N (%)</th>
<th>40-60 N (%)</th>
<th>61-80 N (%)</th>
<th>&gt;80 N (%)</th>
<th>M/F Total N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Specific</td>
<td>Males</td>
<td>2 (1.3)</td>
<td>2 (1.3)</td>
<td>8 (5.3)</td>
<td>4 (2.7)</td>
<td>1 (0.7)</td>
<td>17 (11.3)</td>
<td>58 (38.7)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>2 (1.3)</td>
<td>4 (2.7)</td>
<td>16 (10.7)</td>
<td>14 (9.3)</td>
<td>5 (3.3)</td>
<td>41 (27.3)</td>
<td></td>
</tr>
<tr>
<td>Bimalleolar Fractures</td>
<td>Males</td>
<td>7 (4.7)</td>
<td>3 (2)</td>
<td>5 (3.3)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>16 (10.7)</td>
<td>46 (30.6)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>4 (2.7)</td>
<td>4 (2.7)</td>
<td>12 (8)</td>
<td>10 (6.7)</td>
<td>0 (0)</td>
<td>30 (20)</td>
<td></td>
</tr>
<tr>
<td>Trimalleolar Fractures</td>
<td>Males</td>
<td>4 (2.7)</td>
<td>3 (2)</td>
<td>3 (2)</td>
<td>2 (1.3)</td>
<td>0 (0)</td>
<td>12 (8)</td>
<td>29 (19.3)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>5 (3.3)</td>
<td>4 (2.7)</td>
<td>4 (2.7)</td>
<td>4 (2.7)</td>
<td>0 (0)</td>
<td>17 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Multi Trauma &amp; Ankle Fractures</td>
<td>Males</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (1.3)</td>
<td>4 (2.7)</td>
<td>10 (6.7)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>2 (1.3)</td>
<td>2 (1.3)</td>
<td>6 (4)</td>
<td></td>
</tr>
<tr>
<td>Bilateral Ankle Fractures</td>
<td>Males</td>
<td>2 (1.3)</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (2.7)</td>
<td>5 (3.3)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Closed Ankle Fracture</td>
<td>Males</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Dislocation Fracture</td>
<td>Males</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
</tbody>
</table>
2.9.5 Operative Details

Different procedure type results are displayed in Table 2.6 for the 421 patients. Overall, 84.7% of patients underwent open reduction and fixation surgery (ORIF), with a 62% usage of tourniquets during surgery. Of these patients, 72% received casts postoperatively. In total, 68% of patients received mechanical prophylaxis and 94.7% received pharmacological prophylaxis postoperatively (UH 18.0% and LMWH 76.7%).

Table 2.6 Operative Types by Number of Patients and the 95% CI

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>Number of patients N</th>
<th>Percentage %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed Reduction</td>
<td>70</td>
<td>16.6</td>
<td>0.1 - 0.2</td>
</tr>
<tr>
<td>ORIF</td>
<td>346</td>
<td>82.2</td>
<td>0.8 – 0.9</td>
</tr>
<tr>
<td>External Fixation</td>
<td>13</td>
<td>3.1</td>
<td>0.02 - 0.05</td>
</tr>
<tr>
<td>Debridement</td>
<td>62</td>
<td>14.8</td>
<td>0.1 - 0.2</td>
</tr>
<tr>
<td>Removal of Hardware</td>
<td>24</td>
<td>5.7</td>
<td>0.04 – 0.08</td>
</tr>
<tr>
<td>Unrelated Operation</td>
<td>45</td>
<td>11</td>
<td>0.08-0.15</td>
</tr>
<tr>
<td>Nil</td>
<td>22</td>
<td>5.2</td>
<td>0.03-0.3</td>
</tr>
</tbody>
</table>

The use of tourniquet in VTE group was 58.33%. The mean time for tourniquet use in VTE group was 33.42 minutes. The maximum time used was 100 minutes and the minimum time used was 28 minutes. In the group with VTE events, 91.7% of patients were immobilised for 6 weeks and 8.3 % of patients were immobilised for 8 weeks. All patients, except one, were given a cast or boot. See Table 2.7.
Table 2.7 Use of Moonboot or Cast in Patients with VTE events

<table>
<thead>
<tr>
<th>Moonboot or Cast</th>
<th>n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nil</td>
<td>1 (8.30)</td>
</tr>
<tr>
<td>Cast</td>
<td>1 (8.30)</td>
</tr>
<tr>
<td>Zimmerman</td>
<td>1 (8.30)</td>
</tr>
<tr>
<td>Moonboot</td>
<td>1 (8.30)</td>
</tr>
<tr>
<td>Back-slab</td>
<td>8 (66.70)</td>
</tr>
</tbody>
</table>

During the first operation tourniquets were used on 95% or 64% of patients. 34% or 22.7% of patients required no tourniquet and 17% or 11.3% of patient’s operations were not applicable for tourniquet use. Second tourniquets were used in 3% or 2% patients in the first operation. The mean time of tourniquet use was 59 minutes with standard deviation of 35 minutes. The mean duration of the first surgery was 1 hour 34 min with standard deviation of 0.59 minutes (IQR 1:02 - 1:52). For the first operation, an ASA score of 2 (58%) was most common, (ASA score of 1 was 39 (26%), ASA score of 3 was 28(18.7%), and ASA score of 4 was 4 (2.7%).

Of these surgical patients, 114 (76%) received casts postoperatively. Back-slab, Paris of plaster (POP) was the preferred cast of use with 106 (70.7%) of all casts used. Full cast (POP) was used in 5 (3.3%) of cases and Zimmer and Fiberglass both, each used in one (0.7%) of patients. Refer to Table 2.7. Postoperative 40% of patients required private rehabilitation or follow up with a private doctor.

2.9.6 Type and Prophylaxis Used

In total, 68% (102) of patients received mechanical prophylaxis such as GCS and or IPC and 94.7% (142) received pharmacological prophylaxis. This included UH in 18% (27) and 76.7%
(115) for LMWH. In hospital 70.7 % (106) of patients received 40 mg enoxaparin as initial dose for prophylaxis. In our sample of 150 patients, different pharmacological initial doses were administered. Prophylactic doses of 20mg or 40mg LMWH (enoxaparin) were used on some patients and in some cases 5000U UH was administered. Overall, 5.3% (8) of patients received no pharmacological prophylaxis. Of these, two patients were over 80 years of age and frail. One patient suffered a stroke at the same time as their VTE event. Two patients were in the younger age group (16-45) and two in the 46 to 60 age group with no explicit reason stated in their medical files as to the reason for withholding prophylaxis. Another patient weighed less than 45 kg. Figure 2.2 displays the rates of use of different types of prophylaxis for the study.

Figure 2.2 Type of Pharmacological and Mechanical Prophylaxis Used
2.9.7 Timing of Pharmacological Prophylaxis
Prophylaxis was started without delay in 54.6% of patients and there was a one-day delay in pharmacological administration in 28% of patients. All together 5.3% of patients did not receive prophylaxis and 12% had more than one-day delay before receiving prophylaxis. A deferment of 10 days was experienced by 8.3% of patients. UH 5000U was used as an initial dose in 16.7% of patients. The mean duration of prophylaxis was 27 days in hospital and four days out of hospital.

2.9.8 VTE Incidence
The overall in-hospital VTE incidence was 2.9% (95% CI: 1.3 - 4.4). This included 1.4% (95% CI: 0.3 - 2.5) for non-fatal PE, 0.2% (95% CI: 0.04 - 1.3) for fatal PE, 0.9% (95% CI: 0.4 - 2.4) for DVT and 0.2% (95% CI: 0.04 - 1.3) for patients that developed both DVT and non-fatal PE. At three months post-hospitalisation, our VTE rate was 4.3% (95% CI: 2.3 - 6.2) and the 30-day mortality was at 0.9% (95% CI: 0.4 - 2.4).

Of those patients that developed a VTE event, 25% had previous malignancy, 8.3% had a previous thrombosis such as DVT, 16.7% had type 2 diabetes, 25% had cardiac comorbidities and 41.7% had previous surgery (longer than 3 months before). The median length of hospital stay (LOS) for this group of patients were 27 days (IQR: 16-68 days).

Gender allocation of VTE events were 75% female and 25% male patients. The mean BMI for all patients were 27.4 kg/m². Falls equated 66.7% of VTE events, the combination of both, pedestrians versus car and motor vehicle accidents equated for 33.3% of thrombotic events.
Of the eight patients in hospital that developed a VTE event, only one of those patients was not on a pharmacological prophylaxis. Of the overall number of patients that developed a VTE event (in and out of hospital), four patients had no delay in starting prophylaxis, six had a one day delay in commencing prophylaxis, one patient had a 10 day delay, and a trauma patient with multiple fractures had a 40 day delay due to ongoing surgeries and complications.

Table 2.8 Pharma Prophylaxis Type of All Patients that Developed VTE Events

<table>
<thead>
<tr>
<th>Pharma Prophylaxis Type</th>
<th>Number of Patients</th>
<th>Percentage of VTE Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prophylaxis</td>
<td>1</td>
<td>8.30</td>
</tr>
<tr>
<td>UH</td>
<td>1</td>
<td>8.30</td>
</tr>
<tr>
<td>UH followed by LMWH</td>
<td>2</td>
<td>16.70</td>
</tr>
<tr>
<td>LMWH</td>
<td>8</td>
<td>66.7</td>
</tr>
</tbody>
</table>

When considering the entire data set, patients on only LMWH accounted for the largest group of patients who experienced a VTE event while on pharmacological prophylaxis, even compared to the patients not on any prophylaxis, of which only one patient experienced a VTE event. This complements the findings of a meta-analysis conducted by Calder et al. in 2016, which found that the use of LMWH did not significantly reduce the incidence of VTE events in foot and ankle surgery patients. This cannot, however, be attributed entirely to the use of LMWH, as there are numerous factors involved in the development of a VTE event such as the dosage and timing of the prophylaxis being administered, and individual risk factors that increase the likelihood that someone would develop a DVT or PE. Further, as this sample was from a retrospective study, not a randomised controlled trial, causality cannot be ascertained from the results (see Table 2.8). See Figure 2.3 for a graphical representation of the incidence of VTE in hospital, and three months post-discharge.
2.9.9 Complications

The type of complications following surgery varied. This included one patient with an asthma attack (0.7%), three with DVT (2.0%), and two with PE (1.3%). Post discharge one patient had a PE approximately 14 days postoperatively and another suffered both a PE and CVA. In addition, one patient developed an infection of the wound site and one developed an ulcer. An operation was required by 25 (16.7%) patients. Complications after the second operation included one PE (0.7%), two patients with DVT, one patient with infection and one patient had a “Pre-Arrest Criteria for Escalation” or a PACE call. A third operation was required in 11 (7.3%) patients. One patient had a PE (0.7%) and one (0.7%) had non-healing of wound. Another patient (0.7%) died of respiratory complications. One patient, (who was on warfarin for 11 days after major MVA trauma), died due to perineal and renal bleeding (0.7%). There
were no other major or minor bleeding complications noted and no transfusions were necessary.

2.10 Discussion

It is still a contentious issue whether pharmacological prophylaxis is warranted after foot and ankle surgery. There is no good evidence for prophylaxis due to a lack of high-quality large population–based studies on the incidence rates of VTE after ankle and foot surgery. The incidence of DVT after ankle fractures may not be as low as some studies perceive it to be. It is an acknowledged fact that after immobilisation of the lower limb, thromboembolism is a likely complication. Nevertheless, NICE guidelines continue to recommend thromboprophylaxis for patients undergoing foot and ankle surgery by extrapolating the risk data from joint replacement studies.

Results from this study showed an overall in-hospital VTE incidence of 2.9 % (95% CI: 1.3-4.4). This included 1.4 % (95% CI: 0.3 -2.5) for non-fatal PE, 0.2 % (95% CI: 0.04 -1.3) for fatal PE, 0.9 % (95% CI: 0.4 - 2.4) for DVT and 0.2 % (95% CI: 0.04 -1.3) for patients that developed both DVT and non-fatal PE. Our study had no complications from wound hematoma and poor wound healing. Furthermore, we had no complications from the use of thromboprophylaxis, such as heparin induced thrombocytopenia (HIT) and no patients developed HIT.

