VENOUS THROMBOEMBOLISM RISK ASSESSMENT AND PROPHYLAXIS IN SELECTED PUBLIC SECTOR HOSPITALS IN THE CAPE TOWN METROPOLE

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KEYWORDS

Caprini risk assessment model

Medical inpatient

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Venous thromboembolism risk assessment

ABSTRACT

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Background: Venous thromboembolism (VTE) is reported to be the leading cause of death in hospitalised patients worldwide. Thromboprophylaxis provides a well-established and evidence-based approach to preventing VTE. This approach employs individualised patient risk stratification followed by the provision of pharmacological and/or non-pharmacological prophylaxis. Although various VTE risk assessment models (RAMs) are available, the Caprini RAM offers an objective, evidence-based and validated approach to risk assessment in hospitalised medical patients. Literature findings are indicative of a trend towards both under- and inappropriate VTE prophylaxis prescribing in this patient population. Together with the reported lack of medical practitioner appreciation for VTE risk assessment, the necessity to explore these aspects of practice is evident.

Methods: This study used a retrospective, cross-sectional study design. It was conducted at one regional- and two district-level public hospitals in the Cape Town Metropole in the Western Cape province of South Africa. Medical folders of all adult hospitalised medical patients who were admitted to a general medical ward between January and July 2020 were retrospectively reviewed using a uniquely designed data collection tool. The data collection tool included the 2013 version of the Caprini RAM, which was employed to document VTE risk factors and assess overall VTE risk. Thromboprophylaxis regimens prescribed as well as contraindications to pharmacological thromboprophylaxis were also reviewed.

Results: Among the 383 patients included in the study, 52% were female and the overall mean age was 52 years (ranging between 18 and 96 years of age). Whilst 21% of patients in the sample had their weight recorded, none had their height recorded. The predominant diagnosis identified in the sample was infectious disease (49.2%). Patient currently at bedrest/ restricted mobility for < 72 h (76.3%) and serious infection (67.4%) were the most common VTE risk factors detected in the sample. A total of 369 (97.1%) patients were found to be at a moderate or higher risk of VTE (Caprini score ≥ 2). Of this at-risk group, 71% were prescribed thromboprophylaxis during admission. Of the 266 patients who had thromboprophylaxis prescribed, enoxaparin was prescribed in 98.5% of cases and no mechanical forms of prophylaxis were prescribed in the sample. Contraindications to chemoprophylaxis were identified in 13.4% (n = 51) of patients, of which 19 still received chemoprophylaxis.

Conclusion: Although this study detected a possible trend in improved rates of VTE prophylaxis in hospitalised medical patients, thromboprophylaxis remains under-prescribed in this patient population. This study identified an undesirable ramification of this trend, with inappropriate pharmacological thromboprophylaxis prescribing becoming increasingly apparent. Despite the associated benefits and essential role in specific patient populations, a paucity of mechanical thromboprophylaxis prescribing was detected. VTE RAMs should be adopted and adapted for use in the South African setting, where infectious diseases that confer additional VTE risk are more prevalent. Future research should explore RAM use by medical practitioners as this could inform increased RAM uptake and improved thromboprophylaxis prescribing.

November 2021

DECLARATION

I declare that this study, entitled, *Venous Thromboembolism Risk Assessment and Prophylaxis in Selected Public Sector Hospitals in the Cape Town Metropole,* is my own work, that it has not been submitted for any degree or examination at any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Full name: Alexander Stefan Wehmeyer

Date: 24 November 2021

Signature: 

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DEDICATION

I would like to dedicate this work to the almighty God for giving me the strength to rise from a tumultuous point in my life. Philippians 4:13: *I can do all things through Christ who strengthens me*.

I would also like to dedicate this work to my late grandmother, Ouma Beulah, who continuously inspired me to remain steadfast in my pursuit of knowledge. *U nagedagtenis sal deur ons voortleef.*

LIST OF ABBREVIATIONS AND ACRONYMS

Abbreviation/ Acronym	Description
ACCP	American College of Chest Physicians
aPTT	Activated partial thromboplastin time
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CrCl	Creatinine clearance
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computerised tomography pulmonary angiography
DissolVE-2	Identification of Chinese Hospitalized Patients' Risk Profile for Venous Thromboembolism
DOAC	Direct oral anticoagulants
DVT	Deep vein thrombosis
eCCR	electronic Continuity of Care Record
ENDORSE	Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting
GCS	Graduated compression stockings
HIT	Heparin induced thrombocytopenia
HIV	Human Immunodeficiency Virus
IMPROVE	International Medical Prevention Registry on Venous Thromboembolism
INR	International normalized ratio
IPC	Intermittent pneumatic compression
LMWH	Low molecular weight heparin
PE	Pulmonary embolism
PHC	Primary healthcare
PPS	Padua Prediction Score
PTS	Post-thrombotic syndrome
RAM	Risk assessment model
SC	Subcutaneous
SLE	Systemic lupus erythematosus
SPSS	Statistical Package for Social Sciences
SSA	sub-Saharan Africa
TB	*Mycobacterium tuberculosis*
TF	Tissue factor
TUNE-IN	The Use of VTE prophylaxis in relation to patiEnt risk profiling
UFH	Unfractionated heparin
VTE	Venous thromboembolism
VWF	Von Willebrand factor

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CHAPTER 1: INTRODUCTION

1.1 Introduction

This chapter provides an overview of the study and includes the background and rationale for conducting the study. This is followed by the problem statement, the research question, as well as the study's aim and objectives. The study's importance is discussed thereafter, and an outline of the dissertation concludes the chapter.

1.2 Background and rationale for the study

Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), is regarded as the most preventable cause of inpatient death in hospital settings worldwide (Cohen *et al.*, 2008; Shah *et al.*, 2020; MacDougall & Spyropoulos, 2021). It is a frequent complication that affects both surgical and medical patients during and after admission to hospital (Qatawneh *et al.*, 2019; Nkoke *et al.*, 2020). In addition to the acute risk of mortality, VTE also predisposes patients to long-term complications, including post-thrombotic syndrome (PTS), chronic thromboembolic pulmonary hypertension (CTEPH) and recurrent thrombosis (Rocher *et al.*, 2019; Koren *et al.*, 2020; Ruiz-Talero *et al.*, 2020).

VTE has an estimated annual incidence rate of 1 – 2 cases per 1 000 persons and is regarded as the third most diagnosed cardiovascular disease (CVD) worldwide (Tagalakis *et al.*, 2013; Scheres, Lijfering & Cannegieter, 2018; Hanh *et al.*, 2019). In the USA, the annual incidence of VTE has been estimated at 300 000 to 600 000 people, of which approximately 60 000 to 100 000 will die from associated complications (Serhal & Barnes, 2019). In Europe, literature describing the burden of VTE is reported to be relatively scarce as most data has been generated in the USA (Willich *et al.*, 2018). However, an epidemiological study from 2007, reported 370 012 VTE-related deaths per annum in the EU (Cohen *et al.*, 2007). Furthermore, Preston *et al.* (2020) reported that hospital-associated VTE was responsible for 25 000 to 32 000 deaths per year in the UK alone.

Danwang *et al.* (2017) conducted a systematic review aimed at investigating the epidemiology of VTE and prophylaxis in Africa as estimates were reported to be lacking at a continental level. The authors reported a DVT prevalence ranging from 2.4% to 9.6% in post-surgical patients, and a PE prevalence that ranged from 0.14% to 61.5% in medical inpatients. Moreover, the authors noted that the mortality rate associated with PE in medical inpatients ranged from 40% to 69.5%. In South Africa (SA), the prevalence of VTE is considered to be largely

unknown, since the overall burden of the disease has been poorly characterised. However, it has been hypothesised that the high burden of human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* (TB) in the SA population would inflate the burden of VTE in the country (Moran, 2008; Awolesi, Naidoo & Cassimjee, 2016; Hodkinson & Mahlangu, 2017). The motivation being that both infections possess established associations with VTE development (Bansal, Utpat & Joshi, 2017; Jackson & Pretorius, 2019).

In addition to the associated morbidity and mortality, VTE confers a substantial economic burden on healthcare systems (Horner & Mahan, 2017; Al Mukdad, Al-Badriyeh and Elewa, 2019). Literature relates this burden to VTE's association with increased intensive care unit admission, prolonged hospital stay that is independent of the primary reason for admission, lost economic output and prolonged patient rehabilitation (Gerotziafas *et al.*, 2018; Amin *et al.*, 2019). In the USA, VTE-associated costs are estimated to range from US$5 to US$10 billion each year (Grosse, 2012; Grosse *et al.*, 2016). In 2015, Fernandez *et al.* (2015) conducted a study to provide cost estimates associated with VTE management and care. The authors discovered that VTE treatment costs were increasing more rapidly than general inflation for medical services in the USA in recent years (Fernandez *et al.*, 2015). In SA, a prominent private hospital group reported that their expenditure on VTE prophylaxis and treatment peaked above R195 million in 2017 alone (Du Plessis, Van Blydenstein & Wong, 2020). This, together with cost estimates from the USA and findings from Fernandez *et al.* (2015) lead to the postulation that VTE management is one of the most expensive healthcare strategies worldwide (Van der Merwe, Julyan & Du Plessis, 2020).

Despite VTE's association with significant morbidity and mortality, it can be prevented by providing appropriate pharmacological and non-pharmacological thromboprophylaxis following individualised patient risk assessment (Sachdeva, Dalton & Lees, 2018; Hanh *et al.*, 2019; Yap *et al.*, 2019). This is based on a large body of irrefutable evidence, which clearly demonstrates that appropriate primary prophylaxis in both surgical and high-risk medical patients provides a safe and cost-effective method of reducing PE and DVT (Koren *et al.*, 2020; Nkoke *et al.*, 2020; Yan *et al.*, 2021). Recommendations for using thromboprophylaxis in hospitalised medical patients following individualised patient screening have been implemented as recommended by various clinical practice guidelines, which systematically review and synthesize evidence from the literature (Jacobson *et al.*, 2013; Liew *et al.*, 2017; Schünemann *et al.*, 2018).

Various clinically relevant risk assessment models (RAMs) are available to conduct screenings through assessing thrombotic risk. These include the Padua Prediction Score (PPS), Caprini, International Medical Prevention Registry on Venous Thromboembolism (IMPROVE)

and Geneva RAMs (Stuck *et al.*, 2017; Chen *et al.*, 2018). However, the Caprini RAM provides a comprehensive and simplistic method of measuring VTE risk in both medical and surgical inpatients (Cronin *et al.*, 2019; Rocher *et al.*, 2019; Shah *et al.*, 2020). Moreover, the Caprini RAM has been reported to allow simplistic implementation of the American College of Chest Physicians (ACCP) thromboprophylaxis guidelines, which are typically regarded as the leading VTE prophylaxis guidelines worldwide (Kahn *et al.*, 2012; Zhai *et al.*, 2019).

Jacobson *et al.* (2013) published the SA VTE prophylaxis and treatment guidelines in 2013, which closely mirror the recommendations set out in the ACCP guideline (Rocher *et al.*, 2019; Van der Merwe, Julyan & Du Plessis, 2020). The Caprini RAM, which has undergone several revisions since it was first published in 1991, has been validated in over 250 000 participants in more than 100 trials worldwide (Caprini *et al.*, 1991; Caprini, 2005; Shang *et al.*, 2020). Furthermore, the Caprini RAM has been validated for use in medical inpatients specifically in various studies (Liu *et al.*, 2016; Wang *et al.*, 2019; Zhu *et al.*, 2020).

Various studies have reported an increased incidence of VTE in patients suffering from the coronavirus disease 2019 (COVID-19) (Al-Ani, Chehade & Lazo-Langner, 2020; Wichmann, 2020). A systematic review conducted by Kunutsor and Laukkanen (2020) revealed a high incidence of thromboembolic complications in patients with COVID-19, which ranged from 7.2% to 40.8%. Moreover, the authors concluded that that these complications were underpinned by venous thromboembolic disorders, with PE being the most prevalent. Both literature and practice-based findings provide a clear need for the use of thromboprophylaxis in patients suffering from COVID-19 (Aryal *et al.*, 2020; Bikdeli *et al.*, 2020). However, clarity surrounding risk stratification in this patient population remains controversial as many guidelines recommend that all hospitalised patients with COVID-19 receive pharmacological thromboprophylaxis without risk screening as a pre-requisite (Ali & Spinler, 2021; Patell *et al.*, 2021). In contrast, a multicentre study by Spyropoulos *et al.* (2021) externally validated an adapted form of the IMPROVE RAM, which exhibited significant benefit in discerning VTE risk in hospitalised patients with COVID-19. In addition, a study conducted by Tsaplin *et al.* (2020) showed similar benefits when using an adapted form of the Caprini RAM. These findings highlight the need for tailored thromboprophylaxis regimens in this patient population following individualised VTE risk assessment (Bikdeli *et al.*, 2020).

Despite a growing appreciation for VTE risk assessment and thromboprophylaxis prescription in at-risk medical inpatients, a trend towards under- and inappropriate prescribing has become evident (Pai *et al.*, 2013; Brenner *et al.*, 2019; Yap *et al.*, 2019). Reasons supporting the

under-prescribing of thromboprophylaxis in medical inpatients are unclear and are regarded as being multifactorial. This, together with the low rate of medical practitioner adherence to clinical practice guidelines accentuates the need to clarify these aspects of practice (Bikdeli *et al.*, 2011; Lloyd *et al.*, 2012; Cook *et al.*, 2018).

1.3 Problem statement and research question

Appropriate VTE risk assessment and prophylaxis practices in acute medically ill inpatients have not been fully described in hospital settings worldwide. Despite extensive literature and guideline recommendations available to encourage these practices, their adoption into clinical practice and standardisation has been lacking. Further, a paucity of data relating to VTE risk assessment and adherence to thromboprophylaxis guidelines is evident in the SA public healthcare sector. As VTE is regarded as the most preventable cause of death in this setting, this study will provide valuable insight into the practices of medical practitioners regarding VTE risk assessment and prophylaxis. This insight will have the potential to highlight aspects of VTE risk assessment and prophylaxis that can be further explored and/or developed. Ultimately, this can inform a better standard of thromboprophylaxis-related care being rendered to patients. Thus, the question posed was: "What are the current VTE risk assessment and prophylaxis practices of medical practitioners at public sector hospitals in the Western Cape province of SA?"

1.4 Study aim

This study's aim was to describe the current VTE risk assessment and prophylaxis practices of medical practitioners.

1.5 Study objectives

This study had three main objectives:

1. Conduct a literature review on peer-reviewed published literature concerning VTE risk assessment and prophylaxis by medical practitioners through scientific research;
2. Explore VTE risk assessment practices of medical practitioners in public sector hospitals using a cross-sectional study design; and
3. Analyse and report on findings with recommendations for further research regarding VTE risk assessment and prophylaxis practices.

