Adherence to Prophylaxis Guidelines in Patients that Develop Symptomatic Venous Thromboembolism

A Retrospective Hospital Audit

Literature Review, Data Collection and Analysis

Joseph Benedict De Zylva

Submitted to the Faculty of Education, Health and Science of Charles Darwin University in partial fulfilment of the requirements for the degree of Bachelor of Pharmacy (Honours)

November 2010
Preface

I hereby declare that the work herein, submitted as a thesis for the partial completion of the degree of Bachelor of Pharmacy (Honours) of the Charles Darwin University, is the result of my own investigations, and all references to ideas and work of other researchers have been specifically acknowledged.

I hereby certify that the work embodied in this thesis has not already been accepted in substance for any degree, and is not being currently submitted in candidature for any other degree.

The research which constitutes the subject of this thesis was conducted at the Royal Darwin Hospital and the Faculty of Education, Health and Science under the supervision of Dr Mark Naunton, Associate Professor Pascale Dettwiller and Dr Ferenc Szabo.

Joseph Benedict De Zylva

Monday 7th of November, 2010
Acknowledgements

I would like to acknowledge the support of my principle supervisor Dr Mark Naunton, who has provided me with ongoing support throughout this research project and in a number of units in my undergraduate degree.

I would also like to acknowledge the enthusiastic support of my co-supervisor and disciplinary leader of pharmacy, Associate Professor Pascale Dettwiller, who has provided me with the opportunity to present my findings interstate.

It is also important to mention the significant contributions of Dr Carwyn Davies and Dr Drew Szypowski. They have helped me with editing issues and have reviewed the format and content of my thesis.

I would also like to thank all of my student colleagues for their encouragement. It is my pleasure to be one of the two students in the first Bachelor of Pharmacy (Honours) cohort of the Charles Darwin University, along with Christina Darkadarkis, who has worked hard to uphold the high standards of the university and the pharmacy profession.

A special thanks needs to be mentioned to the support provided to me by staff members of the medical records and the pathology department at the Royal Darwin Hospital. In particular, I would like to express my gratitude to Dr Ferenc Szabo for providing a research opportunity with the Royal Darwin Hospital and for helping me to clinically evaluate my research findings. His recommendations have given me an idea for my next thesis....

Joseph Benedict De Zylva
Table of Contents

1. Coagulation Physiology and Pathophysiology ........................................................ 1
   1.1 Haemostasis, Coagulation and Thrombosis ......................................................... 1
   1.1.1 Platelet Activation ........................................................................................... 1
   1.1.2 Clotting Factor Activation ............................................................................... 1
   1.1.3 Pharmacological Mechanisms of Anticoagulants .............................................. 4
   1.2 Arteriolar and Venous Thrombosis ...................................................................... 5

2. The Incidence and Risk of Venous Thromboembolism ............................................. 8
   2.1 Community Acquired Venous Thromboembolism ............................................... 8
       2.1.1 Age .............................................................................................................. 8
       2.1.2 Sex ............................................................................................................. 8
       2.1.3 Pregnancy and the Use of Oestrogens ......................................................... 9
       2.1.4 Ethnic/Racial Variability ............................................................................ 10
       2.1.5 Smoking and Obesity ................................................................................ 11
       2.1.6 Travelling ................................................................................................... 11
       2.1.7 Anatomical Regions Affected by Deep Vein Thrombosis .............................. 12
   2.2 Hospital Acquired Venous Thromboembolism .................................................... 13
       2.2.1 Surgical Intervention .................................................................................. 13
       2.2.2 Medical Conditions .................................................................................... 17
       2.2.3 Cancer ........................................................................................................ 21
       2.2.4 Drug Induced Venous Thromboembolism .................................................... 23

3. The Treatment and Prevention of Venous Thromboembolism ............................... 25
   3.1 Pharmacological Treatment ............................................................................... 25
   3.2 Non-pharmacological Prophylaxis ...................................................................... 26
   3.3 Pharmacological Prophylaxis ............................................................................ 27
       3.3.1 Unfractionated Heparins and Low Molecular Weight Heparins ................ 27
       3.3.2 Fondaparinux ............................................................................................. 28
       3.3.3 Direct Thrombin Inhibitors ........................................................................ 29
   3.4 Special Considerations in Prophylaxis and Treatment ........................................ 29
       3.4.1 Warfarin and Idiopathic Venous Thromboembolism .................................... 29
7.1 Identification and Classification of VTE Episodes ................................................... 51
7.2 Patient Demographics and Risk Factors ............................................................. 54
7.3 Adherence to Prophylaxis Guidelines in High Risk Patients ............................... 57
7.4 Category A1 – Development of VTE during admission ....................................... 63
7.5 Category B1 – Readmission to RDH for Symptomatic VTE ............................... 65
7.6 Exclusions from the audit .................................................................................... 68
7.7 Medications on Admission ................................................................................. 71

8 Discussion ............................................................................................................. 73
8.1 Adherence to Prophylaxis Guidelines ................................................................. 73
8.2 Medical and Surgical Risk Factors .................................................................... 74
8.3 The Incidence and Anatomical Locations of VTE Episodes ................................ 75
8.4 Medication Induced VTE .................................................................................... 76
8.5 Duplicate Episodes and Potential Coding Errors ............................................... 77
8.6 Increased Risk in Patients with Contraindications or a History of VTE .............. 77
8.7 Patients without Inpatient Admission to RDH within 90 Days of Diagnosis ....... 79
8.8 Limitations of Study Design and Methods of Improvement ............................... 80
8.9 Methods to Improve Adherence Rates ............................................................... 81

9 Conclusion ............................................................................................................. 83

10 Glossary of Acronyms ......................................................................................... 84

11 References ............................................................................................................ 86

12 Appendices .......................................................................................................... 104
12.1 Appendix 1: Ethical Approval .......................................................................... 105
12.2 Appendix 2: Data Collection Sheets ................................................................. 107
12.3 Appendix 3: Royal Darwin Hospital Guidelines 2009 ..................................... 111
List of Tables

Table 1: Clotting factors involved in the propagation of the coagulation pathway. ..........3
Table 2: Proteins involved in the inhibition of the coagulation pathway. .........................4
Table 3: The average incidence of idiopathic VTE and Odds Ratio (OR). .........................10
Table 4: The areas affected by symptomatic DVT. .........................................................12
Table 5: Acquired and Inherited Thrombophilia ..............................................................18
Table 6: The risk of VTE in nephrotic syndrome patients without prophylaxis ...............21
Table 7: The risk of VTE associated with the use of various pharmacological agents ....24
Table 8: Pharmacological agents indicated for the treatment of VTE in Australia. 94, 96, 97 ..25
Table 9: The use of heparins for VTE prophylaxis in medical and surgical patients ........27
Table 10: Comparative studies assessing the efficacy and safety of fondaparinux .........28
Table 11: The risk of VTE in pregnant women with hereditary thrombophilia ..............31
Table 12: Hospital codes used for identification of VTE patients. .................................46
Table 13: The distribution of PE/DVT diagnosed in the 59 medical and surgical patients..52
Table 14: VTE risk classifications according to RDH guidelines. ..................................53
Table 15: The demographics of patients included in the audit. ....................................55
Table 16: The surgical risk factors identified in patients included in the audit .................55
Table 17: The medical risk factors identified in patients included in the audit ................55
Table 20: Thrombophilia testing performed in patients included in the audit ...............56
Table 18: Contraindications to pharmacological prophylaxis .......................................56
Table 19: Contraindications to mechanical prophylaxis ................................................56
Table 21: The median number of days and IQR for confirmed diagnosis in Category A1 ..64
Table 22: The time between hospital discharge and readmission for VTE in Category B1 ..67
Table 23: Episodes of VTE excluded on the basis of potential miscoding .......................69
Table 24: The medications on admission for the 44 patients in Category A ....................72
List of Figures

Figure 1: The Intrinsic and Extrinsic Coagulation Pathways ................................................ 2
Figure 2: Pharmacological Mechanism of Vitamin K Antagonists ........................................... 5
Figure 3: Virchow’s Triad and the Pathogenesis of Thrombosis ............................................... 7
Figure 4: Incidence Rates of DVT Associated with Age and Sex in Australia 2008 ............... 9
Figure 5: Prophylaxis Rates in Patients at Risk (ENDORSE Study) ........................................ 34
Figure 6: The readmission rate within 12 months after surgery ............................................. 37
Figure 7: The total number of VTE episodes identified at RDH from 2005 to 2009 ............... 38
Figure 8: The selection criteria flow chart ............................................................................. 50
Figure 9: Chart of classification categories ............................................................................. 51
Figure 10: The anatomical positions of identified DVT events ............................................. 52
Figure 11: Pharmacological prophylaxis in accordance with hospital guidelines ................... 58
Figure 12: Comparative prophylaxis rates between surgical and medical patients ............... 59
Figure 13: The appropriate use of pharmacological agents .................................................... 60
Figure 14: Mechanical prophylaxis in accordance with hospital guidelines ........................... 61
Figure 15: Mechanical and pharmacological prophylaxis in high risk surgical patients ....... 62
Figure 16: Confirmed diagnosis in patients that develop VTE during admission ................. 64
Figure 17: Confirmed diagnosis in Category B1 ................................................................. 66
Figure 18: The number of days between discharge from RDH and readmission for VTE 67
Figure 19: Distribution chart of primary exclusions from the hospital audit (Category E) .... 69
Figure 20: Distribution chart of Category A2 and B2 patients .............................................. 70
Abstract

Haemostasis is the physiological response to blood loss that is a result of the activation and adhesion of platelets and clotting factors. Damage to the vascular endothelium or stasis of the blood may activate this haemostatic response, potentially leading to clot formation and lumenal obstruction. Anticoagulants prevent clot formation by inhibiting the activation of clotting factors.

Common VTE risk factors include age, pregnancy, obesity, smoking, the use of oestrogen hormonal preparations and genetic predispositions. Hospitalisation confers a greater risk of VTE than travelling. Surgical intervention associated with trauma, orthopaedic, neurologic or major surgery confer a substantial risk. Medical risk factors largely include coagulation disorders, history of VTE, diseases affecting venous perfusion or arterial perfusion, heart failure, inflammation, respiratory disease, diabetic ketoacidosis and nephrotic syndrome. A number of medications are also implicated.

Venous thromboembolism (VTE) is a significant cause of hospital related morbidity and mortality. Evidence based practice is utilised when selecting the appropriate treatment or prophylaxis agent for VTE. This largely includes enoxaparin, dalteparin, unfractionated heparin, warfarin, Factor Xa inhibitors and mechanical devices. There is increasing evidence supporting the use of direct thrombin inhibitors. Special consideration is necessary for pregnancy, renal impairment, and heparin induced thrombocytopenia.

The purpose of this audit was to identify the adherence to hospital VTE prophylaxis guidelines in patients that have developed VTE within 90 days of admission at Royal Darwin Hospital in 2007 to 2009.

A total of 542 episodes of VTE were identified by the Royal Darwin Hospital (RDH) coding department, pertaining to 431 diagnoses. Diagnosis was based on a confirmed compression Doppler ultrasound or computed tomography (CT) angiogram. A total of 123 patients were excluded on the basis of superficial thrombophlebitis (n=49), potential miscoding (n=17), renal ward admission (n=14), intervention in another hospital (n=14), palliative care (n=9), wrong year (n=5), age <18 years (n=11), suspected VTE without confirmation (n=2) and post-mortem diagnosis (n=1). Of the 308 remaining episodes, 14.3% (n=44) developed VTE associated with their current indexed admission and 17.2% (n=53) were readmissions to hospital following an inpatient admission in the previous three months. The remaining 68.5% (n=211) of patients had presented to hospital with a primary diagnosis of VTE without an inpatient admission at RDH in the previous 90 days. Of the 97 patients who developed
VTE associated with their current hospitalisation or readmission within the previous 90 days, 39.2% (n=38) pertained to admissions in the High Dependency Unit (HDU), Intensive Care Unit (ICU), Rapid Assessment Planning Unit (RAPU) or outpatient clinics.

Adherence to VTE prophylaxis guidelines was assessed in 59 medical and surgical patients who developed VTE associated with their current indexed admission (n=32) or within 90 days after discharge (n=27). Across the three years, 46.7% (n=21) received pharmacological prophylaxis with an appropriate agent, dose and duration, 37.8% (n=17) did not receive prophylaxis in accordance with guidelines, and 15.5% (n=7) did not receive pharmacological prophylaxis due to contraindications. A total of 47.6% of high risk surgical (n=10) and 62.5% of high risk medical (n=10) patients without contraindications received the appropriate agent, dose and duration of prophylaxis. Of the high risk surgical patients without contraindications, 61.9% (n=13) received appropriate pharmacological prophylaxis, 47.6% (n=10) received mechanical prophylaxis and 28.6% (n=6) received both methods.

This audit highlights the need for RDH to employ dedicated VTE prophylaxis staff to increase the awareness and adherence to VTE prophylaxis guidelines and reduce the incidence of hospital related VTE.
1. Coagulation Physiology and Pathophysiology

1.1 Haemostasis, Coagulation and Thrombosis

Haemostasis refers to the process of minimising blood loss from the vascular system. This occurs by activation of thrombocytes from a vascular endothelial response to induce platelet aggregation, referred to as the primary haemostatic mechanism. This mechanism is synergistic with the activation of the secondary haemostatic mechanism, which includes the coagulation cascade to form a fibrin clot. These mechanisms are activated under normal physiological conditions in response to vascular injury.

1.1.1 Platelet Activation

Platelets are anuclear fragments that originate from megakaryocytes in bone marrow, with a systemic lifespan of up to ten days. They generally exist within the blood at a concentration of 1.5-4.0 $\times 10^{11}$/L, which may differ in the case of pathophysiological predispositions, leading to thrombocytopenia or thrombophilia. Endothelial damage exposes collagen and the endothelial protein von Willebrand Factor (vWF), which is secreted between the basal membrane and the endothelium. These agents aid in platelet adhesion, with a relatively high concentration of vWF secreted at the site of vascular injury, inducing glycoprotein IIb/IIIa mediated platelet aggregation.

1.1.2 Clotting Factor Activation

The coagulation cascade is activated by the intrinsic and/or extrinsic pathways, which both ultimately result in the conversion of fibrinogen to fibrin, causing the formation of a fibrin clot. Damage to the vascular endothelium releases the cell surface glycoprotein Factor III (Tissue Factor), which causes the formation of an activated enzyme complex with Factor VIIa (Plasma Factor). This is responsible for the initiation of the extrinsic coagulation cascade. The intrinsic pathway, or contact activation pathway, is activated by the exposure of high molecular weight kininogen, prekallikrein or Factor XII to a negatively charged surface. These anionic surfaces may be created as a result of the presence of phospholipids from oxidised lipoprotein particles including Low Density Lipoproteins (LDLs), which are precursors to the formation of atherosclerotic plaques. These activation pathways are illustrated in Figure 1.
Figure 1: The Intrinsic and Extrinsic Coagulation Pathways.
The final common pathway results in the formation of a cross-linked fibrin clot. Adapted from Raghavan et al, 2002.4
**Table 1:** Clotting factors involved in the propagation of the coagulation pathway.

The Roman numerals indicate the order of discovery of various coagulation factors. The activated form of each respective factor is denoted with a subsequent ‘a’ after the designated Roman numeral.

<table>
<thead>
<tr>
<th>Coagulation Factor</th>
<th>Name</th>
<th>Plasma Concentration (mg/L)</th>
<th>Mechanism and primary role of activated form</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Fibrinogen</td>
<td>2,000-4,000</td>
<td>Fibrinogen can bind to platelet glycoprotein IIb/IIIa receptors, forming cross linkages. Fibrin forms haemostatic polymer.</td>
</tr>
<tr>
<td>II</td>
<td>Prothrombin</td>
<td>100</td>
<td>Conversion of fibrinogen to fibrin. Activates PAR receptors on platelets and promotes aggregation. Promotes formation of Factors VIIa, Va, activated protein C and TAFIa.</td>
</tr>
<tr>
<td>III</td>
<td>Tissue Factor (TF)</td>
<td>Subendothelial protein</td>
<td>Released in response to endothelial damage, forms Factor TF:VIIa enzyme complex.</td>
</tr>
<tr>
<td>IV</td>
<td>Calcium ion</td>
<td>46.5 – 52.1</td>
<td>Needed for thrombin generating reactions.</td>
</tr>
<tr>
<td>V</td>
<td>Proaccelerin/Labile Factor</td>
<td>10</td>
<td>Cofactor, forms complex with Factor IV that initiates Factor X activation.</td>
</tr>
<tr>
<td>VII</td>
<td>Proconvertin</td>
<td>0.5</td>
<td>Forms complex with TF, activated FVIIa initiates extrinsic pathway by activation of Factor X.</td>
</tr>
<tr>
<td>VIII</td>
<td>Anti-haemophilic Factor A</td>
<td>0.1</td>
<td>Dissociates with vWF and becomes cofactor to Factor Ixa in activation of Factor X.</td>
</tr>
<tr>
<td>Factor IX</td>
<td>Anti-haemophilic Factor B or Christmas Factor</td>
<td>3</td>
<td>Activates Factor X.</td>
</tr>
<tr>
<td>Factor X</td>
<td>Stuart Prower Factor or prothrombinase</td>
<td>10</td>
<td>Converts prothrombin to thrombin.</td>
</tr>
<tr>
<td>Factor XI</td>
<td>Plasma thromboplastin/ Antihaemophilic Factor C</td>
<td>5</td>
<td>Activates Factor IX in the intrinsic pathway.</td>
</tr>
<tr>
<td>Factor XII</td>
<td>Hageman Factor</td>
<td>20-40</td>
<td>Initiates intrinsic pathway, activated by anionic surface, activates Factor XI.</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>Fibrin stabilising</td>
<td>10-20</td>
<td>Promotes fibrin cross linkage.</td>
</tr>
<tr>
<td>Prekallikrein</td>
<td>Fletcher Factor</td>
<td></td>
<td>Catalyses activation of Factor XII.</td>
</tr>
<tr>
<td>High Molecular Weight Kininogen</td>
<td>Fitzgerald Factor</td>
<td>50</td>
<td>Circulates plasma as bimolecular complex with prekallikrein. Cofactor for kallikrein activation.</td>
</tr>
</tbody>
</table>
Table 2: Proteins involved in the inhibition of the coagulation pathway.

<table>
<thead>
<tr>
<th>Inhibitor Protein</th>
<th>Plasma Concentration</th>
<th>Mechanism of activated factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin</td>
<td>180-300</td>
<td>Inhibits Factors Iia, Xa, Xia and Ixa.</td>
</tr>
<tr>
<td>Protein C</td>
<td>4</td>
<td>Activated by thrombin and thrombomodulin, causes proteolysis of Factors Va and VIIIa.</td>
</tr>
<tr>
<td>Protein S</td>
<td>23</td>
<td>Similar mechanism to Protein C.</td>
</tr>
<tr>
<td>Protein Z</td>
<td>2.3-2.9</td>
<td>Degradation of Factor X.</td>
</tr>
<tr>
<td>Plasminogen</td>
<td>200-400</td>
<td>The proteolytic enzyme plasmin degrades fibrin.</td>
</tr>
<tr>
<td>Plasminogen activators tPA and uPA</td>
<td>5.77 mcg/L for tPA/PAI-1 complex</td>
<td>Tissue-type plasminogen activator (tPA) secreted by the endothelium and urokinase-type plasminogen activator (uPA) by macrophages cleaves plasminogen into plasmin.</td>
</tr>
</tbody>
</table>

1.1.3 Pharmacological Mechanisms of Anticoagulants

Plasmin is produced by tPA from plasminogen and acts to degrade fibrin. The action of plasmin is the rationale underlying the use of synthetic plasminogen activators and thrombolytics. The presence of endogenous plasminogen activator inhibitors limits the action of these agents to the treatment of acute thrombosis. The thrombolytic pathway is inhibited by plasminogen activator inhibitors including Plasminogen Activator Inhibitor 1 (PAI-1), Plasminogen Activator Inhibitor 2 (PAI-2), Protease-Nexin I (PN-I) and α2-antiplasmin. These are responsible for localising the action of tPA to the affected fibrin clot and prevent degradation of other tissue. Heparins are pharmacological agents that exhibit anticoagulant effects by activating the plasma enzyme antithrombin III (AT). AT is responsible for the inactivation of Factor IIa and Factor Xa, thereby preventing fibrin formation. This differs from direct thrombin inhibitors that selectively inhibit Factor IIa (thrombin) and hence prevent the final step in the conversion of fibrinogen to fibrin.

The hepatic synthesis of Factors II, VII, IX and X, proteins C, S and Z is dependent on the presence of vitamin K. This is reduced to vitamin K hydroquinone by the vitamin K epoxide reductase enzyme (VKOR). This allows the gamma-glutamyl carboxylase enzyme to utilise the reduced vitamin K as a cofactor. This results in the conversion of glutamate residues on these clotting factors to functional gamma-carboxyglutamate residues. This process also results in the oxidation of vitamin K hydroquinone to its epoxide form. The inhibition of the VKOR enzyme results in a loss of conversion of vitamin K hydroquinone from its epoxide form to its reduced form and hence increased production of clotting factors with glutamate residues. The factors produced are unable to form linkages with Factor IV (calcium ions) and bind to anionic phospholipid surfaces when activated, reducing their ability to participate in the coagulation cascade. The inhibition of Factor II prevents the thrombin mediated conversion of fibrinogen to fibrin. This is the rationale underlying the use of vitamin K
antagonists (warfarin and phenindione), to inhibit coagulation. The efficacy of warfarin is expressed via the International Normalized Ratio (INR). The INR reflects on the ratio of the time taken for a sample of the patient’s blood to clot with respects to the mean time exhibited by a healthy individual in the absence medication. Hence the INR of a healthy individual is approximately 1. Other pharmacological mechanisms of action include the direct inhibition of Factor Xa or Factor IIa. These anticoagulants are discussed in further detail in Chapter 3. The oxidation and reduction of vitamin K is illustrated in Figure 2.