Our results yielded a fairly low rate of VTE incidence after ankle fractures for patients on prophylaxis, which is in line with the existing literature. Our results have, however, highlighted that there is a delay in the onset of VTE for some patients of up to three months post-hospitalisation, and therefore it is critical that patients continue to be monitored post-
discharge, and that prolonged prophylaxis should be considered. While there is limited information available on VTE events and ankle fractures, studies examining other patient populations, such as those with a spinal cord injury, have similarly noted that there continues to be a delay of up to three months in the development of VTE events for some patients.\textsuperscript{133}

Prolonged prophylaxis continues to be a more cost-effective solution, even considering the low incidence of VTE events in this population, when compared against the high cost of dealing with a VTE event and subsequent complications, as noted in Chapter Three. It appears, however, that certain pharmacological prophylaxis may be more effective than others for ankle fractures. When examining the patients of our study who did go on to develop a VTE event, we noticed that patients on LMWH prophylaxis experienced the highest rate of VTE events, with five patients of the eight who developed VTE in hospital (or approximately 41.7%) receiving LMWH prophylaxis at the time of the VTE event. This result supports the findings from a recent meta-analysis in which LMWH did not demonstrate a significant reduction in the likelihood of developing a VTE event compared to no prophylaxis.\textsuperscript{40} This finding should be interpreted with caution, as our study was not a randomised control trial, and other factors such as dosage, timing, and health comorbidities may have play a role in the development of the VTE event for these patients.

In a multicentre study on VTE following foot and ankle surgery in 1998, Mitzel et al. evaluated 2733 patients for preoperative risk factors and postoperative thromboembolic events. Major bleeding risk associated with pharmacological prophylaxis was reported low in trials (1.5%-4%),\textsuperscript{213} however, clinicians and patients may perceive this risk as significant. However, all pharmacological prophylaxis carries an associated risk of bleeding and in some cases, such as after major trauma, pharmacological prophylaxis may be precluded. Surgeons may be
understandably reluctant to expose patients to the risk of excessive intra- or postoperative bleeding and the subsequent complications, especially in procedures such as joint replacement where bleeding can lead to severe infections and a need for explants of prostheses. When pharmacological prophylaxis cannot be used, mechanical methods may then become crucial for VTE prophylaxis.\textsuperscript{173} Our study had no incidence of major or minor bleeding and no blood transfusion were needed, even though most patients were on pharmacological prophylaxis.

In a study by Shah et al, they concluded that the majority of surgeons did not recommend prophylaxis for foot and ankle surgery in the absence of clear VTE risk factors. Presumably the rationale for this is based on weighing the presumed low incidence of VTE after foot and ankle surgery against the complications of thromboprophylaxis, such as wound haematoma, heparin induced thrombocytopenia (HIT) and poor wound healing.\textsuperscript{133} Our study also reported no HIT complications from any of our patients.

A systematic review by Cochrane, Testroote et al, of six RCT’s with a total of 1490 patients, had incidences of injuries of the lower limb immobilised by a plaster cast or brace. The control group (n=740) received no prophylaxis or placebo, the prophylaxis group (n=750) received LMWH once daily. Major adverse events such as haematoma, acute bleeding, allergy, and thrombocytopenia were rare. Only a few events were reported, the majority of which were bleeding events leading to the discontinuation of LMWH administration; two patients in the treatment group and one in the placebo group had to discontinue the LMWH due to major bleeding events. In the treatment group, minor bleeding events were reported in up to 8% of cases. Although we had one patient die from renal bleeding, it is assumed the patient had long standing illness and was on warfarin before fracture of ankle. We had no other major or minor reports of bleeding. The complications of major bleeding events were extremely rare (0.3%)
and no reports of HIT. Testroote et al. concluded that LMWH should be considered in adult patients with immobilisation of the lower leg to prevent occurrence of venous thromboembolism. It should not only be considered in patients with an above-knee cast but also in patients with a below-knee cast as well. LMWH can safely be used for this indication.\textsuperscript{10}

Testroote et al. also studied the risk of VTE in patients with lower limb injury who had been immobilised in a brace or plaster cast for at least one week and received no prophylaxis. Their findings showed a wide range for the risk of VTE from 4.3\% to 40\%. The authors concluded that use of LMWH in outpatients significantly reduced VTE events when immobilisation of the lower leg was required.\textsuperscript{10} Our study showed a post three month hospital rate of 4.3\%, similar to the lower range of VTE risk of Testroote et al.

In 2017, a systematic literature review by Cochrane, Zee et al. included eight studies and a total of 3680 for their review (until April 2017).\textsuperscript{221} Participants received either a placebo, no preventative treatment or LMWH subcutaneously once daily. The control groups presented with new DVT cases ranging from 4.3\% to 40\%. In the LMWH groups it ranged from 0\% to 37\%, thus for the participants who received LMWH their risk of developing DVT event was lower. When comparing LMWH to no treatment or placebo in the following groups of participants: patients with below-knee casts, conservatively treated patients (non-operated), operated patients, those with fractures, patients with soft-tissue injuries, those with above knee thrombosis, and patients with below-knee thrombosis, analysis showed a reduction in the occurrence of DVT.\textsuperscript{221}

However, for PE no clear differences were found between control and LMWH groups. The control groups had more symptomatic VTEs when compared with the LMWH groups. No
deaths due to PE were reported. In the control group of one study one death was reported. Thus, very few adverse effects were found in the treated patients. A few minor cases of bleeding, such as nose bleeds, blood in urine and dark stools were the only adverse events noted. DVTs in adult patients were reduced with the use of LMWH when immobilisation of the lower limb was required, compared with patients with no prophylaxis or placebo given. Due to the risks of bias in some trials, such as lack of blinding of participants, or unclear reasons for excluding participants from the analyses, a study by Zee et al. downgraded the quality of the evidence to moderate quality. Low quality evidence showed no clear differences between LMWH and the control groups regarding PE. However more symptomatic venous thromboemboli in the control groups. Due to methodological issues and imprecision of the results, Zee et al. downgraded the quality of evidence.\textsuperscript{221} Blanco et al 2017 states that evidence have shown that the use of LMWH might reduce the severity of a VTE event but not the incident.\textsuperscript{228}

It is clear that developing VTE is a complex process and that there are several factors playing a role in the development and also in the prevention of VTE. A patient’s own history and several other risk factors play a role in the acquisition of a VTE. The risk factors from our study varied. Patients that developed VTE in our study were mostly older than 46 years of age (83.3\%). A Study by Basques et al. stated that and age over 60 years of age was associated with an increased rate of VTE.\textsuperscript{229} Patients with previous malignancy accounted for 25\% and patients with cardiac problems, 25\%. Basques et al. also showed that patients with insulin dependent diabetic mellitus (IDDM), were associated with an increased rate of adverse events after ankle fracture ORIF. In our study 16\% of our VTE patients were diabetic type 1 patients. Those who had previous surgery (more than three months before) were 41.7\%. Basques et al. also noted that an ASA classification of three or greater played a role in VTE events. In our study of those patients who had VTE events, 25\% had a higher or equal ASA score of three.
Tobacco consumption plays a role in the development of VTE. It is a known fact that smoking is a well-established risk factor for atherosclerotic disease, and Cheng et al. found that cigarette smoking is associated with a slightly increased risk for VTE. Our study showed that of the patients with a VTE event, 16.7% were ex-smokers and 33.3% were current smokers. This relates to the finding from Cheng et al. The smoking status of 16.7% patients were unknown and 33.3% of the VTE patients never ever smoked. Only one patient who developed a massive postoperative DVT had a previous history of DVT. All patients, except one, received a moonboot or cast and was immobilised. Thromboembolism is a well-recognised complication of cast immobilisation of lower limb. DVT may linger “concealed” under plaster casts of the lower limb and can reveal only upon removal of cast or can manifest itself as a PE. Therefore, it is of utmost importance to risk assess all patients upon presentation to provide prophylaxis to high risk patients. Thus, the risk of VTE and thromboprophylaxis should be discussed with all patients especially whenever treatment entails lower limb immobilisation.

One of the strengths of our ankle fracture study is that after three months post discharge, patients were followed up and included in our data. At three months post-hospitalisation, our VTE rate was 4.3% (95% CI: 2.3 - 6.2) and the 30-day mortality was at 0.9% (95% CI: 0.4 - 2.4).

A potential limitation of the study is a minor amount of missing data, such as a patient’s height and weight. A drawback of the study is the transfer of some patients from the public system into private system for surgery and/or rehabilitation. Some patients might have had their VTE events diagnosed elsewhere and that data from those patients whom were seen in a private setting or who chose to have follow-up care elsewhere, were not able to be captured and it could potentially lead to a reporting information bias. Any patients that died at home from PE
may not be included in the study. Furthermore, routine autopsy is not performed anymore, and PE related deaths may be disguised as heart or respiratory problems and not reported as the cause of death, thus VTE events may be much higher than anticipated. Further research is required on the economic impact on the use of prophylaxis reducing the risk of VTE in hospital and beyond discharge.

According to the meta-analysis by Calder et al., studies that have only assessed for the presence of VTE using clinical assessment have a lower incidence of VTE in foot and ankle surgery patients, with patients on prophylaxis displaying a rate of about 1%.\textsuperscript{40} In contrast, however, they found that ankle and foot surgery patients on prophylaxis who were assessed using radiological assessment displayed a much higher incidence of VTE events, at approximately 7.9%. This suggests that patients who are only clinically assessed are being underdiagnosed for VTE events, which can easily lead a fatal PE event or significant health complications long-term. Overall, our sample was limited to clinically assessed VTE and as such, the true incidence of VTE events in the patient group could have been significantly higher events. As such, studies examining the incidence and outcomes of ankle fracture patients should consider the use of radiological assessment to ensure all VTE events are captured.

\textbf{2.11 Conclusion}

Our in-hospital VTE rates were kept relatively low (2.85\%) with the use of appropriate prophylaxis. Total VTE after three months was 4.3 \% (95\% CI: 2.3 - 6.2) and the 30-day mortality rate was at 0.9\% (95\% CI: 0.4 – 2.4). The rate of PE was higher than that of symptomatic DVTs. Given a 1.5-fold increase in the VTE rate beyond hospitalisation, prophylaxis should be considered and prescribed at an individual level, based on mobility, surgery and underlying thrombosis risk and other individual risk factors.
CHAPTER THREE: Economic Burden of VTE

3.1 Abstract

3.1.1 Introduction

VTE is a common complication during and after hospitalisation for medical and surgical patients such as those requiring orthopaedic surgery. Currently there is limited data on the economic impact of prophylaxis on VTE and bleeding in MOS in the Australian setting and worldwide.

3.1.2 Aims

The objective of this chapter is to highlight the economic burden of orthopaedic-related VTE. It will further review and present updated cost estimates for VTE prevention, treatment, and complications with the use of pharmacological prophylaxis for orthopaedic surgery of the lower limbs, not only as it pertains to the patients, but also its financial impact on the wider community.

3.1.3 Methods

A literature search strategy was performed between the 1st Jan 1998 to 15 Dec 2019 (retrieval period). The searches were performed using OVID that included databases such as EMBASE, PubMed, and Cochrane Database of Systematic Reviews, Health Economic Evaluations Database, Journal Club and Database of Abstracts of Reviews of Effects (DARE). Additional studies were identified by hand searching references of relevant publications.

3.1.4 Results

For major orthopaedic surgery (MOS), findings showed good economic savings when selecting LMWH over UH for pharmacological prophylaxis, however conflicting results for LMWH
compared to DOACs. The cost of treatment of a DVT and/or PE event was high, however this varied between countries due to differences in healthcare systems. The cost of bleeding was found to be consistent between countries.