1.6 Study significance

VTE is considered to be both the leading cause of mortality in hospitalised patients worldwide and the leading cause of maternal morbidity and mortality in developed countries (Cohen *et al.*, 2008; Gassmann *et al.*, 2021). This, together with the increasing prevalence of VTE in aging populations worldwide, is indicative of an expanding public health problem (Tagalakis *et al.*, 2013; Serhal & Barnes, 2019). In SA, a paucity of data concerning VTE risk assessment and prophylaxis practices is evident, notably in the public healthcare sector (Naidoo, Mothilal and Snyman, 2019; Rocher *et al.*, 2019). Therefore, the results of this study could provide valuable insights into VTE risk assessment and prophylaxis practices in SA. This in turn may legitimise innovative strategies aimed at improving VTE risk assessment and prophylaxis practices. In addition, the exploratory approach employed in this study will allow the findings to highlight areas of VTE risk assessment and prophylaxis that can be further developed, specifically in areas where a paucity of data is apparent. Furthermore, these insights can inform future research around these areas of practice.

With the advent of the COVID-19 pandemic in SA, a shift in healthcare resources towards patients presenting with COVID-19 has been evident from the literature (Van Wyk *et al.*, 2021). This, together with the high incidence of thromboembolic events observed in COVID-19 sufferers (Ozsu, Gunay & Konstantinides, 2021), emphasises the need to optimise VTE risk assessment and prophylaxis practices in SA. Therefore, this study has the potential to inform our understanding of the current VTE prophylaxis and risk assessment practices in the SA healthcare setting. This knowledge may be used to enhance the thromboprophylaxis component of the COVID-19 package of care that is rendered to all patients hospitalised with COVID-19.

1.7 Dissertation outline

The outline of the dissertation is presented in the following chapters:

Chapter 1 introduces the study and describes the rationale for its implementation. The research question and the study's aim and objectives are also described. The importance of the study and an overview of the dissertation are also summarised.

Chapter 2 provides a concise review of the available literature that relates to the study topic.

Chapter 3 encompasses the methodology that was employed to conduct the study. Ethical considerations, validity, and reliability as well as bias as it relates to the study are also described in this chapter.

Chapter 4 presents the results of the study and a discussion of the key findings in the form of a published manuscript in a peer-reviewed journal.

Chapter 5 concludes the dissertation with a summary of the overall conclusions and limitations of the study. Recommendations for future research on the study topic are also presented.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This chapter provides a review of published literature pertaining to the study's topic. It begins with an outline of VTE and its various complications. This is followed by a description of the epidemiology and aetiology of the disease. Haemostasis and the pathophysiology associated with VTE are presented and discussed thereafter. Risk factors associated with VTE, VTE risk assessment and various RAMs are introduced and discussed in the next section. A broad overview of thromboprophylaxis, including both pharmacological and non-pharmacological forms of thromboprophylaxis is then provided. The final section provides a concise summary of the chapter.

2.2 VTE

2.2.1 Introduction

VTE is defined as the formation of a thrombus in venous circulation, which manifests as either DVT and/or PE (Heit, Spencer & White, 2016; Schellack, Modau & Schellack, 2020; Galeano-Valle *et al.*, 2021). Thrombi may partially or completely occlude veins or arteries, resulting in localised ischaemic complications. Moreover, thrombi have the potential to embolise to pulmonary circulation or cerebral arteries, leading to severe life-threatening complications, such as PE and/or stroke (Oklu, 2017; Chernysh *et al.*, 2020; Tutwiler *et al.*, 2020). VTE has three potential clinical manifestations: (1) isolated DVT, (2) DVT with resultant PE, or (3) PE alone (Goldhaber & Morrison, 2002; Heit, Spencer & White, 2016). However, VTE is associated with chronic complications, including recurrent VTE, PTS and CTEPH that arise from impaired resolution of pathologic thrombi (Fanikos *et al.*, 2009; Winter, Schernthaner and Lang, 2017).

2.2.2 DVT

DVT is described as the most common manifestation of VTE and is characterised by pathologic clot formation in venous circulation. DVT development occurs more frequently in the lower extremities, specifically in the deep veins located in the calves (Goldhaber & Morrison, 2002; Chan & Weitz, 2020; Ortel *et al.*, 2020). DVTs that originate in the deep veins of the calves are reported to account for approximately half of all DVTs encountered (Galanaud *et al.*, 2012; Utter *et al.*, 2016). However, DVTs can develop in the mesenteric, cerebral and splanchnic venous systems. In addition, DVTs can develop in the deep veins of the upper extremities, which are reported to account for approximately 4% to 10% of all DVT diagnoses. Veins located in the upper

extremities that may be affected include the ulnar, radial, axillary, brachial, subclavian, brachiocephalic and internal jugular veins (Bleker *et al.*, 2016; Heil *et al.*, 2017; Agrati *et al.*, 2021).

Most DVTs originating in the deep veins of the calves will lyse spontaneously. However, it is estimated that 20% of calf-originating DVTs will propagate to the proximal venous system, which comprises the proximal and popliteal veins. The resultant effects include limb ischaemia through blood flow obstruction and proximal pathologic clot propagation resulting in PE (Yoshimura *et al.*, 2012; Chan & Weitz, 2020). Distal DVT, which includes DVT development in the calf and distal veins, has a lower risk of clot propagation and consequential PE. Further, distal DVT is more commonly associated with transient thrombotic events, whilst proximal DVT possesses a stronger association with chronic thrombotic sequalae. Therefore, consideration for the site of DVT development possesses clinical significance as extensive proximal thrombosis is associated with inferior patient health outcomes (Galanaud *et al.*, 2012; Jenkins & Michael, 2014; Mazzolai *et al.*, 2018).

2.2.2.1 Clinical presentation

The clinical presentation of DVT is typically characterised by unilateral limb swelling and acute-onset pain, tenderness as well erythema of the affected extremity. However, these manifestations are nonspecific and result in DVT being clinically indistinguishable from other diseases, including cellulitis, congestive cardiac failure, and superficial thrombophlebitis. Therefore, DVT-associated symptoms should prompt clinicians to employ objective testing to exclude or confirm the diagnosis (Hansrani, Khanbhai & McCollum, 2017; Mazzolai *et al.*, 2018; Tritschler *et al.*, 2018; Bhatt *et al.*, 2020).

2.2.2.2 Diagnosis

DVT-related symptoms possess low sensitivity and specificity when viewed in isolation. However, when symptoms are considered in combination with the use of validated prediction rules, the probability of diagnosing DVT improves. The three-tiered Wells Score provides a validated and simple first step in diagnosing DVT through the assignment of points in relation to findings from a clinical examination (Wells *et al.*, 1995; Modi *et al.*, 2016; Hansrani, Khanbhai & McCollum, 2017; Mazzolai *et al.*, 2018). If a high probability of DVT is detected following the application of a DVT pre-test probability tool, an imaging test, such as duplex doppler ultrasonography should be conducted as this provides a more definitive DVT assessment. Imaging tests are considered to

be the gold standard for detecting DVT. However, in certain circumstances a D-dimer test may be recommended, e.g., in patients who possess a high probability of DVT but lack a positive finding on a duplex doppler ultrasound test. D-dimers are degradation products from plasmin; hence, their association with thrombosis. However, D-dimer tests lack specificity as various conditions may elevate D-dimer levels, including malignancy, pregnancy, trauma and infection (Wells *et al.*, 2003; Hansrani, Khanbhai & McCollum, 2017; Olaf & Cooney, 2017; McLean & James, 2018; Stubbs, Mouyis & Thomas, 2018).

2.2.3 PE

Another clinical manifestation of VTE is a PE, where a clot or portion of a clot embolises to the pulmonary arterial circulation, and becomes lodged and subsequently occludes pulmonary blood flow (Essien, Rali & Mathai, 2019; Schellack, Modau & Schellack, 2020). In most cases, PE originates as a DVT that embolises from the deep veins located in the upper extremities, lower extremities, pelvis, or right side of the heart (Morici, 2014; Duffett, Castellucci & Forgie, 2020). PE can be classified according to anatomic location, presentation, and haemodynamic stability (Rali, Gandhi & Malik, 2016).

Acute PE occurs following the immediate development of signs and symptoms associated with PE, whilst subacute PE is characterised by the progression and worsening of signs and symptoms over several days. In contrast, chronic PE is reported to be prominent in patients with pulmonary hypertension and is associated with a slow symptom progression over a period of years (Rali, Gandhi & Malik, 2016; Simonneau *et al.*, 2017; Witkin, 2017).

A pulmonary embolus that is lodged at the bifurcation of the main pulmonary artery, where it extends into both the left and right pulmonary arteries is termed a saddle PE. Saddle PEs have been reported to be associated with higher rates of major adverse events, including haemodynamic collapse (Sardi *et al.*, 2011; Essien, Rali & Mathai, 2019). Segmental, subsegmental and lobar pulmonary emboli are classified in accordance with the branch of the pulmonary artery in which they are located (Rali, Gandhi & Malik, 2016; Rali & Criner, 2018; Sin *et al.*, 2021).

Further, PE is ranked into two distinct categories on the basis of haemodynamic compromise: massive and submassive PE (Witkin, 2017; Licha *et al.*, 2020). The American Heart Association (Jaff *et al.*, 2011) defines massive PE as:

> "Acute PE with sustained hypotension (systolic blood pressure <90 mm Hg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular [LV] dysfunction), pulselessness, or persistent profound bradycardia (heart rate <40 bpm with signs or symptoms of shock".

Submassive PE is described as an acute PE, which does not fulfil the requirements for massive PE, but does comprise right ventricular failure that is based upon imaging, such as echocardiography and/or pertinent biomarkers, including brain natriuretic peptide (Morici, 2014; Essien, Rali & Mathai, 2019).

2.2.3.1 Clinical presentation

Similar to DVT, diagnosing PE may be challenging due the associated nonspecific signs and symptoms, which include acute onset dyspnoea, cough, tachycardia and pleuritic chest pain. Haemoptysis, as a consequence of pulmonary infarction is also a frequently reported complaint and develops in up to 20% of patients (Stein *et al.*, 2007; Miniati *et al.*, 2012; Doherty, 2017).

2.2.4 Diagnosis

An appropriate approach to diagnosing PE begins with the application of a validated pre-test probability scoring tool, such as the three-tiered Wells or Geneva Scores for PE. Pre-test probability scores offer a standardised method of arranging clinical findings into a formal, point-based classification system. Similar to the Wells Score for DVT, the adapted version for PE employs a scoring system to classify patients as having a low, intermediate or high probability of acute PE; thus, aiding clinicians in excluding or including acute PE as the diagnosis (Doherty, 2017; Hepburn-Brown, Darvall & Hammerschlag, 2019; Duffett, Castellucci & Forgie, 2020; Sin *et al.*, 2021).

Computerised tomography pulmonary angiography (CTPA) is the gold standard test for PE diagnosis and is reportedly the most frequently used imaging test in this regard (Ghaye & Dondelinger, 2008; Hepburn-Brown, Darvall & Hammerschlag, 2019; Licha *et al.*, 2020). A ventilation-perfusion scan may also be used to diagnose PE and is the modality of choice in pregnancy owing to the higher risk of exposure to ionising radiation associated with CTPA testing (Mallick & Petkova, 2006; Tromeur *et al.*, 2019). In addition, chest X-rays are an effective method of excluding alternative diagnoses, including pneumonia, congestive cardiac failure and pneumothorax (Doherty, 2017; Kruger *et al.*, 2019). Further, D-dimer test utility in PE is similar to that in DVT, where a negative D-dimer test can be used to exclude a diagnosis of PE in combination with a low pre-test probability score (Di Nisio *et al.*, 2007; Righini, Robert-Ebadi & Le Gal, 2017).

2.2.5 Chronic complications of VTE

2.2.5.1 PTS

PTS is a long-term complication that develops in approximately 20% to 50% of all patients with DVT. PTS development is underpinned by venous hypertension, which results from valvular reflex and prolonged venous obstruction. Proximal vein DVT has a stronger association with resultant PTS compared to a DVT originating in the popliteal or calf muscle veins. Persistent swelling, pain, cramping and heaviness of the affected extremity are frequently reported symptoms. Clinical signs associated with PTS include ulceration, oedema, hyperpigmentation, lipodermatosclerosis and telangiectasis. Further, symptoms are aggravated during exercise and improve whilst at rest. PTS can develop despite using anticoagulation therapy to treat the initial DVT as this approach prevents extension and embolisation of the thrombus but has no direct action on endogenous thrombolysis. As no gold standard exists for diagnosing PTS, its diagnosis is primarily based upon clinical examination in combination with duplex ultrasound testing (Kahn, 2016; Schleimer *et al.*, 2016; Winter, Schernthaner & Lang, 2017; Rabinovich & Kahn, 2018; Golemi *et al.*, 2019). Primary prophylaxis against the initial DVT is regarded as the most effective method of preventing PTS. The importance of this strategy in high-risk settings is highlighted in various guidelines and reports (Falck-Ytter *et al.*, 2012; Kahn *et al.*, 2012; Pikovsky & Rabinovich, 2018).

2.2.5.2 CTEPH

Opitz and Ulrich (2018) define CTEPH as "symptomatic pulmonary hypertension with persistent pulmonary perfusion defects despite adequate anticoagulation for 3 to 6 months". However, this definition neglects to describe the thromboembolic foundation of the disease as its development is typically provoked by acute PE. The precise pathophysiology of CTEPH is poorly understood, but it is characterised by organised thrombi and fibrosis in the proximal pulmonary arteries and/or small-vessel vasculature. Further, it is associated with anomalous vascular remodelling and residual thrombi in the pulmonary vasculature, which in turn impairs blood flow (Auger *et al.*, 2007; Opitz & Ulrich, 2018; Kim *et al.*, 2019; Papamatheakis *et al.*, 2020; Ranka *et al.*, 2020). CTEPH, along with other disorders that occlude pulmonary arteries, are classified in the World Health Organisation Group 4 pulmonary hypertension (Galiè *et al.*, 2016; Yandrapalli *et al.*, 2018).

Despite CTEPH's classification as a chronic complication of VTE, it lacks a significant association with classic VTE-associated risk factors. However, certain shared risk factors between CTEPH and VTE have been described in the literature, including indwelling venous catheters, chronic inflammatory states, and malignancy. The diagnosis of CTEPH is reported as challenging

owing to the lack of symptoms during the early phase of the disorder and the nonspecific symptoms that develop later during disease progression. However, CTEPH must be considered in all patients presenting with prolonged dyspnoea and decreased exercise tolerance following PE as well as in those in which significant perfusion variations (>15%) are detected following perfusion or ventilation scans (Auger *et al.*, 2007; Winter, Schernthaner & Lang, 2017; Golemi *et al.*, 2019). Using catheter-based pulmonary digital subtraction angiography to evaluate the pulmonary vasculature presents a well-established approach to diagnosing CTEPH (Sugimura *et al.*, 2013; Mullin & Klinger, 2018). In contrast to other forms of pulmonary hypertension, CTEPH can be cured through the removal of obstructive particles from the pulmonary vasculature (Jenkins *et al.*, 2017; Lang *et al.*, 2017).