Figure 2: Pharmacological Mechanism of Vitamin K Antagonists. Vitamin K acts as a cofactor in the production of active clotting Factors II, VII, IX and X and is oxidised to its epoxide form. The Inhibition of the Vitamin K Epoxide Reductase enzyme by warfarin is the pharmacological mechanism of this anticoagulant. Adapted from Schwarz & Stein, 2006.11

1.2 Arteriolar and Venous Thrombosis
A thrombus refers to a clot within the vascular system that is localised as a result of adhesion or blockage of a vessel. This differs from an embolism, which denotes a delocalised thrombus. Hence, the diagnosis of symptomatic venous thromboembolism (VTE) places a patient at high risk of pulmonary embolism (PE) as the clot may dissociate from the venous endothelium.
Although the primary and secondary haemostatic mechanisms are synergistically active, the location can largely influence the mechanism responsible for the thrombus formation and hence the composition of the clot.\textsuperscript{12} Arteriolar thrombi are formed as a result of the inflammatory process involved in the formation of atherosclerotic lesions, which leads to platelet and leukocyte activation, causing the aggregation and adhesion of these cells to the affected vasculature. This is coupled with localised fibrin formation and leads to the formation of a ‘white’ thrombus and is hence the underlying rationale behind the use of antiplatelet therapy in the prevention of arteriolar thrombosis.\textsuperscript{13} These may propagate through the arteries to become lodged within smaller arterioles or capillaries, thereby inhibiting the blood flow to the distal interstitial tissue. This may clinically manifest as a serious complication including myocardial infarction and ischaemic stroke.\textsuperscript{3}

Both the intrinsic and extrinsic pathways may contribute to the formation of a venous thromboembolism. A venous thromboembolism is generally associated with blood stasis, resulting from inadequate venous return, which activates the intrinsic pathway, or from direct vascular injury such as surgery, which provokes the extrinsic pathway. Prolonged stasis increases the contact time between a localised region of the endothelium and the blood. This can trigger the activation of Factor XII by contact adhesion, which causes the subsequent activation of Factor XI and hence triggers the intrinsic activation cascade. This ultimately results in the conversion of fibrinogen to fibrin without the marked platelet activation observed in the formation of ‘white’ thrombi. The fibrin mesh traps the haematic constituents, namely erythrocytes and hence results in the formation of a ‘red’ thrombus.\textsuperscript{13} A deep vein thrombosis (DVT) denotes the formation of this thrombus in the major venous vasculature. This fibrin formation is further potentiated in patients with sustained trauma to the vascular system, which will cause a concurrent activation of the extrinsic coagulation pathway. Hence, the formation of a venous thromboembolism is a function of a reduced venous return and increased activation of clotting factors. Venous thromboembolism prophylaxis is therefore achieved through pharmacological therapy with anticoagulants as opposed to antiplatelets and through mechanical therapy via processes that utilise the skeletal-muscle pump.
The pathogenesis of thrombosis can be summarised in Virchow’s Triad. The components of Virchow’s Triad include blood stasis or turbulence, alteration of the vascular endothelium and alterations in the constitution of the blood causing hypercoagulability, as illustrated in Figure 3. These factors may attribute to thrombosis via more than one method. Surgery may attribute to VTE via blood stasis associated with anaesthesia and direct vascular damage from the procedure. Pregnancy is associated with both reduced peripheral blood flow and increased production of procoagulant mediators.

**Figure 3:** Virchow’s Triad and the Pathogenesis of Thrombosis.
Venous and arterial thrombotic events may be attributed to one or more of the above risk factors for thrombosis.\(^2,^3\)
2. The Incidence and Risk of Venous Thromboembolism

2.1 Community Acquired Venous Thromboembolism
The incidence of community acquired VTE has not appeared to change significantly over the last 35 years. The average incidence of first time symptomatic VTE in the US is estimated at approximately 0.1% of the population per year. Australian based epidemiological studies suggest an average incidence of first time symptomatic VTE, DVT and PE of 0.062%, 0.038% and 0.024% respectively. The overall incidence taking into account recurrent VTE is approximately 0.083%. This would extrapolate to an estimated 18,500 cases across Australia this year with the current population of 22.3 million. These findings are further supported by the Australian Institute of Health and Welfare, which estimates an annual incidence rate of 0.078%.

2.1.1 Age
The risk of VTE generally increases with age. The risk appears to increase exponentially with age, from 0.005% in persons less than 15 year, to 0.5% at 80 years of age. A large cohort study involving 1,464,452 cases of VTE concluded that the risk of symptomatic VTE within 90 days after surgery increases by 9% for every five years above 18 years of age. For hip arthroplasty and neurosurgery, the risk appears to plateau after 60 and 80 years respectively and for vascular surgery, there is no apparent relationship, which may be attributed to the direct vascular damage that elevates the risk of VTE regardless of age.

2.1.2 Sex
A 25-year populated based study in the US suggests that the age adjusted incidence of VTE in males is 0.114% compared to 0.105% in females. This is attributed to a higher incidence of DVT in males compared to females. This trend differs from a 2008 report by the Australian Institute of Health and Welfare, suggesting a higher incidence of both PE and DVT in females than males for all adult age groups as indicated in Figure 4. Discrepancies between different studies may be explained by varying risk factors between different populations. The absolute risk for females is dependent upon a range of factors including pregnancy, menopause and the use of hormonal preparations containing oestrogen.
2. The Incidence and Risk of Venous Thromboembolism

2.1.3 Pregnancy and the Use of Oestrogens

Epidemiological studies suggest an incidence of symptomatic VTE of 0.063% per year in combined oral contraceptive users compared to 0.030% per year amongst those who have never used the pill. This risk varies from 0.054-0.079% per year depending on the oestrogen dose and the type of progestogen used. The increased risk associated with hormone releasing intrauterine devices is relatively minimal (0.036% per year). However, this risk is lower than that associated with pregnancy. Late menopause or the use of post menopausal HRT appears to increase this risk by two fold. One 30 year population based study assessing the epidemiology of symptomatic VTE in pregnant and post partum Caucasian women determined an overall general incidence rate of 0.200% associated with the pregnancy and post-partum period. This consisted of an incidence of 0.095% during and 0.511% after pregnancy. Pulmonary embolism accounted for one third of the cases of symptomatic VTE,
and was fifteen times more common after pregnancy than during pregnancy. This proportion is consistent with the general trend observed in patients that develop symptomatic VTE from other risk factors.\(^{23, 24}\) The higher incidence of symptomatic DVT towards the trimester and post-partum and exponential increase in PE after pregnancy indicates that PE could be the result of a DVT that has developed throughout the progression of the pregnancy. The reasons underlying the increased risk associated with pregnancy and the use of oestrogens are a result of the normal haemostatic changes that prepare the female for pregnancy. This includes an increased production of procoagulant factors, namely Factor VIII, Factor I and von Willebrand Factor, with decreased anticoagulants including protein S, and increased plasminogen activator inhibitors PAI-1 and PAI-2, coupled with the mechanical obstruction caused by foetus upon the inferior vena cava and left iliac vein. Vaginal or operative delivery may also result in venous distension and direct damage to the vascular endothelium.\(^{25}\)

### 2.1.4 Ethnic/Racial Variability

Asian and Pacific Islanders may be at the lowest risk of first time idiopathic VTE from an epidemiological perspective. This is shown in table 3. This is most significant for DVT with a 74% lower associated risk and recurrent VTE with a 35% lower associated risk respectively, compared to the population mean.

**Table 3:** The average incidence of idiopathic VTE and Odds Ratio (OR).

This is expressed as a relative risk compared to Caucasians as determined from an epidemiological study involving 23,564 patients greater than 18 years of age, without hospitalisation within the previous six months or diagnosis of cancer.\(^{26}\)

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Incidence (%)</th>
<th>OR to Caucasian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>0.0230</td>
<td>1</td>
</tr>
<tr>
<td>African Americans</td>
<td>0.0293</td>
<td>1.27</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.0139</td>
<td>0.60</td>
</tr>
<tr>
<td>Asian and Pacific Islander</td>
<td>0.0060</td>
<td>0.26</td>
</tr>
</tbody>
</table>
Genetic predispositions may influence the differences in the incidence rates amongst ethnic groups, although this information is conflicting and further research may be required. There is also little documented information on the prevalence of genetic predispositions of Indigenous Australians, which may suggest avenues for further research.

2.1.5 Smoking and Obesity
A population-based, randomised, controlled study involving 71,729 pregnant and post partum women found that obesity alone is associated with a 2.4 – 5.3 fold increased risk of thromboembolic events, and a further increased risk by 2.7 fold when associated with hypertriglyceridaemia. The risk is 14.9 [95% CI: 1.5 – 4.9] fold greater for pulmonary embolism compared to only 4.4 [95% CI: 1.6 – 11.9] fold for deep vein thrombosis, indicating that obesity is associated with both an increased risk of VTE and a worsened outcome following a venous thromboembolic event. Smoking is associated with an overall increased risk of 2.7 fold.

2.1.6 Travelling
Research suggests that the risk of traveller’s thrombosis may be overly emphasised, however a general consensus is that this risk increases with the duration of the flight. The total incidence of DVT (symptomatic and asymptomatic) after flights with a mean duration of 7.1 hours as determined from a meta-analysis involving randomised controlled trials was 3.72%. This risk was 23.3 times less with the use of graduated compression stockings. The risk of symptomatic VTE also appears to increase with travelling, by a factor of 1.7-2.3 times with travel greater than three hours. Although these figures may appear alarming, the incidence of DVT from the first study was interpreted using venography or ultrasound to assess for evidence of thrombosis. Furthermore the increased risk, although statistically significant appears to represent a total incidence rate of approximately 0.03–0.14% as determined through large scale retrospective cohort studies involving a total of 11,254 people. This risk falls within the interval of the incidence of VTE in the general population. This suggests that patients developing DVT after long distance travel should be

---

*The higher incidence of Factor V Leiden mutation has been associated with the increased risk of VTE amongst Caucasians compared to South East Asians (4.4% versus <1%). However, research has revealed a similar incidence of gene mutation between Africans and Asians, despite the increased risk of VTE amongst Africans and hence other risk factors may be involved. 27. Rees D C, Cox M & Clegg J B. World Distribution of Factor V Leiden. Lancet. 1995;346(8983):1133-4.*
screened or assessed for other underlying risk factors or that patients are unlikely to receive significant risk reduction from VTE prophylaxis unless other risk factors are implicated.

2.1.7 Anatomical Regions Affected by Deep Vein Thrombosis
Although DVT is generally associated with the lower limbs, it may occur in any region of the body. One epidemiological study assessing the incidence of VTE amongst the general population determined that approximately 10% of DVT occurs in areas other than the legs or pelvic region, as summarised in Table 4.

**Table 4: The areas affected by symptomatic DVT.**
This was determined from an epidemiological study involving 151,923 Perth based residents.\textsuperscript{14}

<table>
<thead>
<tr>
<th>Region of the Body</th>
<th>% of Total DVT Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower limbs (including pelvis)</td>
<td>90.7%</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>4.65</td>
</tr>
<tr>
<td>Mesenteric veins</td>
<td>3.46</td>
</tr>
<tr>
<td>Portal vein</td>
<td>1.16</td>
</tr>
</tbody>
</table>
2. The Incidence and Risk of Venous Thromboembolism

2.2 Hospital Acquired Venous Thromboembolism

Reports determining the incidence of VTE associated with particular surgical or medical procedures have often used venography or Doppler ultrasound to assess for evidence of venous thrombosis. Such incidences may be misleading as majority of asymptomatic thrombi detected by routine venography may resolve spontaneously with remission of the patient after the associated surgical or medical procedure. This is further supported by ten multi-centred studies involving 5,796 patient that determined a ratio between symptomatic and asymptomatic DVT after TKR at 1:21 and a ratio of 1:5 for THR, implying that DVT from THR appear to be more problematic and hence asymptomatic DVT is not an accurate predictor of the incidence of symptomatic DVT.

2.2.1 Surgical Intervention

Surgery and trauma, particularly involving lower limb orthopaedic surgery is considered a high risk factor for the development of VTE. This is the result of blood stasis and direct damage to the vascular tissue. The risk of VTE is elevated during surgery or with sustained trauma as a result of endothelial damage, thereby promoting coagulation by the extrinsic pathway. Hence, major general surgery, intra-abdominal, neurologic and other procedures that render the patient immobile or are highly invasive including major gynaecologic and urologic surgery are also considered risk factors. The Million Women Study, a prospective cohort involving 947,454 middle aged women in the United Kingdom between 1996-2001 concluded that the overall risk of developing VTE associated with hospitalisation is 70 fold in the first six weeks after an inpatient operation compared to no surgery. The risk of VTE associated with surgery or injury appears to be insignificant three months after major injury, including surgery associated with spinal cord injury and hence three months is generally used as a cut-off for post-surgical risk assessment.

---

b Information relating to risk factors associated with hospitalisation is focused particularly on factors pertinent to patients with medical conditions or undergoing surgical intervention at Royal Darwin Hospital.

c The reasons of which are a result of the location of each operation as explained in Section 2.2.1.2
2.2.1.1 **Trauma**
Due to the large variation in severity of trauma between patients, risk assessment is generally based on stratification. The risk of developing DVT is as high as 58% in patients without thromboprophylaxis. Acute spinal cord injury follows the greatest risk, with approximately 60-100% of patients developing asymptomatic DVT, and PE is the third most common cause of death in these patients. This risk is followed by leg and pelvic fractures, femoral venous lines, penetrating injuries and prolonged immobility as the greatest risk factors. Those with major trauma generally have a risk of asymptomatic DVT greater than 50%, especially in the case of leg injury, if prophylaxis is not implemented. Pulmonary embolism accounts for approximately one third of deaths from major trauma. The method and duration of prophylaxis requires particular consideration due to risk of VTE associated with vascular damage and inflammation coupled with active bleeding that may be exacerbated by anticoagulants. The use of pneumatic compression devices has shown to reduce the risk of DVT but not significantly for PE. An inferior vena cava (IVC) filter is a mechanical device inserted via the femoral or jugular vein that screens for embolism travelling towards the heart. This may reduce the risk of PE, but may mildly increase the risk of DVT from the increased flow resistance caused by the filter.

Minor trauma may also elevate a person’s risk of VTE with one study concluding a fourfold increased risk of VTE within four weeks post injury. This risk reduces to 3.1 times within ten weeks post injury and is virtually insignificant after 14 weeks. This study was a retrospective analysis involving 2,471 patients with VTE and 3,534 control subjects. Minor trauma was described as trauma not requiring a plaster cast, hospitalisation or extended bed rest for at least 4 days. Muscle or ligament rupture, contusion and sprains accounted for 65% of the reported trauma patients and were the highest risk factors for VTE with respects to minor trauma. This study used asymptomatic DVT as an endpoint of prediction and hence further research is required to correlate this information with the risk of symptomatic VTE.

2.2.1.2 **Orthopaedic and Neurosurgery**
A meta-analysis assessing the risk of VTE events following three months after total hip replacement (THR) and total knee replacement (TKR) concluded that 1 in 5 of these patients developed either symptomatic or asymptomatic DVT. Patients in these cohorts received short term VTE prophylaxis consisting of 7-10 days of LMWH. By comparison, the incidence of non-fatal symptomatic VTE events was 3.2% and the incidence of fatal
2. The Incidence and Risk of Venous Thromboembolism

The incidence of venous thromboembolism (VTE) events was 0.10% as determined by the sample of 6,089 patients. One third of the VTE events occurred within the 7-10 day period of post-surgical VTE prophylaxis. Furthermore, the incidence of asymptomatic DVT as determined by venography was 38.8% in patients with TKR, compared to 16.4% in patients with THR.

These findings are also supported by a multicentre, prospective cohort study involving 1,200 patients with lower leg fractures that did not receive thromboprophylaxis. In this study, patients with major trauma, cancer and previous history of VTE were excluded. 82% of the patients were immobilised by cast but only 7% required surgical correction. Only seven patients experienced symptomatic VTE, consisting of two cases of pulmonary embolism, none of which were fatal, producing a total incidence rate of 0.6%. This study concluded that habitual thromboprophylaxis for patients with lower leg injuries may be undesirable from a cost-effective analysis and may instead be warranted where there is established damage to the vascular endothelium or surgical intervention.44

The incidence of symptomatic VTE after the 7-10 day prophylaxis is twice as high in patients with THR compared to TKR.45 This is supported by a review of hospital medical records in California that concluded the median time of diagnosis of VTE after hip replacement surgery was 17 days (n= 19,586), compared to 7 days after surgery for knee arthroplasty (n= 24,059).46 The reason for the higher incidence of asymptomatic DVT associated with TKR may be due to the distal location of the operation and hence increased blood stasis causing DVT. However, the associated femoral torsion and hip rotation that exists for an extended period of time after surgery appears to contribute to the formation of larger thrombi in patients after THR, which poses a higher risk of symptomatic DVT.45 Hence patients undergoing hip arthroplasty are considered candidates for extended thromboprophylaxis of 28-35 days. Although lower limb surgery is regarded as a major risk factor for DVT, an increased risk of DVT may exist for any region of the body affected by surgery, implying that extended prophylaxis may be warranted for any invasive orthopaedic surgery.

The risk of VTE from major orthopaedic surgery is comparable to the risk after invasive neurosurgery. Asymptomatic DVT appears to develop in one quarter to a third of neurosurgery patients, with 2-3% developing symptomatic DVT if no prophylaxis is delivered. Spinal cord procedures causing paralysis was associated with the highest risk, followed by intracranial procedures. This risk was further increased for patients requiring surgery as the result of a brain tumour.38
2.2.1.3 General, Gynaecologic and Urologic Surgery

The risk of developing VTE associated with general surgical intervention is largely dependent upon the nature of the intervention. Major general surgery (excluding orthopaedic surgery) is regarded as a surgical procedure lasting >45 minutes and/or intra-abdominal or thoracic surgery. Minor surgery appears to bear an associated risk of no more than 2.4% for asymptomatic DVT. The American College of Chest Physicians states that mobilisation of the patient should be encouraged to reduce this risk and routine VTE prophylaxis is unnecessary unless other associated risk factors exist such as obesity, immobility, cancer or age over 40.\textsuperscript{47} The surgical method may also significantly affect the risk of VTE. The incidence of deep vein thrombosis and pulmonary embolism associated with open surgery for cholecystectomy is 5% and 0.4% respectively. A significant risk reduction is achieved via laparoscopic cholecystectomy with an incidence of only 0.03% for symptomatic DVT and 0.02% for PE respectively, as determined from a meta-analysis involving 153,832 patients. Patients with major general surgery including liver, pancreatic, gastric or bowel surgery are at a relatively high risk of pulmonary embolism at 0.8-1.7%. For this reason open intra-abdominal surgery is considered a major risk factor.\textsuperscript{48}

The type and duration of anaesthesia may also affect the incidence of VTE. One retrospective case-control study involving 269 patients found a threshold increased risk of VTE of 3.6 times for patients receiving anaesthesia for greater than 3.5 hours. This associated risk was also higher with patients receiving general or epidural anaesthesia. The increased risk may be due to the associated stasis, dilation of the venous system and the supine position preventing utilisation of the skeletal muscle pump.\textsuperscript{49}

The American Urologic Association associates the following four surgical procedures with a high risk of VTE:

- Transurethral surgery
- Anti-incontinence and pelvic reconstructive surgery
- Laproscopic urologic surgery
- Open urologic surgery

These risk factors were identified largely from non-randomised studies and hence there is insufficient evidence to predict the exact associated risk of each surgical intervention, but evidence is justified for the habitual use of DVT prophylaxis agents in patients undergoing the aforementioned surgical procedures.\textsuperscript{50}
The general increased risk of VTE associated with gynaecologic surgery is 22.7 times compared to no surgery, as determined from the Million Women Study.\textsuperscript{37, 51} The overall risk may be comparable to that of general surgery when following abdominal gynaecologic procedures and is less with vaginal procedures. The risk of DVT (asymptomatic or symptomatic) may vary from 4-38\%, averaging 16\%, and 0.4\% for fatal PE when no prophylaxis is delivered. The risk is highest for patients undergoing surgery associated with cancer.\textsuperscript{34, 47}

2.2.2 Medical Conditions
The risk of VTE in medical patients is often overshadowed by the patient’s presenting medical illness. Retrospective analysis of autopsies has attributed PE to approximately 7.6\% of all non-surgical deaths in hospitals.\textsuperscript{52} There have been several major studies assessing the risk of VTE, the efficacy and safety of prophylactic agents in medical patients.\textsuperscript{d} The duration of therapy in patients with medical illness is generally 6-14 days, until resolution of the acute medical illness or hospital discharge.\textsuperscript{53, 54, 55}

2.2.2.1 History of Venous Thromboembolism and Coagulopathy
A history of VTE is one of the most significant risk predictors for a patient. A previous diagnosis of VTE is associated with a 6 fold increased risk after any surgical procedure.\textsuperscript{18} A strong family history, involving first degree relatives has been associated with a 4-12 fold increased risk. A person with a family history of VTE and genetic predispositions may bear a 64 fold increased risk when undergoing surgery compared to a person with no family history and genetic predisposition. This risk is double where the diagnosis occurs in a relative less than fifty years of age.\textsuperscript{43, 56}

One case control study involving Brazilian patients experiencing VTE without underlying co-morbidities including cancer or hepatic impairment that were less than 70 years of age, found that 20\% of patients experiencing VTE had one or more genetic predisposition of thrombophilia.\textsuperscript{57}

\textsuperscript{d} Information relating to the various trials of prophylactic agents is summarised in Section 3.3.
2. The Incidence and Risk of Venous Thromboembolism

Table 5: Acquired and Inherited Thrombophilia.
Inherited Thrombophilia refers a genetic predisposition to thrombolism.58

<table>
<thead>
<tr>
<th>Acquired Thrombophilia</th>
<th>Inherited Thrombophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus anticoagulant</td>
<td>Antithrombin deficiency</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>Protein C deficiency</td>
</tr>
<tr>
<td>β2-glycoprotein 1</td>
<td>Protein S deficiency</td>
</tr>
<tr>
<td>Plasma homocysteine</td>
<td>Factor V Leiden</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation</td>
<td></td>
</tr>
</tbody>
</table>

Homozygous Factor V Leiden mutation is considered the most prevalent genetic predisposition and has been associated with a 25-50 fold increased risk of VTE, which may be tripled in persons with a positive family history of VTE.56, 59 The incidence of allele mutation is approximately 4.4% amongst Europeans and relatively insignificant amongst Africans and South East Asians. The risk of VTE associated with genetic predispositions and previous history of VTE has formed the basis of thromboprophylaxis in pregnancy.6 The relative risk of VTE associated with each hereditary thrombophilia associated with pregnancy is explained in further detail in Section 3.4.4.