### 3.1.5 Conclusion

These findings reflect the high economic burden for VTE, highlighting the importance of prevention both in-hospital and beyond hospitalisation. This highlights the importance of preventative measures which will lead to significant savings compared to the diagnosis and treatment of VTE, thereby improving quality of life and healthcare costs for VTE at both the individual and global level.

### 3.2 Introduction

Without VTE prophylaxis, the overall VTE incidence ranges up to 40% to 60% in major orthopaedic surgery (such as THR, TKR and hip fracture surgery) and it is as high as 12.2% following ankle fracture and surgery.\(^{40}\) Using routine VTE prophylaxis, fatal PE is uncommon in orthopaedic patients and the rates of symptomatic VTE within three months are in the range of 1.3% to 10%.\(^{165}\)

The reported death rate within one month of diagnosis occurs in approximately 6% of DVT patients and approximately 12% of PE patients.\(^{14}\) Additionally, VTE can result in long term chronic complications such as CTEPH and PTS (usually with poor prognosis). The cumulative ten-year incidence of recurrent VTE reaches 39.9% (35.4% to 44.4%)\(^{15}\) and approximately 5% to 10% of patients with symptomatic DVTs develop severe PTS which may take up to 10 years or more to develop.\(^{6}\) Pharmacological prophylaxis can result in acute complications such as HIT. In addition, surgeons should take care when prescribing pharmacological prophylaxis,
because of the possible risks of bleeding associated with surgical procedures. Given VTE events are not fully comprehended and that limited information on the economic impact of these VTE events is available, more research is needed on the economic impact of VTE of the lower limb orthopaedic patients.

If we try to assess the economic impact of VTE we need to put a monetary value on a human life which in itself is problematic. This value would have to include a person’s economic contribution to society, earning a salary, paying taxes, and participating in the activities of their milieu. An economic value also known as a willingness to pay, is commonly used to quantify the benefit of avoiding a fatality. A reduction in risk to that on average one less person is expected to die from that risk is the appropriate way to estimate that known value. This is known as the value of statistical life (VSL). Previous financial studies into the saving of lives from disease lead to the definition of VSL in the context of environment, health, occupational health and safety, transport and airspace policies and regulation.³⁰

Based on international and Australian research a credible estimate of the value of a statistical life in Australia was $4.2 million dollars and the value of statistical life year in 2014 was estimated to be at $182,000 Australian dollars (AUD). An economic evaluation of this incorporating a 4.44% inflation rate indicates the value of a statistical life as $4.5 million AUD (2019) and the value of statistical life year as $197,000 AUD for 2019 in Australia. The VSL in the United States of America (USA) seems to be much higher. For example, calculations for VSL in USA for 2018 by Kip Viscusi of Princeton University Press, approximated the value as $10 million United States dollars (USD).²³⁰
To estimate the benefit of preventing a disease, it is imperative to calculate the total cost of the disease. VTE is a frequent medical condition that encompasses DVT and PE, including long-term complications such as PTS and CTEPH. VTE is both an acute and chronic disease. It gets more intricate to calculate the value of a life once the cost of morbidity needs to be included. It is therefore very important to note that the economic burden of VTE is not confined to the diagnosis and treatment of the initial event, but also the VTE recurrences and the long-term chronic complications that create additional and future medical costs, e.g. more medicine, rehospitalisation, rehabilitation and long-term complications. Other economic factors include income losses for businesses, for example the cost of mortality, sick days taken, temporary replacement staff needed, loss of time and money invested in training an employee, cost of recruiting and then retraining. Patients may experience job losses and thus loss of income. The government loses out on receiving taxes due to unemployment, and it adds burden on the government to provide social and economic support to people effected by thromboembolism. The community at large may also be negatively influenced due to less disposable income of the patient to participate in their local community. Additionally, the cost of disability and premature death including the cost of funerals needs also to be taken in consideration.\textsuperscript{181} All of the above factors accumulate and add to the increasing cost. In addition to this they play a significant role in the economic burden of VTE, however the limitation is that there is a paucity of data on the total economic burden of PE and DVT worldwide.

Given VTE events are not fully comprehended, and that limited information on the economic impact of these VTE events is available, more research is needed on the economic impact of VTE of the lower limb orthopaedic patients.
3.3 Methodology Literature search

3.3.1 Databases for Literature Retrieval

This systematic literature review was prepared to identify and to explore the economic burden of VTE worldwide, not only the healthcare cost, but also the impact on the economy as a whole. This includes loss of patient income and the consequences of loss of working days due to sickness, tax revenue loss, medical and/or funeral costs. Medical literature was retrieved between the period of 1st January 1998 to 15th of December 2019 using OVID that included databases such as EMBASE, PubMed, Cochrane Database of Systematic Reviews, Health Economic Evaluations Database, Journal Club and Database of Abstracts of Reviews of Effects (DARE).

3.3.2 Search Terms and Selection Criteria

A predefined strategy was employed to search and screen medical published articles with keyword search terms such as “venous thromboembolism”, “venous thrombosis”, “pulmonary embolism”, “orthopedic” or “orthopaedic”, “surgery of lower limb”, “surgery of hip”, “surgery of knee”, "surgery of ankle”, “costs and cost analysis”, “cost-benefit analysis”, “economics, hospital”, “economics, medical”, economics, pharmaceutical”, and/or “cost of illness” to identify burden-of-disease studies, cost-of-illness studies, and cost analyses. Related publications’ reference lists were scrutinised to find supplementary studies related to the topics of interest.
3.3.3 Selection Criteria and Data Extraction

Publications were included if direct or indirect costs for the treatment or management of VTE were reported in monetary terms (refer to Table 3.1). Publications with hospital costs, including hospital LOS, readmission, complications and costs to health care plans and health systems were also utilised. Selected studies included observational design, retrospective analysis of health care claims, randomised controlled trials or meta-analyses of randomised controlled trials comparing at least two different VTE prophylaxis strategies in major orthopaedic surgery.
Table 3.1 Types of Costs Reported in Monetary Terms

<table>
<thead>
<tr>
<th>Direct Costs</th>
<th>Indirect Costs</th>
<th>Intangible Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital in patient cost</td>
<td>Carers’ lost productivity</td>
<td>Patient pain and suffering</td>
</tr>
<tr>
<td>Outpatient and other Healthcare costs</td>
<td>Productivity losses from premature death</td>
<td>Patient life quality decline</td>
</tr>
<tr>
<td>Funeral Costs</td>
<td>Search and hiring costs</td>
<td>Patient possible anxiety and depression</td>
</tr>
<tr>
<td></td>
<td>Reduced workforce participation and absenteeism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Deadweight losses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Taxation revenue forgone from people with VTE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Taxation revenue forgone from informal carer of people with VTE</td>
<td></td>
</tr>
</tbody>
</table>
3.3.4 Results of Literature Search

The literature search identified 182 records. From the 182 potentially relevant citations, 30 were excluded based on title and abstract. The full text versions of 152 manuscripts were retrieved and evaluated. Of these, 133 did not meet the level 1 inclusion criteria. After screening, only 19 studies met the orthopaedic selection criteria. Of these, 16 studies were included from the database searching, and three studies were identified from reviewing reference lists. Two reviewers (AD, KH) independently assessed each of the articles based on the criteria mentioned above.

Figure 3.1 Flow Diagram of Literature search for the Economic Burden of VTE
3.4 Data Extraction Results

A summary of the studies reporting data on VTE economic burden (prevention, complications, and treatment costs) is presented in Tables 3.2 to 3.4. Various study designs were used to assess the costs of managing VTE patients in the inpatient and/or outpatient settings. There were 19 studies identified that were eligible.

3.5 Cost Burden

VTE events have important clinical and economic consequences. The cost associated with VTE events, recurrence and long-term complications is complex and intricate. In 1987 Oster et al. published the first economic analysis of VTE prophylaxis. It included VTE related deaths and clinically detected DVT and/or PE events. It also included asymptomatic VTE events only detected by diagnostic procedures. Unconfirmed clinical suspected events were included to model the diagnostic associated cost. Recurrent VTE, PTS and haemorrhage events were not included in the cost modelling. Wolowacz et al. noted that later modelling included bleeding events and that Markov modelling included long term events.

3.5.1 Cost Comparisons of Pharmacological Prophylaxis

Out of the 19 studies identified in the systematic search, 10 were identified as examining the cost efficacy of different forms of pharmacological prophylaxis for VTE, see Table 3.2 for the complete list of relevant studies. Authors, year, country, costing period, follow up period, design and population, frequency and cost outcomes were presented as headings in the table. In total, there were four reported studies from Europe, one from the UK, three from the USA.
and one from China. Two studies compared the cost efficacy of UH (unfractionated heparin) with LMWH (enoxaparin). One compared the DOAC rivaroxaban with LMWH (enoxaparin). Another three studies compared the cost benefit of fondaparinux and rivaroxaban with LMWH (enoxaparin). Another study compared the cost benefit of two different NOACs (rivaroxaban and dabigatran) with LMWH (enoxaparin). The one study compared the cost efficacy of two different DOACs (apixaban versus dabigatran). The last study compared cost efficacy of enoxaparin (LMWH) with a DOACs (apixaban).

When comparing UH to LMWH, there appears to be a strong economic savings when selecting LMWH. In 2002, cost-modelling revealed a primary net savings of approximately USD$89 per US patient, when utilising LMWH in lieu of UH\textsuperscript{233}, which is likely a higher figure using today’s rates of inflation. In 2004, cost-modelling for the UK noted that utilising LMWH yielded an annual cost of £3.2 million, compared to an annual cost of £4.4 million when using UH.\textsuperscript{234}

Newer studies (both conducted in 2012) assessing the cost of LMWH (enoxaparin) versus a DOAC (rivaroxaban) have garnered mixed results. In the USA rivaroxaban was more cost effective than enoxaparin, resulting in a net savings of between USD $465.74 to USD $511.93 per patient for TKR and THR respectively.\textsuperscript{235} In contrast, in Europe, utilising rivaroxaban was more expensive than utilising enoxaparin in preventing VTE, reducing hospital profit between €20.60 to €31.80 per patient for TKR and THR respectively.\textsuperscript{236} A decade earlier, utilising fondaparinux in Europe, was more cost effective than enoxaparin, providing a cost savings of £27 per (post-orthopaedic surgery) patient per year.\textsuperscript{237} A study in 2011 estimated a cost saving of $162 per patient using rivaroxaban instead of enoxaparin.\textsuperscript{238} However, it was noted that enoxaparin was more cost effective in China in 2016.\textsuperscript{239}
A study conducted in Europe in 2012 compared enoxaparin with two DOACs. This included apixaban and dabigatran both in effectiveness in preventing VTE, and the financial cost.\textsuperscript{239} The results indicated that after five years of use apixaban was both more clinically effective and more cost effective in both TKR and THR.

### 3.5.2 Cost of VTE Treatment Complications

From the 19 studies identified, five were used for the VTE complications cost table in Table 3.3. In total, there were three reported studies from the USA, one from Europe, and one from Canada. Authors, year, country, costing period, time, currency, cost expression, follow up period, design and population, frequency and cost outcomes were presented as headings in Table 3.2. Complications included in this analysis related to two primary areas, PTS following a VTE event, and bleeding as a result of pharmacological prophylaxis, both in prevention and treatment of VTE.