2.3 Epidemiology

VTE is estimated to be the third most diagnosed CVD worldwide (Raskob *et al.*, 2014; Danwang *et al.*, 2017). VTE has an annual incidence ranging from 0.1% to 0.27% and is reported to affect up to 5% of the global population (Wells, Forgie & Rodger, 2014; Patel *et al.*, 2017; Bungard *et al.*, 2018). It is also reported to be one of the leading causes of hospital-related morbidity worldwide, with up to 50% of patients with DVT being at risk of developing long-term sequalae (Agrati *et al.*, 2021; Xu, Siegal & Anand, 2021). This is compounded by the estimate that 18% to 65% of all VTE-related deaths are preventable (Chen *et al.*, 2021).

The Centers for Disease Control and Prevention (2020) estimate that 60 000 to 100 000 people die each year from VTE in the USA. However, Goldhaber (2012) reported a higher rate, where a conservative mortality rate is 100 000 to 180 000 deaths occurring annually in the USA. In addition to mortality, VTE is reported to account for more than 500 000 hospital admissions each year in the USA (Xu, Siegal & Anand, 2021). In Europe, a scarcity of VTE-related epidemiological data has been reported. However, Cohen *et al.* (2007) conducted a large epidemiological study across six European nations to estimate the EU's burden of VTE. The authors reported that over 600 000 cases of VTE occurred annually in the EU with more than 300 000 VTE-related deaths.

Kanchanabat *et al.* (2014) conducted a systematic review and meta-analysis aimed at analysing the incidence and mortality associated with postoperative VTE in Asia. The authors reported a 13.4% rate of DVT and a 0.4% rate of PE, which were markedly low in comparison to estimates from western populations (Kanchanabat *et al.*, 2014). In contrast, emerging evidence

from other epidemiological studies in Asia describe a trend towards similar rates of VTE in medical inpatients when compared to western populations (Liew *et al.*, 2017).

Despite a high burden of VTE worldwide, a paucity of data concerning the epidemiology of VTE in low- and middle- income countries has been reported (Duncan, 2009; Goldstein & Wu, 2018). With the aim to ascertain the epidemiology of VTE in Africa, Danwang *et al.* (2017) conducted a systematic review across the continent, which revealed a PE prevalence ranging from 0.14% to 61.5% in medical inpatients. In addition, the authors reported a PE mortality rate between 40% and 69.5% in this population.

Limited VTE-related epidemiological data is evident in SA, despite the postulation that the high dual burden of HIV and TB would inflate the prevalence of VTE in the country (Naidoo, Mothilal & Snyman, 2019; Van der Merwe, Julyan & Du Plessis, 2020). Despite the lack of data, Awolesi, Naidoo and Cassimjee (2016) reported that more than 200 000 South Africans are diagnosed with DVT annually, despite the true incidence being unknown. Furthermore, it has been noted that 20 000 deaths occur each year in the country due to thromboembolic disease (Awolesi, Naidoo & Cassimjee, 2016; Van der Merwe, Julyan & Du Plessis, 2020).

VTE is considered to be a disease of older age, owing to the exponential increase in VTE incidence as individuals age. However, incidence rates differ with age in each gender, with substantial increases noted in men aged 45 years and older and in women of childbearing age (Heit, Spencer & White, 2016; Patel *et al.*, 2017). The age-adjusted incidence rate is 105 per 100 000 persons for women and 114 per 100 000 persons for men, which is indicative of a greater VTE risk in men. In addition, inter-racial differences in VTE rates have been reported, with black persons having the greatest risk, compared to Asians with the lowest risk (Heit, Spencer & White, 2016; Xu, Siegal & Anand, 2021).

Worldwide, VTE is reported to be the leading cause of mortality in pregnant patients in developed countries, with PE alone accounting for 13.8% of deaths in this population (Rybstein & DeSancho, 2019; Gassmann *et al.*, 2021). Moreover, data from the World Health Organisation revealed that PE accounts for 3.2% of all maternal deaths worldwide (Say *et al.*, 2014). Further, VTE accounted for 15% of maternal mortality between 2003 and 2011 in the USA (Dado, Levinson & Bourjeily, 2018). In Africa, an annual VTE prevalence ranging from 380 to 480 per 100 000 births was reported in pregnant and postpartum women (Danwang *et al.*, 2017). In SA, data lacks in this regard, despite VTE being considered one of the top 10 leading causes of preventable maternal death in the country (Wessels, 2019).

The rate of VTE increases with hospital admission, with approximately 50% of all VTE diagnoses being associated with current or recent hospitalisation (Lewis *et al.*, 2018; Schünemann *et al.*, 2018). The risk of VTE is not limited to surgical patients, as previously thought, as the estimated incidence of VTE in medical inpatients ranges from 10% to 40%, which is equivalent to patients undergoing a general surgical procedure (Alikhan & Spyropoulos, 2008; Preston *et al.*, 2020). Moreover, medical inpatients possess an eight-fold greater risk of developing VTE compared to the general population (Al Yami *et al.*, 2018; Skeik & Westergard, 2020). This increased risk is purportedly linked to an increased incidence of VTE risk factors in this population. This is evidenced by the estimates that 78% of all medical inpatients possess more than one risk factor and 20% have more than three risk factors (Nkoke *et al.*, 2020). In addition, medical inpatients are reported to contribute 74% of all VTE diagnoses as compared to only 26% of surgical patients (Khoury *et al.*, 2011). Furthermore, 75% of all fatal VTE-related events occur in medical inpatients and the VTE re-admission risk of survivors in this population peaks at 28% six months post-admission (Khoury *et al.*, 2011; Skeik & Westergard, 2020).

The elevated risk of VTE in medical inpatients has been well-described in the literature (Koren *et al*., 2020). The Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting (ENDORSE) study was a multinational epidemiological study that investigated the prevalence of VTE risk in acute hospital settings. The study was conducted across 32 countries and included 68 183 patients from across 358 hospitals. Cohen *et al.* (2008) found that 51.8% of patients were at-risk of VTE and of these, 41.5% were medical inpatients. In China, the Identification of Chinese Hospitalized Patients' Risk Profile for Venous Thromboembolism (DissolVE-2) study was a large, cross-sectional study that aimed to determine the prevalence of VTE risks in the Chinese population. A total of 13 601 patients from 60 different Chinese hospitals were included in the study, of which 45.2% were found to be at-risk of VTE. However, a lower proportion of medical inpatients were found to be at-risk, making up only 36.3% of the overall at-risk group in the study (Zhai *et al.*, 2019).

Although the ENDORSE study encompassed African countries, it neglected to include any countries from sub-Saharan Africa (SSA), prompting Kingue *et al.* (2014) to carry out a similar study across five SSA countries. The authors reported a higher proportion of medical inpatients (62.3%) being at-risk of VTE in this setting. In SA, The Use of VTE prophylaxis in relation to patiEnt risk profiling (TUNE-IN) study was conducted to assess the use of VTE prophylaxis in relation to patient risk in SA private hospitals. More than 600 patients were included in the study, with 54.1% of patients in the sample being reported as at-risk of VTE. Further, a large proportion

of medical inpatients were also found to be at-risk, with 70.9% of this group being grouped into the high and highest risk categories (Wessels & Riback, 2012).

2.4 Aetiology

2.4.1 Virchow's Triad

In 1856, Virchow first hypothesised that pathologic thrombosis was multifactorial in its aetiology and was underpinned by three main factors: venous stasis, hypercoagulability and vessel wall or endothelial injury. More than 150 years later, Virchow's Triad remains a fundamental approach to understanding the factors encompassing arterial and venous thrombosis (Anderson & Spencer, 2003; Key, 2013; Louw & Ntusi, 2019). Figure 2.1 presents Virchow's Triad.

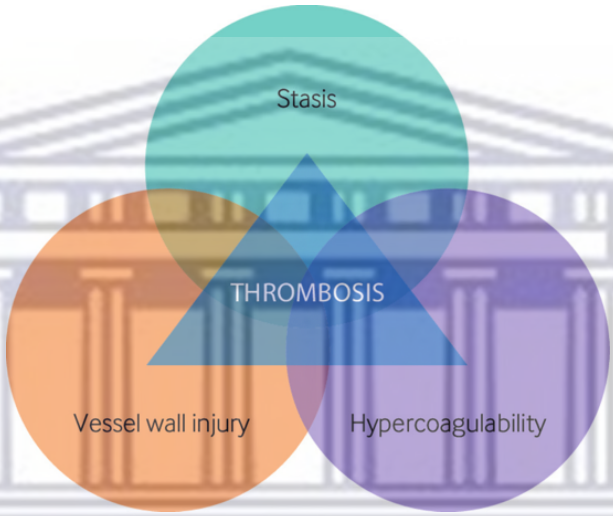

Figure 2.1: Virchow's Triad of factors associated with thrombosis (Khan, Vaillancourt & Bourjeily, 2017).

Together with the contraction of the calf and thigh muscles, one-way valves located in the deep veins of the lower extremities ensure that blood flows back to the pulmonary and cardiac vasculature. However, prolonged immobility and injured venous valves can result in blood stasis and altered blood flow (Hochauf, Sternitzky & Schellong, 2007; Moore, Gohel & Davies, 2011). Valve pockets located in the large veins of the lower extremities are predominantly susceptible to alterations in blood flow; thus, resulting in turbulent flow or complete venous stasis. Moreover, these valve pockets are regarded as the main sites from which venous thrombi originate. Prolonged stasis in these valve pockets is associated with local hypoxia through the induction of a diminishing oxygen concentration gradient. The resultant oxidative stress promotes the recruitment of platelets, granulocytes, and monocytes, which cause the subsequent release of proinflammatory mediators. This then leads to the increased local exposure to tissue factor (TF), which in turn initiates the extrinsic coagulation pathway, resulting in thrombosis. The intrinsic coagulation pathway can also

be initiated from the actions of activated platelets and damaged granulocytes. Collectively, the induction of these pathways results in a proinflammatory and procoagulant state with subsequent venous thrombosis (Turpie & Esmon, 2011; Reitsma, Versteeg & Middeldorp, 2012; Byrnes & Wolberg, 2017; Stone *et al.*, 2017).

A hypercoagulable state can be induced by various factors, including cancer, chemotherapy agents, oestrogen-containing oral contraceptives, pregnancy, and thrombophilia. Moreover, literature findings suggest that TF-bearing microparticles, which are associated with specific diseases, such as cancer and congestive cardiac failure, contribute to the induction of a hypercoagulable state (Turpie & Esmon, 2011; Monie & DeLoughery, 2017). In addition, prothrombotic diseases, such as hyperhomocysteinaemia subject fibrinogen to abnormal post-translational modifications, resulting in dysfibrinogenaemia and consequential coagulation. Other mechanisms underpinning hypercoagulability include leukocyte-mediated coagulation, whereby leukocytes are recruited to combat pathogens, but result in an unintended procoagulant state with pathologic thrombosis (Mackman, 2012; Byrnes & Wolberg, 2017).

Although endothelial or vessel wall injury is known to be associated with pathologic clot formation, the exact underlying mechanism is not well understood (Lurie *et al.*, 2019). However, it is understood that vessel wall disruption results in increased TF expression, which allows for the activation of the extrinsic pathway and subsequent coagulation. In response to injury, activated endothelial cells upregulate the expression of TF, which is a procoagulant, and downregulate the expression of endogenous anticoagulants, including thrombomodulin. Moreover, activation leads to the expression of adhesion molecules, such as P-selectin on endothelial surfaces, which ultimately lead to the capture of leukocytes and further promote coagulation (Geenen *et al.*, 2012; Mackman, 2012; Stone *et al.*, 2017). In addition, TF-bearing microparticles have been shown to promote thrombosis when endothelial injury occurs. The underlying mechanism includes the attachment of these microparticles to endothelial cells, followed by activation and subsequent transfer of TF; thus, promoting thrombosis (Turpie & Esmon, 2011).

2.5 Pathophysiology

2.5.1 Haemostasis and the coagulation cascade

Haemostasis, which consists of primary and secondary haemostasis are defined as the process by which the circulatory system maintains its integrity following blood vessel injury (Xu *et al.*, 2016; Periayah, Halim & Mat Saad, 2017; Grover & Mackman, 2019). Primary haemostasis refers to the process of platelet plug formation at the site of endothelial cell injury following interactions

between the platelets, adhesive proteins, and the endothelial cell wall. Secondary haemostasis involves the deposition of an insoluble fibrin mesh to reinforce the pre-formed platelet plug following activation of the coagulation cascade (Gale, 2011; Palta, Saroa & Palta, 2014). Haemostasis is characterised by three stages: (1) vasoconstriction of the affected blood vessel, (2) platelet adhesion and aggregation to form a platelet plug, as well as (3) activation of the coagulation cascade to form a fibrin clot (Hiller, 2007; Winter, Flax & Harris, 2017).

The classical concept of the coagulation cascade was first proposed in 1964, where the process was introduced as a "waterfall" and "cascade" sequence (Davie & Ratnoff, 1964; Macfarlane, 1964). Davie and Ratnoff (1964) explained that this concept was developed to "explain the function of the various protein clotting factors during the formation of the fibrin clot". In this approach blood coagulation is presented as a series of stepwise reactions involving the activation of zymogens, which ultimately lead to the formation of fibrin (Hoffman, 2003; Grover & Mackman, 2019). Three pathways are described within this approach, which are the parallel running intrinsic and extrinsic pathways that eventually converge at the common pathway (Adams & Bird, 2009; Palta, Saroa & Palta, 2014). Figure 2.2 displays the classical concept of the coagulation cascade.

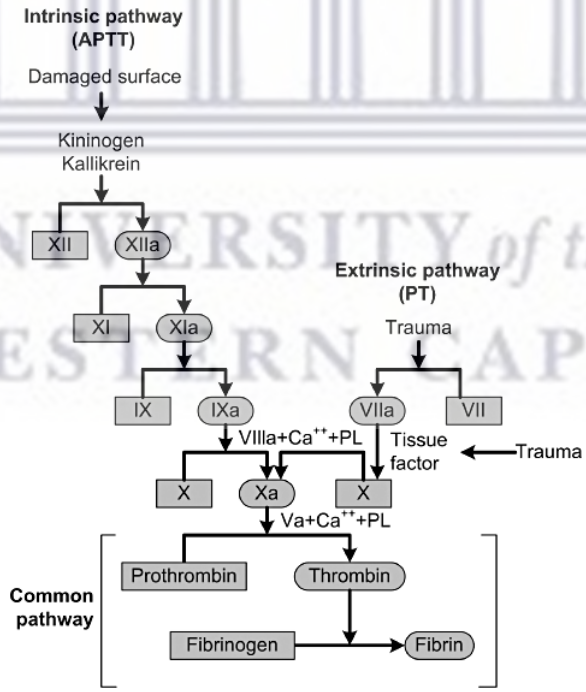

Figure 2.2: Classic waterfall idea of the coagulation process (Adams & Bird, 2009).