2.2.2.2 Venous Insufficiency and Varicose Veins
There is little documented evidence to assess the absolute risk caused by the presence of varicose veins. This is because the severity of the varicosities is subjective and the risk appears to be inversely proportional to the age at which a person presents with varicose veins. The odds ratio is 4.2 times if varicosities are present at 45 years of age compared to 1.9 times if present at 60 years of age and no associated risk if present at 75 years.42 It is unclear if the varicosities directly contribute to an increased risk of VTE or if the association is due to similarities between the risk factors for VTE and varicosities. These include obesity, pregnant women and occupations associated with long periods of orthostasis, which are also associated with VTE.61 In chronic venous insufficiency, there is a dysfunction in the venous valves, which may have resulted from phlebitis, intense pressure and genetic predispositions. The resulting insufficiency reduces the efficiency of the venous skeletal muscle pump, which may result in stasis of the blood in susceptible individuals and hence lead to DVT.61, 62

6 Anticoagulants increase the risk of bleeding and hence may predispose the foetus to haemorrhage. Furthermore, all heparins are classed as ADEC category C drugs and warfarin as category D. Hence thromboprophylaxis is considered necessary for pregnant women with >10% risk according to RDH guidelines 60. Northern Territory Drugs and Therapeutics Committee. Venous Thromboembolism Prophylaxis Guidelines, 2009.
2.2.2.3 *Heart Failure and Atrial Fibrillation*

Heart failure reflects on the insufficiency of the heart to maintain tissue perfusion and is hence a risk factor for VTE independent of surgery, immobility or cancer. This is especially significant during the phase of decompensated heart failure due to the increased fluid stasis. Randomised audits of hospitals suggest that the risk of VTE in hospitalised heart failure patients is often neglected as the patient’s presenting complaints are addressed. This is reflected in the relatively low adherence to VTE prophylaxis guidelines for hospitals at 15.8% as determined from a US based study involving 34,286 heart failure patients that were considered candidates according to the guidelines outlined by the American College of Chest Physicians (ACCP).^63^

The risk of venous thromboembolism associated with heart failure inversely correlates with the left ventricular ejection fraction (LVEF). A 5% increase in the risk of VTE is observed per 18% reduction in the LVEF. One tenth of all deaths attributed to pulmonary embolism are linked to patients with coexisting heart failure, indicating that adequate VTE prophylaxis in heart failure patients may significantly reduce the total number of deaths attributed to VTE.^54^

Atrial Fibrillation (AF) is a major contributor to thromboembolic events, largely including ischaemic stroke. The rapid and uncoordinated contraction of the atrial myocardium caused by recurrent excitation may lead to thrombosis, which may embolise and occlude small blood vessels. A population-based study of 23,796 autopsies directly associated 4.0% of all pulmonary embolisms to intracardiac thrombosis arising from the right side of the heart.^64^ A twofold risk of deep vein thrombosis is associated with AF patients.^65^ Although there is an increased risk of PE associated with AF, the rationale for anticoagulant therapy is based on reducing the risk of stroke, as AF accounts for approximately 15-20% of all ischaemic strokes. This is largely attributed to the anatomical position of the left atrial appendage, which forms a compartment for thrombosis during AF.^66^ Treatment of persistent or permanent atrial fibrillation often includes control of the ventricular rate and hence the patient may remain at an elevated risk of thromboembolic complications without the use of anticoagulants. For this reason, anticoagulant therapy is warranted for patients with AF.
2.2.2.4 *Infection, Inflammation and Respiratory Disease*

A meta-analysis assessing the use of thromboprophylaxis in medically ill patients that developed VTE found that 29.4% of medical patients that developed symptomatic VTE in hospital were admitted for acute infection or inflammation. This study did not attribute infection or inflammation to the specific cause of VTE and the high prevalence may simply reflect on a relatively high total proportion of hospitalised patients with acute infection or inflammation in the sample. However, randomised, double-blind trials have shown that acute infection and respiratory disease each present independent risk factors of 1.26 and 1.5 fold respectively for VTE. Chest and systemic infections appear to increase this risk up to 1.75-1.95 fold. The higher associated risk is because infection and inflammation lead to procoagulant changes including a 4-5 fold increased expression in tissue factor and reduced thrombomodulin and protein C response. Inflammation has shown to inhibit fibrinolysis by increasing PAI-1 and promote thrombosis by interleukin 6 mediated platelet activation. Low dose unfractionated heparin therapy has been shown from randomised, double blind, multicentre trials to reduce the risk of DVT in these patients from 26% without prophylaxis to 4% with appropriate dose and duration.

2.2.2.5 *Ischaemic Stroke and Myocardial Infarction*

Ischaemic stroke, especially when associated with hemiplegia creates a very high risk of VTE. Up to 75% of these patients develop DVT and 20% develop PE without prophylaxis, attributing VTE to approximately 25% of deaths in acute stroke patients. The PREVAIL study was an open-label multicentre randomised study involving 1,762 patients with acute ischaemic stroke, which found that 10% of patients develop DVT and 0.15% develop PE after 40mg once daily dosing of enoxaparin, compared to 17% and 0.90% respectively for 5,000 IU of unfractionated heparin every twelve hours. The duration of prophylaxis for both agents was 10 +/- 4 days. Furthermore, there was no difference in the occurrence of bleeding (8%) or the frequency of symptomatic intracranial haemorrhage (1%).

The results are further supported by the ESSENCE study, which demonstrated that enoxaparin reduces the incidence of both arterial and venous thrombosis. The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events (ESSENCE) study was a prospective, multicentre, randomised, double-blind trial involving 10 countries that concluded enoxaparin reduces the frequency of recurrent angina, myocardial infarction and death in patients with unstable, recurrent or non-Q wave MI. Similar results were
demonstrated with the use of enoxaparin when used in acute myocardial infarction in the Treatment of Acute ST-segmented Elevation Myocardial Infarction Patients Ineligible for Reperfusion (TETAMI) study.\textsuperscript{74}

2.2.2.6 **Diabetic Ketoacidosis and Nephrotic Syndrome**

Although diabetes mellitus is not recognised as a major independent risk factor for VTE, retrospective analysis has revealed that complications of diabetes mellitus may place patients at an increased risk. Diabetic ketoacidosis appears to increase the risk of arterial thrombosis and to a smaller extent, venous thrombosis. The absolute risk factor caused by this condition has not been fully elucidated and information is largely based on anecdotal case studies.\textsuperscript{75}

Nephrotic syndrome potentiates the risk of DVT and renal vein thrombosis (RVT), both of which may lead to pulmonary embolism. The exact mechanism in which nephrotic syndrome promotes hypercoagulability is unknown. It is hypothesised that the proteinuria as a result of the damaged nephrotic tissue promotes an increase in the renal excretion of plasma inhibitory coagulation proteins and increased levels of von Willebrand Factor. This also promotes platelet aggregation and hence both arterial and venous thrombosis are complications of this condition.\textsuperscript{76} Warfarin has found to be the most effective therapy for the prevention and treatment of RVT, however the safety and efficacy of different treatments has not been assessed with large randomised controlled trials. Heparins are required in relatively high doses due to the increased antithrombin III levels observed in these patients.

Table 6: The risk of VTE in nephrotic syndrome patients without prophylaxis. RVT is often the first manifestation of VTE that progresses into DVT and/or PE.\textsuperscript{76}

<table>
<thead>
<tr>
<th>VTE complication</th>
<th>Proportion of Nephrotic Syndrome Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVT</td>
<td>22%</td>
</tr>
<tr>
<td>DVT</td>
<td>15%</td>
</tr>
<tr>
<td>PE associated with RVT</td>
<td>21%</td>
</tr>
<tr>
<td>PE independent of RVT</td>
<td>10%</td>
</tr>
</tbody>
</table>

2.2.3 **Cancer**

A higher incidence of VTE has been documented amongst patients diagnosed with active cancer, with an even greater risk for those with associated cancer surgery or chemotherapy. The absolute risk is dependent upon the stage and type of tumour, however the diagnosis of cancer has been associated with a fourfold increased risk and chemotherapy with a six to seven fold increased risk.\textsuperscript{77} Hypercoagulability is particularly associated with active or
malignant cancer and it has been stipulated that neoplastic cells may achieve this via direct or indirect stimulation of endothelial cells, leukocytes or platelets. Increased levels of von Willebrand Factor and reduced protein C activity have been demonstrated through randomised collection of blood samples in patients with DVT and active cancer versus patients with DVT and no diagnosis of cancer. Studies have also suggested that recurrent VTE may be indicative of undiagnosed malignancy. Large prospective studies have found that approximately 4 – 6.5% of patients with venous thromboembolic disease later present with previously undiagnosed cancer.

The @RISTOS project was a prospective multicentre observational study of 2,373 patients that underwent general, urologic or gynaecologic surgery for cancer and compared the overall risk of developing symptomatic VTE within 35 +/- 5 days after surgery. Thromboprophylaxis was given to 81.7% of patients, with LMWH as the selected agent in approximately 75% of patients. Other agents included unfractionated heparins and heparinoids. Only 10.4% of patients received mechanical prophylaxis. Symptomatic DVT was diagnosed in 0.42%, non-fatal pulmonary embolism in 0.88% and fatal pulmonary embolism in 0.80%, accumulating a total incidence of symptomatic venous thromboembolism at 2.1%. This risk was highest with general cancer surgery (2.83%), followed by gynaecologic surgery (2.0%) and was lowest with urologic surgery (0.87%). The risk of developing VTE was greatest at 1-5 days post surgery and significantly decreased up to the 16-20 day interval. This risk then paradoxically increased after 21 days and was elevated for the remainder of the study. This increase may be the result of only 23.3% of patients receiving prophylaxis for greater than 21 days. From this study, it is evident that cancer patients may be considered candidates for extended VTE prophylaxis. A major criticism of this study is that the observational period of 35 days post surgery was relatively narrow and a three month post assessment may have determined the period of time in which the risk of developing VTE remained elevated in these patients and would hence allow the desired length of thromboprophylaxis to be determined. The risk of VTE with concurrent cancer diagnosis is not limited to surgical cancer patients, with a multicentre epidemiological case-control study concluding that the risk of VTE is 2.3 times greater in hospitalised medical patients with a concurrent diagnosis of cancer.
2.2.4 Drug Induced Venous Thromboembolism
Evidence suggesting associated risks between pharmacological agents and the development of venous thromboembolism is largely based on case-control studies. The increased risk of VTE associated with the use of pharmacological oestrogens has been established through multi-centred, randomised, double-blind, placebo-controlled trials, which has led to the inclusion of these agents in current guidelines as independent risk factors for VTE. Similar evidence has been published for selective oestrogen receptor modulators including raloxifene and tamoxifen. Agents that stimulate erythropoiesis increase the risk of VTE by increasing the haematocrit and viscosity of the blood. The risk of VTE associated with pharmacological agents may be subjective to the disease states in which the drugs are indicated to treat. The associated incidence of VTE in patients using tamoxifen is 1.7% – 3.5% in patients with non-metastatic cancer and up to 8.4% of patients with metastatic cancer. The relatively high risk is also the result of additional risk factors such as malignancy and advanced age in patients undergoing treatment. The risk of VTE associated with various pharmacological agents is indicated in Table 7.
Table 7: The risk of VTE associated with the use of various pharmacological agents. The absolute risk may vary according to other factors including dose, sex, weight, malignancy and age.84, 85, 86, 87, 88, 89, 90, 91, 92, 93

<table>
<thead>
<tr>
<th>Pharmacological Agent</th>
<th>Study/Trial</th>
<th>Participants (N)</th>
<th>Subject Category</th>
<th>Associated Risk of VTE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline*</td>
<td>Population based, randomised, case control.</td>
<td>3,867</td>
<td>&lt;70 years, first time diagnosis of VTE.</td>
<td>1.7 (1.2–2.4)</td>
</tr>
<tr>
<td>Clozapine or Quetiapine†</td>
<td>Retrospective cohort, case control.</td>
<td>132,018</td>
<td>Antipsychotic use and hospitalisation from VTE.</td>
<td>2.68 (1.15–6.28)</td>
</tr>
<tr>
<td>Olanzapine†</td>
<td>Population based, case control.</td>
<td>132,018</td>
<td>Antipsychotic use and hospitalisation from VTE.</td>
<td>1.87 (1.06–3.27)</td>
</tr>
<tr>
<td>Risperidone†</td>
<td>Population based, case control.</td>
<td>29,952</td>
<td>&lt;60 years, first time VTE.</td>
<td>1.98 (1.40–2.78)</td>
</tr>
<tr>
<td>Chlorpromazine or Thoridazine†</td>
<td>Population based, case control.</td>
<td>29,952</td>
<td>&lt;60 years, first time VTE.</td>
<td>24·1 (3·3–172·7)</td>
</tr>
<tr>
<td>Haloperidol†</td>
<td>Population based, case control.</td>
<td>45,390</td>
<td>Female, diagnosis of osteoporosis.</td>
<td>1.32 (0.98–1.78)</td>
</tr>
<tr>
<td>Etidronate</td>
<td>Population based, case control.</td>
<td>45,390</td>
<td>Female, diagnosis of osteoporosis.</td>
<td>1.32 (0.98–1.78)</td>
</tr>
<tr>
<td>Erythropoietin or Darbepoetin</td>
<td>Meta-analysis of randomised, placebo controlled trials.</td>
<td>4,610</td>
<td>9-24 weeks treatment for anaemic cancer patients with concomitant chemotherapy.</td>
<td>1.57 (1.31–1.87)</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Multicentre, randomised, placebo controlled.</td>
<td>9,795</td>
<td>50-75 years with type 2 diabetes mellitus.</td>
<td>1.66 (1.35–2.04)</td>
</tr>
<tr>
<td>Oestrogen (oral)‡</td>
<td>Meta-analysis of randomised, double-blind, placebo controlled trials.</td>
<td>38,795</td>
<td>Post menopausal women, first time VTE.</td>
<td>2.1 (1.4–3.1)</td>
</tr>
<tr>
<td>Oestrogen (transdermal)</td>
<td>Meta-analysis of randomised, double-blind, placebo controlled trials.</td>
<td>38,795</td>
<td>Post menopausal women, first time VTE.</td>
<td>1.2 (0.9 to 1.7)</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Multicentre, randomised, double-blind, placebo controlled.</td>
<td>7,705</td>
<td>&lt;81 years, post menopausal, diagnosed osteoporosis.</td>
<td>3.1 (1.5–6.2)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Multicentre, randomised, double-blind, placebo controlled.</td>
<td>7,152</td>
<td>Female, increased risk of breast cancer.</td>
<td>2.4 (1.5–4.4)</td>
</tr>
</tbody>
</table>

*Significant for amitriptyline >25mg per day. There is no evidence to indicate a risk of VTE associated with the use of other antidepressants.
†An odds risk of 1.54 (95% CI: 0.99–2.40) is associated with former users of antipsychotics. This may suggest that lifestyle is a contributing factor in the association between antipsychotic use and VTE.
‡Oral oestrogen doses ranged from 0.625 mg/day to 2.5mg/day.f

fThe increased risk of VTE associated with HRT including the combined oral contraceptive is explained in Section 2.1.3.
3. The Treatment and Prevention of Venous Thromboembolism

3.1 Pharmacological Treatment

There have been numerous trials assessing the efficacy and safety of different pharmacological agents in the prevention and treatment of VTE. The action of thrombolytics is generally limited to patients with acute pulmonary embolism with unstable haemodynamics. Warfarin (INR 2-3) is considered the agent of choice for the treatment of VTE and is initiated concurrently with heparin due to the delay of 5-6 days before the appropriate pharmacodynamic response is established. Treatment is generally indicated for 3-6 months in the case of provoked risk factors including surgery and for at least 6 months for idiopathic VTE. This may be extended in the case of concurrent risk factors such as cancer or history of VTE. The pharmacological agents indicated in the treatment of VTE are outlined in Table 8. There is new evidence emerging for the use of direct thrombin inhibitors. The RE-COVER study, published in 2009, was a multicentre, randomised, double-blind, placebo controlled trial involving 2,564 patients with symptomatic DVT and/or PE. This study found no clinically significant difference between dabigatran 150mg bd and warfarin (target INR 2-3) in terms of efficacy and safety for the treatment of venous thromboembolism when given for a period of six months.

Table 8: Pharmacological agents indicated for the treatment of VTE in Australia.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Name</th>
<th>Indication</th>
<th>Usual Dose*</th>
<th>Usual Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinolytic</td>
<td>Alteplase</td>
<td>Acute treatment with severe right ventricular dysfunction or haemodynamic</td>
<td>10 mg bolus IV, then 90mg IV infusion over 2 hours.</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Streptokinase</td>
<td>instability.</td>
<td>250 000 IU IV over 30 mins, then 100 000 IU per hour for 24 to 48 hours.</td>
<td></td>
</tr>
<tr>
<td>Unfractionated Heparin</td>
<td>Dalteparin</td>
<td>Acute management (minimum 5 days) until INR 2-3 achieved with warfarin.</td>
<td>Bolus 80 U/kg IV, then continuous IV infusion or bolus (bd or tds).</td>
<td>IV or SC†</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin</td>
<td>OR Long term monotherapy if warfarin is contraindicated.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Molecular</td>
<td>Dalteparin</td>
<td>Dalteparin</td>
<td>100 IU/kg bd or 200 IU/kg od.</td>
<td>SC</td>
</tr>
<tr>
<td>Weight Heparin</td>
<td>Enoxaparin</td>
<td>Factor Xa Inhibitor</td>
<td>1mg/kg bd or 1.5mg/kg od.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fondaparinux</td>
<td>Vitamin K Antagonist</td>
<td>7.5mg od.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Secondary prevention and long term treatment.</td>
<td>5mg orally od for 2 days then adjust daily dose according to INR (Target INR 2-3).</td>
<td>Oral</td>
</tr>
</tbody>
</table>

*Subject to variation according to body weight, renal function and pregnancy.
†SC – Subcutaneous
3.2 Non-pharmacological Prophylaxis

Non-pharmacological prophylaxis is highly recommended in patients at high risk of VTE or increased risk of bleeding and as the sole method of therapy in pregnant women with a risk of less than 3%. First line non-pharmacological therapy is to encourage mobilisation if possible. Graduated Compression Stockings (GCS) and Intermittent Pneumatic Compression (IPC) devices are mechanical agents recommended in Royal Darwin Hospital for VTE prophylaxis (60). Studies from a meta-analysis concluded that IPC devices do not reduce the risk of DVT when used alone compared to no prophylaxis.40 However, a 70% reduction in the development of asymptomatic DVT is observed with the concomitant use of GCS and IPC devices compared to GCS alone. Mechanical prophylaxis does not create a risk of bleeding and may be used as adjunct therapy to anticoagulants.56 Contraindications to therapy outlined by the RDH guidelines are as follows:

- Severe peripheral arterial disease
- Recent skin graft
- Severe peripheral neuropathy
- Severe leg deformity

These contraindications exist to prevent exacerbation or worsening of the above conditions in susceptible patients from the applied pressure.60 Ideally, the GCS should extend from the ankle to at least the knee and create a pressure of 16-20mmHg at the ankle when in supine position.98
3.3 Pharmacological Prophylaxis

3.3.1 Unfractionated Heparins and Low Molecular Weight Heparins

Enoxaparin delivered once daily has demonstrated superior efficacy to Unfractionated Heparin (UFH) delivered three times a day for thromboprophylaxis in medical patients. Enoxaparin has also been shown to reduce the release of the procoagulant mediator von Willebrand Factor unlike UFH. These studies concluded that enoxaparin 40mg SC once daily is safe and effective for VTE prophylaxis in high risk medical patients and 20mg once daily in low risk patients. Significant studies assessing the use of these agents are outlined in Table 9.

### Table 9: The use of heparins for VTE prophylaxis in medical and surgical patients.

These major studies assessing safety and efficacy, have formed the basis of guidelines including the ACCP guidelines.

<table>
<thead>
<tr>
<th>Study/Trial Name</th>
<th>Study Type</th>
<th>Subjects</th>
<th>Patient Category</th>
<th>Assessment</th>
<th>Efficacy (VTE risk)</th>
<th>Safety (major bleeding risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDENOX</td>
<td>Randomised, double-blind, placebo controlled.</td>
<td>1,102</td>
<td>Medical (Severe)</td>
<td>Enoxaparin 40mg od vs placebo.</td>
<td>Enoxaparin reduces risk (5.5% vs 15%).</td>
<td>Enoxaparin increases risk (1.7% vs 1.1%).</td>
</tr>
<tr>
<td>PRIME</td>
<td>Multicentre randomised, double-blind, controlled, comparative.</td>
<td>885</td>
<td>Medical</td>
<td>Enoxaparin 40mg od vs UFH 5,000 U tds.</td>
<td>Enoxaparin reduces risk (0.2% vs 1.4%).</td>
<td>Enoxaparin reduces risk (0.4% vs 1.5%).</td>
</tr>
<tr>
<td>PRINCE</td>
<td>Multicentre, randomised, controlled, open.</td>
<td>665</td>
<td>Medical (CHF and RD*)</td>
<td>Enoxaparin reduces risk (8.4% vs 10.4%).</td>
<td>Equal (0.3%).</td>
<td></td>
</tr>
<tr>
<td>PREVENT</td>
<td>Multicentre, randomised, double-blind, placebo controlled.</td>
<td>3,706</td>
<td>Medical (acute)</td>
<td>Dalteparin 5,000 IU vs placebo.</td>
<td>Dalteparin reduces risk (2.77% vs 4.96%).</td>
<td>Dalteparin increases risk (0.49% vs 0.19%).</td>
</tr>
<tr>
<td>ENOXACAN</td>
<td>Multicentre, double-blind, placebo controlled.</td>
<td>1,115</td>
<td>Surgical (cancer)</td>
<td>Enoxaparin 40mg od vs UFH 5,000U tds.</td>
<td>Enoxaparin reduces risk (14.7% vs 18.2%).</td>
<td>Enoxaparin increases risk (4.1% vs 2.9%).</td>
</tr>
<tr>
<td>ENOXACAN II</td>
<td>Multicentre, double-blind, placebo controlled.</td>
<td>332</td>
<td></td>
<td>Enoxaparin 40mg od vs placebo.</td>
<td>Enoxaparin reduces risk (12% vs 4.8%).</td>
<td>Enoxaparin mildly increases risk (1.2% vs 0.4%).</td>
</tr>
</tbody>
</table>

*RD = Respiratory Disease

These studies evaluated asymptomatic DVT through venography as the assessment endpoint and hence the incidence of symptomatic VTE is likely to be lower than the risk indicated above.
3. The Treatment and Prevention of Venous Thromboembolism

3.3.2 Fondaparinux

Fondaparinux is a direct Factor Xa inhibitor. The safety and efficacy of fondaparinux for thromboprophylaxis has been demonstrated through a number of multicentre, randomised, double-blind, placebo controlled phase III studies. Prophylaxis was initiated post operatively in all trials and continued for 5-9 days in the EPHESUS, PENTHIFRA and PEGASUS trials, for 6-14 days in the ARTEMIS trial and for 25-31 days in the PENTHIFRA Plus trial.\(^g\)

Table 10: Comparative studies assessing the efficacy and safety of fondaparinux. The randomised trials below included subcutaneous fondaparinux 2.5mg once daily started post operatively, versus control.\(^{105, 106}\)

<table>
<thead>
<tr>
<th>Study/Trial Name</th>
<th>Study Type</th>
<th>Subjects</th>
<th>Patient Category</th>
<th>Assessment Control</th>
<th>Efficacy (VTE risk)</th>
<th>Safety (major bleeding risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPHESUS</td>
<td>Multicentre, randomised, double-blind.</td>
<td>2,309</td>
<td>Surgical (major orthopaedic).</td>
<td>Enoxaparin 40mg bd started post operatively.</td>
<td>FX* reduces risk (4.1% vs 9.2%).</td>
<td>No significant difference (0.4% vs 0.3%).</td>
</tr>
<tr>
<td>PENTHIFRA</td>
<td></td>
<td>1,711</td>
<td></td>
<td></td>
<td>FX* reduces risk (8.3% vs 19.1%).</td>
<td>No significant difference (0.2% vs 0.3%).</td>
</tr>
<tr>
<td>PENTHIFRA Plus</td>
<td></td>
<td>656</td>
<td></td>
<td></td>
<td>FX* reduces risk (1.4% vs 35%).</td>
<td>Same (0.6%).</td>
</tr>
<tr>
<td>ARTEMIS</td>
<td>Multicentre randomised, double-blind, placebo controlled.</td>
<td>849</td>
<td>Immobile Medical (acute).</td>
<td>Placebo.</td>
<td>FX* reduces risk (5.6% vs 10.5%).</td>
<td>Same (0.2%).</td>
</tr>
<tr>
<td>PEGASUS</td>
<td>Multicentre, randomised, double-blind.</td>
<td>2,927</td>
<td>High risk abdominal surgery.</td>
<td>Dalteparin 2,500 IU post operatively then 5,000 IU once daily [5-9 days].</td>
<td>FX* reduces risk (4.6% vs 6.1%).</td>
<td>FX* increases risk (3.4% vs 2.4%).</td>
</tr>
</tbody>
</table>

*FX – Fondaparinux

\(^g\) Other major trials include the PENTATHLON and PENTAMAKS trials. These trials used enoxaparin dosing regimens that are not recommended for venous thromboembolism prophylaxis according to RDH guidelines Source: 105. Eikelboom J W. Effect of fondaparinux 2.5 mg once daily on mortality: a meta-analysis of phase III randomized trials of venous thromboembolism prevention. Eur Heart J (Suppl). 2008;10:C8-C13.
3.3.3 Direct Thrombin Inhibitors
The METHRO III and the EXPRESS trials assessed the safety and efficacy of the direct Factor IIa inhibitor melagatran, given as 3mg subcutaneously and its oral prodrug ximelagatran given as 24mg twice a day. The trials proved the superiority of these drugs in terms of their antithrombotic effect compared to enoxaparin but with an increased risk of haemorrhagic complications. Other direct thrombin inhibitors including dabigatran, bivalirudin and lepirudin have become available, although with the exception of dabigatran, their efficacy and safety as agents for venous thromboembolism prophylaxis have not been shown to be superior to enoxaparin. This is also attributed to the higher risk of bleeding complications associated with direct thrombin inhibitors, as the pharmacodynamic response to direct thrombin inhibitors cannot be rapidly reversed in the case of overdose or haemorrhagic complications. Warfarin may be reversed with vitamin K and heparins with the use of protamine that binds to form a stable inactive complex. Dabigatran has been approved for the prevention of VTE after total hip or knee replacement after the RENOVATE study found similar efficacy between oral dabigatran etexilate 150mg once daily, or 220mg once daily and enoxaparin 40mg once daily when given for one month for VTE prophylaxis after total hip replacement.