Of the five studies identified, two related to bleeding events after the use of prophylaxis and three were related to the cost of treatment of PTS. When evaluating the cost of bleeding, figures were produced for post orthopaedic surgery patients, who were on prophylaxis in 2007 in the US, ranging from approximately $29,500 to $31,100.\textsuperscript{240} This fits in with findings from a 2011 Canadian study which found that for those on treatment for prophylaxis in the study, the cumulative cost was $183,000 000, when divided by the amount of patients, (4849 who developed bleeding events), receiving this treatment, this translated to roughly $38,000 per bleeding event per patient.\textsuperscript{241}

In the studies that examined the cost of PTS, a secondary syndrome associated with VTE, the expenditure was broken down by cost in the first year versus the cost from the second year
onwards. In 2003, for patients with moderate or mild PTS, the findings were that most people had costs around the $839 USD per year and thereafter $341 per year.\textsuperscript{242} Severe PTS cost $3817 for first year and then $1677 thereafter.\textsuperscript{242} This ties in with a French study in 2006 for inpatients that estimated the cost of PTS as €3778 per year. Their yearly cost of PTS for inpatients were estimated by Tilleul et al. as €16, 6 million (2006 Euro).\textsuperscript{243} Total annual costs of VTE associated with major orthopaedic surgery from the French Health Fund were estimated to be about 60 million € over one year with 28 million € for inpatient care and 30 million € for recurrences and PTS.\textsuperscript{243}

### 3.5.3 Treatment Cost

In Table 3.4, 10 of the initial 19 studies were used for the VTE treatment cost table. Of these, seven reported data from the USA, one from Europe, one from the UK, and one from Canada.

Three USA studies from the early 2000s reported the VTE cost as split between primary DVT and PE. The initial two studies provided cost figures that ranged from $4,159 to $7,560 USD for DVT and $5,567 to $10,485 USD for PE patients.\textsuperscript{244} In contrast, the most recent of the American studies provided a much higher cost figure, at $17,114 for DVT and $18,521 USD for PE, almost $10,000 dollars difference.

Other studies based in the mid 2000’s reported costs as inpatient or outpatient costs for VTE treatment. In the USA, the cost of VTE as an inpatient was around $50,000 per patient and as outpatient around $41,000 per patient.\textsuperscript{202, 231} A European study reported the total VTE cost of inpatient at around €9,444,812, and total outpatient costs as €5,910,829.\textsuperscript{243} In 2008 the cost of DVT compared to non-DVT orthopaedic surgery patients found that DVT patients incurred a
### Table 3.2 Cost Comparison of Pharmacological Prophylaxis

<table>
<thead>
<tr>
<th>Authors, year, country</th>
<th>Costing period</th>
<th>Study Design</th>
<th>Population</th>
<th>Time of Period</th>
<th>Type of cost</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottman MF et al. 2002, USA</td>
<td>Short term 7 days. Long term from event to death of 100 years (when ever comes first)</td>
<td>Decision-analytic model</td>
<td>THR and any VTE events and/or PTS (cerebral modelling performed)</td>
<td>1983-2001</td>
<td>Compare enoxaparin with Warfarin (USD)</td>
<td>Primary net cost enoxaparin $138/patient and $64.67/PTES/patient, and a net savings of $89 per patient on Enoxaparin. Enoxaparin vs Warfarin $27722/ Qaly saved. Cost avoided 1983/VT events $1728 and cost avoided $34.47/ death. Enoxaparin reduced VTE events by 77 cases/ 1000 surgical procedures &amp; VTE-related deaths from 11 to 7 (7/1000 procedures)</td>
</tr>
<tr>
<td>Giroud LS et al. 2003 Europe</td>
<td>Short term 7 days. Long term 5 years</td>
<td>Decision analysis model and weighted cohort</td>
<td>132,000 patients with THR, TKR and hip fractures. Comparison enoxaparin versus fondaparinux cost effectiveness</td>
<td>2000-2005</td>
<td>Cost saving €27/year with fondaparinux. At 5 years expected to be 23.2 fewer clinical VTE events &amp; 5.9 fewer VTE related deaths/ 1000. Fewer VTE events for THR (15.0) &amp; TKR (19.5). Fewer VTE related deaths (8.8 for THR &amp; 0.7 for TKR)/ 1000 procedures . Cost savings, THR €173, TKR (€58) HFS (€129)</td>
<td></td>
</tr>
<tr>
<td>Reeves et al. 2004s United Kingdom</td>
<td>12 months</td>
<td>Decision tree model</td>
<td>Major orthopaedic surgery as acute medical intervention/treatment of diagnosed VTE</td>
<td>2002</td>
<td>Comparison of UH and LMWH Mean cost of prophylaxis (UK £)</td>
<td>LMWH annual estimated cost £8.2 million and UH annual estimated cost £4.4 million</td>
</tr>
<tr>
<td>Short AF et al. 2007 USA</td>
<td>The study period for all outcomes encompassed index hospitalisation + two months postdischarge or until inhospital death, whichever came first.</td>
<td>Retrospective observational cross-section, cohort analysis of inpatient billing data after orthopaedic surgery</td>
<td>Inpatient after orthopaedic surgery</td>
<td>2007-2008</td>
<td>Total mean costs of anti-coagulants, comparing UH, LMWH, dalteparin and fondaparinux</td>
<td>No complication mean cost $18,376 - $14,934. VTE $31,607 - $34,692. Major bleeding $30,109 - $29,540. Mean cost UH most costly ($20,815) and fondaparinux lowest cost ($18,019).</td>
</tr>
<tr>
<td>Kwong LM 2011 USA</td>
<td>Short term 10-14 days and longterm 31-39 days</td>
<td>Prospective study</td>
<td>Post-orthopaedic surgery/arthroplasty population</td>
<td>2007-2008</td>
<td>Total mean costs, comparison of prophylaxis/rivaroxaban versus enoxaparin</td>
<td>Sa691/patient with enoxaparin &amp; 3607 rivaroxaban, a cost saving of $162/patient. THA, 35 days of rivaroxaban saved $5945 symptomatic event avoided vs 14 days enoxaparin and a cost saving of $82 perennial vs 35 days enoxaparin. In TKA, 12 days of rivaroxaban a cost saving of $249 and 16 fewer symptomatic events per 1000 patients vs 12 days of enoxaparin twice daily &amp; per-patient savings of $284 &amp; 18 fewer symptomatic events/1000 patients vs enoxaparin 40 mg once daily.</td>
</tr>
<tr>
<td>Gómez-Cordero JS et al. 2012 Europe</td>
<td>Short term 90 days. Long term 5 years</td>
<td>Decision-analytic model</td>
<td>TKR or THR</td>
<td>2003-2004</td>
<td>Compare apixaban vs dabigatran &amp; mean cost of prophylaxis (Euro €)</td>
<td>Apixaban lower costs per patient in TKR - €14. Additional cost in THR €15. In 5 years apixaban was cheaper and more effective in both TKR and THR</td>
</tr>
<tr>
<td>Dunin A et al. 2012 USA</td>
<td>Short term Long term 5 years</td>
<td>Decision-analytic model</td>
<td>RECORD III trials (three studies) for THR or TKR</td>
<td>Short and long term</td>
<td>Compare enoxaparin vs rivaroxaban &amp; mean cost of prophylaxis (USD)</td>
<td>Cost savings rivaroxaban was $511/58/patient, prevents 0.145 symptomatic VTE events/patient in THR. THR: $2085/patient, prevents 0.105 symptomatic VTE events/patient</td>
</tr>
<tr>
<td>Zidile S et al. 2012 Europe</td>
<td>Short term 7 days. Long term (event death or 100 year which ever comes first)</td>
<td>Decision tree model</td>
<td>THR or TKR (RECORD I and II trials)</td>
<td>Short and long term</td>
<td>Rivaroxaban versus enoxaparin for VTE prevention (Euro €)</td>
<td>Compare enoxaparin vs rivaroxaban reduced profit €31.80/patient in THR (preserving 0.74 symptomatic VTE events) and reduced profit in TKR €52.60/patient, preventing 0.005 symptomatic VTE events/patient. For THR prophylaxis non significant cost effectiveness ratio of 0.875/ VTE event avoided and the expenditure was €5.7 million for THR with potential saving for TKR (€4.7 million)</td>
</tr>
<tr>
<td>Moncuny M et al. 2014 Europe</td>
<td>Short term and long term</td>
<td>Decision analytic model and literature review</td>
<td>THR and TKR patients in Europe</td>
<td>5 years</td>
<td>Comparison of enoxaparin and rivaroxaban costs/dabigatan. Mean cost of prophylaxis.</td>
<td>Rivaroxaban reduced profit €30.46/patient vs enoxaparin (THR) vs dabigatan the incremental cost ranges €5.7-€11.6. In TKR incremental cost against enoxaparin ranges from €65.5-€137., versus dabigatan that ranges from €6.6-€28</td>
</tr>
<tr>
<td>Yan X et al. 2016 China</td>
<td>Short term and long term</td>
<td>Decision tree model and Markov modeling</td>
<td>Patients after TKR in China</td>
<td>5 years</td>
<td>Comparison of enoxaparin and apixaban. Mean cost of prophylaxis.</td>
<td>Apixaban more costly (USD 50/sh patient). Enoxaparin is more cost effective in China</td>
</tr>
</tbody>
</table>
total cost of $9,251, whilst non DVT patients incurred only $7,182 per event, providing an increase of over $2,069.\textsuperscript{245}

In the latter part of 2000s, procedures with VTE events were broken down into procedure costs. For example, THR with VTE was about $53,000 USD and TKR with VTE about $78,000 USD (2017).\textsuperscript{246} A major Canadian study had 7974 patients who developed a VTE event with a cumulative all-cause healthcare costs of $292,690,000 Canadian dollars. Most recently, a study from the UK focused on VTE direct costs, (£25 for VTE) overnight costs of £17,860 (including bed costs). VTE cost was estimated at £7,000 for ED admission.\textsuperscript{247}
<table>
<thead>
<tr>
<th>Authors, year, country</th>
<th>Costing period</th>
<th>Time, Currency, Cost Expression</th>
<th>Follow up period</th>
<th>Design and population</th>
<th>Frequency</th>
<th>Cost Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botteman MF et al., 2002, USA</td>
<td>Short term 7 days. Long term from event to death age 100 years</td>
<td>2002 USD</td>
<td>From surgery until death or age 100 years</td>
<td>Decision-analytic model. THA and any events and/or PTE, compare enoxaparin vs warfarin</td>
<td>31.5% severe PTE with open ulcer, 68.5% severe PTE with healed ulcer, 20.8% of recurrent VTEs is PE.</td>
<td>Enoxaparin reduced PTE by 21 cases/1000 initial surgeries and reduction from 89 to 69 idiopathic cases. $222/patient extra savings with enoxaparin, net lifetime savings $889/patient.</td>
</tr>
<tr>
<td>Caprini et al., 2003, USA</td>
<td>12 months</td>
<td>2003 USD</td>
<td>12 months</td>
<td>Retrospective study and Markov modelling, patients with THA vs prophylaxis over 12 months</td>
<td>Long-term complications of a primary DVT (with prophylaxis) was 5% to 20% and without prophylaxis was 50% in THRs.</td>
<td>Mild-moderate PTE, $859 1st year, then $354/year; PTE, $3817 1st year, then $1677/year; DVT, $3796; PE, $60644. Mean lifetime cost of DVT complications ranged between $2091 - $4279 (mean $3069).</td>
</tr>
<tr>
<td>Tilead P et al., 2006, Europe</td>
<td>12 months</td>
<td>1999 Euro</td>
<td>12 months</td>
<td>Retrospective analysis of annual costs of VTE associated with MOS using a decision tree and various data sources 216,916 patients hospitalised for major orthopaedic surgery DVT, n=280; PE n= 665. THA &amp; TKR surgery.</td>
<td>No Prophylaxis DVT rates 45% - 65%, (99% THA and 53% TKR). No Prophylaxis PE rates 16% (94% THA &amp; 2% TKR). With prophylaxis DVT rates for THA a mean of 19% (15% - 31%) and TKR a mean of 31% (9% - 40%). PE was 0.7% with prophylaxis and Fatal PE 0.1%.</td>
<td>PTS cost €3,778/patient. PTS cost in France (impacts) yearly €16.6 million. Annual cost of 30 million € for VTE recurrences and PTS.</td>
</tr>
<tr>
<td>Short AP et al., 2007 USA</td>
<td>The index hospitalisation + two months postdischarge or until in-hospital death, whichever came first.</td>
<td>2005 S US Dollars</td>
<td>Two months post discharge</td>
<td>Retrospective observational cross section, cohort analysis of inpatient billing data after orthopaedic surgery (500+ hospitals)</td>
<td>Major orthopaedic surgery without prophylaxis has a VTE risk of 40-60%. 1.1% to 1.9% of patients had a major bleeding episode. With prophylaxis 1.4% &amp; 2.8% develop DVT &amp; 0.8% - 1.2% will experience PE.</td>
<td>Regardless of prophylaxis, No complication mean cost $18,376 - $14,934. VTE $31,067 - $34,692. Major bleeding $50,109 - $29,540. Mean cost fondaparinux lowest $18,019. IH most costly ($20,835).</td>
</tr>
<tr>
<td>Veikemanis P et al., 2011 Canada</td>
<td>2004-2008</td>
<td>2005 Canadian Dollars</td>
<td>From index event to 3 months</td>
<td>Retrospective claims data. Patients with THA, TKR with VTE and bleeding</td>
<td>Among all patients with THA/TKA, 197 (6.6%) experienced VTE and $849 ($102) had a bleeding event, including 232 (1.85%) patients with a major bleeding event. Some patients had both VTE and bleeding events.</td>
<td>After THA/TKA surgery, the risk of VTE, any bleeding, or major bleeding was 6.7, 4.8 and 1.9 events respectively (100 patients. Up to 3 months after THA/TKA, the mean healthcare costs/patient/month for VTE bleeding, and major bleeding were $2729, $2696, and $4404, respectively. All healthcare costs was $183,254,000 for bleeding events. The healthcare cost for major bleeding events was $93,570,000.</td>
</tr>
</tbody>
</table>
### Table 3.4 VTE Treatment Cost