This classical theory of the coagulation cascade is useful for understanding blood coagulation from an *in vitro* coagulation testing perspective. However, this approach fails to appreciate the

significant role of cellular elements, notably activated platelets in the *in vivo* blood coagulation process (Hoffman & Monroe, 2005; Ferreira *et al.*, 2010; Palta, Saroa & Palta, 2014).

Contemporary approaches, which are also termed 'cell-based models' appreciate the role of cellular elements in blood coagulation and recognise that the intrinsic pathway is not an independent and parallel running pathway. Moreover, these approaches emphasise the role of the intrinsic pathway in augmenting thrombin production that is generated by the extrinsic pathway. Further, cell-based models involve three phases: initiation, amplification and propagation (Hoffman, 2003; Adams & Bird, 2009; Smith, 2009; Ferreira *et al.*, 2010).

The initiation phase is characterised by the expression TF in an injured blood vessel in response to an initial insult or injury. TF binds to factor VIIa to form a TF-VIIa complex, which in turn activates factors IX and X. The activation of factor IX serves as the link between the traditional intrinsic and extrinsic pathways. Thrombin, also termed factor IIa is produced on the surface of TF-bearing cells following the binding of factors Xa and II. However, thrombin produced during this step is reported to be insufficient to exert its full effect and may be easily repressed by circulating TF pathway inhibitor (Hoffman, 2003; Smith, 2009; Ho & Pavey, 2017).

The amplification phase takes place to compensate for the insufficient quantities of thrombin produced in the initiation stage. The small quantity of thrombin produced during the previous stage now functions to activate platelets, which promote the release of partly activated forms of factor V onto their surfaces. Thrombin mediates the activation of factors VIII and V on platelet surfaces. This results in VIII/von Willebrand factor (VWF) complex dissociation; thus, allowing VWF to mediate additional platelet aggregation and adhesion at the site of blood vessel injury. Last, thrombin mediates the activation of factors XI to XIa on platelet surfaces (Veldman, Hoffman & Ehrenforth, 2003; Romney & Glick, 2009; McMichael, 2012).

During the propagation phase a large quantity of activated platelets are recruited to the site of injury in the blood vessel. The tenase complex is formed on platelet surfaces following the binding of factor IX to factor VIIIa. The prothrombinase complex is formed following the rapid association between factors Xa and Va on platelet surfaces. The completion of the prothrombinase assembly leads to the conversion of substantial quantities of prothrombin to thrombin, which in-turn cleaves fibrinogen into fibrin monomers (Hoffman & Monroe, 2005; Ferreira *et al.*, 2010; McMichael, 2012). Last, the fibrin monomers are covalently linked together through activation of factor XII, which is responsible for stabilizing fibrin strands following their incorporation into and around the platelet plug (Lasne, Jude & Susen, 2006; Adams & Bird, 2009; Romney & Glick,

2009). Figure 2.3 presents the various phases of coagulation in line with the cell-based model of the coagulation.

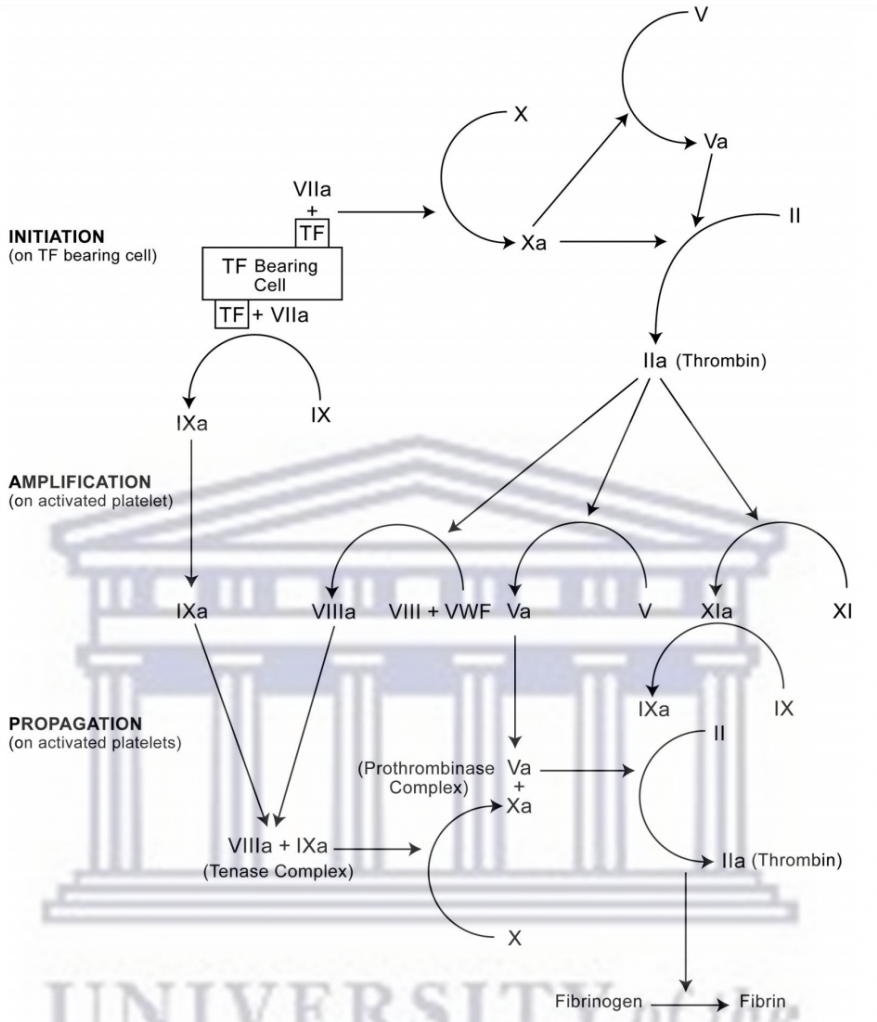

Figure 2.3: Summary of the coagulation process according to the cell-based approach (Vine, 2009).
TF – Tissue factor
VWF – Von Willebrand factor

Fibrin or haemostatic clots promote bleeding cessation and subsequently dissipate following fibrinolysis. Activation of the fibrinolytic system during the wound healing process results in clot dissolution through fibrin cleavage by the operative enzyme (Boon, 1993; Ogedegbe, 2002; Winter, Flax & Harris, 2017). However, dysregulation of the coagulation process can result in the formation of intravascular clots, which underpin various pathological thrombotic disorders, including VTE (Gale, 2011; Palta, Saroa & Palta, 2014; Grover & Mackman, 2019). In contrast to haemostatic clots, pathologic clots do not always remain localised to endothelial walls and often result in complete blood vessel occlusion and consequent tissue ischaemia and death. In addition,

pathologic VTE frequently develops without endothelial wall injury and is initiated by TF-bearing microparticles (Smith, Travers & Morrissey, 2015; Xu *et al.*, 2016).

2.6 Risk factors for VTE

2.6.1 Classifying risk factors

VTE can be classified as being provoked or unprovoked in nature, which influences the risk of recurrent thrombosis as well the duration of thromboprophylaxis (Phillippe, 2017; Agrati *et al.*, 2021; Galeano-Valle *et al.*, 2021). Unprovoked or idiopathic VTE is referred to as a thrombotic event that is not associated with acquired or environmental VTE risk factors. In contrast, provoked VTE is described as a thrombotic event, which develops as a result of an acquired or environmental VTE risk factor (Di Nisio, Van Es & Büller, 2016; Ellis & Avnery, 2021). Risk factors associated with provoked VTE can be categorised as either transient or persistent, where transient risk factors are anticipated to resolve following the provocation of the thrombotic event (Phillippe, 2017; Satpanich & Rojnuckarin, 2019; Tritschler & Wells, 2019). It has been reported (Kearon *et al.*, 2016; Prins *et al.*, 2018; Ageno *et al.*, 2021) that the risk of VTE recurrence can be estimated by clinicians in accordance with the categorisation of the thrombotic event, which is significant as previous VTE is an independent risk factor for recurrence. Figure 2.4 provides a visual representation of the potential recurrence of a thrombotic event in line with risk factor categorisation.

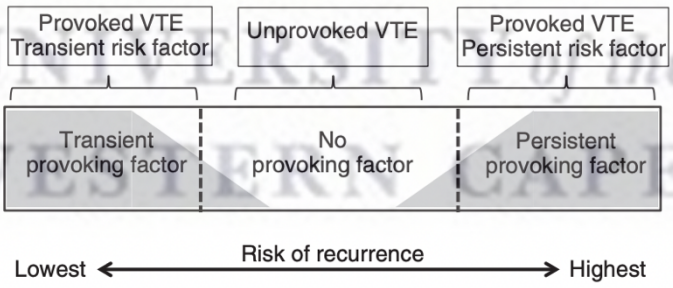

Figure 2.4: Risk of VTE recurrence in line with categorising VTE risk factors (Kearon *et al.*, 2016).
VTE – Venous thromboembolism

The utilisation of VTE risk factor categorisation to predict recurrence has been described as controversial (Baglin *et al.*, 2010). Albertsen, Piazza and Goldhaber (2018) argue that a paucity of data hinders the precise estimation of risk in this regard. This postulation may be valid when considering the results of a nationwide cohort study in Denmark, where recurrence rates per 100-person years at a six-month follow-up were 6.80 and 6.92 for provoked and unprovoked VTE,

respectively (Albertsen, Piazza & Goldhaber, 2018). In contrast to this argument, a systematic review conducted by Iorio *et al.* (2010) concluded that risk categorisation should still be employed to guide clinicians in estimating the duration of thromboprophylaxis. Moreover, various other studies have demonstrated the robust association between VTE risk factor categorisation and the risk of recurrent thrombosis (Kovacs *et al.*, 2010; White *et al.*, 2010; Tosetto *et al.*, 2012).

2.6.2 Thrombosis-related risk factors

VTE is described as a multifactorial disease that occurs as a consequence of a complex set of interactions between genetic predispositions and environmental exposures (Ariëns *et al.*, 2002; Heit, Spencer & White, 2016; Brenner *et al.*, 2019). Risk factors can be characterised according to their association with the three components of Virchow's Triad; namely, venous stasis, vessel wall injury and hypercoagulability (Patel *et al.*, 2017; Witt, Clark & Vazquez, 2020). Table 2.1 summarises various risk factors associated with VTE development.

Table 2.1: Risk factors for developing VTE (Anderson & Spencer, 2003; Heit, Spencer & White, 2016; Patel et al., 2017; Witt, Clark & Vazquez, 2020; Agrati *et al.*, 2021).

Risk factor classification	**Examples**
Venous stasis	• Surgery • Immobility (e.g., plaster cast, spinal cord injury, acute medical illness requiring hospitalisation, paralysis, long-haul air travel > 4 h) • Obesity • Congestive cardiac failure
Hypercoagulability	• Malignancy • Acquired or inherited thrombophilia • Antiphospholipid syndrome • Nephrotic syndrome • Pregnancy • Medication use (e.g., oestrogen-containing contraceptives, hormone therapy, cancer chemotherapy) • Acute infections (e.g., COVID-19 infection) • Chronic infections (e.g., TB, HIV) • Chronic inflammatory diseases (e.g., Rheumatoid arthritis)
Vessel wall injury	• Surgery (e.g., major orthopaedic surgery) • Trauma (e.g., fracture of pelvis, long bones and/or hips) • Indwelling venous catheters • Previous VTE • Varicose veins • Smoking

VTE – Venous thromboembolism

COVID-19 – Coronavirus disease 2019

TB – *Mycobacterium tuberculosis*

HIV – Human Immunodeficiency Virus

Venous stasis-related risk factors are based primarily upon an established form of immobility, such as paralysis and/or hospitalisation for acute medical illness. However, this group of risk factors also comprises congestive cardiac failure, which develops primarily as a result of

increased venous pressure (Piazza *et al.*, 2009; Turpie & Esmon, 2011; Mackman, 2012). Further, hospitalisation for acute medical illness is reported to be one of the most significant VTE risk factors. This is evidenced by the estimate that inpatients have an eight-fold greater risk of developing VTE as compared to non-hospitalised patients (Darzi *et al.*, 2020; Skeik & Westergard, 2020). Despite hospitalisation being an independent risk factor for VTE, the risk in medical inpatients has also been attributed to the elevated prevalence of other risk factors in this patient population. These risk factors include congestive cardiac failure, pneumonia, stroke, cancer, respiratory failure, and myocardial infarction (Cohen *et al.*, 2005; Ageno & Hunt, 2018). Congestive cardiac failure's association with VTE development is typically linked to venous stasis, which arises from low cardiac output with the consequential creation of areas, where blood pooling and stasis occurs. However, congestive cardiac failure is also considered to induce vessel wall injury through its association with endothelial and vascular remodelling, which damages endothelial cells. Moreover, it has been reported to cause abnormalities in the coagulation system, resulting in the induction of a hypercoagulable state (Dean & Abraham, 2010; Zhu, Hu & Tang, 2017; Goldhaber, 2020).

Various studies have found obesity (Body mass index [BMI] > 30 kg/m^2) to be an independent risk factor for VTE development (Borch *et al.*, 2009; Steffen *et al.*, 2009). These findings are further evidenced by the findings from a meta-analysis conducted by Ageno *et al.* (2008), which evaluated the association between cardiovascular risk factors and VTE development. The authors included nine studies with 8 125 patients and found that obese patients possessed a two-fold greater risk of suffering from VTE compared to patients with a normal BMI. The risk conferred by obesity is reported to occur as a result of its association with inactivity, chronic inflammation, elevated levels of VWF and fibrinogen as well as impaired fibrinolysis, which all result in a prothrombotic state. Further, associations between elevated BMI (>25 kg/m^2) and increased risk of VTE have also been described (Yang, De Staercke & Hooper, 2012; Hotoleanu, 2020).

Although long distance travel has been found to be a risk factor for VTE development, the incidence is purportedly uncommon. Long distance travel has been shown to increase the risk of VTE nearly three-fold, with an 18% increase to the overall risk for each additional two-hours of travel added to a trip (Chandra, Parisini & Mozaffarian, 2009; Gavish & Brenner, 2011). The available data suggests that VTE risk is not only limited to air travel, yet the association between flights > 4 h and thrombosis have been established (Watson & Baglin, 2011; Patel *et al.*, 2017; Koh, 2021). In 2007, the landmark World Health Organisation Research Into Global Hazards of

Travel project report (2007) was published, which revealed that the incidence of VTE increases two-fold for those on flights exceeding four hours. Further, the authors described a linear relationship, where VTE risk rises as the duration of travelling increases.