3.4 Special Considerations in Prophylaxis and Treatment
3.4.1 Warfarin and Idiopathic Venous Thromboembolism
The issue of prophylaxis and treatment is problematic in patients presenting with VTE that is unprovoked by underlying medical illness or associated with surgical intervention. The recurrence rate in these patients appears to be greater than 5% per year in the absence of pharmacological prophylaxis. This highlights the need to screen patients to detect high risk patients and ensure the appropriate prophylaxis is implemented. There have been several randomised trials comparing the recurrence rate of VTE using a range of treatment periods. A six month course of anticoagulants has been shown to half the risk of recurrent VTE compared to six weeks. However, there appears to be no effect in the long term risk reduction of VTE after cessation of VTE prophylaxis or treatment in patients with recurrent idiopathic VTE. Hence, such patients may be candidates for extended prophylaxis. Long term prophylaxis with low dose warfarin (INR 1.5-2.0) has shown to reduce the risk of recurrent VTE from 7.2% per year to 2.6% per year, with the risk of major bleeding at 2% over two years as demonstrated in the double-blind, placebo controlled, Prevention of
3. The Treatment and Prevention of Venous Thromboembolism

Recurrent Venous Thromboembolism (PREVAIL) study. The Extended Low-intensity Anticoagulation for Thromboembolism (ELATE) study concluded that a further risk reduction by 63% is observed with the use of an INR range 2.0-3.0 compared to 1.5-1.9 with no difference in the risk of major bleeding complications. Access to INR monitoring is a significant barrier to the optimal use of warfarin. This is highly applicable to patients residing in rural settings. Self-monitoring INR therapy using calibrated equipment has proven to be a safe and efficacious technique that allows the patient to assume a more active role and reduces the number of follow-up assessments. This has been demonstrated in an analysis of 169 patients in north Queensland, South Australia and Tasmania, using warfarin for the long term management of atrial fibrillation. This technique may be similarly adopted to assist out-patients in the management of DVT.

3.4.2 Post-Thrombotic Syndrome

Post-thrombotic (post-phlebitic) syndrome is a complication of DVT, especially when untreated, which occurs in one quarter to one half of patients within two years after the diagnosis of deep vein thrombosis. Post-thrombotic syndrome (PTS) condition is characterised by symptoms including recurrent pain and cramping upon calf compression, pruritus and paraesthesia. Signs include calf oedema, hyperpigmentation, erythema, swelling, and venous ulceration. Elastic graduated compression stockings with an ankle pressure gradient of 30-40 mmHg are recommended by the ACCP guidelines for a minimum of two years for the management of PTS. The use of IPC devices is recommended to treat venous ulcers, although this recommendation is based on Grade 2B evidence.

3.4.3 Renal Impairment

The selection of the appropriate pharmacological agent in patients with renal insufficiency requires special consideration. LMWHs and fondaparinux are two agents that are primarily excreted through the kidneys and hence increased bleeding may be a complication of the use of these agents in patients with compromised glomerular filtration. Unfractionated heparins are often the agent of choice however, dalteparin appears safe and effective to use in
patients with creatinine clearance <30 mL/min and doses of 5,000U four times a day have not shown evidence of accumulation.\(^h\)

3.4.4 Pregnancy and Post-Partum

Prophylaxis in pregnancy is based on the absolute risk of developing venous thromboembolism. This is highly relevant to pregnant women with a history of VTE or diagnosed hereditary thrombophilia. According to the Royal Darwin Hospital Guidelines, a risk greater than 20% warrants therapeutic anticoagulant treatment. Pharmacological prophylaxis is recommended with a risk of 10% and 20% and considered negotiable with a risk between 3-10%. Anticoagulants may be unnecessary if the risk is less than 3\(^{60,98}\).

Table 11: The risk of VTE in pregnant women with hereditary thrombophilia.

This stratification is used to necessitate VTE prophylaxis during pregnant or post-partum. These categories are based on the Australian and RDH prophylaxis guidelines.\(^{60,117}\)

<table>
<thead>
<tr>
<th>Personal History of VTE</th>
<th>Antithrombin</th>
<th>Protein C deficiency</th>
<th>Protein S deficiency</th>
<th>FVL or PGM homozygous</th>
<th>FVL or PGM heterozygous</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30%</td>
<td>10-20%</td>
<td>10-20%</td>
<td>10-20%</td>
<td>10-20%</td>
<td>3-10%</td>
</tr>
<tr>
<td>10-30%</td>
<td>10-20%</td>
<td>10-20%</td>
<td>10-20%</td>
<td>10-20%</td>
<td>3-10%</td>
</tr>
<tr>
<td>10-30%</td>
<td>10-20%</td>
<td>3-10%</td>
<td>3-10%</td>
<td>&lt;3%</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>10-30%</td>
<td>10-20%</td>
<td>&lt;3%</td>
<td>&lt;3%</td>
<td>&lt;3%</td>
<td>&lt;3%</td>
</tr>
</tbody>
</table>

\(^h\) RDH guidelines recommends no more than 20mg of enoxaparin SC daily for patients with CrCl<30mL/min for all risk categories 60. Northern Territory Drugs and Therapeutics Committee. Venous Thromboembolism Prophylaxis Guidelines, 2009.
3.4.5 Heparin-Induced Thrombocytopenia

The use of heparins may also lead to Heparin-Induced Thrombocytopenia (HIT) in susceptible individuals. HIT refers to an immunologic antibody mediated response to heparins, causing platelet activation and thrombin formation, promoting a paradoxical hypercoagulable state. This is characterised by two non-specific signs of thrombocytopenia and thrombosis, which may be difficult to distinguish in patients with acute blood loss. HIT is induced by activated anti-H-PF4 antibodies binding to endothelial cells and leukocytes to promote the formation of platelet-monocyte-neutrophil aggregates. Thromboprophylaxis in patients with HIT require immediate stoppage of heparin therapy. Vitamin K antagonists may induce venous gangrene and skin necrosis when given during acute HIT and the use of direct thrombin inhibitors (lepirudin and agatroban), and Factor Xa inhibitors (danaparoid) are often necessitated. Danaparoid is a heparinoid and may exhibit cross sensitivity in patients with HIT; however it also has a highly predictable dose response relationship. The risk of developing HIT has been estimated at 0.2% with LMWH and 2.6% with UFH through meta-analysis of prospective randomised controlled trials in orthopaedic patients.
4. Adherence to Venous Thromboembolism Prophylaxis Guidelines

4.1 The Burden of Venous Thromboembolism in Australia
A 2008 report by Access Economics estimated the total financial cost of VTE at $1.72 billion in Australia and the direct financial cost to the Australian healthcare system at $148 million. Although the incidence of the disease increases with age, the cost associated with premature mortality is greater than that of other cardiovascular disease, cancer or osteoporosis. VTE prophylaxis is also necessary to enhance the overall outcome of hospitalisation. This has been demonstrated in patients with heart failure. A poor prognosis is associated with heart failure patients that develop pulmonary embolism with a 2.4 fold longer period of hospitalisation and a 1.6 fold increase in the risk of death and rehospitalisation within 3 months.

4.2 Rates of Adherence
The ENDORSE study was one of the most significant multinational hospital audits, published in 2008, consisting of more than 60,000 patients that assessed the risk of VTE and prophylaxis rates according to the ACCP guidelines across 32 countries, including Australia. This study estimated that 52% of hospitalised patients are at risk of VTE, requiring prophylaxis, consisting of 42% of medical and 64% of surgical patients. However, only 40% of medical and 59% of the surgical patients that are considered at risk receive the recommended prophylaxis. The ENDORSE study demonstrated that VTE prophylaxis is largely under implemented in hospitals and that a significant proportion of hospital acquired venous thromboembolic events are preventable. A meta-analysis of the rate of prophylaxis across 227 hospitals in the US found an average prophylaxis rate of 61.8% in patients at risk, however only 54.9% of these patients received the appropriate thromboprophylaxis in accordance with the ACCP guidelines. Adherence to prophylaxis in patients after discharge was also neglected with 34.8% of discharged patients at risk receiving no further prophylaxis. The underutilisation of VTE prophylaxis guidelines is also apparent in RDH. A 2007 retrospective cohort study in RDH determined that approximately 30.8% of cancer patients admitted to RDH without contraindications to therapy receive the appropriate pharmacological agent, dose and duration of prophylaxis in accordance with the guidelines approved by RDH. The study also indicated that mechanical prophylaxis is underutilised, with an adherence rate of 19.2% in the absence of contraindications.
4. Adherence to Venous Thromboembolism Prophylaxis Guidelines

Figure 5: Prophylaxis Rates in Patients at Risk (ENDORSE Study).
The percentage of at risk patients that received the recommended prophylaxis in accordance with the ACCP guidelines, for each respective country. Adapted from Cohen et al. 2008. 122

4.3 Intervention Methods
The lack of adherence to prophylaxis guidelines may be attributed to a lack of awareness amongst clinicians, differences between or within institutions, complexity of the guidelines and the risk of adverse effects including bleeding associated with anticoagulants. Prophylaxis rates are often higher in academic and teaching based hospitals compared to other community hospitals. A one week intervention of verbal teaching to clinicians has proven sufficient to almost double prophylaxis rates.124 These are further supported by an Australian based hospital study that found an increase in adherence to prophylaxis guidelines from 48% to 74% resulting in a 27% decrease in the annual rate of VTE. Interventions largely included staff education and the integration of a hospital-wide risk assessment tool.125 These results are further supported by an Australian hospital based research study that found an increase in adherence to VTE prophylaxis guidelines from 27% to 85% over four years (2005-2009) after the employment of a VTE Clinical Nurse Consultant in collaboration with a vascular physician to execute a VTE prophylaxis program that lead to increased awareness and up skilling of staff to identify patients at risk and to implement prophylaxis where appropriate.126 Anticoagulant therapy has shown to significantly reduce the risk of developing symptomatic VTE, although some controversy exists with as to which patients should receive VTE prophylaxis due to the risk of adverse effects, particularly bleeding, and unnecessary financial burden. 103, 127
5. **Background to Data Collection and Analysis**

5.1 **Venous Thromboembolism, Deep Vein Thrombosis and Pulmonary Embolism**

Venous thromboembolism (VTE) in the form of deep vein thrombosis (DVT) is a condition characterised by the formation of a thrombus or ‘blood clot’ in the deep veins, responsible for the return of deoxygenated blood to the heart. The right ventricle of the heart pumps the venous return through the pulmonary arteries for oxygenation. A pulmonary embolism (PE) is characterised by the formation of a thrombus in the pulmonary vasculature. VTE was attributed to approximately 7% of all deaths in Australian hospitals in 2005. In 2008, the direct financial cost to the Australian healthcare system was estimated to be $148 million; a further $162 million is attributed to the indirect financial costs from the loss of efficiency and required government expenditure.\(^{121}\)

5.2 **Pathogenesis and Risk Factors**

Rudolph Virchow in 1884 proposed that the pathogenesis of thrombosis is attributed to factors that cause endothelial damage, blood stasis or changes in blood constitution resulting in hypercoagulability.\(^{128, 129, 130, 131}\) These factors activate the coagulation cascade and result in the formation of a fibrin clot, or thrombosis.\(^3\) A thrombotic occlusion in a deep vein may embolise and travel from the site of thrombosis to the pulmonary artery and cause an occlusion in the pulmonary vasculature, leading to a PE. A pulmonary occlusion may lead to an increase in the right ventricular afterload and may cause haemodynamic instability, decreasing systolic blood pressure and potentially leading to circulatory collapse. This event may be abrupt in the event of a saddle PE.\(^{132, 133}\) Such patients are candidates for thrombolytic therapy, including the plasminogen activator tenecteplase, which is used at the Royal Darwin Hospital (RDH). The RDH has produced evidence based guidelines outlining the major risk factors for VTE and the recommended prophylaxis.\(^{134}\) Orthopaedic surgery, major surgery and major trauma have been attributed as major risk factors.\(^{38}\) There is increasing evidence of the risk of developing VTE in patients with acute medical conditions including acute ischaemic stroke, myocardial infarction, decompensated cardiac failure, respiratory failure, inflammatory and infectious disease.\(^{135, 136}\) Approximately 80% of fatal pulmonary embolisms occur in patients who have not undergone recent surgery.\(^{137}\) Epidemiological studies have shown an increased risk in patients with certain chronic conditions or using medications; the most prominent of which include active cancer, obesity and the use of pharmacological oestrogen.\(^{138}\) There is increasing evidence correlating the use
of antipsychotics with VTE, although this information has not been incorporated into international guidelines.\textsuperscript{139}

Hereditary thrombophilia are major factors in determining the risk of developing idiopathic VTE, especially in pregnant women. These have impacts on both the health of the mother and the outcome of pregnancy, with hereditary or acquired thrombophilia found in approximately 65\% of women with pre-eclampsia, unexplained still birth, placental abruption, intrauterine growth restriction and unexplained late pregnancy loss.\textsuperscript{140} The most prominent hereditary thrombophilia risk factors include Factor V Leiden mutation, prothrombin G20210A mutation, deficiencies in protein C, S and antithrombin. Acquired risk factors include anticardiolipin antibodies, lupus anticoagulant (lupus antibody) and plasma homocysteinaemia. A homozygous Factor V Leiden mutation increases the risk of VTE during pregnancy by 34 fold. Prothrombin mutation is associated with a 9 fold increased risk of postoperative PE.\textsuperscript{141} Routine screening for hereditary thrombophilia is not recommended in patients unless there is a personal or family history of VTE due to its cost-effectiveness. Routine screening of pregnant women will detect thrombophilia in approximately 2,921 per 10,000.\textsuperscript{141} The incidence of VTE associated with pregnancy is only approximately 20 per 10,000 woman-years.\textsuperscript{22} Therefore, thrombophilia screening is most clinically useful in patients that experience unprovoked or recurrent episodes of VTE, or pregnant women that develop VTE.

5.3 Detection and Diagnosis
Venography (phlebography) is considered the diagnostic standard for the detection of DVT. This technique employs a contrast media such as iodine, which is injected as a solution into the observed limb and its diffusion through the vasculature imaged via radiography. This technique is disfavoured as a first line method of detection in clinical practice as it is invasive and exposes the patient to radiation. Venous access may be restricted in some patients and there is also the potential of an idiosyncratic reaction to the contrast media.\textsuperscript{142} Diagnostic ultrasonography is a non-invasive technique of medical imaging. Blood flow through the deep veins can be assessed by compression of the deep veins and the concomittant use of ultrasonography. Computed Tomography (CT) pulmonary angiography utilises x-rays to visualise the internal organs and soft tissue. This method allows imaging of the pulmonary vessels to assess for thrombotic occlusions.\textsuperscript{143} These techniques are the first line methods
used in the detection of DVT and PE in RDH. Hospital related VTE events may manifest in patients during their admission and may be evident during or after discharge.

For patients that develop VTE secondary to an acute risk factor such as surgery, the risk of developing VTE will be highest within the first few days following the acute risk factor. This implies that the risk of developing VTE secondary to an acute risk factor will decrease as the number of days after the recovery period increases. Figure 6 shows the cumulative rate of readmission to hospital for patients that develop VTE secondary to surgery. This study demonstrated that over a twelve month period, 80% of patients are readmitted within the first three months. Therefore, three months (90 days) post-discharge will be used as the cut-off for assessing patients that develop VTE secondary to hospitalisation in this study.

**Time to Readmission Within 12 Months Following Surgical Procedure.**

![Graph](image)

**Figure 6:** The readmission rate within 12 months after surgery. This data reflects on a Perth hospital based study involving 5,670 VTE episodes. The rate of readmission for VTE following a provoked risk factor such as surgery, decreases as the as the time after the provoked risk factor increases. Approximately 80% of readmissions for VTE within 12 months following acute provoked risk factors occur within the first three months (90 days). Adapted from National Institute of Clinical Studies, 2005.144
5. Background to Data Collection and Analysis

The total number of VTE episodes identified at RDH has increased in the period from 2005 to 2007 and has decreased since 2007. This may reflect on a change in the method and proficiency of diagnosis or an increase in the awareness of VTE. The previous audits conducted at RDH have not quantified the proportion of VTE events that are associated with hospitalisation versus the total number of diagnosed VTE events. Therefore, it is unknown whether the change shown in Figure 7 is a result of an increase in hospital related episodes or admissions to RDH for VTE.

![Total Number of VTE episodes Identified at RDH 2005-2009](image)

**Figure 7:** The total number of VTE episodes identified at RDH from 2005 to 2009. The number of DVT and superficial thrombophlebitis events were calculated together due to ambiguity between the two coded events.

5.4 Pharmacological Prophylaxis

Unfractionated heparin (UFH) was the major pharmacological prophylactic agent until the introduction of low molecular weight heparins (LMWHs). UFH was disfavoured due to its twice or thrice daily dosing required, but offers an alternative to patients with compromised renal clearance. The LMWH enoxaparin (Clexane®) is considered the first line agent for pharmacological prophylaxis at RDH.60 This agent is administered subcutaneously as a once per day dose of 20 mg and 40 mg in low and high risk VTE patients respectively. This agent
is cleared through the kidney and hence a maximal dose of 20mg once a day is used in patients with a creatinine clearance <30 mL/min. Other agents, namely the direct thrombin inhibitor dabigatran and the Factor Xa inhibitors fondaparinux and rivaroxaban, have been indicated for VTE prophylaxis, with studies largely assessing their safety and efficacy in patients receiving knee and hip replacements.\(^94\)

5.5 **Mechanical Prophylaxis**

Mechanical prophylaxis agents are beneficial in patients unable to use pharmacological agents on the basis of contraindications, including active bleeding. The mechanical prophylaxis agents indicated in the Australian guidelines include the following:

- Graduated compression stockings (GCS): These are designed to provide 16-20mmHg of pressure at the ankle in supine position, with a graduated proximal reduction in pressure.
- Intermittent pneumatic compression (IPC): An inflatable garment for the legs with an electrical pneumatic pump that deflates with cycles to compress the leg and/or ankle, thereby stimulating circulation in the extremities.
- Foot impulse technology (FIT): This stimulates the skeletal muscle pump by imitating the physiological movement of the foot.
- Inferior vena cava (IVC) filter: This device requires surgical intervention and is inserted into the inferior vena cava to prevent an embolism migrating from the periphery to the lungs.

GCS and IPC devices are indicated for routine prophylaxis in RDH. Contraindications to these methods include severe leg deformity, limb ischaemia, peripheral neuropathy and recent skin graft.\(^i\)

5.6 **The Efficacy of VTE Prophylaxis Agents Used in RDH**

Orthopaedic surgery, major vascular surgery and neurosurgery are associated with the highest risk of VTE in the absence of prophylaxis. Trials assessing the efficacy of new VTE prophylactic agents are generally performed in patients receiving knee or hip arthroplasty as

\(^i\) The contraindications for mechanical prophylaxis are outlined in Appendix 3.
5. Background to Data Collection and Analysis

approximately 40-60% of these patients develop DVT in the absence of prophylaxis.\textsuperscript{39} UFH reduces the risk of asymptomatic DVT by 0.51 (95% CI; 0.32 – 0.81) versus placebo, with a number needed to treat (NNT) of 8, in patients receiving total hip replacement. The risk of reducing proximal DVT is 0.26 (95% CI; 0.08 – 0.87) versus placebo, with a NNT of 4. LMWH reduces the risk of asymptomatic DVT by 0.51 (95% CI; 0.38 – 0.68) compared to placebo with a NNT of 10. The risk reduction associated with GCS in patients receiving hip arthroplasty is 0.60 (95% CI; 0.45 – 0.79) for asymptomatic DVT, with a NNT of 7. The risk reduction for proximal DVT is 0.68 (95% CI; 0.41 – 1.14) and for PE 0.35 (95% CI; 0.01 – 1.25). There is no statistically significant difference between IPC and GCS.\textsuperscript{145} This indicates that mechanical prophylaxis is more effective in preventing lower limb DVT than proximal DVT or PE.