<table>
<thead>
<tr>
<th>Authors, year, country</th>
<th>Time of period</th>
<th>Design</th>
<th>Population</th>
<th>Costing period</th>
<th>Type of cost</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edelberg J et al. 2001 USA</td>
<td>1973 - 2001</td>
<td>Literature review</td>
<td>THR and TKR patients</td>
<td>Inpatient, outpatient and for long term (5 years for VTE)</td>
<td>Total mean direct costs</td>
<td>Diagnosis and inpatient cost for DVT $7,360 and PE $40,493 (2000 USD). The estimated total cost of treating VTE/patient was approximately $11,600.</td>
</tr>
<tr>
<td>Botteman MF et al. 2002 USA</td>
<td>1996-2002</td>
<td>Literature-based, decision-analytic model</td>
<td>Cost-Effectiveness of enoxaparin vs warfarin for prophylaxis of DVT. Associated long-term complications in THR surgery in the United States</td>
<td>Short term 7 days and long term from the time of the surgery until age 100 years or death.</td>
<td>Total mean direct costs, enoxaparin vs warfarin</td>
<td>Primary DVT cost $4,159. Primary PE cost $5,267. Secondary DVT cost $3,798. Secondary PE cost $6,404.</td>
</tr>
<tr>
<td>Ollechford DA et al. 2002 USA</td>
<td>January 1998 to June 1999</td>
<td>Retrospective Cohort study</td>
<td>Patients with major orthopaedic surgery from 220 hospitals, discharges 105,362 patients</td>
<td>Mean cost whilst in hospital after THR, TKR or hip fracture repair</td>
<td>Mean total costs</td>
<td>Primary DVT cost $17,114 in patients. Primary PE cost $18,521 in patients. Hip fracture repair $12,256 for DVT and $11,019 for PE. TKR (VTE $32,995) and THR (PE $8,859).</td>
</tr>
<tr>
<td>Oster G et al. 2004 USA</td>
<td>January 1993 to December 1998</td>
<td>Claims data retrospective cohort study</td>
<td>Patients with THRs, major knee surgery, hip fracture repair (n=11,960)</td>
<td>At index admission and at 90 days</td>
<td>Mean total costs</td>
<td>In hospital VTE before 90 days $52,037 vs $34,485 control, in hospital VTE at 90 days VTE $55,480 vs $35,640 control post discharge VTE $41,411 vs $35,640 control.</td>
</tr>
<tr>
<td>Tilleul P et al. 2005 Europe</td>
<td>1999-2002</td>
<td>Retrospective analysis, decision tree</td>
<td>216,916 patients hospitalised for major orthopaedic surgery. DVT, n=287; PE n=665</td>
<td>12 months</td>
<td>Mean annual all-cause medical cost/patient/event</td>
<td>Cost of VTE at hospital £9,444,812, out patient £5,910,829, new readmission £4,480,160. Total costs £18,835,801. Total annual costs of VTE associated with major orthopaedic surgery: 50 million euros over 1 year with £28 million euros for inpatient care and £30 million euros for recurrences and PTS.</td>
</tr>
<tr>
<td>Netteso RA et al. 2008 USA</td>
<td>January 2002 to 31st March 2006</td>
<td>Retrospective analysis</td>
<td>Patients with major orthopaedic surgery with DVT within the first month, followed for cost after 6 months</td>
<td>6 months</td>
<td>Total 6 month cost and resource utilisation</td>
<td>6 months cost were significant higher for patients with DVT, with an incremental increase of over $2,069. DVT $9,251 vs non DVT $7,182.</td>
</tr>
<tr>
<td>Veleman F et al. 2011 Canada</td>
<td>2004-2008</td>
<td>Retrospective claims data</td>
<td>Patients with THR, TKR with associated VTE and bleeding</td>
<td>From index event to 3 months</td>
<td>Cumulative all-cause cost</td>
<td>A total of 119,729 patients who underwent THR/TKR, the cumulative all-cause healthcare costs were $292,690,000 for the 7,974 patients who developed a VTE event.</td>
</tr>
<tr>
<td>Kwong L.M. 2011 USA</td>
<td>2007-2008</td>
<td>Prospective Study</td>
<td>Post-orthopaedic surgery/arthroplasty population</td>
<td>Short term 10-14 days and long term 31-39 days</td>
<td>Total mean costs, comparison of prophylaxis (warfarin/low molecular weight heparin)</td>
<td>Estimated US costs for the treatment of symptomatic VTE range from $9805-$14,146 per event.</td>
</tr>
<tr>
<td>Shali A et al. 2017 USA</td>
<td>2002 - 2011</td>
<td>Retrospective</td>
<td>Nation wide inpatients (THR, TKR &amp; VTE)</td>
<td>Ten years</td>
<td>Additional costs of TKR or THR when VTE occurs.</td>
<td>The median charge for TKR was $88,791 (37,873-99,938). With VTE increased to $55,307 (51,392-55,470). A $14,515 net increase. In revision TKR, median charges changed from $49,667 - $78,100 ($29,433 increase). The median charges for primary TKR was $41,203 - $62,263 with VTE and in revision: THR, the median cost increased from $30,165 - $78,065 (difference $29,844).</td>
</tr>
<tr>
<td>Tucker A et al. 2018 United Kingdom</td>
<td>2016</td>
<td>Prospective consecutive cohort study</td>
<td>Patients with THR and TKR readmitted to hospital</td>
<td>12 months</td>
<td>Total VTE cost for readmission. VTE £29 readmissions for DVT/PE, VTE direct cost &amp; overnight £5,050. VTE £17,660 bed cost. VTE £7,670 for ED</td>
<td></td>
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</table>
3.6 Ankle Study Costs Results

Results from chapter two showed a median hospital LOS of 7.0 (IQR: 3.0-16.0) days in ankle fracture patients. This reflects an estimated cost of $15,466.92 ($6628.68-$35,352.96) AUD when incorporating a 4.44% inflation rate for 2019. The per patient estimated inpatient expenditure for DVT and PE is predicted to range from $6,129 to $150,174 and $419,823 to $3,265,594 AUD, respectively. At three months, post-hospitalisation, our VTE rate was 4.3% (95% CI: 2.3-6.2). In per capita terms, the current financial cost per person with VTE is estimated to be $146,199 AUD (2019). These findings are based from previous economic VTE Burden in Australia report that was published in 2008.248

3.7 Discussion

To put a monetary value on a human life is problematic. This monetary value should encompass a person’s entire economic contribution, earning money and paying taxes and supporting local businesses etc. A willingness to pay is an economic value, used to quantify the benefit of avoiding a fatality. A reduction in risk to that on average one less person is expected to die from that risk, is used to estimate that value, namely the value of statistical life (VSL). The definition of VSL in the context of environment, health, occupational health and safety, transport and airspace policies and regulation was derived from previous financial studies into the saving of lives from disease. 30

There are complicating postulations used to derive these estimates so a sensitivity analysis should be undertaken as part of the cost-benefit analysis of VSL. Based on international and Australian research a credible estimate of the value of a statistical life in Australia was $4.2 million dollars and the value of statistical life year was $182,000 dollars in 2014. This includes an economic evaluation incorporating a 4.44% inflation rate. This indicates the value of a
statistical life at $4.5 million dollars. The value of statistical life year is estimated at $197,000 dollars for 2019 in Australia. The VSL in the USA is approximated at $10 million dollars (USD).²³⁰

When calculating the value of a life, the cost of morbidity needs to be included. The economic burden of VTE is not confined to the diagnosis and treatment of the initial event, but also includes the VTE recurrences and the long-term chronic complications that create additional and future medical costs. Major economic factors include sick days taken, temporary replacement staff needed, loss of time and money invested in training an employee, cost of recruiting and then retraining. Furthermore, income losses for businesses due to staffing. The cost of mortality is also high. Patients may experience job losses and thus loss of income. The government loses out on receiving taxes due to unemployment and it adds burden on the government to provide social and economic support to people effected by thromboembolism. The community at large may also be negatively influenced due to less disposable income of the patient to participate in their local community. Additionally, the cost of disability and premature death including the cost of funerals needs also to be taken in consideration.¹⁸¹ All of the above factors accumulate and add to the increasing cost. In addition to this, they play a significant role in the economic burden of VTE, however the limitation is that there is a paucity of data on the total economic burden of PE and DVT worldwide.

VTE events continue to be an avoidable and costly burden to patients, the wider community, and global economy. Pharmacological prophylaxis is a widely available and effective form of prevention and treatment for VTE events. Economic modelling has revealed that certain types of pharmacological prophylaxis are more cost effective than others. Generally, LMWH is the most utilised in treatment, but newer DOACs have been proven to be more cost effective over
time. Economic modelling across the world has demonstrated significant long-term cost savings of preventing VTE recurrences and complications, such as PTS and CTEPH. Complications related to prophylaxis include HIT and bleeding, however the risk and cost of bleeding not to mention HIT can be balanced by identifying and only administering prophylaxis to patients at high risk of VTE. Research examining the cost of HIT appears to be lacking, as no papers were identified in our current literature review.

The literature outlining total VTE treatment costs is varied, as studies have had no consensus on how to determine and present cost figures. Overall, it appears that VTE events of orthopaedic surgery patients are quite costly, in terms of hospital LOS, patient impact such as time off work, financial cost to the patient and the wider community. Globally, any patient can develop VTE, as VTE has numerous risk factors including surgery, cancer, and trauma, to name a few. A patient in hospital is 100 times more likely to experience a VTE event than a person in the wider community.

A large financial report on total VTE cost burden to the Australian economy was estimated to be AUD$1.72 billion for the year 2008.\textsuperscript{249} In today’s terms, this equates to $2.1 billion AUD in 2018. The total hospital expenditure in Australia for 2019 has been estimated to be at an excessive amount, (approximately, $ 101, 500, 000 million AUD). The direct health care system cost was estimated at $185 million AUD and the per patient estimated inpatient expenditure for DVT and PE ranged from $6,129 to $150,174 and $419,823 to $3,265,594 AUD, respectively. In per capita terms, the current financial cost per person with VTE was estimated to be $146,199 AUD. Current estimates suggest that VTE deaths account for roughly 10% of all deaths in Australia.\textsuperscript{249} The percentage of VTE deaths could be higher due to current trends of not routinely performing autopsy. VTE is an enormous cost to society as most VTE
deaths are preventable. Therefore, it is very important to communicate that VTE is the most preventable cause of all hospital deaths.