Various inherited and acquired conditions have been shown to induce a hypercoagulable state. These include various forms of thrombophilia, cancer and cancer chemotherapy, infections, and chronic inflammatory disorders (Witt, Clark & Vazquez, 2020; Agrati *et al.*, 2021).

Thrombophilia may be defined as a coagulation disorder in which abnormal blood coagulation occurs with a consequential increased risk VTE. Inherited thrombophilia occurs as a result of one or more genetic mutations or genetic risk factors. Thrombophilia-associated mutations include mutations in prothrombin and factor V genes, which cause prothrombin G20210A and factor V Leiden blood clotting disorders, respectively. Genetic risk factors include deficiencies in endogenous anticoagulant proteins, including protein S, protein C, and antithrombin (Alli *et al.*, 2020; Colucci & Tsakiris, 2020). Factors that are indicative of inherited thrombophilia include a first degree relative with a history of VTE, VTE occurrence prior to 40 years of age, VTE recurrence and VTE occurrence in the presence of weak or entirely absent provoking risk factors (Connors, 2017; Ashraf *et al.*, 2019).

The association between various forms of cancer, chemotherapies and VTE development has been established. Cancer sufferers have been reported to possess a five- to seven-fold increase in their risk of developing VTE, and up to 20% of cancer patients will develop VTE in their lifetime (Sud & Khorana, 2009; Razak *et al.*, 2018; Kraaijpoel & Carrier, 2019). Cancer patients have been described as possessing a prothrombotic state due to possible venous stasis resulting from tumour compression, vessel wall injury from intravasation of cancer cells as well as hypercoagulability resulting from the release of cancer cell-mediated procoagulant factors. However, the underlying pathophysiology of cancer-associated thrombosis has been predominantly linked to the increased expression of TF and resultant blood hypercoagulability (Zwicker *et al.*, 2009; Khalil *et al.*, 2015). Varying cancers have been linked to differences in the risk of VTE development, with pancreatic, lung, ovarian and stomach tumours carrying the highest risk (Lyman, 2011; Cohen *et al.*, 2017). Further, various cancer chemotherapies have also been associated with thrombosis, including cisplatin, thalidomide, and tamoxifen (Heit, Spencer & White, 2016; Razak *et al.*, 2018).

Various infections have been shown to predispose patients to VTE through the induction of a hypercoagulable state. Both chronic and acute infections caused by a variety of viruses and bacteria have established associations with thrombosis as independent risk factors. The underlying pathophysiology is theorised to be associated with both the direct actions of pathogens as well the

host's immune response, both of which result in deleterious activation of coagulation with a resultant procoagulant state. The hyperactivation of immune cells, such as monocytes and lymphocytes result in greater systemic inflammation and subsequent activation of the coagulation pathway. Further, depressed levels of the natural anticoagulant, TF pathway inhibitor, have also been observed in septic patients (Schmidt *et al.*, 2012; Epaulard, Foote & Bosson, 2015; Cohoon *et al.*, 2018; Beristain-Covarrubias *et al.*, 2019). Although all infections carry an increased risk of VTE, variations in the risk of VTE associated with acute infections have been reported in the literature. Pneumonia, bloodstream and intra-abdominal infections as well symptomatic urinary tract infections have been reported to confer the highest risk (Smeeth *et al.*, 2006; Grimnes *et al.*, 2018). COVID-19-induced coagulopathy has emerged as a critical and frequent complication associated with the disease. Various organs have been shown to be affected by this complication, including the vasculature of the brain, lungs, lower limbs, and spleen. Moreover, DVT and PE have been reported to be the most frequently encountered thrombotic events in this patient population and resultant multi-organ failure is frequently reported. Although the underlying pathophysiology of COVID-19-induced coagulopathy is not well understood, it is hypothesised that the excessive systemic inflammation and resultant endothelial cell damage is the leading factor associated with increased thrombosis (Ali & Spinler, 2021; Kyriakoulis *et al.*, 2021; Ozsu, Gunay & Konstantinides, 2021). This hypothesis is also evidenced by the extensive inflammatory response observed in COVID-19 patients who experience the release of a large quantity of pro-inflammatory cytokines, termed cytokine storm (Huang *et al.*, 2020; Ragab *et al.*, 2020). In addition, the multisystem inflammatory syndrome in children observed in paediatric patients suffering from COVID-19 is also indicative of a potential, independent COVID-19-induced coagulopathy occurring in this patient population (Ali & Spinler, 2021). The incidence of VTE in patients with COVID-19 has been reported to range from 15% to 35%, whilst autopsy-based studies have reported estimates as high as 60% (Manolis *et al.*, 2021). Di Minno *et al.* (2020) conducted a meta-analysis aimed at investigating the association between thrombotic events and COVID-19. A total of 20 studies comprising 1 988 patients were included in the analysis, where a weighted mean prevalence of 31.3% was detected (Di Minno *et al.*, 2020).

Patients infected with TB have been shown to possess a 1.5-fold increased risk of developing VTE when compared to uninfected individuals (Dentan *et al.*, 2014). However, this added risk remains underappreciated as an independent VTE risk factor, despite the extensive prevalence of the disease. Further, it has been well-established that TB, like other chronic infections, induces a hypercoagulable state primarily through inflammation (Epaulard, Foote & Bosson, 2015; Azdaki,

Moezi & Farzad, 2018; Hariz *et al.*, 2019). The apparent slow resolution of symptoms and possible diagnostic delays have also been reported to compound and prolong the exposure to chronic inflammation in TB sufferers (Borjas-Howard *et al.*, 2017). In addition, the coagulopathy associated with TB has also been linked to decreasing endogenous anticoagulant proteins, including proteins S and C, increasing procoagulant factors, such as fibrinogen, as well intrathoracic venous compression (Turken *et al.*, 2002; Dentan *et al.*, 2014).

TB has also been frequently associated with underlying HIV infection; thus, compounding the risk of VTE. The inflammatory burden is theorised to double in patients co-infected with HIV and TB. Thus, HIV also possesses a strong association with thrombosis (Epaulard, Foote & Bosson, 2015; Borjas-Howard *et al.*, 2017). Numerous studies have described a higher incidence of VTE in patients infected with HIV, with reports of a two- to ten-fold greater risk of VTE when compared to the general population (Ahonkhai *et al.*, 2008; Bibas, Biava & Antinori, 2011). The underlying pathogenesis of HIV-associated hypercoagulability is multifactorial and is related to the upregulation of proinflammatory cytokines. Moreover, it is thought to be perpetuated by deficiencies in endogenous anticoagulant proteins and antithrombin, the presence of procoagulants, including antiphospholipid antibodies and lupus anticoagulant antibodies as well as increased levels of VWF and fibrinogen. In addition, HIV-related opportunistic infections and neoplasms and antiretroviral medications have been hypothesised to further predispose patients with HIV to VTE (Louw, Jacobson & Büller, 2008; Rasmussen *et al.*, 2011; Jackson & Pretorius, 2019; Alli *et al.*, 2020; Agrati *et al.*, 2021).

Inflammation has been established as a key component in VTE development, which is further evidenced by the strong association between VTE and chronic inflammatory diseases. Inflammatory bowel diseases, systemic lupus erythematosus (SLE), psoriasis and rheumatoid arthritis have been demonstrated to possess a higher rate of VTE when compared with that of the general population (Saghazadeh & Rezaei, 2016; Ogdie *et al.*, 2018; Galloway *et al.*, 2020). Moreover, antiphospholipid antibodies are commonly associated with SLE sufferers, which are known to induce a hypercoagulable state (Bazzan, Vaccarino & Marletto, 2015). Lee and Pope (2014) conducted a meta-analysis to assess the risk of VTE in patients suffering from various inflammatory rheumatologic diseases, including rheumatoid arthritis and SLE. The authors found that patients suffering from these diseases were three times as likely to develop VTE as compared to the general population.

Vessel wall injury results from damage to the endothelium, which exposes collagen and sub-endothelial TF to blood in circulation, which in turn leads to thrombosis and clot formation. This

damage can result from physical injuries including trauma, intravenous drug use, surgery and indwelling venous catheters (Van Stralen, Rosendaal & Doggen, 2008; Patel *et al.*, 2017; Witt, Clark & Vazquez, 2020). Surgery is a well-established risk factor for VTE due to the resultant post-operative immobility in certain cases and endothelial injury (Beavers & Wayne, 2020; Segon *et al.*, 2020). Although all surgical procedures are associated with a risk of VTE development, the risk differs substantially between the varying types of surgeries. Furthermore, surgeries associated with the greatest risk of VTE include major orthopaedic surgery, such as knee and hip arthroplasty, major vascular surgery and invasive neurosurgery (Lewis *et al.*, 2018; Anderson *et al.*, 2019). This is evidenced by the finding that in the absence of thromboprophylaxis, approximately 50% of all patients undergoing total hip or knee arthroplasty will develop VTE (Anderson & Spencer, 2003). In addition, a relationship between the length of the surgical procedure and VTE risk has been reported (Hardy *et al.,* 2014). Kim *et al.* (2015) conducted a retrospective cohort study, which investigated the relationship between the duration of surgery and the incidence of VTE. The authors included more than 1 432 855 patients and demonstrated that patients undergoing the longest types of surgical procedures had a 1.27-fold increase in their odds of developing VTE.

Although no measures can be employed to circumvent non-modifiable risk factors, such as age, ethnicity, sex, and genetics, understanding the mechanisms underpinning these risk factors is key to improving VTE-related care. The incidence of VTE is reported to increase exponentially with age, although it can develop at any age (Crous-Bou, Harrington & Kabrhel, 2016; Lacruz *et al.*, 2019). Moreover, paediatric patients are also at risk of VTE, albeit far lower when compared to the elderly. Further, predisposing risk factors are reported to be prominent in paediatric patients presenting with VTE (Branchford *et al.*, 2012; Rühle & Stoll, 2018; Jinks & Arana, 2019). This is supported by the estimate that 90% of paediatric patients possess a minimum of two VTE risk factors at the time of the thrombotic event (Rühle & Stoll, 2018).

Patients older than 40 years have been reported to possess a significantly increased risk of VTE, after which the risk is estimated to double with each passing decade (Anderson & Spencer, 2003). This is supported by a study conducted by Stein *et al.* (2004), which revealed that PE diagnosis in patients > 70 years of age was 6.2 times the rate of those younger than 70 years. Further, the authors reported that DVT diagnosis in patients aged 70 to 79 years was 12.7 times greater than that in patients whose age fell between 20 and 29 years (Stein *et al.*, 2004). Therefore, age is considered to be an independent risk factor for VTE development (Alikhan & Spyropoulos, 2008). It has been postulated that the increasing incidence of VTE with age is underpinned by a

higher prevalence of provoking risk factors in this population, including surgery, hospitalisation, immobility and cancer (Luxembourg *et al.*, 2009; Crous-Bou, Harrington & Kabrhel, 2016).

The notion that men possess a greater risk of VTE development in comparison to women remains controversial (Yoshikawa *et al.*, 2019). However, literature findings are indicative of trend towards men having a greater propensity of recurrent thrombosis (White *et al.*, 2006). Further, differing annual incidences in women of childbearing age have been reported. This has been attributed to the greater impact of hormonal exposures during childbearing years, such as oral contraceptive use and pregnancy itself, which predisposes patients to VTE through its influence on all three components of Virchow's Triad (Stein & Matta, 2010; Heit, Spencer & White, 2016; Khan, Vaillancourt & Bourjeily, 2017). Further, the incidence of VTE has been found to increase in men following midlife, yet the reasons for this increase are unclear. Hypotheses that have been proposed for this increased risk include differences in body height and increased VTE-associated risk factors that are related to lifestyle (Crous-Bou, Harrington & Kabrhel, 2016; Zöller *et al.*, 2017).

Ethnoracial differences in the incidence of VTE have also been reported, where black individuals have been found to possess the greatest risk of VTE compared to individuals form other ethnicities (White & Keenan, 2009; Goldhaber, 2014). Various epidemiological studies have reported a trend, where the incidence of VTE is lower in East Asian individuals as compared to those from North America and Western Europe. In addition, this trend extends across countries with a similar income status, which further supports the hypothesis that VTE incidence is lower in Asian individuals (Xu, Siegal and Anand, 2021).

2.7 Assessing VTE risk

2.7.1 Introduction

VTE prevention has been described as a multifaceted and complex approach involving a multi-step process (Durieux *et al.*, 2000; Cayley, 2007; Basey *et al.*, 2012). Lau *et al.* (2018) describes the process of VTE prevention in four phases:

1. Each patient's individual risk of VTE must be evaluated.
2. Clinicians must prescribe a tailored VTE prophylaxis regimen in accordance with the individual patient's risk profile and consideration should be given to possible contraindications.
3. Patients must be willing to accept the prescribed prophylaxis regimen.
4. Each prophylaxis regimen must be administered as prescribed by nursing personnel.

VTE risk assessment comprises a fundamental component of VTE prevention and is described as an approach to assessing and estimating a patient's risk of developing VTE (Streiff *et al.*, 2012; Obi *et al.*, 2015). Risk assessment procedures are typically based upon clinician knowledge of VTE risk factors at a patient level. Following the risk assessment process, patients are targeted for select VTE prophylactic measures in accordance with their projected risk of VTE. The benefits of VTE risk reduction are typically weighed against the risk of adverse effects, cost, and patient preference (Maynard, Jenkins & Merli, 2013; Watts & Grant, 2013; Preston *et al.*, 2020).

Previously, VTE risk assessment was predominantly conducted through a group-specific risk assessment strategy. This strategy would allow clinicians to assign patients to specific risk groups, including low, moderate, and high-risk groups, based upon predisposing risk factors, such as surgery or medical illness. This strategy was reported to be appealing due to its simplicity as well as the apparent lack of knowledge regarding VTE risk factors and their exact impact on inducing thrombosis in previous years (Durieux *et al.*, 2000; Geerts *et al.*, 2004; Spyropoulos, 2010). However, Spyropoulos, McGinn and Khorana (2012) noted various limitations associated this strategy:

1. The lack of capacity to stratify VTE risk of patient groups with complex VTE risk factors, including those hospitalised with acute medical illness.
2. The inability for precise VTE risk measurement in cases where narrower benefit versus risk profiles is evident.
3. The inability to account for individualised, patient-centred outcomes, such as current symptomatic VTE in place of surrogate outcomes, including venographic VTE.

Further, Caprini (2010) argued that group-specific risk assessment strategies were based off "older studies, arbitrary age cut-off levels, and inexact definitions". These shortcomings were mirrored by Geerts *et al.* (2008), who, despite being in favour of a group-specific approach, also noted that this approach failed to quantify the risk conferred by each individual risk factor.