One meta-analysis involving 12,391 medically ill patients in randomised, controlled trials, compared the efficacy of LMWH, UFH and fondaparinux in reducing the risk of VTE. The acute illnesses consisted of congestive heart failure (29.4%), acute respiratory disease (22.4%), acute infection or inflammation (24.7%) and other or multiple reasons (2.1%). LMWH/fondaparinux significantly reduced the risk of VTE when compared with placebo by 59% (95% CI; 47 – 74%). There was a statistically insignificant difference when comparing the odds risk (OR) of VTE associated with LMWH/fondaparinux versus UFH, at 0.89 (0.54 – 1.46), suggesting similar efficacy between the pharmacological agents. The NNT for LMWH/fondaparinux was 60 compared to the number needed to harm (NNH) at 58; however this largely comprised of minor bleeding, with the NNH for minor bleeding at 45.\textsuperscript{67}

5.7 VTE Treatment and Secondary Prevention

VTE treatment is generally initiated with LMWHs or UFHs and concomitant administration of warfarin until a therapeutic international normalised ratio (INR) of 2-3 is achieved. Warfarin is the main treatment agent for patients that develop symptomatic VTE. The average duration of treatment is three to six months for VTE provoked by acute events such as surgery in otherwise healthy individuals. A first episode of idiopathic VTE may require treatment of at least six months and lifetime prophylaxis may be considered in patients with recurrent events, especially if the onset is idiopathic.\textsuperscript{146} This agent however significantly increases the risk of bleeding compared to heparins.\textsuperscript{145} Warfarin is a selective inhibitor of vitamin K dependent clotting factors II, VII, IX and X. The pharmacodynamic response of a
patient to a particular dose of this drug varies depending on genetic polymorphism, dietary vitamin K intake and concomitant use of other drugs and herbs. These factors and the cost-effectiveness of the ongoing monitoring and dosage adjustments required to maintain the therapeutic INR make this agent less favourable compared to LMWH for the primary prevention of VTE. One meta-analysis comparing ten randomised, controlled trials found the risk of developing DVT associated with enoxaparin at 13.6% (95% CI; 10.9 – 16.3%) compared to warfarin at 20.6% (95% CI; 17.4% to 23.8%) and the cost per patient was six times less with enoxaparin than warfarin.\textsuperscript{147} Malignancy is both an independent risk factor for the development of recurrent VTE and bleeding associated with the use of anticoagulants.

There is greater difficulty in achieving and maintaining stable INR values in patients with malignancy due to the use of complex drug regimens, malnutrition, vomiting and liver dysfunction.\textsuperscript{148} The results from two multicentre, randomised studies with a total of 1,303 participants found that the use of warfarin for VTE treatment in patients with malignancy is associated with 13.3 bleeding events per 100 patient-years (95% CI; 5.4 – 27.5) compared to 2.1 per 100 patient-years (95% CI; 0.7 – 5.0) in patients without anticoagulation. This study determined the risk of recurrent VTE at 27.1 per 100 patient-years (95% CI; 14.8 – 45.4) with malignancy and 9.0 per 100 patient-years (95% CI; 5.6 – 13.8) without malignancy.\textsuperscript{149} The reduced risk of bleeding and increased survival rates in cancer patients using long term LMWH versus warfarin implies that LMWH is favourable for VTE prophylaxis and treatment in patients with active cancer.\textsuperscript{150, 151}

5.8 Standardisation of VTE Prophylaxis Guidelines

The evidence based guidelines developed by the International Union of Angiology (IUA) and the American College of Chest Physicians (ACCP) form the international standards for VTE prophylaxis and treatment.\textsuperscript{36, 152} The National Health and Medical Research Council (NHMRC) and the Australian & New Zealand Working Party (ANZWP) on the Management and Prevention of Venous Thromboembolism have developed national clinical practice guidelines for the prevention of hospital related VTE based on these guidelines.\textsuperscript{98, 145} The RDH specific guidelines from 2007 to 2009 have been developed to account for the medical and surgical interventions that are relevant to RDH and are based on the ANZWP 2007 guidelines. The ANZWP guidelines indicate the use of enoxaparin 40 mg daily as a first line agent and that fondaparinux 2.5 mg daily is suitable for total hip replacement (THR) or total knee replacement (TKR), major trauma, hip fracture surgery or other surgery with a history
of VTE or active cancer. Likewise, dalteparin 5000 U daily may be used for the aforementioned patients, including major surgery in patients over 40 years of age. FIT may be considered in orthopaedic patients where GCS or IPC devices are unavailable. The RDH specific guidelines do not indicate the use of fondaparinux and dalteparin for routine pharmacological prophylaxis and FIT for routine mechanical prophylaxis. This implies that adherence to the RDH guidelines will reflect on adherence to the ANZWP guidelines as the treatment agents, doses and durations indicated in RDH for the respective surgical and medical risk factors are endorsed by the ANZWP guidelines. The following first line recommendations in the 2009 NHMRC guidelines differ from the 2009 RDH guidelines:

- Incorporation of new oral anticoagulants agents (rivaroxaban and dabigatran etexilate) as options for thromboprophylaxis following elective hip or knee replacement, although enoxaparin may still be used first line.
- Thromboprophylaxis continued up to 35 days in THR or hip fracture surgery (recommended 28-35 days in RDH and ANZWP guidelines).
- LMWHs are indicated for all patients admitted to hospital with a lower leg fracture or injury with immobilisation in brace or plaster cast for the entire period of immobilisation. (RDH guidelines recommend to consider enoxaparin and/or GCS in these patients).
- The use of thromboprophylaxis for five to nine days following intra-abdominal surgery (RDH guidelines recommend five to ten days).
- Thromboprophylaxis guidelines following specific intra-thoracic and neurosurgical procedures that are not applicable to RDH surgical procedures.
- Thromboprophylaxis guidelines following specific cancer surgical procedures. (RDH guidelines recommend considering long term prophylaxis with enoxaparin 40mg daily in patients with active cancer).
- Specific thromboprophylaxis guidelines for pregnant or post-partum women who deliver by caesarean or have other thrombophilia risk factors. (This section is negligible as there were no pregnant or post-partum women identified in the audit).
- The use of heparinoids, namely danaparoid in patients with heparin-induced thrombocytopenia. (This indication is absent from RDH guidelines).
5.9 **Increasing Adherence to Guidelines and the Use of VTE Prophylaxis**

The American College of Chest Physicians (ACCP) recommend the development of a formal, active strategy and a written standard policy for thromboprophylaxis in each general hospital. The efficacy and implementation rates of these guidelines should be assessed through periodic audits and feedback methods. Previous audits conducted in RDH have consisted of cross-sectional ward based analyses, assessing the adherence rates and consistency to VTE prophylaxis guidelines. Various studies have been conducted in Western Australia specifically in VTE patients to identify the proportion of idiopathic VTE disease in comparison to provoked events associated with medical and surgical risk factors. These studies have been used to identify subgroups that account for the major burden of disease. Such studies have not been conducted in RDH and may be useful in potentially identifying areas where prophylaxis guidelines are not implemented or are ineffective. This may also allow RDH to implement strategies such as the employment of a dedicated VTE prophylaxis nurse to increase adherence to VTE guidelines and to target clusters of high risk patients that exist in spite of the current guidelines. One Brisbane based cross-sectional clinical audit involving 2,063 hospitalised patients proved that the employment of dedicated VTE prophylaxis nurses increases hospital adherence rates by three fold.
5. Background to Data Collection and Analysis

5.10 Investigation Aims
- To identify patients who developed symptomatic VTE associated with inpatient admissions at RDH in 2007-2009.
- To assess the adherence to current RDH VTE prophylaxis guidelines amongst surgical and medical patients with symptomatic VTE within 90 days of hospital discharge, based on the risk factors for VTE in each of these patients.
- To identify the percentage of patients that developed VTE and did not use prophylaxis based on contraindications.

5.11 Definition of Patients
Surgical patient: Any patient with indexed inpatient admission to ward 2A, 2B, 2E or 3A and/or admission at RDH with associated surgical intervention.

Medical patient: Any patient with indexed inpatient admission not associated with surgical, paediatric or renal wards, Rapid Assessment Planning Unit (RAPU), Intensive Care Unit (ICU), High Dependency Unit (HDU), or palliative care; and indexed admission not limited to the Emergency Department (ED) or short stay unit.

HITH patient: Any patient with indexed admission associated with the Hospital In The Home (HITH) setting.
Method

6.1 Legislative Protocols
Approval for the research project was sought from and granted by the RDH general manager. Ethical approval for the research project was given by the Menzies School of Health Research. Provisional access to paper files and the electronic databases including JadeCare Clinicals® and MedChart® was also granted by the General Manager of the Royal Darwin Hospital.

All collected data was transcribed to a password-protected electronic Excel® spreadsheet, which was accessed exclusively by the research team. At the conclusion of the audit, all paper notes produced by the research team, which contained patient specific information, were shredded and the data was stored in a locked cabinet in accordance with NHMRC guidelines.

6.2 Episode Identification
The coding system used by Northern Territory public hospitals was used to identify episodes of VTE in patients admitted to Royal Darwin Hospital in 2007 to 2009. This was used to produce a list, containing the Health Record Number (HRN) of each patient to be included in the audit.

The JadeCare Clinicals® program was used to compare the admission and discharge dates specified by the hospital’s coding system to the admission and discharge dates specified in the patient’s discharge summary. The actual number of VTE episodes was adjusted by subtracting the duplicate episodes identified through JadeCare Clinicals® from the total number identified by the coding system.

---

1 Menzies School of Health Research ethical approval is attached in Appendix 1.
2 The diagnostic codes used to identify patients with venous thromboembolism in RDH are outlined in Table 1.
Table 12: Hospital codes used for identification of VTE patients. These codes were used to identify the HRNs of patients required for the audit. A total of 542 admissions at RDH for VTE were identified, including 111 duplicate admissions.

<table>
<thead>
<tr>
<th>Description of Diagnosis</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism with acute cor pulmonale</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary embolism without acute cor pulmonale</td>
<td>111</td>
<td>67</td>
<td>47</td>
</tr>
<tr>
<td>Phlebitis &amp; thrombophlebitis in other deep vessel legs</td>
<td>49</td>
<td>71</td>
<td>63</td>
</tr>
<tr>
<td>Phlebitis &amp; thrombophlebitis in legs unspecified</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Phlebitis &amp; thrombophlebitis in other sites</td>
<td>17</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Phlebitis &amp; thrombophlebitis in unspecified site</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Embolism and thrombosis of vena cava</td>
<td>2</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Embolism and thrombosis of renal vein</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Embolism &amp; thrombosis of other specified veins</td>
<td>28</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>Embolism &amp; thrombosis of unspecified vein</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>217</strong></td>
<td><strong>187</strong></td>
<td><strong>138</strong></td>
</tr>
</tbody>
</table>

6.3 **Categorisation of Episodes and Criteria for Data Exclusion**

Patient discharge summaries, Emergency Department (ED) notes and progress notes were assessed to identify the reason for admission at RDH and the date of diagnosis relative to each patient’s admission. Episodes were classified according to the patient’s reason for admission to RDH, date of diagnosis of VTE relative to admission, and the number of days since the patient’s last discharge from RDH.

- An episode was classed as Category A, if the development of VTE was associated with the same admission where the patient was hospitalised at RDH for a reason other than VTE.
- An episode was classed as Category B, if the patient was admitted at RDH for VTE and was an inpatient at RDH within the last 90 days of readmission.
- An episode was classed as Category C, if the patient was admitted at RDH for VTE and there was no inpatient admission at RDH within 90 days. These patients were excluded from further data collection.
- An episode was classed as Category D, if the coded event related to the same event for the same patient, which had been previously coded in another category.
Episodes were classed as Category E (exclusion), if one or more of the following conditions were identified. These patients were excluded from further data collection:

- Age <18 years.
- VTE event identified as superficial thrombophlebitis with no evidence of PE or DVT.
- VTE event associated with an inpatient in palliative care or the Renal Ward (7A).
- The date of admission to RDH was not within the specified time frame (2007-2009).
- The suspected DVT/PE was not supplemented with a confirmed compression Doppler ultrasound or CT angiogram.
- The patient was coded with a VTE episode with no indication of VTE in the patient’s medical notes, including discharge summaries, progress notes, electronic notes or radiography notes.
- The patient was transferred to RDH from another hospital for symptomatic VTE or was identified as an inpatient in another hospital within 90 days prior to the development of VTE.
- Post-mortem diagnosis of VTE.

6.4 **Audit of VTE Prophylaxis**

Patients in Categories A and B were further subdivided according to the ward of admission. The following wards/units were excluded from the audit of adherence to VTE prophylaxis guidelines. Patients in Categories A and B from the following wards were labelled as Category A2 and B2 patients respectively.

- 7A (Renal Hospital Dialysis and Renal Ward).
- Rapid Assessment Planning Unit (RAPU).
- Intensive Care Unit (ICU).
- High Dependency Unit (HDU).
- Palliative Care.
- Short Stay Unit.
6. Method

The audit of adherence to VTE prophylaxis guidelines was therefore based on the remaining wards/units in RDH, which corresponds to medical and surgical patients in episodes labelled as Category A1 and Category B1.

The episodes in Category A1 and B1 were analysed and the following information was recorded from the patients’ medical notes:

- Date of admission to RDH.
- Dates of previous admissions and discharges to RDH (Category B1 specific).
- Reason for admission to RDH.
- Reasons for previous admissions to RDH (Category B1 specific).
- Ward/s of admission prior to the diagnosis of VTE.
- Evidence of PE/DVT as confirmed via Doppler ultrasound or CT angiogram.
- Risk factors for VTE and contraindications to VTE prophylaxis, in accordance with the Royal Darwin Hospital Venous Thromboembolism Prophylaxis Guidelines 2009. This was in association with the current admission (Category A1) or previous admission/s (Category B1) within 90 days to RDH.\(^1\)
- The use of VTE (pharmacological and mechanical) prophylactic agents in accordance with the guidelines. In Category A1, this reflected on the interval between admission and the confirmation of VTE via Doppler ultrasound or CT angiogram. In Category B1, this reflected on the use of VTE prophylaxis in the previous (<90 days) admissions to RDH.

6.5 Statistical analysis

The median and interquartile ranges for the ages of the patients in the audit were calculated. The recommended prophylaxis for each patient in Categories A1 and B1 with the respective medical or surgical risk factors during hospitalisation was compared to the prophylaxis administered to the respective patient. Adherence to prophylaxis guidelines was expressed as the percentage of patients adhering to the recommended mechanical or pharmacological prophylaxis in the specified ward/s. Patients that did not receive prophylaxis on the basis of contraindications were isolated as a separate category to patients that received or did not receive prophylaxis in accordance with guidelines. This data was represented using column graphs.

\(^1\) A copy of the 2009 VTE prophylaxis guidelines for RDH are available in Appendix 3.
6. Method

The data was placed in an Excel© spreadsheet and the 95% confidence interval was calculated based on binomial distribution, to reflect on the proportion of patients that either received or did not receive prophylaxis in accordance with guidelines. The adherence rates were combined between the three years due to the relatively small sample sizes and the overall prophylaxis rate in medical and surgical patients was assessed using the Fisher’s Exact Test. This method was also utilised to compare the anatomical distribution of DVT events between the three years. A significance level of p<0.05 was used for all confidence intervals and statistical tests.
6. Method

Categorisation of VTE Episodes

VTE Episodes identified by RDH Coding 2007-2009 (n=542)

Duplicate episode coded for the same VTE event? → Yes → Category D
No (n=431)

Criteria for Primary Exclusion
(age<18, no diagnostic CT chest scan or Doppler ultrasound, patient in palliative care or renal ward)

→ Yes → Category E
No (n=308)

VTE Event on Admission

No (n=44)

Yes (n=264)

Category A

VTE Event in RAPU/ICU/HDU

No (n=32)

Yes (n=12)

Category A2

Category A1
Inclusion in VTE Audit

VTE Risk

High (n=26)

Low (n=6)

Surgical (n=16)

Medical (n=10)

Last RDH Inpatient Admission >90 Days Ago

No (n=53)

Yes (n=211)

Category C

Category B

VTE Event in RAPU/ICU/HDU or Outpatient only

No (n=27)

Yes (n=26)

Category B2

Figure 8: The selection criteria flow chart. This was used to isolate the 59 patients included in the audit.
7. Results

7.1 Identification and Classification of VTE Episodes

The 542 diagnostic episodes as identified via the hospital coding system were classified according to the reason for admission to RDH and prior admissions to RDH. The removed sections of the pie chart indicate the patients included in the audit. The classification categories used in the above chart are as follows:

- **Category A1**: DVT/PE in indexed admission, other wards/units. (n=32, 6%)
- **Category A2**: DVT/PE in indexed admission, RAPU/ICU/HDU or outpatient. (n=12, 2%)
- **Category B1**: Readmission for DVT/PE, RDH inpatient <90 days ago, other wards/units. (n=27, 5%)
- **Category B2**: Readmission for DVT/PE, RDH inpatient <90 days ago, RAPU/ICU/HDU or outpatient. (n=26, 5%)
- **Category C**: DVT/PE on admission, without hospitalisation in RDH <90 days ago. (n=211, 39%)
- **Category D**: Duplicate episode coded. (n=111, 20%)
- **Category E**: Criteria for primary exclusion. (n=123, 23%)

**Figure 9**: Chart of classification categories. The 542 diagnostic episodes as identified via the hospital coding system were classified according to the reason for admission to RDH and prior admissions to RDH. The removed sections of the pie chart indicate the patients included in the audit.
Table 13: The distribution of PE/DVT diagnosed in the 59 medical and surgical patients.

<table>
<thead>
<tr>
<th>VTE Event</th>
<th>Medical</th>
<th>Surgical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>9</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>PE + DVT</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>DVT</td>
<td>8</td>
<td>24</td>
<td>32</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>39</td>
<td>59</td>
</tr>
</tbody>
</table>

This includes a total of 37 DVT events identified in 59 patients included in the audit. Adapted from Phillips RE, 2009.154

Figure 10: The anatomical positions of identified DVT events. This includes a total of 37 DVT events identified in 59 patients included in the audit. Adapted from Phillips RE, 2009.154
Table 14: VTE risk classifications according to RDH. This classification is based on the risk factors for the development of VTE. A total of 61 admissions were identified in the 59 patients outlined in Figure 8.

<table>
<thead>
<tr>
<th>VTE Risk</th>
<th>Patient Group</th>
<th>VTE in Indexed Admission</th>
<th>Readmission for VTE</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2007</td>
<td>2008</td>
<td>2009</td>
</tr>
<tr>
<td>High</td>
<td>Medical</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Medical (HITH)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical (general/vascular)</td>
<td>1</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Surgical (orthopaedic)</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical (specialist/other)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Medical</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical (general/vascular)</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical (orthopaedic)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical (specialist/other)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>9</td>
<td>10</td>
<td>13</td>
</tr>
</tbody>
</table>

* One high risk (medical) patient was readmitted after 14 days as a high risk (medical HITH) patient.
† One high risk (general/vascular surgical) patient self-discharged and was readmitted after one day as a low risk (general/vascular surgical) patient.
7. Results

7.2 Patient Demographics and Risk Factors
The median age of the audited patients was 62 years (Interquartile Range [IQR]; 52-72 years). The median age and IQR in each year was as follows:

- 62 (55-73) years in 2009
- 59 (51-71) years in 2008
- 65 (51-71) years in 2007

The audit identified 18 patients in 2007, 15 patients in 2008 and 26 patients in 2009 with symptomatic VTE in the wards of inclusion. The ‘total’ column refers to the total over the three year period, as identified in the 59 audited patients. Table 15 indicates that no pregnant or postpartum women with VTE over the three year period could be identified in the audit. Only one patient using oral pharmacological oestrogen (Premarin®) was identified. Tables 16 and 17 outline the percentage of patients with surgical and medical risk factors for each respective year. The row titled ‘None of the Above’ indicates the percentage and number of patients in each respective year without any of the surgical or medical risk factors. Tables 18 and 19 indicate the percentage of patients in each respective year with contraindications to prophylaxis in accordance with the RDH guidelines. A total of 7 of the 59 patients in the audit were tested for thrombophilia risk factors, as shown in Table 20.
Table 15: The demographics of patients included in the audit.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2007 % (n)</th>
<th>2008 % (n)</th>
<th>2009 % (n)</th>
<th>Total % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Sex</td>
<td>61 (11)</td>
<td>60 (9)</td>
<td>58 (15)</td>
<td>59 (35)</td>
</tr>
<tr>
<td>Aboriginal or Torres Strait Islander</td>
<td>17 (3)</td>
<td>20 (3)</td>
<td>12 (3)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Pregnant or postpartum</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Oestrogen or HRT</td>
<td>0 (0)</td>
<td>7 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table 16: The surgical risk factors identified in patients included in the audit.

<table>
<thead>
<tr>
<th>Surgical Risk Factor</th>
<th>2007 % (n)</th>
<th>2008 % (n)</th>
<th>2009 % (n)</th>
<th>Total % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Trauma</td>
<td>6 (1)</td>
<td>33 (5)</td>
<td>8 (2)</td>
<td>14 (8)</td>
</tr>
<tr>
<td>Hip Arthroplasty</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>8 (2)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Knee Arthroplasty</td>
<td>0 (0)</td>
<td>13 (2)</td>
<td>15 (4)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Hip Fracture Surgery</td>
<td>0 (0)</td>
<td>7 (1)</td>
<td>0 (0)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Major Surgery*</td>
<td>6 (1)</td>
<td>7 (1)</td>
<td>8 (2)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Minor Surgery</td>
<td>44 (8)</td>
<td>13 (2)</td>
<td>27 (7)</td>
<td>29 (17)</td>
</tr>
<tr>
<td>Ceasarean section</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>None of the Above</td>
<td>44 (8)</td>
<td>33 (5)</td>
<td>46 (12)</td>
<td>42 (25)</td>
</tr>
</tbody>
</table>

*Intra-abdominal or >45 minutes.

Table 17: The medical risk factors identified in patients included in the audit.