3.8 Conclusion

Preventing VTE could lead to substantial savings to health care systems and governments, and to significant reductions in morbidity and mortality. The estimated dollar findings from our ankle study reflects the high economic burden for VTE, highlighting the importance of prevention (in-hospital and beyond hospitalisation). This will lead to significant savings compared to the diagnosis and treatment of VTE improving quality of life and healthcare costs. Hospitals have the potential to reduce the national cost burden of VTE and meet new quality initiatives by ensuring that VTE events are prevented via the use of evidence-based guideline recommendations for prophylactic methods in patients identified to be at risk for VTE.250

The Australian Commission on Safety and Quality in Health Care is enroute to reduce and eliminate all unnecessary hospital acquired DVT events and prevent premature deaths from PE. Thus, the key to saving lives, improving patient outcomes, and reducing the huge financial cost to individuals and the nation lies in prevention of this disease. Evidence-based findings from well-designed studies have clearly shown that prevention is possible.13, 117
CHAPTER FOUR: Summary, Gaps in the Literature and Future Directions

4.1 Introduction

The incidence of asymptomatic DVT (venographically confirmed) without pharmacological prophylaxis is high after THR and TKR. The VTE incidence after THR is 40% to 60% and after TKR it is 40% to 85%.\(^{39}\) Fatal PE is uncommon if routine thromboprophylaxis is used, although symptomatic VTE continues to be reported in 1% to 10% of patients within three months post-surgery.\(^{39}\) Currently, with the use of anticoagulants, the risks after hip and knee arthroplasty appear to be about 2.5% for deep vein thrombosis, 1% for non-fatal PE, and a few tenths of 1% for fatal PE over a three-month period following surgery.\(^{244}\) Recurrent VTE, PTS, which includes chronic pain, swelling, and ulceration of the legs, can result in considerable morbidity and mortality. Without thromboprophylaxis, the incidence of fatality is approximately one patient in 300 surgeries for THA. Non-fatal PE can also have considerable consequences and may result in chronic thromboembolic pulmonary hypertension (CETPH), a severe disease linked with advanced incapacity and severe risk of mortality.\(^{251,252}\) It is accepted protocol to treat patients with major orthopaedic surgeries with pharmacological and mechanical prophylaxis for the prevention of VTE events. The incidence of VTE after ankle fracture and surgery is less clear, as it is not well defined because there are a wide range of results from different foot and ankle studies. Results range from 12.2% without prophylaxis to 0.6% with prophylaxis.\(^{40}\)

Most authors are of the opinion that the low rate of VTE does not warrant pharmacological prophylaxis. A study in 2018 by Robinson et al. performed a cost effective analysis and they were of the opinion that the risk of VTE is low for foot and ankle surgeries.\(^{253}\) Another 2015 study by Mangwani et al. did a systematic review of the English literature and came to conclusion that the overall incidence of symptomatic VTE in foot and ankle surgery is low, 0%
to 0.55%. They concluded patients with two risk factors, but no history of VTE should not receive prophylaxis. Patients with three risk factors, no history of VTE, should receive pharmacological prophylaxis until weight bearing status conferred. A recent study by Bikdeli et al. concluded that their data cast doubt on the usefulness of VTE prophylaxis in unselected younger patients undergoing foot and ankle surgery in the general adult population.

However, there are still some patients from that group of patients that develop DVT and/or PE and suffer long term complications or even death. The ENDORSE study (which enrolled over 68,000 medical and surgical patients in 32 countries, including Australia) showed that 51.8% of hospital inpatients were at risk of VTE, but only 58.5% of at-risk surgical patients and 39.5% of at risk medical patients received VTE prophylaxis. This is consistent with the findings of a prospective audit carried out by the National Health and Medical Research Council (NHMRC) National Institute of Clinical Studies in Australian hospitals in 2005–2006.

The general consensus among orthopaedic surgeons are that the risk after ankle fracture surgery is insignificant and that the cost of prophylaxis does not warrant it. The incidence of VTEs are mostly on the lower side, however the important fact to remember is that each patient has different risk factors for VTE, as discussed in chapter one. It is important to consider that postoperative DVT is often asymptomatic and that a fatal PE is the first clinical manifestation of postoperative VTE in many patients. Therefore, it is critical that all patients be individually VTE risk assessed at hospital admission and on discharge in order to provide appropriate prophylaxis in those patients identified to be at risk. This is emphasised in chapter two where the overall in-hospital incidence of VTE in our study was 2.9% (95% CI: 1.3 - 4.4), compared to 4.3% (95% CI: 2.3 -6.2) at three months post hospitalisation. This represents a 1.5-fold
increased VTE risk beyond discharge reinforcing the importance of VTE prevention and extended prophylaxis in patients identified to be at high risk.

4.2 Rates of Readmission

A recent study by Secemsky et al. in 2018 showed a readmission rate of 6.6% at 7 days, 8.7% at 10 days, and 14.0% at 20 days after VTE events. A major study by Nutescu et al. in 2014 revealed that approximately 4% of 214,901 patient admissions identified with a diagnosis of DVT or PE at hospital admission, were readmitted with a diagnosis of PE (8217) or DVT (9138). Of the initial DVT diagnosed readmitted patients, 66% were re-hospitalised with diagnosis of DVT and 34% were re-hospitalised with a diagnosis of PE. Of the initial admission patients, diagnosed with PE, 63% of them were re-hospitalised with a PE diagnosis and 37% of those patients were diagnosed with DVT. Of the readmission patients with PE diagnosis, 62% occurred within 30 days of initial event and likewise patients with DVT, 58% occurred within 30 days of initial event. The DVT and/or PE burden is huge, because not only of the index event, but also of the high readmissions (> half of that occurs within 30 days). The rate of recurrent VTE from the above studies are high and the cost of recurrent DVT and PE are mostly double. Long-term complications such as PTS and CEPTH also needs to be considered.

4.3 VTE Prevention

Given that some patients with ankle fractures still go on to develop VTE, prophylaxis needs to be considered once a risk assessment has been performed. It is recommended that every patient admitted to the hospital is VTE risk assessed. Prophylaxis includes mechanical prophylaxis such as GCS and/or IPC and pharmacological prophylaxis. Studies have compared different pharmacological prophylaxis such as LMWH versus UH versus warfarin, or LMWH such as
enoxaparin with DOAC such as apixaban or dabigatran. Choice of prophylaxis should be determined according to the patient’s individual risk factors and presentation. Consideration should be given to factors such as patients experiencing kidney failure, those already on anticoagulants, those allergic to heparin, or for cases when mechanical prophylaxis is not feasible due to body habitus, surgery, or injury status.

In 2002 Wang et al.\textsuperscript{219} noted that DVT often develops weeks after surgical patients have been discharged, and that the danger of DVT or PE persist up to five or six weeks following surgery. This study concluded that the use of extended prophylaxis postoperatively in the outpatient setting may also be beneficial for ankle surgery patients who present with additional VTE risk factors.\textsuperscript{219} In a 2014 Cochrane systematic review, Testroote et al.\textsuperscript{10} found risk of venous thromboembolism from 4.3\% to 40\% in patients with lower limb injury who had immobilisation in a plaster cast or a brace for at least one week and received no prophylaxis. They concluded that use of LMWH in outpatients significantly reduces VTE when immobilisation of the lower leg was required. In another review, Nokes and Keenen found significant risk reduction of DVT with use of LMWH and concluded that all patients with lower limb cast immobilisation should at least be risk assessed and thromboprophylaxis to be provided to those having high risk of DVT.\textsuperscript{258}

As noted above, risk assessment has become a vital part of holistic patient care. In best practice, patients are assessed and then categorised into low, moderate, and high risk for VTE. This is of utmost importance so the patients at risk can be appropriately prescribed prophylaxis (mechanical and pharmacological) and thus prevent unnecessary VTE and its associated complications. The NSW health Department has a VTE risk assessment policy in place, where all patients need to be risk assessed within 24 hours of hospital admission. In NSW, there is a
related policy to further reinforce the prevention of Hospital Acquired Complications (HACs), where hospitals are financially penalised for any patients that acquire thrombosis whilst in hospital, Hospital Acquired Thrombosis (HATs), however this is not standardised across Australian states and territories.

These policies, while important, only apply to inpatient care, and ongoing outpatient VTE prevention remains less structured, with some believing that ambulant outpatients do not require ongoing prophylaxis. Studies have evaluated the effect of ankle joint immobilisation on venous blood in the lower limb. Results of these studies have demonstrated that ambulating non-weight bearing is not associated with significant increases in venous blood flow above resting levels. To stop pharmacological prophylaxis once a patient is ambulating irrespective of weight-bearing status is therefore not justified. In contrast, both partial and full weight bearing resulted in a significant increase in venous flow compared with resting levels, irrespective of whether the ankle joint was immobilised. However venous blood flow remained significantly lower with partial weight-bearing (50%) compared with full weight-bearing. When comparing venous blood flow among full weight-bearing exercises, a significant reduction with the ankle joint in equinus compared with no ankle joint immobilisation were observed. These results demonstrate that venous blood flow return to normal levels when the subjects were permitted to fully weight bear in below knee casts or walking boots, provided the ankle was not in equinus. It was also noted that both active and passive ankle plantar flexion also increase the venous return from the lower limb. However, utilising these techniques is not possible when the joint is immobilised using a cast or pneumatic boot.

More recently the use of calf muscle pump, in the presence of a plaster cast, was examined demonstrating that a simple strategy of toe and ankle exercises can maintain venous return
despite below-knee cast immobilisation. The study recommended that all patients with a below-knee casts are given a program of exercises that can be comfortably performed with the cast; this could provide a useful, inexpensive, and safe thromboprophylactic strategy acting at the site of greatest risk and targeting a major cause of VTE.\textsuperscript{260} Recent practices in Australia have focused on encouraging faster hospital discharges by encouraging outpatient VTE prevention, through self-administered prophylaxis. Patients are discharged earlier and instructed to self-inject or have a community healthcare professional administer LMWH, or they are given new oral anticoagulants for extended periods of time (for example, taking apixaban for 15 days post-discharge). Australia wide there continues to be major preventable VTE events, and standardised policies and regulations regarding VTE prevention for both inpatient and outpatient settings would benefit the patients, healthcare system and taxpayers of Australia alike.

Globally regulations and policies regarding VTE preventative care remains obsolete, ad-hoc, and at times non-existent. In addition, current guidelines, such as the 2012 American College of Chest Physicians (ACCP) Antithrombotic Guidelines, suggest no prophylaxis for orthopaedic patients with lower limb immobilisation, due to surgery or trauma.\textsuperscript{11, 261} These guidelines, therefore, do not account for individualised risk assessments, and in many countries, rates of risk assessment and prophylaxis are still low. This is likely due to poor integration of literature into evidence-based practice guidelines, and limited knowledge by hospital regulators of current VTE literature, as well as the high cost of accessing pharmacological prophylaxis in many countries. In addition, prophylaxis is often underutilised and under prescribed by many surgeons. Many surgeons still have the outdated perception that the postoperative bleeding risk is too high to justify implementing pharmacological prophylaxis, especially after joint replacements and in lower limb orthopaedic surgery.
Furthermore, the fact that pharmacological prophylactic measures carry an associated risk of bleeding and in some cases, such as after major trauma, may contribute to the precluding of pharmacological prophylaxis by the orthopaedic surgeons. Many clinicians and patients may perceive this bleeding risk as significant. Surgeons may be understandably reluctant to expose patients to the risk of excessive intra- or postoperative bleeding and the subsequent complications, especially in procedures such as joint replacement where bleeding can lead to severe infections and a need for explants of prostheses.