Individualised VTE risk assessment strategies, such as point-based VTE risk stratification are the generally accepted standard of VTE prevention and are recommended by various organisations and guidelines (Jacobson *et al.*, 2013; Rosenberg *et al.*, 2014; Schulman, Ageno & Konstantinides, 2017; National Department of Health, 2019). These strategies determine the risk of VTE in each individual patient, based on their predisposing risk factors as well the risk related to their current procedure or disease. The composite risk of VTE is used to guide individualised thromboprophylaxis prescribing. Further, these strategies aim to determine VTE risk more

accurately through the use of individualised VTE risk scoring systems (Geerts *et al.*, 2008; Caprini, 2010; Nicholson *et al.*, 2020). However, individualised VTE risk assessment is complex, owing to the expanding number of VTE risk factors and knowledge thereof. Further, the varying levels of VTE risk conferred by each VTE risk factor further complicates the assessment process. Therefore, it may be deduced that individualised VTE risk assessment can be challenging for clinicians when considering the growing number of VTE risk factors with varying risk profiles (Durieux *et al.*, 2000; Beck *et al.*, 2011; Golemi *et al.*, 2019).

A frequent misconception among clinicians is that individualised VTE risk assessment strategies are more time consuming and cumbersome when compared to group-specific risk assessment strategies. Yet, individualised VTE risk assessment strategies are simplistic in their design, which simply accumulate patient information from general patient histories and physical examinations (Geerts *et al.*, 2004; Caprini, 2010). Moreover, various studies have shown that individualised VTE risk assessment strategies, such as those using point-based models, can be effectively and reliably employed by physicians, pharmacists and nursing personnel in clinical settings (Beck *et al.*, 2011; Yap *et al.*, 2019; Yan *et al.*, 2021).

2.7.2 VTE RAMs

A VTE RAM can be defined as a risk prediction or prognostic model that employs a standardised amalgamation of established VTE risk factors to predict the VTE risk of individuals (Darzi *et al.*, 2020; Pandor *et al.*, 2021). Point-based VTE risk stratification, which employs a risk-factor weighting, function through the allocation of points for various VTE risk factors during patient assessment. This process is preceded by the determination of each patient's cumulative VTE risk through tallying up the assigned points. Patients will then be classified according to their individual risk of VTE depending on their overall risk score, which will ultimately guide thromboprophylaxis prescribing (Maynard & Stein, 2010; Beck *et al.*, 2011; Golemi *et al.*, 2019). Numerous VTE RAMs, which utilise point-based risk stratification systems, have been developed and adopted for use in a variety of patient populations, including both surgical and hospitalised medical patients. These models serve as adjunct clinical decision-making tools to aid clinicians in risk stratification as well as to inform appropriate thromboprophylaxis prescribing (Rosenberg *et al.*, 2014; Stuck *et al.*, 2017; Chen *et al.*, 2018).

Various concepts defining the characteristics of an ideal VTE RAM have been described in the literature (Grant *et al.*, 2016; Shang *et al.*, 2020). Of these concepts, Spyropoulos, McGinn and Khorana (2012) provide a comprehensive synopsis, explaining that an ideal RAM should:

- Reliably identify all patients at-risk of VTE based on their meeting of set thresholds for VTE development in the absence of thromboprophylaxis.
- Predict a precise level of VTE risk in individual patients, which allows for the individualisation of thromboprophylaxis regimens.
- Accurately exclude patients who possess an unfavourable VTE risk/benefit ratio.
- Undergo external validation and be underpinned by robust evidence from the literature.
- Be simplistic to utilise in clinical practice settings.

Furthermore, recommendations from a systematic review conducted by Huang *et al.* (2013) mirrored the aforementioned qualities of an ideal VTE RAM. However, the authors also noted that an ideal RAM should state the specific point in time during patient care that thromboprophylaxis use will be appropriate and that RAMs must exclude predicative VTE factors, which are not available at the point of care.

Various VTE RAMs have been developed, in part, to circumvent barriers associated with VTE prophylaxis, including the underestimation of VTE risk, concerns of bleeding risk and lack of adherence to VTE prevention guidelines and policies (Maynard & Stein, 2010; Alckmin *et al.*, 2013; Mlaver *et al.*, 2020). The most notable of these RAMs include the PPS, IMPROVE, Intermountain, Kucher, Rogers and Caprini RAMs (Serhal & Barnes, 2019; Shang *et al.*, 2020). The PPS as well as the IMPROVE, Geneva, Kucher and Intermountain RAMs were reported to be developed specifically for use in hospitalised medical patients (Barbar & Prandoni, 2017; Gerotziafas *et al.*, 2018). In contrast, the Rogers RAM was originally developed for use in patients undergoing various surgical procedures, including thoracic, general and vascular surgeries (Jacobs & Pannucci, 2017; Cronin *et al.*, 2019; Tian *et al.*, 2019). In addition, VTE RAMs have been designed for use in other populations, such as the Khorana RAM, which was designed for assessing VTE risk in patients suffering from cancer. Further, the Khorana RAM has been proven to be effective in predicting VTE risk in both in- and outpatients with cancer (Hu *et al.*, 2020; Li *et al.*, 2021).

Despite numerous reviews of the various RAMs' capacity to accurately predict the risk of VTE, a lack of consensus regarding the preferred RAM is evident (Stuck *et al.*, 2017; Van der Merwe, Julyan & Du Plessis, 2020). This is further compounded by the lack of suitable external validation of RAMs in prospective studies. Despite this lack, several RAMs have been evaluated in impact analysis studies, which are not considered to produce robust evidence for validation (Barbar *et al.*, 2010; Darzi *et al.*, 2020). Further, Rosenberg *et al.* (2014) expands on this by stating that suitable external validation of VTE RAMs should be done in "settings and patient populations

different from the populations from which the model was derived". The resultant benefits of suitable external validation would ensure reproducible accuracy and extensive clinical use of selected RAMs (Spyropoulos, McGinn & Khorana, 2012; Barbar & Prandoni, 2017).

Despite the lack of external validation, several RAMs have been studied more extensively and have undergone external validation, including the PPS, IMPROVE, Caprini and Geneva RAMs (Nendaz *et al.*, 2014; Chamoun *et al.*, 2019; Arpaia *et al.*, 2020; Darzi *et al.*, 2020). This was also reflected in a systematic review conducted by Pandor *et al.* (2021), which aimed to measure the comparative accuracy of various RAMs at predicting VTE in hospitalised patients. The investigators reported that the PPS was evaluated in 16 studies, the IMPROVE RAM in eight studies and the Geneva and Kucher RAMs in four studies, respectively. Although the investigators included 51 studies, which were inclusive of 24 distinct RAMs, they concluded that insufficient evidence was available for RAM preference. However, the investigators did find that the Caprini RAM was the most extensively evaluated, with it being assessed in 22 different studies (Pandor *et al.*, 2021).

2.7.3 Caprini RAM

The Caprini RAM is reported to be the most extensively used and validated RAM in clinical practice worldwide (Obi *et al.*, 2015; Jacobs & Pannucci, 2017; Hu *et al.*, 2020). Moreover, the RAM's worldwide adoption is reported to be underpinned by its simplistic VTE risk estimation that is based on a categorical stratification system. The Caprini RAM derives VTE risk from a consolidation of clinical expertise and experience as well as published evidence (Laryea & Champagne, 2013; Hanh *et al.*, 2019). It was originally designed by Joseph Caprini to replace outdated VTE risk prediction indices, such as group-specific risk assessment, which failed to achieve widespread acceptance and use. Further, it has been postulated that these outdated VTE risk stratification approaches possessed poor uptake due to their failure to account for individual patient VTE risks and compulsory laboratory testing (Caprini, 2005; Geerts *et al.*, 2008; Jeong *et al.*, 2014).

The Caprini RAM has been used in clinical practice since the 1980s and has undergone extensive modifications over the years, resulting in novel versions that incorporate contemporary VTE risk information. The RAM was first published in 1991, with subsequent versions being published in 2005, 2009 and 2013 (Caprini, 2010; Cronin *et al.*, 2019). Furthermore, the initial version of the Caprini RAM was developed by a multidisciplinary team consisting of nurses, scientists and physicians that were led by Caprini (Caprini *et al.*, 1991). The benefit of a

multidisciplinary team-based design may be further appreciated when considering a key concept of RAM application, where various members of the team can be actively involved in VTE risk assessment (Streiff *et al.*, 2016; Nana *et al.*, 2020). Maynard and Stein (2010) expand on this further by stating that VTE RAMs can be administered by any healthcare professional, most notably nurses and pharmacists, after which the presiding physician can be informed of the results. Lastly, the Caprini RAM has undergone validation in more than 250 000 patients, including both surgical and medical patients, in over 100 trials globally (Krauss *et al.*, 2019; Shang *et al.*, 2020).

The Caprini RAM uses a total of 39 individual VTE risk factors, including weight, age, and comorbidities, including HIV, to assign patients to specific VTE risk categories. Moreover, each risk factor is correlated with a point value, where the weighting is based upon published literature. Ultimately, all points assigned are tallied up to obtain an aggregate score, which is used to classify patients into highest, high, moderate or low VTE risk categories (Cronin *et al.*, 2019; Golemi *et al.*, 2019). Table 2.2 provides a visual representation of the 2013 version of the Caprini RAM, where risk factors and their quantitative risk weighting are grouped together.

Table 2.2: 2013 version of the Caprini RAM (Caprini, 2005; Cronin et al., 2019; Rocher et al., 2019).

Each risk factor corresponds to one point	**For women only: Each risk factor corresponds to one point**	**Each risk factor corresponds to two points**	**Each risk factor corresponds to three points**	**Each risk factors corresponds to five points**
Age 41–60 years	Current use of birth control therapy or hormone replacement therapy	Age 61–74 years	≥ Age 75	Elective major lower extremity arthroplasty
Minor surgery planned (< 45 min)	Pregnant or conceived in the last 30 d	Current or past malignancies (excluding skin cancer, but including melanoma)	History of thrombosis, either DVT; PE or superficial venous thrombosis	Hip, pelvis, or leg fracture
Past major surgery (> 45 min) in last 30 d	History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxaemia or growth restricted infant	Planned major surgery lasting longer than 45 minutes (including laparoscopic and arthroscopic surgeries)	Family history of thrombosis (up to third-degree relatives)	Multiple trauma
Visible varicose veins		Use of nonremovable plaster cast that prevents leg movement in last 30 d	Personal or family history of genetic or acquired thrombophilia	Spinal cord injury with resultant paralysis
History of inflammatory bowel disease		Use of tube in blood vessel in neck or chest that delivers blood or medicine directly to the heart in the last month (e.g., central venous access)		Stroke
Swollen legs (current)		Confined to bed for 72 h or more (unable to ambulate		

		continuously for 30 feet)		
BMI > 25 kg/m^2				
Myocardial infarction				
Congestive cardiac failure				
Serious infection (requires hospitalisation and antibiotic[s])				
Chronic respiratory disease e.g., COPD				
Currently at bed rest or restricted mobility, including the use of removable leg brace for < 72 h				

RAM – Risk assessment model

DVT – Deep vein thrombosis

PE – Pulmonary embolism

BMI – Bodymass index

COPD – Chronic obstructive pulmonary disease

Each risk category is correlated with pre-specified VTE prophylaxis recommendations, which are based upon VTE risks from the literature (see Table 2.3). Depending on the level of VTE risk detected through the application of the RAM, varying types and degrees of VTE prophylaxis are recommended (Caprini, 2005; Krauss *et al.*, 2019).

Table 2.3: Caprini RAM risk categorisation and recommended thromboprophylaxis regimen (Caprini, 2005; Rocher *et al.*, 2019).

Total risk factor score	**DVT incidence (%)**	**Associated risk level**	**Recommended thromboprophylactic regimen**
0–1	< 10	Low	No specific interventions; early ambulation
2	10–20	Moderate	GCS or IPC or UFH, or LWMH
3–4	20–40	High	IPC or UFH, or LMWH alone or in combination with GCS or IPC
≥ 5	40–80	Highest	Pharmacological: UFH, LMWH, Warfarin, or factor Xa inhibitor alone or in combination with GCS or IPC

RAM – Risk assessment model

DVT – Deep vein thrombosis

GCS – Graduated compression stockings

IPC – Intermittant pneumatic compression

UFH – Unfractionated heparin

LMWH – Low molecular weight heparin

Several arguments against the use of the Caprini RAM are apparent in the literature (Darzi *et al.*, 2020). Among these, a notable limitation was described by Gharaibeh, Albsoul-Younes and Younes (2016), who reported that the RAM overestimates the risk of VTE, with this effect being more pronounced in medical inpatients. In contrast, a study conducted by Chamoun *et al.* (2019)

found that the Caprini RAM was effective at discriminating between patients at low and high risk of VTE. Another possible limitation is the extensive list of VTE risk factors that must be considered when applying the RAM, which could be challenging to adopt for use in clinical practice. However, each risk factor included is based off published evidence; thus, necessitating the need for their inclusion in the RAM to ensure optimal patient care (Stuck *et al.*, 2017; Golemi *et al.*, 2019). In addition, the use of patient-friendly versions of the RAM have been proposed as a means to circumvent the potential time-constraints associated with the use of the RAM (Veith *et al.*, 2019). Moreover, Paz Rios *et al.* (2018) conducted a validation study, which revealed a significant level of agreement between patient and physician Caprini RAM scores.

2.8 VTE prophylaxis

2.8.1 Introduction

VTE risk assessment only forms the initial phase of the comprehensive thromboprophylaxis-related package of care rendered to hospitalised patients. Patients at risk of VTE should be rapidly identified and counselled around the benefits and risks associated with thromboprophylaxis, followed by clinician-led selection, prescribing and administration of the most appropriate prophylactic agent available (Bonner, Coker & Wood, 2008; Gerakopoulos, 2015; Key, Bohlke & Falanga, 2019). To ensure effective and safe VTE prophylaxis, each stage of this approach requires meticulous consideration and thorough execution (Preston *et al.*, 2020). Anderson and Spencer (2003) expand on this concept further by stating that when considering VTE prophylaxis clinicians need to account for the:

1. Relative and absolute risks associated with VTE development in each individual.
2. Possible benefits associated with the available prophylactic agents.
3. Potential complications and adverse effects, specifically bleeding.
4. Associated costs of thromboprophylaxis.

VTE prophylaxis can be defined as the measures employed to reduce the risk of VTE development in at-risk individuals (Lederle *et al.*, 2011; Routhier & Tagalakis, 2021). VTE prophylaxis is grouped as either primary or secondary prophylaxis. Primary prophylaxis refers to a proactive approach to prevent VTE and is considered the preferred method by various guidelines. In contrast, secondary prophylaxis is a reactive approach and encompasses early detection of sub-clinical VTE through screening, diagnosis and subsequent VTE treatment (Diep & Garcia, 2020; Shah *et al.*, 2020).