<table>
<thead>
<tr>
<th>Medical Risk Factor</th>
<th>2007 % (n)</th>
<th>2008 % (n)</th>
<th>2009 % (n)</th>
<th>Total % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic stroke</td>
<td>6 (1)</td>
<td>7 (1)</td>
<td>4 (1)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>History of VTE</td>
<td>11 (2)</td>
<td>7 (1)</td>
<td>12 (3)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Family History of VTE</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decompensated Cardiac Failure</td>
<td>6 (1)</td>
<td>0 (0)</td>
<td>12 (3)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Acute MI</td>
<td>6 (1)</td>
<td>13 (2)</td>
<td>19 (5)</td>
<td>14 (8)</td>
</tr>
<tr>
<td>Active Cancer</td>
<td>17 (3)</td>
<td>27 (4)</td>
<td>12 (3)</td>
<td>17 (10)</td>
</tr>
<tr>
<td>Acute on Chronic Lung Disease</td>
<td>17 (3)</td>
<td>20 (3)</td>
<td>0 (0)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Acute Inflammatory Disease</td>
<td>6 (1)</td>
<td>7 (1)</td>
<td>8 (2)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Chest Infection</td>
<td>11 (2)</td>
<td>33 (5)</td>
<td>12 (3)</td>
<td>17 (10)</td>
</tr>
<tr>
<td>Diabetic Ketoacidosis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nephrotic Syndrome</td>
<td>0 (0)</td>
<td>7 (1)</td>
<td>8 (2)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Myeloproliferative Disorders</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CrCl &lt;30mL/min</td>
<td>17 (3)</td>
<td>0 (0)</td>
<td>8 (2)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>None of the Above</td>
<td>39 (7)</td>
<td>33 (5)</td>
<td>58 (15)</td>
<td>46 (27)</td>
</tr>
<tr>
<td>Other Risk Factors*</td>
<td>39 (7)</td>
<td>20 (3)</td>
<td>15 (4)</td>
<td>25 (15)</td>
</tr>
</tbody>
</table>

*Other risk factors included: (uncontrolled) Atrial fibrillation (3), sepsis (3), permanent immobility (3), cellulitis/septic-arthritis/osteomyelitis with immobility >3 days (5).
## Results

Table 18: Contraindications to pharmacological prophylaxis.

<table>
<thead>
<tr>
<th>Contraindication</th>
<th>2007 % (n)</th>
<th>2008 % (n)</th>
<th>2009 % (n)</th>
<th>Total % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Bleeding</td>
<td>17 (3)</td>
<td>20 (3)</td>
<td>12 (3)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Haemophilia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6 (1)</td>
<td>7 (1)</td>
<td>0 (0)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>History of GI Bleeding</td>
<td>6 (1)</td>
<td>7 (1)</td>
<td>12 (3)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Severe Hepatic Disease with INR&gt;1.3</td>
<td>0 (0)</td>
<td>7 (1)</td>
<td>0 (0)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Very High Risk of Falls</td>
<td>6 (1)</td>
<td>0 (0)</td>
<td>8 (2)</td>
<td>5 (3)</td>
</tr>
</tbody>
</table>

Table 19: Contraindications to mechanical prophylaxis.

<table>
<thead>
<tr>
<th>Contraindication</th>
<th>2007 % (n)</th>
<th>2008 % (n)</th>
<th>2009 % (n)</th>
<th>Total % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Peripheral Arterial Disease</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Recent Skin Graft</td>
<td>11 (2)</td>
<td>0 (0)</td>
<td>4 (1)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Severe Peripheral Neuropathy</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Severe Leg Deformity</td>
<td>0 (0)</td>
<td>13 (2)</td>
<td>0 (0)</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>

Table 20: Thrombophilia testing performed in patients included in the audit.

A standard or normal test result is indicated as ‘n’, a positive thrombophilia test result is indicated by a positive marker and an invalid test is indicated as ‘N/A’.

<table>
<thead>
<tr>
<th>Thrombophilia Test</th>
<th>2007 (n=3)</th>
<th>2008 (n=4)</th>
<th>2009 (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus Anticoagulant a</td>
<td>n</td>
<td>n</td>
<td>N/A</td>
</tr>
<tr>
<td>Anticardiolipin antibodies (ACA) b</td>
<td>n</td>
<td>n</td>
<td>N/A</td>
</tr>
<tr>
<td>Antithrombin Deficiency c</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Protein C Deficiency d</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Protein S Deficiency</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Factor V Leiden Gene Mutation e</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Prothrombin Gene Mutation</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Hyperhomocysteinaemia f</td>
<td>N/A</td>
<td>N/A</td>
<td>n</td>
</tr>
</tbody>
</table>

The tests conducted in each of the twelve patients are indicated in the columns above.

- a One invalid test as the patient was receiving warfarin.
- b 2007 - Invalid test as the patient was receiving warfarin. 2008 - One a mild positive result detected.
- c The positive test was attributed to acute thrombosis.
- d Tests performed when patient was readmitted for PE after diagnosis of DVT; patient was receiving both warfarin and enoxaparin.
- e The positive test identified one patient with a heterozygous Factor V Leiden mutation.
- f No fasting state was provided in two homocysteine tests.
7.3 **Adherence to Prophylaxis Guidelines in High Risk Patients**

Figures 11, 12, 13, 14 and 15 relate to patients in Category A1 and Category B1. Figure 11 shows the use of pharmacological prophylaxis in high risk medical and surgical patients who developed symptomatic VTE. This relates to the risk stratification outlined in Table 14. The ‘% Administered’ refers to the percentage of patients that received the appropriate pharmacological and/or mechanical prophylaxis.

Figures 11, 12 and 13 pertain to high risk medical and surgical patients identified in the audit. A total of 43 high risk medical and surgical patients were identified, pertaining to 45 episodes. This is because two high risk medical patients (2009 and 2008) were discharged twice from RDH within 90 days of the diagnosis of symptomatic VTE. The diagnosed symptomatic VTE events in the 43 high risk medical and surgical patients were as follows:

- PE 36% (n=16)
- DVT 52% (n=22)
- PE + DVT 11% (n=5)

Figure 11 relates to all high risk medical and surgical patients and specifically outlines the percentage of patients with contraindications to prophylaxis. The cumulative sum of the ‘n=21’, ‘n=17’ and ‘n=7’ columns equals the total number of events in the audit. Figure 12 compares the pharmacological prophylaxis given to 37 high risk medical and surgical patients, and excludes seven patients with contraindications. Figure 15 shows the percentage of patients in each respective year that received the appropriate pharmacological agent, dose and duration. The appropriate duration in this figure is irrespective of the appropriate agent or dose. The fourth column of each year shows the percentage that received all three parameters in accordance with RDH guidelines.

Figures 14 and 15 pertain to high risk surgical patients, as routine mechanical prophylaxis is recommended in these patients unless contraindicated. The diagnosed symptomatic VTE events identified in the 25 high risk surgical patients included in Figure 14 were as follows:

- PE 32% (n=8)
- DVT 60% (n=15)
- PE + DVT 8% (n=2)
Results

Figure 11: Pharmacological prophylaxis in accordance with hospital guidelines. This represents the appropriate pharmacological agent, dose and duration of therapy in accordance with hospital guidelines for high risk medical and surgical patients who developed symptomatic VTE. Two high risk medical patients (2009 and 2008) were discharged twice from RDH within 90 days of the diagnosis of symptomatic VTE.
Figure 12: Comparative prophylaxis rates between surgical and medical patients. The adherence to prophylaxis guidelines is expressed as a percentage of the total number of high risk medical and surgical patients in the audit. The fractions represent the number of patients that received prophylaxis (numerator) compared to the total number of patients in the respective year and risk category (denominator). Three patients in 2009, two patients in 2008 and two patients in 2007 were omitted from this graph on the basis of contraindications to pharmacological prophylaxis.
Figure 13: The appropriate use of pharmacological agents in high risk patients without contraindications to pharmacological prophylaxis.
7. Results

**Figure 14:** Mechanical prophylaxis in accordance with hospital guidelines. One high risk surgical patient in 2009 was omitted due to contraindications.
Figure 15: Mechanical and pharmacological prophylaxis in high risk surgical patients. A total of 25 high risk surgical patients were identified in the audit. Patients with contraindications to either mechanical or pharmacological prophylaxis were omitted from Figure 15. This includes one patient in 2007, one patient in 2008 and two patients in 2009.
7.4 Category A1 – Development of VTE during admission.

Figure 16 and Table 21 relate to patients admitted to RDH for reasons other than symptomatic VTE and subsequently diagnosed with DVT/PE after admission (Category A1). Figure 16 indicates the length of hospitalisation prior to confirmation of VTE via compression Doppler ultrasound or CT angiogram. The date of hospital admission is represented as day 0. The length of hospitalisation after the diagnosis of VTE was not displayed in Figure 16 as some patients are transferred to the HITH after the diagnosis of VTE. Table 21 shows the median number of days and IQR for each respective year, for the data relating to Figure 16. These patients were within the range of 3 and 103 days after hospitalisation.
7. Results

Figure 16: Confirmed diagnosis in patients that develop VTE during admission. One CT angiogram in 2007 was conducted 103 days after admission and is not visible in this figure.

Table 21: The median number of days and IQR for confirmed diagnosis in Category A1.

<table>
<thead>
<tr>
<th>Year</th>
<th>DVT (Median number of days, IQR)</th>
<th>PE (Median number of days, IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>7 (6 – 8)</td>
<td>10 (4 – 26)</td>
</tr>
<tr>
<td>2008</td>
<td>11 (8 – 16)</td>
<td>8 (5 – 11)</td>
</tr>
<tr>
<td>2009</td>
<td>7 (6 – 15)</td>
<td>4 (4 – 8)</td>
</tr>
<tr>
<td>Total</td>
<td>8 (6 – 13)</td>
<td>7 (4 – 13)</td>
</tr>
</tbody>
</table>
7.5 **Category B1 – Readmission to RDH for Symptomatic VTE.**
Figures 17 and 18, and Table 22 relate to patients with a previous inpatient hospitalisation from the ward/s of inclusion, less than 90 days prior to their readmission for VTE (Category B1). Figure 17 reflects on the diagnosis rate for patients presenting to hospital with symptomatic VTE. All patients received a diagnostic compression Doppler ultrasound or CT angiogram within two days of presentation to RDH for symptomatic VTE. Day 0 indicates the day of admission to RDH. Figure 18 shows the number of days between discharge and readmission for VTE for patients that received a discharge from RDH <90 days prior to readmission to RDH and did not receive inpatient admissions in other hospitals in this period of time. A greater length of time between admission and readmission confers a lower association between the previous hospitalisation and the development of VTE. Of the 27 readmissions to RDH, 21 (44.4%) were within the first 30 days.
Figure 17: Confirmed diagnosis in Category B1. This depicts the number of days between readmission and confirmation of VTE for patients readmitted to RDH for a suspected DVT or PE. Day 0 indicates that the Doppler ultrasound or CT angiogram was conducted on the day of readmission to RDH.
Figure 18: The number of days between discharge from RDH and readmission for VTE. Two patients in 2009 were admitted as inpatients twice within the 90 days preceding the diagnosis of symptomatic VTE. The most recent admission prior to the diagnosis of VTE is shown in this figure.

Table 22: The time between hospital discharge and readmission for VTE in Category B1. DVT and PE episodes were not individually compared in Table 11 due to the low number of Category B1 episodes in 2008.

<table>
<thead>
<tr>
<th>Year</th>
<th>Median number of days (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>17 (6 – 33)</td>
</tr>
<tr>
<td>2008</td>
<td>29 (10 – 68)</td>
</tr>
<tr>
<td>2009</td>
<td>7 (4 – 15)</td>
</tr>
<tr>
<td>Total</td>
<td>10 (6 – 29)</td>
</tr>
</tbody>
</table>
7.6 **Exclusions from the audit**

Figures 19 and 20, and Table 23 relate to patients excluded from the audit. Figure 19 indicates the number of patients that did not match the initial criteria for inclusion in the audit as outlined in section 6.3. This figure illustrates the percentage of patients corresponding to each criteria of the exclusion (Category E). Approximately 40% of patients were excluded on the basis of a diagnosis of superficial thrombophlebitis. This percentage may be greater with consideration of the renal patients, as the most common VTE event in renal patients included superficial thrombophlebitis of the cannula.

Figure 20 shows the distribution of secondary exclusions. These were identified as Category A2 patients if admitted to a ward of exclusion during admission and prior to the diagnosis of VTE, or Category B2 patients if admitted to a ward of exclusion within the previous admission to RDH. All of the identified ICU/HDU patients were Category A2 patients.
Figure 19: Distribution chart of primary exclusions from the hospital audit (Category E). A total of 17 episodes were excluded on the basis of potential miscoding.

Table 23: Episodes of VTE excluded on the basis of potential miscoding.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear Doppler ultrasound or CT angiogram</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary Abscess</td>
<td>3</td>
</tr>
<tr>
<td>Lung cell carcinoma without diagnosed PE</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary Hypertension with clear CT angiogram</td>
<td>2</td>
</tr>
<tr>
<td>No Doppler ultrasound or CT angiogram</td>
<td>1</td>
</tr>
<tr>
<td>No VTE event identified in medical notes</td>
<td>1</td>
</tr>
<tr>
<td>PE from previous admission</td>
<td>1</td>
</tr>
<tr>
<td>SVC stenosis associated with TIVAS*</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
</tr>
</tbody>
</table>

*Totally implantable venous access system
Figure 20: Distribution chart of Category A2 and B2 patients. This consists of patients that developed VTE associated with admission to ICU/HDU/RAPU or short stay and patients that received outpatient treatment only within the 90 days preceding the diagnosis of VTE.
7. Results

7.7 Medications on Admission
Table 24 shows the medications on admission for patients in Category A. This also includes the patients that developed symptomatic VTE in the wards of inclusion (Category A1, n=32) and the wards of exclusion (Category A2, n=12). It represents all patients that developed symptomatic VTE during their indexed hospital admission. Medications used by Category B patients were not recorded as these received numerous alterations during their hospital admissions prior to the development of VTE. Medications of the same therapeutic class were grouped according to the guidelines for the Anatomical Therapeutic Class (ATC) classification. A total of 93 medications were identified in the 44 patients in Category A.
### Table 24: The medications on admission for the 44 patients in Category A.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Patients Using Particular Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet aggregation inhibitor (aspirin and/or clopidogrel)</td>
<td>11</td>
</tr>
<tr>
<td>ACE inhibitor*</td>
<td>7</td>
</tr>
<tr>
<td>Beta blocking agent</td>
<td>7</td>
</tr>
<tr>
<td>HMG CoA reductase inhibitor</td>
<td>6</td>
</tr>
<tr>
<td>PPI †</td>
<td>6</td>
</tr>
<tr>
<td>Vitamins/minerals (zinc, calcium, iron, vit B1, D)</td>
<td>5</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>4</td>
</tr>
<tr>
<td>COX-2 selective inhibitor (NSAID)‡</td>
<td>4</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>3</td>
</tr>
<tr>
<td>Paracetamol (without combination)</td>
<td>3</td>
</tr>
<tr>
<td>Salmeterol + fluticasone propionate</td>
<td>3</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonents</td>
<td>2</td>
</tr>
<tr>
<td>Non-selective COX inhibitor (NSAID) ‡</td>
<td>2</td>
</tr>
<tr>
<td>Frusemide</td>
<td>2</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>2</td>
</tr>
<tr>
<td>Opioids (paracetamol or ibuprofen + codeine =2)</td>
<td>5</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>2</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>1</td>
</tr>
<tr>
<td>Dexchlorpheniramine</td>
<td>1</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1</td>
</tr>
<tr>
<td>Digoxin</td>
<td>1</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>1</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>1</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>1</td>
</tr>
<tr>
<td>Lithium</td>
<td>1</td>
</tr>
<tr>
<td>Metformin</td>
<td>1</td>
</tr>
<tr>
<td>Prazosin</td>
<td>1</td>
</tr>
<tr>
<td>Oestrogen (Premarin®) oral</td>
<td>1</td>
</tr>
<tr>
<td>Probenecid</td>
<td>1</td>
</tr>
<tr>
<td>Risedronate</td>
<td>1</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>1</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>2</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>1</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1</td>
</tr>
</tbody>
</table>

*ACE – Angiotensin Converting Enzyme  
† PPI – Proton Pump Inhibitor  
‡ NSAID – Non-Steroidal Anti-inflammatory Drug
8. Discussion

8.1 Adherence to Prophylaxis Guidelines
A total of 59 patients developed VTE associated with hospitalisation (<90 days) in RDH. This number, isolated from RDH alone is insufficient to provide an accurate comparison of the prophylaxis rates in patients that developed hospital related VTE from 2007 to 2009, as only fifteen patients were identified in 2008. As an average over the three year period in patients without contraindications to prophylaxis, 61.9% (51.3 – 72.5%) of high risk surgical patients received mechanical prophylaxis and 47.5% (36.7 – 58.5%) received the appropriate pharmacological prophylaxis. The concomitant use of both prophylaxis measures is only half as common, at 28.5% (18.7 – 38.4%), as illustrated in Figure 15. Therefore a recommendation should be made to clinicians at RDH to remind them of the concomitant use of both prophylaxis measures in high risk surgical patients. The average prophylaxis rate according to guidelines in high risk medical patients who developed VTE in 2007 to 2009 as indicated by Figure 12 was 62.5% (50.4 – 74.6%). There is no statistically significant difference between the prophylaxis rates of medical and surgical patients (two-tailed Fisher’s exact test, p>0.05). Previous VTE prophylaxis audits in RDH have been conducted through cross-sectional methods to assess the adherence rates in all medical and surgical inpatients present in the hospital at a particular period of time, without a specific focus on patients that developed symptomatic VTE. Previous audits have indicated adherence rates of 68% (27 of 40 patients) in September 2007, 56% (13 of 23 patients) in May 2007, and 46% (16 of 19 patients) in 2005, in high risk medical and surgical patients.134 This suggests that the prophylaxis rate in high risk patients who develop VTE may be similar to the prophylaxis rate in all high risk patients in the medical and surgical wards; however this is inconclusive due to the differences in the study designs between this audit and previous audits as the patients included in this audit represent a specific subgroup of hospitalised medical and surgical patients.

Of the 59 audited patients, 17 were high risk medical or surgical Category B1 patients. Therefore, 28.8% (14.5 – 19.5%) of the patients that developed VTE associated with hospitalisation in 2007-2009 were recently discharged (<90 days) high risk medical or surgical patients. Figure 17 suggests that 96.3% (92.7 – 99.9%) of patients in this category received a compression Doppler ultrasound or CT angiogram within one day of readmission to RDH.
This audit was unable to qualify the adherence to VTE prophylaxis guidelines in low risk surgical and medical patients. This is because routine prophylaxis is recommended in all high risk patients without contraindications and is only considered in low risk patients on a patient-by-patient basis depending on the number of minor risk factors. One 2007 cross-sectional audit of medical and surgical patients at RDH recommended to reduce the use of pharmacological prophylaxis in patients considered at low risk of VTE according to RDH guidelines. The recommendation is neither supported, nor refuted by this audit, as it may be an appropriate recommendation from a pharmacoeconomic perspective, taking into consideration the NNT. Of the 61 identified events, 16 (26.2%) occurred in low risk patients. This percentage is irrelevant without information relating to the total number of low risk medical and surgical patients at RDH per year, as this would indicate the incidence of VTE in low risk patients. This information was unavailable at the time of data collection and is beyond the scope of this investigation. Sepsis and lower limb infections were identified in eight patients. These criteria are not part of the general RDH prophylaxis guidelines, outlined in Appendix 3. Therefore, a review of the criteria may be necessary to outline VTE prophylaxis in patients with infectious conditions.

### 8.2 Medical and Surgical Risk Factors

Minor surgery accounted for the majority of surgical admissions, as indicated in Table 16. These procedures mainly included laparoscopic surgery and debridement. Major trauma was the second most common surgical risk factor, although this figure may be underestimated by the exclusion of major trauma patients who were transferred to ICU or HDU upon admission to RDH. Active cancer and chest infection were the most prevalent medical risk factors, affecting 16.9% (12.1 – 21.8%) of the patients in the audit, or almost 1 in 6 patients who developed VTE.

Thirteen patients in 2009 were readmitted for VTE, compared to only five patients in 2008 and nine patients in 2007, as shown in Figure 18. Table 22 also shows that the median and IQR for the number of days between discharge and readmission was also less in 2009 compared to 2008 or 2007. The proportion of low risk medical or surgical patients in Category B1 was relatively similar between the three years, at 33.3% (17.6 – 49.0%) in 2007, 40% (18.2 – 61.9%) in 2008 and 38.5% (25.0 – 52.0%) in 2009. Further investigation with a larger sample size is required to ascertain if the fewer number of days between admission and
discharge in 2009 was a result of increased awareness of VTE in discharged patients, or if the prophylaxis rate has decreased in these patients since 2007. These figures may also suggest an increase in the total number of hospital admissions since 2007. Data relating to the occupancy of the wards and the number of patients discharged from RDH, per year from 2007 to 2009 was unavailable at the time of data collection.

Of the 59 patients included in the audit, 7 were tested for thrombophilia risk factors. The relatively low proportion is due to the identification of surgical risk factors in 58% of patients and medical risk factors in 54% of the patients in accordance with RDH guidelines. Thrombophilia testing is generally reserved for patients with suspected idiopathic VTE or patients with recurrent VTE episodes. Patients with hereditary thrombophilia risk factors are unlikely to know of their condition prior to the development of VTE. Furthermore, thrombophilia test results may be affected by the presence of acute thrombosis or pharmacological treatments for thrombosis. False positive lupus anticoagulant results have been reported. One placebo controlled study found that the effect of warfarin on the dilute Russell’s viper venom time (DRVVT) used to assess for a positive lupus anticoagulant is minimal, although this study employed a relatively small sample size (n=35). Protein S and protein C are vitamin K dependent clotting factors and hence false deficiencies may be observed in a patient receiving warfarin therapy or within a week of ceasing the drug.