VTE has many presentations and is diagnosed and cared for by multiple providers and also in multiple settings (inpatient and outpatient) and the orthopaedic surgeon might not even realise any of his patients had a VTE event. This is despite recent literature indicating that the risk of post-operative bleeding is lower than previously thought and research now suggests that the benefits for high risk VTE patients receiving prophylaxis outweighs the risk of post-operative bleeding. Results from chapter two reflects a low bleeding rate which emphasises this point.

As mentioned in chapter one, a multinational cross-sectional survey performed in 2008 which enrolled over 68,183 patients in 358 hospitals across 32 countries, including Australia called the ENDORSE (Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting) survey assessed the prevalence of VTE risk in the acute hospital care setting and determined the proportion of at-risk patients who receive effective prophylaxis. 116

Findings showed that 58.5% of at-risk surgical patients received appropriate prophylaxis as per ACCP recommended guidelines compared to 39.5% of at-risk medical patients. The ENDORSE study showed that, worldwide, more than half of all hospitalised patients are at risk
for VTE, and that surgical patients seem to be at higher risk than medical patients. They also indicated that only half of at risk patients received an ACCP-recommended methods of prophylaxis (ranging between 2% to 84%) with poor use in the medical group.\textsuperscript{116}

Furthermore, findings reflected limited differences between countries regarding the proportion of patients at risk for VTE, but there were definite differences in the use of the ACCP recommended guidelines regarding the type of prophylaxis used between countries.\textsuperscript{117, 118} Factors, such as the availability of VTE guidelines, education resources, reimbursement, physician awareness and national health-care resources may have contributed to these findings. The ENDORSE study highlighted the importance of VTE prevention and the global need to increase awareness on the use of hospital-wide strategies to ensure that those patients at risk receive appropriate prophylactic strategies.\textsuperscript{113, 119}

Risk factors causing VTE often result in vessel wall damage, venous stasis and increased clot activation that can lead to PE.\textsuperscript{262} Conditions in which venous stasis is a major component, include immobilisation, major surgery, trauma, pregnancy, obesity, decompensated cardiac failure and lower limb venous valvular incompetence with ensuing varicose veins and chronic venous disease. It is well known that immobilisation of a limb is one of the main causes of DVT.

Individualised risk assessment is critical in maximising VTE prevention and patient care as it enables differentiation of those at high risk, who would benefit from prophylaxis, compared to those at low risk of VTE. This is preferable to a model in which prophylaxis is administered as part of standard care to all patients, particularly given the known low risks of VTE in ankle fractures for most patients, preventing unnecessary prophylaxis costs. By preventing VTE in
the subset of high-risk patients, economic costs are reduced, length of hospital stays are shorter (thus freeing up critical beds needed), and long-term complications such as PTS and fatality are avoided.

4.4 Economic Burden of VTE

From chapter three, most of the economic studies focus on the costs of VTE as a disease and also on post-operative VTE events following major orthopaedic surgeries. Very little is available on the cost of VTE after ankle fractures. The paucity of economic impact data in the literature for VTE and the estimated cost for VTE events and complications predicted the ankle fracture results (chapter three). This highlights the need for further investigation, particularly given the effectiveness of prophylaxis in preventing VTE events.

4.5 Gaps in the Literature

The majority of VTE literature focuses on MOS such as hip and knee replacement as well as hip fracture surgery. Patients undergoing these types of procedures are considered to be at particularly high risk of VTE and routine prophylaxis is the standard care. The incidence of PE in major orthopaedic surgery in the absence of prophylaxis is around 8.6%. Given the scarcity of literature on lower limb prophylaxis, the American Orthopaedic Foot and Ankle Society (AOFAS) currently have no uniform guidelines for or against routine VTE prophylaxis for patients undergoing foot and ankle surgery.

The potential risk of VTE may be increased after foot and ankle surgery and lower limb injury, however the incidence of VTE of the distal lower limbs are poorly understood and require further investigation. This is at least partly due to the wide range of procedures and injuries encountered in this area. There is a multitude of different procedures and surgeries, all with
varying levels of complexity that are performed on the lower extremities. The aftercare protocols vary from immediate weight bearing or total non-weight bearing for a certain time period, making it difficult to generalise results from researching across these types of procedures in lower limb VTE.\textsuperscript{207}

Another area that is poorly researched is the incidence of VTE of diabetes patients with foot ulcers. Patients with foot ulcers are mostly immobile and as immobility is a major risk factor, the question arises whether the patients with foot ulcers who receive TCC for the healing of these ulcers are at higher risk of developing DVT and/or PE. To date there is limited information and literature that specifically addressed the incidence of DVT in immobile patients with TCC.

Overall, it appears that pharmacological and mechanical prophylaxis play an important role in the prevention of VTE, not only in major orthopaedic surgeries, but also in lower limb immobilisation.\textsuperscript{10} New research should further examine the factors surrounding VTE and prophylaxis in lower limb immobilisation, in order to obtain a more complete and relevant understanding. This would allow for the development of more effective model to prevent, diagnose and treat VTE in the future. It appears that VTE is a real risk in certain patients with immobilisation, notwithstanding only a small number of studies have been done on below the knee lower limb prophylaxis. In patients with full plaster casts it is difficult to use mechanical prophylaxis and is therefore necessary to provide other anticoagulation alternatives and antiplatelet drugs in these patients.
4.6 Future Directions – Total Contact Cast and VTE

There are still significant gaps in the research and barriers to the implementation of a standardised protocol of VTE prevention in ankle and lower limb fractures. A less researched factor in the development of VTE events in this population is the extent to which the timing of prophylaxis impacts upon the risk of developing a VTE. Future research should consider any delays that occurred in the start of both mechanical and/or pharmacological prophylaxis, which will better inform clinicians of the relative risks when weighing up factors such as extra post-operative bleeding versus increased risk of VTE events. In our study the patients that presented with VTE events had varied timing in the commencement of prophylaxis due to factors such as ongoing surgical interventions and medical complications. Further, studies in ankle and lower limb fractures should consider the use of radiological diagnostic screening in addition to clinical assessments, as the bulk of the research has relied heavily on clinical assessment only. Past research has revealed that studies utilising radiological assessment show a much higher prevalence of VTE in patients, suggesting that clinical assessment may miss some DVT events that are current and/or asymptomatic. This is problematic as research has indicated that many asymptomatic DVTs result in fatal PE.

Given the significant gap identified in the literature review of this thesis and the risk of VTE in patients with lower limb immobilisation due to lower limb injuries such as ankle fractures led to the development of a research protocol (Appendix C) and ethics approval (Appendix D). This is a prospective TCC study, designed to determine rates of VTE events from TCC patients presenting to the Diabetic Foot Ulcer clinic at Westmead Hospital, in NSW, Australia. This study was reviewed and ethically approved by the Western Sydney Local Health District Human Research Ethics Committee. However, due to time constraints it has not yet commenced. This study will be required to address the critical gap in VTE not only for diabetic
foot patients with TCC, but also those with lower limb immobilisation. This research could inform practices that significantly reduce economic costs, save lives, and improve the quality of life for many ulcer and immobile patients by preventing the development of VTE.
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## Appendix A: VTE Ankle Data Collection Form

### Demographics

<table>
<thead>
<tr>
<th>Gender: Male ☐</th>
<th>Female ☐</th>
<th>Age:</th>
<th>Height:</th>
<th>Weight:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission Date: / /</td>
<td>Discharge Date: / /</td>
<td>LOS: days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Injury: / /</td>
<td>Type of Injury:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CO-MORBIDITIES (pre-existing conditions: not complications)

<table>
<thead>
<tr>
<th>Smoking Status: Current ☐</th>
<th>Ex-smoker ☐</th>
<th>Never ☐</th>
<th>Unknown ☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy: Yes ☐</td>
<td>No ☐</td>
<td>If yes details:</td>
<td></td>
</tr>
<tr>
<td>Previous DVT: Yes ☐</td>
<td>No ☐</td>
<td>If yes details:</td>
<td></td>
</tr>
<tr>
<td>PE: Yes ☐</td>
<td>No ☐</td>
<td>If yes details:</td>
<td></td>
</tr>
<tr>
<td>DVT &amp; PE: Yes ☐</td>
<td>No ☐</td>
<td>If yes details:</td>
<td></td>
</tr>
<tr>
<td>Diabetic: Type 1 ☐</td>
<td>Type 2 ☐</td>
<td>Gestational ☐</td>
<td></td>
</tr>
<tr>
<td>Ulcer: Yes ☐</td>
<td>No ☐</td>
<td>If yes details:</td>
<td></td>
</tr>
<tr>
<td>Cardiac History: Yes ☐</td>
<td>No ☐</td>
<td>If yes details:</td>
<td></td>
</tr>
<tr>
<td>Thrombophilia: Yes ☐</td>
<td>No ☐</td>
<td>If yes details:</td>
<td></td>
</tr>
<tr>
<td>Protein C ☐</td>
<td>Protein S ☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FV Leiden ☐</td>
<td>Other:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous Surgery: Yes ☐</td>
<td>No ☐</td>
<td>If yes details:</td>
<td></td>
</tr>
<tr>
<td>Previous Trauma: Yes ☐</td>
<td>No ☐</td>
<td>If yes details:</td>
<td></td>
</tr>
</tbody>
</table>

### MEDICATIONS: (not Prophylaxis)

| Anticoagulant: Yes ☐ | No ☐ | If yes details: |
| Aspirin: Yes ☐ | No ☐ | If yes details: |
| NSAID: Yes ☐ | No ☐ | If yes details: |

VTE Ankle Data Collection Form Version 1 2016/08/18

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IMAGING:

DVT:
- Duplex Ultrasound: [ ] Yes [ ] No
- If yes: Date of US: __/__/____, Time of US: __:__
- Region of US: _______________
- Right [ ] Left [ ]
- Proximal [ ] Distal [ ]
- Result of Ultrasound: _______________________

D-Dimer:
- [ ] Yes [ ] No
- If yes: Details: _______________________
- Result of D-Dimer: _______________________

PE:
- CTPA: [ ] Yes [ ] No
- If yes: Date of CT: __/__/____, Time of CT: __:__
- Region of CT: _______________________
- Result of CT: _______________________

VQ Scan:
- [ ] Yes [ ] No
- If yes: Result: _______________________

Operation Details:

- Surgery: [ ] Yes [ ] No
- If yes: Start time: __:__ End Time: __:__ Duration: __________

- Date of Operation: __/__/____
- Time of operation: _______________________

- American Society of Anaesthesiology Score (ASA Score): [ ] I [ ] II [ ] III [ ] IV [ ] V [ ]

- Tourniquet: [ ] Yes [ ] No
- If yes: Start time: __:__, End Time: __:__, Duration: __________

- Immobilise: [ ] Yes [ ] No

- Cast: [ ] Yes [ ] No

- Moonboot: [ ] Yes [ ] No

- Immobilisation period: Details: _______________________

---

VTE Ankle Data Collection Form Version 1 2016/08/18
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**COMPLICATIONS:**


**PROPHYLAXIS:**

**Mechanical:**

- [ ] Yes  [ ] No  If yes: Stockings only  [ ] Stockings and IPC  [ ] Period prescribed: 

**Pharmacological:**

- [ ] Yes  [ ] No  If yes: Start time:  End Time:  Duration: 

- [ ] UH  [ ] LMWH  Dose:  Comments:

**Deep Venous Thrombosis:**

- [ ] Yes  [ ] No  If yes: Proximal:  [ ] Yes  [ ] No  Distal:  [ ] Yes  [ ] No

**Pulmonary Embolism**

- [ ] Yes  [ ] No  If yes: Non-Fatal:  [ ] Yes  [ ] No  Fatal:  [ ] Yes  [ ] No
<table>
<thead>
<tr>
<th>Readmission:</th>
<th>Yes</th>
<th>No</th>
<th>If yes Admit Date:</th>
<th>Discharge Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT:</td>
<td>Yes</td>
<td>No</td>
<td>If yes:</td>
<td>Proximal</td>
</tr>
<tr>
<td>PE:</td>
<td>Yes</td>
<td>No</td>
<td>If yes:</td>
<td>Fatal</td>
</tr>
<tr>
<td>DVT &amp; PE:</td>
<td>Yes</td>
<td>No</td>
<td>If yes details:</td>
<td></td>
</tr>
<tr>
<td>Pain:</td>
<td>Yes</td>
<td>No</td>
<td>If yes where:</td>
<td>Upper Body</td>
</tr>
<tr>
<td>If lower limbs:</td>
<td>Right</td>
<td>Left</td>
<td>Proximal</td>
<td>Distal</td>
</tr>
<tr>
<td>Redness:</td>
<td>Yes</td>
<td>No</td>
<td>If yes where:</td>
<td>Upper Body</td>
</tr>
<tr>
<td>If lower limbs:</td>
<td>Right</td>
<td>Left</td>
<td>Proximal</td>
<td>Distal</td>
</tr>
<tr>
<td>Oedema:</td>
<td>Yes</td>
<td>No</td>
<td>If yes where:</td>
<td>Upper Body</td>
</tr>
<tr>
<td>If lower limbs:</td>
<td>Right</td>
<td>Left</td>
<td>Proximal</td>
<td>Distal</td>
</tr>
</tbody>
</table>

**COMMENTS:**

---

VTE Ankle Data Collection Form  Version 1  2016/08/18

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Appendix B: Ethical Approval for Ankle Fracture Study

26 September 2016

Associate Professor Kerry Hitos
Department of Surgery
Westmead Hospital

Dear A/Prof Hitos

Project Title: ‘The incidence of Deep Vein Thrombosis (DVT) in Ankle Fracture Patients with or without internal fixation’

Thank you for submitting the above research project to the WSLHD Human Research Ethics Committee for ethical review, received on Wednesday 21 September 2016.