A well-established body of evidence has clearly demonstrated the efficacy, feasibility, acceptability, safety and cost-effectiveness of primary prophylaxis in reducing the incidence of VTE in at-risk surgical and medical inpatients (Francis, 2007; Sachdeva, Dalton & Lees, 2018; Schünemann *et al.*, 2018; Koren *et al.*, 2020). Furthermore, this body of evidence includes a study by Bump *et al.* (2009), who conducted a meta-analysis of randomised controlled trials to determine whether VTE prophylaxis reduced clinically significant VTE events in hospitalised general medical patients. The authors reported that thromboprophylaxis regimens comprising pharmacological agents resulted in a significant reduction in both DVT and PE. The investigators also noted that despite the tendency of pharmacological prophylaxis to increase the risk of bleeding, there was no increased risk of major bleeding (Bump *et al.*, 2009). Further, the cost-effectiveness of various forms of VTE prophylaxis have been reported in various studies (Dawoud *et al.*, 2018; Torrejon Torres, Saunders & Ho, 2019).

As primary VTE prophylaxis possesses substantial benefit to patient care, the use of standardised risk stratification and prevention protocols are typically regarded as key indicators of patient safety and quality care in hospital settings worldwide (Bonner, Coker & Wood, 2008; Encke, Haas & Kopp, 2016). This concept has been supported by various healthcare societies, commissions and organisations worldwide, including the American College of Surgeons, Centers for Medicare and Medicaid Services, the UK Care Quality Commission, Australian Commission on Safety and Quality in Health Care (Goldsmith, Whitelaw & Cannaday, 2008; Lau *et al.*, 2018).

As numerous pathological mechanisms have been demonstrated to underpin VTE, a multifaceted approach to prophylaxis, where the targeting of multiple components of Virchow's Triad is recommended (Byrnes & Wolberg, 2017; Mehta, Calcaterra & Bassareo, 2020). Venous stasis may be reduced through the use of mechanical methods of VTE prophylaxis, which result in limb compression and increased blood movement (Leme & Sguizzatto, 2015; Weinberger & Cipolle, 2016). Similarly, hypercoagulability may be targeted through the use of various anticoagulants, which inhibit clot formation at various points during the coagulation process (Turpie & Esmon, 2011; Monie & DeLoughery, 2017).

Various reports concerning the effectiveness of VTE prophylaxis regimens indicate that combination therapy with both mechanical and pharmacological methods of prophylaxis capacitate improved VTE prevention (Laryea & Champagne, 2013; Nicholson *et al.*, 2020). These reports are evidenced by the systematic review and meta-analysis conducted by Fan *et al.* (2020), which assessed the effect of adjunct intermittent pneumatic compression (IPC) in hospitalised patients receiving pharmacological thromboprophylaxis. The authors found that pharmacological

thromboprophylaxis with adjunctive IPC conferred a moderate benefit in reducing the risk of VTE in surgical inpatients (Fan *et al.*, 2020). However, various guidelines and commissions typically regard pharmacological prophylaxis alone as the gold standard when preventing VTE in both surgical and medical inpatients without major risks of bleeding (Jacobson *et al.*, 2013; Liew *et al.*, 2017; Schünemann *et al.*, 2018; National Institute for Health and Care Excellence., 2019).

2.8.2 Pharmacological thromboprophylaxis

2.8.2.1 Introduction

Standardised pharmacological thromboprophylaxis regimens have been widely accepted by healthcare institutions and are advocated for use as first-line thromboprophylaxis by various authoritative commissions and guidelines globally (Maynard & Stein, 2010; Naidoo, Mothilal & Snyman, 2019; National Institute for Health and Care Excellence., 2019; Bartlett *et al.*, 2020). Further, these recommendations are not only pertinent to surgical patients, but to at-risk medical inpatients too, where significant benefit has been demonstrated (Cayley, 2007; Kahn *et al.*, 2012; Park *et al.*, 2016; Ageno & Hunt, 2018).

Pharmacological thromboprophylaxis comprises various anticoagulants, which exert their effect through the inhibition of one or more clotting factors in the coagulation process (Brien, 2019; Myers & Lyden, 2019). The mechanisms of these agents vary widely, including indirect and direct inhibition of clotting factors as well as inhibition of vitamin K-dependent clotting factors (Bonner, Coker & Wood, 2008; Ho, Van Hove & Leng, 2020). Osuch and Marais (2019) reported that these inhibitory effects of anticoagulants possess two key outcomes, which are to prevent:

1. Propagation of existing thrombi, and
2. Formation of new thrombi.

Despite the lack of clarity around the involvement of platelet activation in the pathophysiology of VTE, antiplatelet agents, such as aspirin have also been studied for use in VTE prophylaxis. However, their effectiveness at preventing VTE in hospitalised medical patients is unclear, owing to a lack of evidence in this population (Lacut *et al.*, 2008; Kahn *et al.*, 2012). Although aspirin has shown benefit in preventing VTE following orthopaedic surgery, comparability data with anticoagulants is reported to be lacking (Bartlett *et al.*, 2020). This, together with the substantial body of evidence supporting the use anticoagulants in VTE prophylaxis has led to several guidelines recommending against the use of aspirin in favour of anticoagulants in at-risk medical inpatients (Jacobson *et al.*, 2013; Schünemann *et al.*, 2018; Diep & Garcia, 2020). Various anticoagulants are available for VTE prophylaxis in both hospitalised

surgical and medical patients, including vitamin K antagonists, heparins, fondaparinux and direct oral anticoagulants (DOACs) (Julia & James, 2017; Lim, 2018).

2.8.2.2 Vitamin K antagonists

Vitamin K antagonists, such as warfarin, exert their anticoagulant effects through the competitive inhibition of vitamin K epoxide reductase, an enzyme that is required for the activation vitamin K-dependent clotting factors. Initially, vitamin K antagonists result in a pro-thrombotic effect through the inhibition of proteins C and S, followed by a delayed anticoagulant effect once factors II, VII, IX, and X are inhibited (Hirsh *et al.*, 2003; Harter, Levine & Henderson, 2015). Warfarin is made of a racemic mixture of the R-isomer and the S-isomer, which is reported to be three to five times more potent than the R-isomer (Gong *et al.*, 2011; Eriksson & Wadelius, 2012). Further, warfarin is administered once-daily orally and is used for the secondary prevention and treatment of VTE as well as other thromboembolic diseases. Routine international normalized ratio (INR) monitoring is integral when assessing the safety and effectiveness of warfarin therapy as the pharmacodynamic response of the agent is challenging to predict and largely variable. For the majority of indications, a target INR range of 2.0 to 3.0 is desirable; however, exceptions are also apparent for certain diseases. In response to the preliminary procoagulant effect induced by warfarin, an adjunctive parenteral anticoagulant, such as a low molecular weight heparin (LMWH), will need to be administered until a therapeutic INR is achieved and is stable for 48 h (Horton & Bushwick, 1999; Kuruvilla & Gurk-Turner, 2001; Jaffer & Bragg, 2003).

The pharmacokinetics and pharmacodynamics of warfarin present another key limitation, which is the agent's association with numerous clinically significant drug-drug and drug-food interactions. These are related primarily to the active S-isomer, which is predominantly metabolised by cytochrome P450 2C9; thus, prompting inducers or inhibitors of this pathway to result in significant interactions (Holbrook *et al.*, 2005; Xue *et al.*, 2017). In addition, consuming varying quantities of foods containing vitamin K when using vitamin K antagonists can result in clinically significant drug-food interactions, where the anticoagulant effects of the agent may be reduced. As warfarin use is associated with an increased risk of bleeding as the primary adverse effect, vitamin K is a natural antidote and has been well-established as a reversal agent in patients with supratherapeutic INR levels (Baglin, 1998; Ebright & Mousa, 2015).

2.8.2.3 Heparins

Heparins, which comprise unfractionated heparin (UFH) and LMWHs, are considered the most widely used class of anticoagulants in the treatment and prevention of VTE in clinical practice today. Heparin derivatives, including LMWHs, were developed to produce agents with improved and more predictable pharmacokinetic profiles (Hemker, 2016; Qiu *et al.*, 2021).

UFH is a naturally occurring and ubiquitous polysaccharide that is found in mast cells. The molecule was first isolated from animal tissues and was considered one of the greatest advancements in medicine when introduced to clinical practice in the 1930s. Owing to its extensive use for decades, the structure and mechanism of activity of UFH have been studied and researched (Page, 2013; Oduah, Linhardt & Sharfstein, 2016). UFH exerts its anticoagulant effect through its binding and induction of allosteric changes to antithrombin III, which ultimately inhibits factors Xa and IIa (thrombin). Through the inactivation of thrombin, UFH antagonises the conversion of fibrinogen to fibrin; thus, preventing clot formation. In addition, UFH has also been shown to inactivate other clotting factors, including XIa, XIIa and IXa (Harter, Levine & Henderson, 2015; Hemker, 2016). UFH is administered as a subcutaneous (SC) injection two to three times per day at a fixed low dose when used for VTE prophylaxis and as a continuous intravenous infusion when used to treat VTE. As UFH possesses a nonlinear anticoagulant response at therapeutic doses, owing to its clearance via a saturable mechanism, strict monitoring of activated partial thromboplastin time (aPTT) for dose adjustments is recommended. Key advantages of UFH include the lack of dose adjustment required in patients with renal impairment, rapid onset of action and the lack of need for routine monitoring when used at lower doses for VTE prophylaxis (Hirsh *et al.*, 2001; Douketis, 2010; Ihaddadene & Carrier, 2016).

LMWHs, including enoxaparin and dalteparin possess shorter polysaccharide chains, lower molecular weights and are produced from UFH through fractionation or depolymerisation. From these processes, LMWHs possess structural heterogeneity and polydispersity, resulting in a more favourable pharmacodynamic and pharmacokinetic profile. When compared to UFH, they possess less nonspecific binding to proteins, improved anticoagulant predictability, higher bioavailability, better dose-response relationships, longer half-lives and less heparin induced thrombocytopenia (HIT) (Weitz, 1997; Oduah, Linhardt & Sharfstein, 2016; Qiu *et al.*, 2021). Further, LMWHs exert their anticoagulant effects in a similar manner to UFH through the inactivation of factor Xa. However, LMWHs have less effect on thrombin as compared to UFH (Brien, 2019; Padayachee, Schoeman & Schellack, 2021). Due to the enhanced pharmacokinetic profiles and safety of LMWHs, they are typically preferred over UFH in most cases where VTE prophylaxis is indicated.

Furthermore, LMWHs are administered as fixed-dose SC injections on the basis of body weight for the treatment and prophylaxis of VTE without the need for routine monitoring of anti-factor Xa levels (Harter, Levine & Henderson, 2015; Minze, Kwee & Hall, 2016; Onishi *et al.*, 2016). However, UFH still possesses other favourable characteristics, such as a rapid onset of action and simplistic reversal that are desirable in specific clinical circumstances. LMWHs possess several distinct disadvantages, including their need for dose adjustments in patients with chronic kidney disease or acute kidney injury and the finding that protamine sulphate as a reversal agent does not achieve a full reversal effect against their actions (Merli & Groce, 2010; Boonyawat & Crowther, 2015; Di Nisio, Van Es & Büller, 2016).

In addition to bleeding, HIT is also a notable adverse effect associated with both UFH and LMWHs. Further, HIT is regarded as the most clinically pertinent non-haemorrhagic adverse effect associated with heparins (Linkins, 2015; Arepally, 2017). Two types of HIT have been described in the literature, which vary in clinical significance as well as underyling pathogensis (Bailly *et al.,* 2021). Non-immune HIT is more common and causes a mild reduction in blood platelet counts, which is not considered harmful. In contrast, immune-mediated HIT is life-threatening and results in severe thrombocytopenia with the additional risk of thrombosis, which occurs in up to 50% of sufferers. HIT typically develops 5 d to 10 d following heparin exposure and is more frequently associated with UFH as opposed to LMWHs. Management of HIT is typically characterised by the discontinuation of heparin, heparin flushes and switching to an alternative anticoagulant, such as a DOAC or fondaparinux (Baroletti & Goldhaber, 2006; Joseph *et al.*, 2019; Hogan & Berger, 2020).

2.8.2.4 Fondaparinux

Fondaparinux is a synthetic pentasaccharide that possesses a chemically similar structure to that of LMWHs. Its mechanism of action occurs through antithrombin III-mediated, selective and indirect inactivation of factor Xa, without having any effect on thrombin (Brien, 2019; Osuch & Marais, 2019). Findings from the literature are suggestive of an association between HIT and minimum molecular weights and polysaccharide chain lengths, where anticoagulants with values above set parameters are more likely to result in HIT-related antigen synthesis (LaMuraglia, Houbballah & Laposata, 2012). Interestingly, fondaparinux possesses a lower molecular weight and shorter polysaccharide chain compared to other LMWHs; thus, it has demonstrated a lack of cross reactivity with the serum of patients suffering from HIT. These findings have ensured its

safety as an alternative anticoagulant agent for use in HIT sufferers (Spyropoulos, Magnuson & Koh, 2008; Leme & Sguizzatto, 2015; Linkins, Hu & Warkentin, 2018).

Fondaparinux is typically administrated via SC injection as a fixed once daily dose for the prevention of VTE. As fondaparinux possess a favourably predictable dose-response effect with limited inter- and intra-subject variability, the need for routine dose adjustments and coagulation monitoring can be disregarded. However, if coagulation testing is warranted, anti-factor Xa levels may be monitored. Despite the agent's favourable pharmacokinetic and safety profile, it is contraindicated in patients suffering from severe renal impairment, where the creatinine clearance (CrCl) is less than 30 mL/min, owing to its near complete excretion in the urine by the kidneys (Samama & Gerotziafas, 2003; Nadar *et al.*, 2009; Harter, Levine & Henderson, 2015). Although fondaparinux possesses this shortcoming, a review conducted by Turpie (2008) noted that the agent "exhibits a very positive benefit-risk ratio in the prevention of VTE in both surgical and acutely ill medical patients at risk of thrombosis". In addition, this finding has been replicated in various patient populations in other studies (Cohen *et al.*, 2006; Dempfle *et al.*, 2021).

2.8.2.5 DOACs

DOACs, which were initially referred to as new oral anticoagulants, are relatively novel anticoagulants that have been widely adopted for the prevention and treatment of venous and arterial thrombotic diseases (Barnes *et al.*, 2015; Almarshad *et al.*, 2018). DOACs are comprised of two main classes of anticoagulants: direct oral factor Xa inhibitors, which include rivaroxaban, betrixaban, edoxaban and apixaban, and direct oral thrombin inhibitors, which includes dabigatran. These agents have been increasingly preferred over vitamin K antagonists due to their more favourable safety profiles, fixed dosing without the need for intensive monitoring, rapid onset of action, shorter half-lives and lower association with drug-drug and drug-food interactions (Makam *et al.*, 2018; Chen, Stecker & Warden, 2020; Wadsworth *et al.*, 2021). Although DOACs possess favourable safety profiles, anticoagulant-associated bleeding still remains a key adverse effect to consider when prescribing these agents (Julia & James, 2017; Lavalle *et al.*, 2020). This concept is evidenced by findings from various studies (Romanelli *et al.*, 2016; Lin *et al.*, 2019), where dabigatran was found to possess a greater association with gastrointestinal bleeding compared to warfarin.