8.3 The Incidence and Anatomical Locations of VTE Episodes
The symptomatic VTE episodes identified in the patients identified in the audit are indicated in Table 13 and Figure 10. Medical patients accounted for 33.9% (27.7 – 40.0%) of VTE episodes and 44.4% (34 – 54.0%) of PE episodes identified in the audit. A total of 89.2% (84.1 – 94.3%) of the identified DVT episodes occurred in the pelvis and legs, which coincides with a Perth based epidemiological study of 151,923 episodes of VTE, indicating that 90.7% of DVT events occur in these anatomical regions. DVT occurred more commonly in the left leg than in the right leg (one-tailed Fisher’s exact test, p<0.05), with 25 of the 37 episodes isolated in the left leg. There is unlikely to be a significant variation in the outcome of a DVT event, whether it is isolated in the left or right lower limb. One 2007 population-based case-control study involving 483 DVT events found that the most common risk factor for upper extremity DVT is the recent placement of a central venous catheter, compared to surgery in lower limb DVT. The study also found no significant difference in
8. Discussion

the risk mortality between upper and lower limb DVT, however the risk of recurrence is 1.7 fold greater in patients with upper extremity DVT.\textsuperscript{158}

Further data collection may be required to explain if this variation is the result of a greater number of total knee and hip joint replacements or musculoskeletal injuries on the left side of the body. The variation may also be attributed to the anatomical positions of the iliac veins. The right common iliac artery transverses the left common iliac vein, increasing the susceptibility to DVT and varicose veins in the left leg, due to the pressure applied by the common iliac artery that results in a reduction in venous return. This has been supported by epidemiological studies in pregnant women.\textsuperscript{159, 160, 161} Although pregnancy per se was not an identified risk factor in the audit, the anatomical variation between the left and right iliac vasculature will predispose the lower left limb to a higher risk of DVT compared to the lower right limb.

8.4 Medication Induced VTE

There was no evidence to suggest any relationship between the medications on admission and the risk of VTE in this study. The most commonly reported medications on admission include platelet aggregation inhibitors (n=11), ACE inhibitors (n=7) and beta blockers (n=7). The lack of association is because the method of this audit was designed to isolate patients that have developed VTE associated with hospitalisation. Of the 44 patients in Category A, 86.3\% (81.2 – 91.5\%) were classed as high risk medical or surgical patients based on their risk factors. Only one patient reported using oral HRT (oestrogen) prior to admission. Although this medication is indicated in the guidelines as a risk factor for VTE; major gynaecological surgery and the absence of any VTE prophylaxis were the likely contributing factors to the development of PE in this patient. One patient was identified with chlorpromazine upon admission to RDH. This patient was admitted to RDH for elective TKJR and only received pharmacological prophylaxis, despite the recommendation of routine mechanical prophylaxis. One nested case-control study involving 31,612 patients with identified VTE events found an odds ratio of 1.77 (1.27 – 2.48) for patients using chlorpromazine compared to controls.\textsuperscript{139} Although this issue appears relatively minor in this audit, this highlights the need for pharmacists and medical staff to be vigilant in identifying patients with increased risks of VTE secondary to medication use.
The information in Table 24 represents a control group. This is because these patients were most likely to develop VTE associated with a major medical or surgical risk factor. This asserts that the relationship between medication use and the development of VTE may be explored in further detail by comparing the information in Table 24 to patients in Category C. This category represents the patients with the lowest association between hospitalisation and the development of VTE. One area of future research may include a follow up of the patients in Category C and the control group, with each patient’s community pharmacy to determine the number of days on each medication and the development of VTE.

8.5 Duplicate Episodes and Potential Coding Errors
A total of 431 episodes of VTE were identified from the 542 coded episodes supplied by the coding department. The difference in the figures accounts for patients with duplicate coding, which is often associated with relocation to other wards in the hospital or the confirmation of a VTE from a previous hospital admission. Duplicate coding was also evident in patients with a prolonged (>1 month) stay in hospital. The JadeCare Clinicals® hospital program was used to identify the admission and discharge dates for each patient and to adjust the dates supplied by the coding department accordingly, if duplicate coding was identified. One example includes a patient with a six month admission that was coded for seven episodes of thrombophlebitis and seven episodes of DVT, pertaining to a single episode of thrombosis in the left cephalic vein. The 111 patients with identified with duplicate coding as shown in Figure 9 may either reflect on systematic errors from the hospital’s coding department or the accuracy of the staff members in the coding department. The 17 potential miscoded episodes shown in Table 23 pertain to the remaining 431 duplicate-adjusted episodes identified in RDH. Hence, approximately one in twenty-five coded events were identified as erroneous. This highlights that RDH should consider increasing the training or supervision delivered to junior staff members of the coding department to increase the coding accuracy.

8.6 Increased Risk in Patients with Contraindications or a History of VTE
Previous audits conducted at RDH assessed the use of thromboembolic prophylaxis in accordance with guidelines and rated the instigated prophylaxis as ‘consistent’ or ‘inconsistent’ with guidelines. In this audit, patients in whom prophylaxis was withheld due to contraindications were specifically indicated and other patients in whom there were no
identified contraindications to prophylaxis were grouped according to whether or not prophylaxis was instigated in accordance with guidelines. This is because patients with contraindications to prophylaxis are adherent to RDH protocols but do not receive adequate VTE prophylaxis and therefore remain elevated risk of VTE. A total of 13.3% (8.2 – 18.4%) of high risk patients did not receive pharmacological prophylaxis due to contraindications and 2.2% (0.0 – 4.4%) refused to receive VTE prophylaxis. A total of 8% (2.6 – 13.4%) of high risk surgical patients did not receive mechanical prophylaxis on the basis of contraindications. Although no comparative audits could be identified in Australian literature, specifying the percentages of medical and surgical patients with contraindications to prophylaxis, these figures are lower than those found in ICU patients. One 2007 prospective audit of VTE prophylaxis in ICU patients across thirty Australian and New Zealand hospitals found an average prophylaxis rate of 55% and 69% for pharmacological and mechanical prophylaxis respectively. A total of 57% of patients that did not receive pharmacological prophylaxis had contraindications; implying that 26% of patients overall had contraindications to pharmacological prophylaxis. Patients admitted to ICU and HDU were excluded from this audit. Of the 44 patients that developed VTE during their indexed admission (Category A), 11 were associated with admission to ICU/HDU, indicating that ICU/HDU patients are at a high risk of VTE and it may have been necessary to include these patients in the audit.

A history of VTE was identified in 10.2% (6.2 – 14.1%) of patients across the three years. Five of the six patients with a reported history of VTE had experienced an event within the previous year. One 2007 retrospective analysis involving 32,193 episodes of VTE assessed the economic burden of VTE and the rates of hospital readmission. The readmission rate identified in the 2007 study was 5.3% for primary and 14.3% for secondary VTE within one year of diagnosis. In this audit, of five patients with a recent history of VTE, two were already receiving VTE treatment, one received prophylaxis in accordance with RDH guidelines following major surgery and two did not receive prophylaxis on the basis of active bleeding. Of the two patients that did not receive pharmacological prophylaxis, neither patient received mechanical prophylaxis despite guideline recommendations and both patients developed DVT. A similar trend was observed for all patients with contraindications to prophylaxis. Mechanical prophylaxis was instigated in only two of the nine patients with active bleeding and consequently, six patients developed DVT in the lower limbs. This indicates that a check list may need to be instigated whereby clinicians are reminded to
8. Discussion

instigate mechanical prophylaxis in patients with contraindications to pharmacological prophylaxis; particularly in patients with risk factors including a history of VTE.

8.7 Patients without Inpatient Admission to RDH within 90 Days of Diagnosis.
Category C represents the patients that did not experience VTE secondary to an intervention in RDH within the last 90 days. The 211 patients in this category represent 49% of the duplicate adjusted admissions to RDH and 68.5% of the duplicate and primary exclusion adjusted admissions to RDH. This indicates that two out of three patients with an identified PE or DVT (excluding Category E) did not develop their condition associated with hospitalisation in RDH in the last 90 days. Of the patients admitted to Category C, 19.0% in 2007 (n=15), 22.4% in 2008 (n=17), and 19.6% in 2009 (n=11), were identified according to medical notes as ‘travellers’ or Northern Territory residents that have ‘recently travelled’ prior to the diagnosis of VTE. Patients in this category would be most likely to receive a diagnosis of primary (idiopathic) VTE, although further investigation would be required for each patient to determine if they received interventions in other hospitals or if the VTE event is associated with recent trauma. The investigation of idiopathic VTE outside of the hospital setting is beyond the scope of this investigation.

Category C includes patients that received outpatient only admissions. Patients without additional risk factors that receive outpatient only interventions, including laparoscopic surgery and minor gynaecologic or urologic surgery are not considered to be at a significant risk of VTE and hence routine prophylaxis is not recommended in accordance with the RDH, national or international guidelines.\textsuperscript{36, 60, 152} Outpatient interventions were therefore omitted from this study; although the VTE episodes identified in Category C patients may have been provoked by outpatient surgical procedures conducted in patients with other minor risk factors. One Perth based audit of patients with diagnosed VTE events found that outpatient procedures account for 35% of hospital procedures and only 3.2% of VTE events.\textsuperscript{164} The total of 431 VTE events (excluding duplicate coding) would imply that VTE may be linked to approximately 14 outpatient procedures over the three year period. One example of a high risk outpatient procedure includes cancer chemotherapy, where the odds ratio of VTE in cancer patients is four times that of patients without cancer; this ratio increases to 6.5 with associated chemotherapy.\textsuperscript{77} 18% (n=7) of the patients readmitted to hospital following an inpatient admission <90 days prior to diagnosis in a ward or unit of exclusion (Category B2)
were cancer chemotherapy patients that received interventions in other hospitals. One patient also reported receiving an abdominoplasty in another hospital eight days prior to admission to RDH for PE. Circumferential abdominoplasty is associated with a 3.40% risk of VTE. This highlights the issue of patients in all categories potentially receiving interventions other than at Royal Darwin Hospital, which may not be evident in medical notes. Such information may alter the VTE risk for the patient as perceived by clinicians and alter the recommended VTE prophylaxis.

8.8 Limitations of Study Design and Methods of Improvement

VTE prophylaxis audits are generally conducted as cross-sectional prospective audits, as this allows a more comprehensive analysis of the patients’ medical and surgical risk factors. Immobility in the absence of any other risk factors is a minor risk factor for the development of VTE. It is however, a major risk factor in patients with co-morbidities including lower limb trauma or thrombophilia. The OR for VTE associated with air travellers in the absence of prophylaxis is 2.0 fold (1.5 – 2.7) compared to non-travellers. Comparatively, the risk of VTE associated with hospitalisation or nursing home confinement is 8.0 (4.5 – 14.2), suggesting that VTE associated with hospitalisation is multifactorial and is attributed to immobility in addition to other risk factors, which are not implicated in the general population of travellers. A cross-sectional design may increase the accuracy of the documented contraindications to prophylaxis. The audit was unable to assess the period of time in which contraindications to pharmacological prophylaxis such as active bleeding persisted in each patient. Figure 19 and Table 23 demonstrate that a number of patients were excluded from the audit on the basis of potential miscoding. This indicates a number of patients who have developed hospital associated VTE may have been miscoded for other conditions with similar descriptions from medical notes. Patients admitted to hospital with a suspected VTE and later diagnosed with another condition appeared to be coded as VTE patients. A prospective method would provide the most accurate data in terms of clinical assessment and follow-up, however this would require sufficient time to reassess the patients at specific time intervals, which is beyond the limitations of this investigation. Furthermore, upon resolution of the acute medical or surgical risk factors, patients that develop symptomatic VTE in RDH generally receive further treatment by a nurse via the HITH setting and may be referred to their local general practitioner for continuing care, which is beyond the scope of the data that may be obtained from the RDH medical records.
The original design of the audit intended to include patients admitted to RDH from January to June 2010. These admissions were unavailable at the time of data collection. A total of 821 VTE episodes were identified by the coding department from 2007 to 2009 across all NT public hospitals, implying that this study (n=542) accounted for approximately 66.0% of all identified episodes in the NT. The number of VTE episodes included in the audit may have been increased by including patients with diagnosed VTE episodes across all Northern Territory public hospitals. The VTE prophylaxis guidelines for RDH are applicable to all NT public hospitals. This method would require a larger research team or an extension of the research period.

8.9 Methods to Improve Adherence Rates
This audit is consistent with previous RDH audits that suggest new methods are necessary for RDH to increase adherence to prophylaxis guidelines and reduce the incidence of hospital related VTE. One 2006 comparative study involving 444 patients assessed the efficacy of pharmacist-initiated screening of patients on adherence to VTE prophylaxis. This study involved daily monitoring of patients by pharmacists to assess the safety and efficacy of prescribed VTE prophylaxis. Pharmacists were also involved in making recommendations to physicians and providing continual education to hospital staff. This resulted in an increase in the appropriate use of VTE prophylaxis from 37% to 85% (p<0.05).167 The impact of a dedicated VTE prophylaxis nurse has been demonstrated in both Australian and international studies.126, 168 VTE clinical nurse consultants are capable of assessing patients based on their risk of VTE, assessing the use of VTE prophylaxis in accordance with guidelines and providing hospital staff with continual education and awareness of prophylaxis guidelines.169, 170 Continual education and risk assessment may include seminars, the adoption of electronic VTE risk assessment programs and checklists. An alternative approach may include the mandatory teaching of VTE risk assessment to all junior nursing staff, as recommended by UK based senior nurse consultants.171

It is essential for RDH to adopt a multidisciplinary approach to identify patients at risk of VTE and increase adherence to VTE prophylaxis guidelines. This will require the employment of dedicated VTE prophylaxis staff, including a clinical nurse consultant who is empowered to provide risk assessment of patients, reviews of the current practice, evidence based recommendations and continual education to hospital staff. The Australian Institute of
Health and Welfare estimated the cost of VTE in 2008 at $10,007 per episode, with 59% of these costs attributed to hospitalisation.\textsuperscript{1} The 59 patients identified with hospital related VTE in this audit indicates that RDH should consider the employment of a nurse consultant as a clinically beneficial option.
The number of VTE events isolated from RDH is insufficient to accurately assess the adherence to VTE prophylaxis guidelines in each respective year, in patients who develop symptomatic VTE.

The adherence rate to VTE prophylaxis in accordance with hospital guidelines in high risk patients without contraindications to prophylaxis who were admitted to RDH in 2007 to 2009 and subsequently developed VTE is as follows:

- 61.9% (51.3 – 72.5%) for mechanical prophylaxis in surgical patients.
- 47.5% (36.7 – 58.5%) for pharmacological prophylaxis in surgical patients.
- 28.5% (18.7 – 38.4%) for both prophylaxis methods in surgical patients.
- 62.5% (50.4 – 74.6%) for pharmacological prophylaxis in medical patients.

The percentage of high risk patients who developed VTE associated with hospitalisation and did not receive prophylaxis for reasons accepted by guidelines was as follows:

- 13.3% (8.2 – 18.4%) of medical and surgical patients with contraindications to pharmacological prophylaxis.
- 8% (2.6 – 13.4%) of high risk surgical patients with contraindications to mechanical prophylaxis.
- 2.2% (0.0 – 4.4%) refused to receive VTE prophylaxis.

A total of 96.3% (92.7 – 99.9%) of patients who are readmitted to RDH with a suspected VTE receive a compression Doppler ultrasound or CT angiogram within the following day of admission.

RDH should consider the employment of a VTE clinical nurse consultant to improve adherence to prophylaxis guidelines and reduce the incidence of hospital related VTE events. The major areas of practice requiring improvement as identified from this audit include the adherence rate to VTE prophylaxis in high risk patients, the use of mechanical prophylaxis in patients with contraindications to pharmacological prophylaxis and the use of VTE prophylaxis in immobile patients with lower limb infections.
10. Glossary of Acronyms

ACCP  American College of Chest Physicians
ACE  Angiotensin Converting Enzyme
AF  Atrial Fibrillation
ANZWP  Australia and New Zealand Working Party
APTT  Activated Partial Thromboplastin Time
ATC  Anatomical Therapeutic Class
ATSI  Aboriginal or Torres Strait Islander
bd  bis die (twice a day)
BMI  Body Mass Index
CCU  Coronary Care Unit
CHF  Chronic Heart Failure
CT  Computed Tomography (chest/pulmonary angiogram)
DRVVT  Dilute Russell’s Viper Venom Time
DVT  Deep Vein Thrombosis
ED  Emergency Department
FIT  Foot Impulse Technology
GCS  Graduated Compression Stockings
HDU  High Dependency Unit
HITH  Hospital In The Home
HRN  Health Record Number
HRT  Hormone Replacement Therapy
ICU  Intensive Care Unit
INR  International Normalized Ratio
IPC  Intermittent Pneumatic Compression (Device)
IVC  Inferior Vena Cava
IUA  International Union of Angiology
LDL  Low Density Lipoprotein
LMWH  Low Molecular Weight Heparin
LVEF  Left Ventricular Ejection Fraction
MI  Myocardial Infarction
NHMRC  National Health and Medical Research Council
NNH  Number Needed to Harm
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNT</td>
<td>Number Needed to Treat</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drug</td>
</tr>
<tr>
<td>od</td>
<td>once daily</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Risk</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary Embolism</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton Pump Inhibitor</td>
</tr>
<tr>
<td>qid</td>
<td>quater in die (four times a day)</td>
</tr>
<tr>
<td>RAPU</td>
<td>Rapid Assessment and Planning Unit</td>
</tr>
<tr>
<td>RDH</td>
<td>Royal Darwin Hospital</td>
</tr>
<tr>
<td>RVT</td>
<td>Renal Vein Thrombosis</td>
</tr>
<tr>
<td>SC</td>
<td>Subcutaneous (administration)</td>
</tr>
<tr>
<td>tds</td>
<td>ter die sumendus (to be taken three times a day)</td>
</tr>
<tr>
<td>THR</td>
<td>Total Hip Replacement</td>
</tr>
<tr>
<td>TIVAS</td>
<td>Totally Implantable Venous Access System</td>
</tr>
<tr>
<td>TKR</td>
<td>Total Knee Replacement</td>
</tr>
<tr>
<td>UFH</td>
<td>Unfractionated Heparin</td>
</tr>
<tr>
<td>VKOR</td>
<td>Vitamin K Epoxide Reductase</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous Thromboembolism</td>
</tr>
</tbody>
</table>
11. References


4. Raghavan SAV, Dikshit M. Recent advances in the status and targets of antithrombotic agents. Drugs Fut. 2002;27(7):669.


References


11. References


11. References


References


11. References


11. References


11. References


153. Cheng C-S, Szabo F. An Audit of Thromboprophylaxis in Hospitalized Surgical and Medical Patients at the Royal Darwin Hospital, NT: University of Queensland, School of Medicine, Brisbane; 2008.


11. References


12. Appendices

12.1 Appendix 1: Ethical Approval .......................................................... 105
12.2 Appendix 2: Data Collection Sheet ................................................... 107
12.3 Appendix 3: Royal Darwin Hospital Guidelines 2009 ....................... 111
04th June 2010

Dr Mark Naunton  
Senior Lecturer  
Charles Darwin University  
School of Science  
Casuarina NT 0810

Dear Dr Naunton,

Re: HREC-2010-1388 - Adherence to Prophylaxis guidelines in Patients that Develop symptomatic Venous thromboembolism - a retrospective hospital audit.

Thank you for submitting the research application titled "Adherence to Prophylaxis guidelines in Patients that Develop symptomatic Venous thromboembolism - a retrospective hospital audit" for review. The application was assessed to be a low risk study and sent for expedited external review. The Fast Track Committee have reviewed and approved this application and is satisfied that the research proposal meets the requirements of the NH&MRC National Statement on Ethical Conduct in Human Research, 2nd ed, 2007.

Please note: The Committee would comment that the requirements of this study does not lend itself to the need for the HRN to be collected. Quality control is not a sufficient reason to collect HRN for a small number of records. Please remove HRN for data collection.

Full approval is now granted. This approval will be ratified at the next meeting of the Human Research Ethics Committee to be held 16th June 2010. Please note that HREC approval applies only to research conducted after the date of this letter.

Approved Project timeline: 4/6/2010 to 31/12/2010

This approval is for a period of six (6) months. A project progress report is required on or before 31/12/2010

Please note the terms under which ethical approval is granted:

1. The safe and ethical conduct of this project is entirely the responsibility of the investigators and their institution(s).

2. Researchers should report immediately anything which might affect continuing ethical acceptance of the project, including:
   a) adverse effects of the project on subjects and the steps taken to deal with these,
   b) other unforeseen events,
   c) new information that may invalidate the ethical integrity of the study.
   d) Proposed Changes in the project

3. Approval for a further twelve months will be granted if the HREC is satisfied that the conduct of the project has been consistent with the original protocol.

4. Confidentiality of research participants should be maintained at all times as required by law.
5. The Patient Information Sheet and the Consent Form shall be printed on the relevant site letterhead with full contact details.

6. The Patient Information Sheet must provide a brief outline of the research activity including, risks and benefits, withdrawal options, contact details of the researchers and must also state that the Human Research Ethics Secretary can be contacted (telephone and email) for information concerning policies, rights of participants, concerns or complaints regarding the ethical conduct of the study.