Your project has been assigned the file number (4888). This number must be quoted in all correspondence with the HREC.

Should you require any further information, please contact the Research Office at WSLHD-ResearchOffice@health.nsw.gov.au or on 9845 9007.

Yours faithfully,

[REDACTION]

Sree Chinta Khind
Administration Officer
WSLHD Human Research Ethics Committee

HUMAN RESEARCH ETHICS COMMITTEE
Research Office, Level 2, REN Building
Westmead Hospital, Hawkesbury & Darcy Roads, Westmead NSW 2145
Telephone 02 9845 7193 Facsimile 02 9845 8353
Email: WSLHD-ResearchOffice@health.nsw.gov.au

WESTERN SYDNEY LOCAL HEALTH DISTRICT
ABN 49 702 384 764
WSLHD Office, Westmead Hospital Campus
Institute Road, Westmead NSW 2145
PO Box 533, Westmead NSW 2145
Telephone 02 9845 5555

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Appendix C: Total Contact Cast Study Protocol

A.1 Study Setting/Location

The location of where the study will be conducted is at Westmead Diabetic Foot Ulcer clinic and Westmead Specialist Vascular Services. This would be a multicentre study.

A.2 Study Population

Eligible patients attending the Diabetic Foot Ulcer clinic at Westmead hospital that need a TCC, will be recruited for this study. We plan to recruit 150 patients for this study.

A.3 Eligibility Criteria

Patients will be older than 18 years of age, have a foot ulcer and need to get a TCC as treatment for the foot ulcer. Patients who currently have a DVT will be excluded. If they had a DVT in the past, they can take part as long as they are not taking anticoagulant for it currently.

A.3.1 Inclusion Criteria

Patients need to be over 18 years of age with a foot ulcer. They need TCC as treatment for the foot Ulcer. They must not have a known DVT. They must not be on any anticoagulant treatment.

A.3.2 Exclusion Criteria

Patients younger than 18 will be excluded. Patients with a current DVT and on anticoagulant for it, may not take part. Patients who do not need TCC for foot ulcer will also be excluded.
A.4 Study Outcomes

A.4.1 Direct Benefit

The direct benefit of this study is that if the patient develops a DVT, asymptomatic or symptomatic, the patient will be treated immediately.

A.4.2 Indirect Benefit(s)

Literature review showed a gap in research data around lower limb and the incidence of DVT in the lower limb. There has been no research done on the incidence of DVT and the use of TCC. This study will contribute to the information pool of lower limb research. Depending on the results of the study it may or may not change the treatment of such patients in the future.

A.4.3 Study Procedures

Patients may be recruited from the Diabetic Foot Ulcer clinic at Westmead Hospital. If they are eligible, patients will be invited to take part in the study. It will be explained to them and they will also receive and information and consent sheet in layman's terms what the study is about. If the patient agrees to take part in the study, they will receive a Doppler ultrasound of both legs before they receive the TCC. After 3 weeks, 6 weeks and 3 months in TCC they will receive Doppler ultrasound at each of the time points. If they still have TCC at 6 months, they will receive a final Doppler ultrasound then. However, if the patient at any time experience any of the following symptoms, redness of skin, swelling of the limb, or pain, they will receive a Doppler ultrasound and if they have a DVT, it will be treated accordingly. If the patient experience shortness of breath or chest pain, they need to go to a Hospital Emergency Department immediately as they may have a PE. Similarly, if they experience a headache, slurring of words or numbness on one side of the body, they need to go to a Hospital Emergency Department immediately as they may have a stroke.
A.4.4 Recruitment of participants

Potential participants will be recruited from the Diabetic foot ulcer clinic at Westmead hospital. An information sheet /consent form will be given to them. After reading the info, they may decide to join the study. They can sign consent and also inform their own general practice doctor that they will take part in the study. We aim to recruit 150 patients and it will roughly take 3 to 6 months for study to be complete for each patient.

A.4.5 Study procedure

In total, 150 patients with TCC will be recruited. If they consent, they will receive a referral for a venous Doppler scan of both legs. They will be scanned at a third-party centre and reported on. Their data will also be collected from medical records. This will include demographic information (age, gender), acquired risk factors (obesity, smoking status, contraceptives,) and any hereditary factors (thrombophilia), length of immobility, malignancy, cardiac history, previous thromboembolic risk. Any prophylaxis provided (before or after) and if any incidence of DVT occurred would be recorded.

A.4.6 Data Collection and Statistical Analysis

Data will be collected on specific data collection form. All data analysis will be descriptive and analysed using SPSS version 20.0 (SPSS, Inc. Chicago, USA). Nonparametric continuous data will be analysed using the Mann Whitney Test. Logistic regression modelling will be used for analysis of trend DVT. Categorical data will be analysed using the Chi squared test. Predictors reaching statistical significance will be reported as odds ratio with their corresponding 95% confidence intervals and their associated P values. All significant tests be two tailed and differences considered to be statistically significant at a P<0.05 level.
A.4.7 Safety considerations/Patient safety

The safety of research participants will be important. Adequate information on how the safety of research participants will be ensured. This would include procedures for recording and reporting adverse events (and serious adverse events) and their follow-up.

A.5 Ethical Considerations

This study will be a medical record review and prospective (patients will receive bilateral ultrasounds of their legs). The medical record number of each patient will identify the record for review. The proforma will NOT contain the medical record number or any other potential identifiable information. Each proforma will have a de-identified code attached from the patient’s medical record number and kept under lock and key in a locked room and locked cabinet as per Westmead Hospital security procedures protocol.

Computer data files will be password protected, with tracking features and firewalls as per Information Technology Services Department Protocol. Access will only be available to the investigators for this study. Consent will be obtained from all patients taking part in this study. Consent from all treating surgeons will be obtained and no information will be used that is detrimental to the patient or the treating surgeon as all data will be de-identified and anonymity will be kept.

Data collection forms will be kept for a minimum of seven years after the completion of the study. Thereafter the forms will be shredded by the investigators. Publications of results will be in terms of de-identified data presented epidemiologically in terms of trends per year.
A.6 Outcomes and Significance

The results of this study will be published in a peer reviewed journal. An electronic search of medical databank OVID confirmed that there is no research done on the incidence of DVT in patients with TCC or any other similar studies. Literature review showed a gap in research data around lower limb and the incidence of DVT in the lower limb. This study will contribute to the information pool of lower limb research. Depending on the results of the study it may or may not change the treatment of such patients in the future. The direct benefit of this study is that if the patient whilst on the study, develops a DVT, asymptomatic or symptomatic, the patient will be treated immediately.
Appendix D: Ethical Approval Letter for TCC Study

Research Office File No: [4379]
HREC Ref: AU RED HREC/15/WMEAD/339
SSA Ref: AU RED SSA/15/WMEAD/345

4 April 2017

Dr Mauro Vicarietti
Department of Vascular Surgery
Westmead Hospital

Dear Dr Vicarietti,

Project title: The Incidence of Deep Vein Thrombosis (DVT) in the lower extremity in patients with Foot ulcers with Total Contact Cast (TCC), DVT in Patients with TCC

Thank you for Dr Anna de Wet’s correspondence addressing the matters raised in the HREC’s letter dated 28 September 2016 following single ethical review of the above project at its meeting held on 27 September 2016.

This HREC has been accredited by the NSW Department of Health as a lead HREC to provide the single ethical and scientific review of proposals to conduct research within the NSW public health system. This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council’s National Statement on Ethical Conduct in Human Research and the CPMP/ICH Note for Guidance on Good Clinical Practice.

This proposal meets the requirements of the National Statement and I am pleased to advise that the HREC has now granted ethical approval of this multicentre research project to be conducted by you at:

- Westmead Hospital
- Westmead Specialist Vascular Services

The following documentation has been reviewed and approved by the HREC:

- NEAF submission code AU/1/432835
- Protocol, version 1, dated 12 July 2016
- Participant Information and Consent Form, version 2, dated 21 February 2017
- Data Collection Form, version 1, dated 13 March 2017
Please note the following conditions of approval:

- The Chief Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.
- For clinical trials of implantable medical devices only – The Chief Investigator will confirm to the HREC that a process has been established for tracking the participant, with consent, for the lifetime of the device and will immediately report any device incidents to the Therapeutic Goods Administration (TGA).
- The Chief Investigator will immediately report any protocol deviation / violation, together with details of the procedure put in place to ensure the deviation / violation does not recur.
- The Chief Investigator will provide to the HREC in the specific format, proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, must be provided to the HREC to review in the specific format. Copies of all amendments when approved by the HREC must also be provided to the Research Governance Officer.
- The Chief Investigator must notify the HREC, giving reasons, if the project is discontinued at a site before the expected date of completion.
- The Coordinating Chief Investigator must provide an annual report to the HREC and a final report at completion of the study, in the specified format. HREC approval is granted for a period of 12 months and ongoing approval is contingent upon annual submission. Annual Reports for all studies should be submitted in November, they will be processed and presented to the HREC at their January meeting. A copy of the Annual / Final Research Report Form can be obtained electronically from the Research Office on request.
- The HREC has the discretion to adopt other appropriate mechanisms for monitoring depending on the complexity, design and risk perceived including
  1. Discussion of relevant aspects of the project with investigators, at any time,
  2. Random inspection of research sites, data or consent documentation,
  3. Interview with research participants or other forms of feedback from them, and
  4. Request and review reports from independent agencies such as a Data Safety Monitoring Board.
- If your research project is an interventional trial, please ensure it is registered on one of the clinical trial registries eg http://www.actr.org.au
- It should be noted that compliance with the ethical guidelines is entirely the responsibility of the Chief Investigator.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained. Copies of this letter, together with any approved documents as enumerated above, must be forwarded to all site investigators for submission to the relevant Research Governance Officer.
Should you have any queries about the HREC's Terms of Reference, Standard Operating Procedures or membership, please contact the Acting Research Ethics Manager through the Research Office on 9845 8183 or emailing kellie.hansen@health.nsw.gov.au.

In all future correspondence concerning this study, please quote Research Office File Number (4829).

The HREC wishes you every success in your research.

Yours sincerely

Mrs Kellie Hansen
Manager, Research Office
WSUHD Research & Education Network

cc Ms Margaret Piper, Research Governance Officer