7. The Committee must also be notified at the completion of the project.

Yours sincerely,

Dr Michael Nixon
Chair
Human Research Ethics Committee
of NT Dept of Health & Families
and Menzies School of Health Research
### Appendix 2: Data Collection Sheets

#### Patient Demographics

<table>
<thead>
<tr>
<th>Date of Admission</th>
<th>Date of Discharge</th>
<th>Not Discharged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ward</td>
<td>Ward</td>
<td>Ward</td>
</tr>
<tr>
<td>Age (not &lt;18 years*)</td>
<td>Age (not &lt;18 years*)</td>
<td>Age (not &lt;18 years*)</td>
</tr>
<tr>
<td>Sex</td>
<td>Sex</td>
<td>Sex</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI</th>
<th>20-25</th>
<th>25-30</th>
<th>&gt;30</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aboriginal or Torres Strait Islander</th>
<th>Aboriginal or Torres Strait Islander</th>
<th>Aboriginal or Torres Strait Islander</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Aboriginal</td>
<td>Torres Strait Islander**</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>A&amp;TSI</td>
<td>A&amp;TSI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy</th>
<th>Yes</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
<td>Postpartum</td>
</tr>
</tbody>
</table>

#### Surgical Risk Factors within 3 months

| Major Trauma | Yes |
| Hip or knee arthroplasty | Yes |
| Hip fracture surgery | Yes |
| Major Surgery (Intra-abdominal or >45mins): | Yes |
| Other (Minor) Surgery | Yes |
| Caesarean section performed | Yes |

#### Medical Risk Factors

<table>
<thead>
<tr>
<th>History of VTE</th>
<th>No</th>
<th>DVT</th>
<th>PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE event during pregnancy</td>
<td>No</td>
<td>DVT</td>
<td>PE</td>
</tr>
<tr>
<td>Date of previous VTE (if available):</td>
<td>(D)</td>
<td>(M)</td>
<td>(Y)</td>
</tr>
<tr>
<td>Acute MI</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Acute cancer</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Acute or chronic lung disease</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Acute inflammatory disease</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Chest Infection</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Decompensated cardiac failure</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Myeloproliferative disorders</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

*Criteria for exclusion from analysis

** Torres Strait Islander
### Other Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>1-3 days</th>
<th>&gt;3 days</th>
<th>&gt;1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immobility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paralysis of lower limbs</td>
<td>No</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>CrCl &lt;30mL/min</td>
<td>No</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Oestrogen (HRT or Pill)</td>
<td>No</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Family history of VTE (first degree relative)</td>
<td>No</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>VTE episode/s in family member</td>
<td></td>
<td>Isolated</td>
<td>Spontaneous</td>
<td>Recurrent</td>
</tr>
<tr>
<td>Positive Lupus anticoagulant and/or anticardiolipin antibodies (ACA)</td>
<td>Negative</td>
<td>Weak Positive</td>
<td>Moderate-strong positive</td>
<td></td>
</tr>
<tr>
<td>History of Thrombophilia</td>
<td>No</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Thrombophilia Risk Factors (Below)</td>
<td>None</td>
<td>Personal</td>
<td>1st degree relative</td>
<td>Distant relative</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated Protein C resistance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other lower level thrombophilia risk factors: prothrombin (Factor II) gene mutation, hyperhomocysteinaemia, lupus anticoagulant, antiphospholipid antibodies, myeloproliferative disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Contraindications to Anticoagulant Prophylaxis

<table>
<thead>
<tr>
<th>Condition</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active bleeding</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Haemophilia</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>History of GI bleeding</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Severe Hepatic Disease</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Severe Hepatic Disease With INR &gt;1.3</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Adverse reaction to heparin (inc. Allergy)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Very high risk of falls</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Other: (Specify)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Contraindications to Mechanical Prophylaxis

<table>
<thead>
<tr>
<th>Condition</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe peripheral arterial disease</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Recent skin graft</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Severe peripheral neuropathy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Severe leg deformity</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Venous Thromboembolism Prophylaxis Specific

<table>
<thead>
<tr>
<th>Recognised VTE episode</th>
<th>PE</th>
<th>DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of recognised VTE episode</td>
<td>(D)</td>
<td>(M)</td>
</tr>
</tbody>
</table>

Anticoagulant prophylaxis use PRIOR to admission (specify number of days on therapy)

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin</th>
<th>20mg</th>
<th>40mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondaparinux (dose):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH (dose):</td>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anticoagulant prophylaxis DURING admission (specify number of days on therapy)

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin</th>
<th>20mg</th>
<th>40mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondaparinux (dose):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH (dose):</td>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anticoagulant prophylaxis AFTER admission (specify number of days on therapy)

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin</th>
<th>20mg</th>
<th>40mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondaparinux (dose):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH (dose):</td>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mechanical prophylaxis prescribed

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>GCS</th>
<th>IPC</th>
</tr>
</thead>
</table>

Period for mechanical prophylaxis

<table>
<thead>
<tr>
<th>From</th>
<th>To</th>
</tr>
</thead>
</table>

### Venous Thromboembolism Treatment Specific

<table>
<thead>
<tr>
<th>Treatment initiated in RDH</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
</table>

Date of treatment initiation

| (D) | (M) | (Y) |

Treatment Ceased

| (D) | (M) | (Y) |

p/c for hospital admission

| PE | DVT | Other |

Symptomatic VTE to be treated

| None | PE | DVT | Post Treatment |

Anticoagulant treatment prior to admission (specify number of days on therapy)

| Enoxaparin | 20mg | 40mg | Other: |
| Fondaparinux (dose): |  |
| Warfarin |  |
| UFH (dose): | Other |
| Other | None |

Anticoagulant treatment during admission (specify number of days on therapy)

| Enoxaparin | 20mg | 40mg | Other: |
| Fondaparinux (dose): |  |
| Warfarin |  |
| UFH (dose): | Other |
| Other | None |

Anticoagulant treatment with discharge (specify number of days on therapy)

| Enoxaparin | 20mg | 40mg | Other: |
| Fondaparinux (dose): |  |
| Warfarin |  |
| UFH (dose): | Other |
| Other | None |

UFH – Unfractionated Heparin

p/c – Presenting Complaint

110
12. Appendix 3: Royal Darwin Hospital Guidelines 2009

VENOUS THROMBOEMBOLISM PROPHYLAXIS Guidelines, 2009

Based on Best practise guidelines for Australia and New Zealand 4th edition 2007

Target Audience

Areas applicable:
All NT Public Hospital Clinical Staff.

Abbreviations

- GCS = graduated compressive stockings
- IPC = intermittent pneumatic compression
- DVT = deep venous thrombosis
- PE = venous thrombo-embolism

Guideline on next page

Disclaimer for reformatting: Format has been changed to accommodate technical requirements, content has not been altered.

Alternative Search Words

Venous thromboembolism, prophylaxis, DVT, deep vein thrombosis, PE, pulmonary embolism, surgery, orthopaedic, GCS, graduated compression stockings, IPC, intermittent pneumatic compression, enoxaparin, heparin, pregnancy, obstetric, travel, oestrogen, hormone replacement therapy, thrombophilia, anaesthesia.

Prompt Doc No: RDH0000513 v2 Approval Date: 15/07/2009 Due for Review: 15/07/2010
## Table 1. Recommended prophylaxis in all surgical patients (Orthopaedics, general and vascular surgery, gynaecology and urology)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Clinical Features</th>
<th>Recommended prophylaxis</th>
</tr>
</thead>
</table>
| **High**      | • Hip or knee arthroplasty*  
                • Major Trauma*        | Enoxaparin 40mg/day for 5-10 days.  
                        EXCEPT  
                        28-35 days for hip arthroplasty*  
                        **And**  
                        GCS &/or IPC. |
| **High**      | • Other surgery with prior VTE &/or active cancer.  
                • Hip fracture surgery* | Enoxaparin 40mg/day  
                        Or Heparin 5000iu TDS  
                        For 5-10 days  
                        EXCEPT  
                        28-35 days for hip fracture surgery.*  
                        **And**  
                        GCS &/or IPC. |
| **High**      | • Major surgery ** and age >40 years. | Enoxaparin 20mg/day  
                        Or Heparin 5000iu BD or TDS for 5-10 days.  
                        **And**  
                        GCS &/or IPC. |
| **Low**       | • All other surgery* | Consider Enoxaparin  
                        20mg/day or Heparin 5000iu BD or TDS if additional risk factors. ***  
                        Consider GCS. |

*For further information on thromboembolism prophylaxis in orthopaedic surgery, refer to RDH Orthopaedic Department protocol.

* Major surgery is any intra-abdominal operation and all other operations lasting more than 45 minutes.

**Additional VTE risk factors: immobility, thrombophilia, oestrogen therapy, pregnancy or puerperium, active inflammation, strong family history of VTE and/or obesity.
<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Clinical features</th>
<th>Recommended prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>• Age &gt;60 years</td>
<td>Enoxaparin 40mg/day</td>
</tr>
<tr>
<td></td>
<td>• Ischaemic stroke</td>
<td>Or Heparin 5000iu BD</td>
</tr>
<tr>
<td></td>
<td>• History of VTE</td>
<td>or TDS.</td>
</tr>
<tr>
<td></td>
<td>• Decompensated</td>
<td>Until resolution of</td>
</tr>
<tr>
<td></td>
<td>• Active cancer</td>
<td>acute medical illness</td>
</tr>
<tr>
<td></td>
<td>• Acute on Chronic</td>
<td>or hospital discharge.</td>
</tr>
<tr>
<td></td>
<td>• Acute inflammatory disease</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>• None of the above features.</td>
<td>None required.</td>
</tr>
</tbody>
</table>

- While patients aged over 60 years are currently classified as high risk, those that are otherwise well and ambulant may not be at high risk for DVT in the absence of other risk factors.
- The NT Drugs and Therapeutics Committee have agreed that enoxaparin will be the low molecular weight heparin of first choice.
- LMWH favoured over low-dose unfractionated heparin (LDUH) for ischaemic stroke.
- **Dose adjustment is required for enoxaparin in patients with renal impairment.**
  - If CrCl <30ml/min reduce dose to 20mg daily for all risk categories
- **Contraindications to anticoagulant prophylaxis include:**
  - Active bleeding / high risk of bleeding eg. Haemophilia, thrombocytopenia, history of GI bleeding.
  - Severe hepatic disease (INR >1.3) / adverse reaction to heparin.
  - On current anticoagulation.
  - Other eg. very high falls risk and palliative management.
- **Contraindications to mechanical prophylaxis include:**
  - Severe peripheral arterial disease
  - Recent skin graft
  - Severe peripheral neuropathy
  - Severe leg deformity
Table 3. Recommended Prophylaxis in pregnant women

This section of the guidelines is currently under review. Please contact the O&G Registrar or Consultant on-call for advice.

### a) Thromboprophylaxis against recurrent venous thromboembolism (DVT/PE) in pregnant women with previous DVT/PE and no identified thrombophilia, according to estimated pregnancy related risk of thrombosis

<table>
<thead>
<tr>
<th>Thrombosis history</th>
<th>Recurrent DVT/PE</th>
<th>Single episode of DTE/PE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history of DVT/PE in one or more 1st degree relatives</strong></td>
<td>Prophylaxis (option therapeutic)</td>
<td>Prophylaxis</td>
</tr>
<tr>
<td><strong>No family history of DVT/PE</strong></td>
<td>Prophylaxis</td>
<td>Negotiable</td>
</tr>
</tbody>
</table>

* Risk factors present such as surgery.

### b) Anticoagulation to prevent venous thromboembolism (DVT/PE) in pregnant women testing positive for lupus coagulant or anticardiolipin antibodies (ACA), according to estimated pregnancy-related risk of thrombosis.

<table>
<thead>
<tr>
<th>Thrombosis history</th>
<th>Lupus anticoagulant and/or ACA IgG moderate-strong</th>
<th>ACA IgG weak positive,* ACA IgM positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recurrent DVT/PE in pregnancy despite prophylaxis</strong></td>
<td>Therapeutic</td>
<td>Therapeutic</td>
</tr>
<tr>
<td><strong>Recurrent DVT/PE outside pregnancy</strong></td>
<td>Therapeutic</td>
<td>Therapeutic</td>
</tr>
<tr>
<td><strong>Previous DVT/PE</strong></td>
<td>Prophylaxis</td>
<td>Negotiable</td>
</tr>
<tr>
<td><strong>No previous DVT/PE</strong></td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>

* Based on the highest-ever titre measured in the individual patient.

### c) Preventing venous thromboembolism (DVT/PE) in pregnant women with established thrombophilia, according to estimated pregnancy-related risk of thrombosis.

<table>
<thead>
<tr>
<th>Thrombosis History</th>
<th>Antithrombin deficiency (Very rare)</th>
<th>Protein C deficiency (Rare)</th>
<th>Protein S deficiency (Rare)</th>
<th>FVL* or PGM+ homozygous (Uncommon)</th>
<th>FVL* or PGM+ heterozygous (Common)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Personal history of DVT/PE independent of family history</strong></td>
<td>Therapeutic</td>
<td>Prophylaxis</td>
<td>Prophylaxis</td>
<td>Prophylaxis</td>
<td>Negotiable</td>
</tr>
<tr>
<td><strong>Family history of DVT/PE in one or more 1st degree relatives</strong></td>
<td>Therapeutic/Prophylaxis</td>
<td>Prophylaxis</td>
<td>Prophylaxis</td>
<td>Prophylaxis</td>
<td>Negotiable</td>
</tr>
<tr>
<td><strong>Family history of DVT/PE in a distant relative</strong></td>
<td>Therapeutic/Prophylaxis</td>
<td>Prophylaxis</td>
<td>Negotiable</td>
<td>Negotiable</td>
<td>Nil</td>
</tr>
<tr>
<td><strong>No personal or family history of DVT/PE</strong></td>
<td>Therapeutic/Prophylaxis</td>
<td>Prophylaxis</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>


KEY TO MANAGEMENT RECOMMENDATIONS

**Therapeutic** - Therapeutic anticoagulation necessary throughout pregnancy and postpartum – very high risk (>20%)

**Prophylaxis** - Prophylaxis necessary throughout pregnancy and puerperium – high risk (10%-20%)

**Negotiable** – Need for prophylaxis negotiable on a case by case basis until further data becomes available – moderate risk (3%-10%)

**Nil** – Postpartum prophylaxis or no prophylaxis – low risk (<3%)
1. GENERAL CONSIDERATIONS

Adequate hydration and ambulation are important principles in all patients.

2. PHARMACOLOGIC PROPHYLAXIS

2.1 Dosage (Note: 1mg enoxaparin is equivalent to 100 units anti-Xa activity)

Enoxaparin (40 mg administered subcutaneously daily) provides safe and effective prophylaxis for patients undergoing general surgery.

2.2 Timing of Administration in Surgical Patients

- General anaesthesia:
  First dose (20 to 40 mg subcutaneously) pre-operatively, no sooner than 1 hour after uncomplicated spinal injection, followed by 20-40mg administered subcutaneously daily thereafter.

- Spinal anaesthesia (no in-dwelling catheter):
  First dose (20 to 40 mg subcutaneously) intra-operatively, no sooner than 1 hour after uncomplicated spinal injection, followed by 20-40 mg subcutaneously daily thereafter.

- In-dwelling epidural catheter
  First dose (20 to 40 mg subcutaneously) intra-operatively, no sooner than 1 hour after uncomplicated spinal injection. Post surgery, monitor patient in Recovery until observed return of monitor and sensory function, before return to ward. Continue administration of 20-40 mg subcutaneously daily thereafter.

- Timing of removal of epidural catheter
  Not sooner than 10 hours after administration of enoxaparin, and no less than 2 hours before a dose is due to be administered.

2.3 Route of Administration

Subcutaneous: Severe bruising may result if an incorrect injection technique is used. The injection should be made in the abdominal wall or thigh, into a skin fold pinched up between thumb and forefinger. Pressure should then be applied to the site with the palm of the hand for 5 minutes. Care must be taken to avoid injecting the pre-operative dose into skin at the probable site of surgical incision.

2.4 Duration of therapy

The optimum length of VTE prophylaxis and treatment requires further research. Decisions regarding time of commencement and duration of prophylaxis should be made for each patient individually. However, in most studies, prophylaxis was used for at least 10 days in high-risk patients, 10 days or more in patients with knee replacement and 28-35 days in patients with hip replacement or hip fracture. In medical patients, prophylaxis should continue until resolution of their acute medical illness or hospital discharge.

2.5 Laboratory control

It is not necessary to monitor therapy to measurement of an effect on blood tests. However, platelet counts should be monitored weekly to detect heparin-induced thrombocytopenia.
3. GRADUATED COMPRESSION STOCKINGS (GCS)

GCS reduce the incidence of DVT. Studies have generally involved full-length stockings. Although it is anticipated that below knee stockings, should also provide a degree of protection against DVT, there are few comparative studies.

There are two distinct and non-interchangeable types of graduated compression stockings (GCS): one for DVT prophylaxis and the other treatment for cardio-vascular insufficiency.

In order to achieve optimal benefit from the use of GCS, some general recommendations are provided (Table 4).

**Table 4. General Recommendations for the use of graduated compression stockings for DVT prophylaxis**

- Should be worn from the time of immobility to the return of full ambulation
- Should be worn continuously during the period of immobility
- Should be measured and fitted for the individual patient
- Patient compliance is essential e.g. ensuring stockings not rolled down etc
- Are contraindicated in critical limb ischaemia

There are a wide variety of GCS available in Australia and New Zealand. However, there are no Australian standards regulating their manufacture and clinical performance. The ideal characteristics for GCS are laid out in table 5. It is also essential that the prophylactic stockings available are applied to appropriate patients, using the risk categories described in this booklet guide.

**Table 5. Ideal characteristics for the selection of graduated compression stockings for DVT prophylaxis**

- Evidence of clinical efficacy
- Pressure of 16mmHg to 20mmHg at the ankle in the supine position with graduated compression to the knee or above
- Appropriate and individual sizing for each patient
- Sizing range should be suitable for a large percentage of the population and the window of coverage should be clearly defined
- Washing and reuse guidelines should be provided
- Appropriate manufacturing standards to ensure quality control
- Independent testing and compression profile of each stocking brand using internationally accepted methods
4. INTERMITTENT PNEUMATIC COMPRESSION (IPC)

IPC using sequential compression reduces the incidence of DVT and is more effective than GCS in high risk patients in combination with anticoagulants are contraindicated.

Foot impulse technology in combination with GCS has been shown to reduce the incidence of proximal DVT following hip and knee surgery.

The use of IPC devices for DVT prophylaxis is similar to the GCS recommendations in that they should be used from the time of immobility to the return of full ambulation and not used in limbs with critical ischaemia.

5. COMBINATION THERAPY

Combinations of agents (for example subcutaneous enoxaparin with GCS and/or IPC) may be more effective than single interventions alone. Although the studies have generally been too small to draw strong conclusions for prophylaxis in high risk patients, a combination of subcutaneous enoxaparin and GCS with or without IPC is recommended.

6. RISK STRATIFICATION AND APPROPRIATE PROPHYLAXIS

6.1 Surgery

The risk of DVT is increased by obesity, increasing age, malignancy, prior VTE, smoking, varicose veins, oestrogen preparations or the presence of thrombophilia. The duration and type of operation is most important (e.g. intra-abdominal and intra-thoracic versus non-body cavity surgery). Additional risk factors include immobility, dehydration, and the presence of sepsis. The risk classification based on the International Consensus Statement is shown in Table 1.

6.2 Ambulant and short stay patients

The risk of developing VTE when undergoing day surgery or minor surgery is considered to be generally low. However, in some day surgery including laparoscopic and arthroscopic surgery, the intra-operative procedures can be relatively prolonged or the patient is already at high risk. In either circumstance, full VTE prophylaxis should be considered.

Early discharge patients may spend a considerable amount of time resting at home. They may not be truly ambulant and thus may be at increased risk of DVT. There is no conclusive evidence to form recommendations for ambulatory patients. Nevertheless, it is important to be cautious with early discharge patients as they may still be at risk and may need continued prophylaxis during their convalescence. Patient groups where the value of extended prophylaxis has been demonstrated and where prophylaxis should be continued for 28-35 days include patients following hip fracture or hip replacement surgery and possibly major curative surgery for cancer.

6.3 Medical Patients

Up to 75% of fatal PE in general hospitals occur in non-surgical patients immobilised by medical illness, yet there are fewer trials on DVT prophylaxis for hospitalised medical patients as compared to surgical patients. Available data suggest that prophylaxis can prevent two thirds of DVT cases in medical patients, a reduction rate similar to prophylaxis in surgical patients.

Patients suffering an acute stroke with paralysis of a lower limb are at high risk of DVT and subsequent PE. Those with acute congestive cardiac failure, previous VTE, or intensive care admission are also at high risk (Table 2). Patients suffering acute myocardial infarction have a moderate risk of DVT and PE, but are considered high risk if advanced age or cardiac failure are present.

Other medical patients at moderate risk of VTE include those with chest infection, diabetic ketoacidosis, cancer, nephrotic syndrome, inflammatory bowel disease, and myeloproliferative disorders.
6.4 Age

The risk of VTE increases substantially with age and this applies to all categories of patients.

6.5 Pregnancy & postpartum

Several factors increase the risk of VTE during pregnancy including Caesarean section, obesity, advanced maternal age and thrombophilia (Table 3). Although there is insufficient data on optimal timing and dosage, enoxaparin is commonly used in pregnant women with a history of VTE, thrombophilia or other high-risk factors. Prophylaxis should be continued for four weeks into the post-partum period. In addition, peri-operative and post-partum prophylaxis should be considered for women undergoing Caesarean section who are obese or aged over 35 years.

6.6 Obstetric Patients

As discussed in 6.3, pregnancy is an additional risk for those patients with pre-existing risk factors for DVT. These patients require consideration for prophylaxis both during their pregnancy and in the post-partum period. Peri-operative and post-partum prophylaxis should also be used for women undergoing Caesarean section who are obese, aged over 35 years or who have thrombophilic states.

6.7 Oestrogen Preparations

It is considered prudent to stop hormone replacement therapy (HRT) and the oral contraceptive pill if the patient is in high risk category. In the absence of other risk factors, there is insufficient evidence to support routine pre-operative cessation or oral contraceptives or HRT. Appropriate prophylaxis should be used when these agents have not been stopped. Ideally, the oral contraceptive pill should be ceased the cycle before planned surgery. HRT should cease six weeks before planned surgery.

6.8 Thrombophilia

There are many types of thrombophilia (Table 6) but the presence of thrombophilic factors alone does not greatly increase the risk of VTE. However, patients with thrombophilia and a strong family history of VTE, recurrent DVT, or documented unexplained thrombosis before the age of 40 years are at increased risk of VTE and should receive prophylaxis during any surgical or medical condition. Screening for thrombophilia before surgery is not required and specialist advice should be sought before screening is considered.

<table>
<thead>
<tr>
<th>Table 6. Causes of thrombophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher Level of Risk:</td>
</tr>
<tr>
<td>• Antithrombin III deficiency</td>
</tr>
<tr>
<td>• Protein S deficiency</td>
</tr>
<tr>
<td>• Protein C deficiency</td>
</tr>
</tbody>
</table>

| Lower Level Risk:                |
| • Activated protein C resistance (Factor V Leiden) |
| • Prothrombin gene mutation      |
| • Hyperhomocystinaemia           |
| • Lupus anticoagulant            |
| • Antiphospholipid antibodies    |
| • Myeloproliferative disease     |
6.9 Epidural anaesthesia

The use of epidural anaesthesia has been increasing in recent times. The risk of DVT and the importance of prophylaxis, however, has not diminished with the use of epidural anaesthesia. Lately, anaesthetics have become increasingly concerned about the complication of epidural haematoma in patients who are receiving anti-coagulant therapy.

It is important for the individual patient that the risk of VTE is weighed against the risk of an epidural haematoma and discussions between the anaesthetist and the surgeon should take place early enough for appropriate planning of prophylaxis. While not being able to provide definitive recommendations from the literature, options for the management of such patients would include delaying pharmacological anti-coagulant therapy until after the insertion of the epidural catheter or ensuring that no anti-coagulant agent is administered within 12 hours prior to the insertion or withdrawal of an epidural catheter.

6.10 Travel related thrombosis

The risk of DVT is not confined to air travel. There is little information available in the literature with recent studies indicating that the incidence of travel-related PE appears to be small and is estimated to be about 1:70,000 arrivals for flights longer than 12 hours. Further studies are required to fully define the risk of travel related VTE.

Considered at high risk are those travellers with a history of previous VTE, those with known pro-thrombotic states, recent surgery, significant medical illness or with multiple risk factors. In these patients the administration of prophylactic LMWH and use of properly measured and fitted GCS (20-25mmHg) is suggested. Lower compression (eg 16-20mmHg) does not offer adequate protection when the legs are in a dependent position. Non-graduated stockings are not recommended.

Aspirin is not likely to be appropriate as at best it may have a weak protective effect and in some people excess bleeding may negate any benefit.