Direct oral factor Xa inhibitors, such as rivaroxaban exert their effects through the direct and reversible inhibition of factor Xa. Direct thrombin inhibitors, such as dabigatran act further downstream in the coagulation pathway, where they reversibly and selectively inhibit thrombin

(factor IIa). Further, the pharmacokinetic profiles of the various DOACs are reported to differ extensively. Therefore, clinicians should individualise and tailor therapy with these agents for each patient on the basis of comorbidities, concurrent medication use and indication (Lee, 2016; Wu *et al.*, 2020; Roberti *et al.*, 2021).

As all DOACs are renally eliminated to differing degrees, with dabigatran undergoing the most renal elimination, where this pathway accounts for 80% of its elimination. This is followed by edoxaban, rivaroxaban, apixaban and betrixaban, where 50%, 35%, 27% and 11% of each agent are renally eliminated, respectively (Yeh, Gross & Weitz, 2014; Padrini, 2019). Based on this concept, clinicians need to be aware of renal clearance alterations when prescribing these agents and are encouraged to frequently monitor renal function. Renal dose adjustments with DOACs, which include decreased frequency of administration and decreased dose, are recommended in accordance with renal function estimates using the Cockcroft-Gault CrCl equation. Furthermore, DOACs are reported to be effective and safe in patients with moderate renal impairment, where CrCl values range from 30 mL/min to 50 mL/min. Further, rivaroxaban, dabigatran and edoxaban are noted to require renal dose adjustments and are not recommended for use in patients with severe renal impairment, where CrCl values are less than 30 mL/min (Weber, Olyaei & Shatzel, 2019; Chen, Stecker & Warden, 2020; Roberti *et al.*, 2021).

Routine coagulation monitoring is not typically recommended for patients using DOACs. However, special circumstances may require coagulation testing to ensure the safety and effectiveness of the regimen. Ecarin assay and thrombin time testing may be used to assess the anticoagulant actions of dabigatran, while anti-factor Xa testing may be used to evaluate that of apixaban and rivaroxaban (Douketis, 2010; Lee, 2016).

Table 2.4 presents various anticoagulants prescribed for VTE prophylaxis in different patient populations.

Table 2.4: Anticoagulants used for VTE prophylaxis in adults and their respective properties (Ryan, 2013; Hogg & Weitz, 2017; Weitz, 2018; Witt, Clark & Vazquez, 2020).

Class	Example(s)	Monitoring	Recommended prophylactic dose	Renal dose adjustment (VTE prophylaxis)	Adverse effects	Reversal agent
Vitamin K antagonist	Warfarin	INR monitoring required, especially when initiating.	Dose individualised according to INR	Not required	Bleeding from any site on the body Bruising of the skin Skin necrosis Foetal abnormalities	Vitamin K_1
Heparins	Enoxaparin (LMWH)	No routine monitoring recommended. Anti-factor Xa can be used.	40 mg 24-hourly/ 30 mg 12-hourly	If CrCl <30 mL/min, then reduce dose to 30 mg 24-hourly	Bleeding from any site on the body Bruising of the skin HIT (less than UFH) Other thrombocytopenia Hyperkalaemia Osteoporosis	Protamine sulphate (partial activity)
	Fondaparinux*	No routine monitoring recommended. Anti-factor Xa can be used.	2.5 mg 24-hourly	Use with caution when CrCl 30–49 mL/min Avoid use when CrCl < 30 mL/min	Bleeding from any site on the body	No specific agent
	UFH	aPTT should be monitored when therapeutic doses are administered. aPTT monitoring not recommended when used for prophylaxis.	5 000 International Units 8 to 12-hourly	Not required	Bleeding from any site on the body HIT Other thrombocytopenia Hyperkalaemia Osteoporosis	Protamine sulphate
Direct Oral Factor Xa Inhibitors	Rivaroxaban	No routine monitoring recommended. Anti-factor Xa can be used.	10 mg daily for hip or knee arthroplasty	Use with caution when CrCl 30 – 49 mL/min Avoid use when CrCl < 30 mL/min	Bleeding from any site on the body Greater risk of gastrointestinal bleeding compared to warfarin Less risk of intracranial bleeding compared to warfarin Bruising of the skin Thrombocytopenia	Andexanet alfa
Direct Oral Thrombin Inhibitors	Dabigatran	No routine monitoring recommended. Ecarin assays or thrombin times can be used.	110 mg 1-4 h post-surgery; then, switch to 220 mg 24-hourly	Reduce the dose if CrCL 15–30 mL/min Avoid use when CrCl <30 mL/min	Risk of major bleeding is like that of warfarin Greater risk of gastrointestinal bleeding compared to warfarin Less risk of intracranial bleeding compared to warfarin Anaemia Allergic oedema Thrombocytopenia	Idarucizumab

*Synthetic pentasaccharide, which is chemically similar to LMWHs

VTE – Venous thromboembolism

INR – International normalized ratio

LMWH – Low molecular weight heparin

CrCl – Creatinine clearance

HIT – Heparin induced thrombocytopenia

UFH – Unfractionated heparin

aPTT – Activated partial thromboplastin time

2.8.3 Non-pharmacological thromboprophylaxis

2.8.3.1 Introduction

Non-pharmacological thromboprophylaxis comprises various mechanical methods of VTE prophylaxis. These methods function through mirroring the natural contraction of the limbs; thus, facilitating venous filling and blood flow through compression. Various forms of mechanical prophylaxis have been described in the literature, including early ambulation, IPC devices, venous foot pumps and graduated compression stockings (GCS) (Geerts *et al.*, 2008; Gaspard *et al.*, 2015; Hanison & Corbett, 2016). Mechanical methods of VTE prophylaxis confer significant and distinct benefit in their applicability of use in patients who cannot utilise anticoagulants, such as those at risk of major bleeding. Additional advantages of these modalities include the lack of need for laboratory monitoring and lack of association with any significant adverse effects (Geerts *et al.*, 2004; Caprini, 2009). However, these methods also present several disadvantages, such as the associated difficulty with their implementation and maintenance as well as patient discomfort stemming from limited movement. In addition, mechanical thromboprophylaxis is contraindicated in several circumstances, including ulceration or infection of the lower limbs, exposed fractures as well as severe arterial and cardiac insufficiencies (Leme & Sguizzatto, 2015; Weinberger & Cipolle, 2016; Flevas *et al.*, 2018).

2.8.4 Early ambulation

Early ambulation and mobilisation are regarded as the most simplistic and feasible methods of thromboprophylaxis (Sadeghi *et al.*, 2012; Bircher & Chowdhury, 2020). In addition to reducing the incidence of VTE in hospitalised patients, early ambulation is associated with numerous benefits, including shorter length of hospital stay, enhanced functional status and recovery time in postoperative patients following major surgery. Further, various VTE prophylaxis guidelines accentuate the importance of early ambulation as a core component of VTE prophylaxis regimens. Additionally, the importance of early ambulation is more pronounced in low-risk patients, where it is typically the only form of prophylaxis recommended (Cayley, 2007; Kahn *et al.*, 2012; Chindamo & Marques, 2019).

It has been reported that the majority of symptomatic VTE occurring in hospitalised patients develop following patient mobilisation. Thus, early ambulation in isolation is not considered sufficient VTE prophylaxis in hospitalised patients at moderate or higher risk of VTE (Geerts *et al.*, 2008). This concept was reflected in a systematic review conducted by Lau *et al.* (2020), who

synthesised all available literature available that supported the use of early ambulation as thromboprophylaxis among hospitalised patients. The authors included a total of 18 studies and reported that no high-quality evidence was available to indicate that early ambulation alone was effective VTE prophylaxis. Moreover, the authors noted that the incidence of VTE was lowest when ambulation was combined with pharmacological thromboprophylaxis (Lau *et al.*, 2020).

2.8.5 IPC

IPC devices comprise fabric or plastic sleeves attached to a pump that wrap around limbs and produce intermittent periods of inflation and deflation, resulting in muscle compressions. This periodic cycle of inflation and deflation are theorised to reproduce the ambulation-driven pumping action on the calf and thigh muscles. Further, these actions result in increased venous velocity and help circumvent venous stasis (Chen *et al.*, 2001; Talec, Gaujoux & Samama, 2016; Greenall & Davis, 2020). IPC devices are developed to exert pressures ranging from 35 mm Hg to 55 mm Hg with active compression cycles that last 10 s to 35 s. After each active compression cycle, a deflation interval of 1 min is actuated to allow for venous return in the limb (Kohro *et al.*, 2005; Caprini, 2009; Weinberger & Cipolle, 2016).

It has also been reported that the evidence supporting the use of IPC devices for VTE prophylaxis is more robust as compared to that of GCS (Guéroult *et al.*, 2020). Furthermore, the efficacy of IPC devices in combination with pharmacological thromboprophylaxis have been demonstrated in various studies, including a Cochrane systematic review, which was conducted by Kakkos *et al.* (2016) and a meta-analysis that was conducted by Fan *et al.* (2020). However, this benefit has only been established in surgical patients due to the lack of studies evaluating their efficacy in medical inpatients (Holleck & Gunderson, 2019).

2.8.6 Venous foot pumps

Venous foot pumps are similar to IPC devices in their underlying mechanism of action. However, their exertion of intermittent compressions is applied to the plantar venous plexus, which is located in the feet. The reduced compressibility of the foot muscles results in increased pressure requirements as compared to those of the calf muscles. The resultant consequence of this added compression amplifies the discomfort and pain when applying venous foot pumps, which is reported to lead to poor adherence (Charalambous *et al.*, 2003; Anand & Asumu, 2007; Bircher & Chowdhury, 2020). Furthermore, the efficacy of venous foot pumps in clinical practice settings has also been debated. A randomised controlled trial, conducted by Sakai *et al.* (2016) revealed

that the A-V Impulse System foot pump did not reduce the incidence of DVT when used in conjunction with pharmacological thromboprophylaxis in patients undergoing total knee arthroplasty. Further, several VTE prophylaxis guidelines do not make any specific mention regarding their use (Jacobson *et al.*, 2013; Al-Hameed *et al.*, 2016; Liew *et al.*, 2017).

2.8.7 GCS

GCS have been shown to exert a graded circumferential pressure that extends from the distal region to the proximal region of the lower limbs to which they are applied. The resultant effect of this pressure is increased venous flow velocity toward the heart, reduced diameter of veins and increased venous return from the applicable extremities. Venous velocity is correlated with the pressure profile exerted by the specific GCS, where the standard pressure profile of 8 mm Hg at the thigh, 14 mm Hg at the calf and 18 mm Hg at the ankle are described as the optimal pressure profiles (Caprini, 2009; Lim & Davies, 2014; Weinberger & Cipolle, 2016). The efficacy of GCS in preventing DVT is considered to be sufficient and is recommended as an alternative to pharmacological prophylaxis in select patients by various national and international guidelines (Jacobson *et al.*, 2013; Schünemann *et al.*, 2018; National Institute for Health and Care Excellence., 2019). This efficacy has also been demonstrated in a Cochrane systematic review, which evaluated the safety and efficacy of GCS in preventing VTE in hospitalised patients. The investigators pooled data from 20 randomised controlled trials and found that the incidence of DVT was 9% in the GCS group as compared to 21% in the control group, who did not have GCS as part of their regimen. Further, it should be noted that only one of the trials included medical inpatients in their cohort. Therefore, the investigators concluded that high-quality evidence indicated that GCS was effective at reducing DVT in surgical patients with or without other forms of thromboprophylaxis. However, they described a paucity of data surrounding the use of GCS in medical inpatients (Sachdeva, Dalton & Lees, 2018).

2.9 Summary

In summary, VTE is a serious and life-threatening condition with the potential to result in long-term sequelae. VTE RAMs offer an efficacious, simplistic, and cost-effective approach to VTE risk stratification in various patient populations, including hospitalised medical patients. Furthermore, VTE RAMs may be correlated with specific VTE prophylaxis regimens, such as pharmacological and non-pharmacological methods with established efficacy, safety, and cost-effectiveness. Yet, a gap was identified in the literature concerning the uptake and use of these

tools as well appropriate thromboprophylaxis prescribing in hospitalised medical patients, particularly in SA. Thus, findings from this literature review were indicative of the need to further explore and describe these aspects of practice in SA. The chapter that follows provides an overview of the methodology employed in the execution of this current study.

CHAPTER 3: METHODOLOGY

3.1 Introduction

This chapter provides an overview of the methodology employed in the execution of this study. It begins with a description of the study design, study sites as well as the study population and sampling procedures used. A description of the data collection tool used as well as the measures employed to ensure validity and reliability of the data collection tool follows. This is followed by a detailed description of the data collection process and data analysis procedures that were conducted. An overview of the ethical considerations relating to the study and the dissemination of study findings conclude the chapter.

3.2 Study design

The study comprised a quantitative, observational, descriptive, exploratory cross-sectional design. This design was used to conduct a retrospective medical folder review in public sector hospitals in the Cape Town Metropolitan district of SA's Western Cape province. A quantitative research approach is reported to be associated with rigorous quality criteria, including reliability, internal validity, and generalisability, which may afford more robust findings (Williams, 2007; Wisdom *et al.*, 2012; Daniel, 2016). Moreover, this approach emphasises objective measurement and statistical analysis of data to achieve study outcomes, which reduces the time and resources required for study implementation (Williams, 2007; Daniel, 2016; Boeren, 2018). Therefore, a quantitative approach was used in this study due to its association with robust findings and reduced time and resources required for implementation.

Observational studies are characterised by the examination of naturally occurring relationships between exposures and outcomes. Further, observational studies do not lend themselves to methods that influence study participants or their environments through intervention or manipulation. Observational studies may be classified as being descriptive, where the aim of the study is to describe the current distribution of one or more variables, without regard for any causal or alternative hypothesis (Grimes & Schulz, 2002; Thiese, 2014; Aggarwal & Ranganathan, 2018). Grimes and Schulz (2002) expound descriptive studies further through expressing their 'important roles' in clinical research and their significance in prompting more rigorous research into specific areas of study. Descriptive studies are distinguished by several advantages, including ease and low cost associated with their implementation as well as their ability to identify temporal and/or geographic variations of variables (Ranganathan & Aggarwal, 2018). Based on the

aforementioned advantages, an observational descriptive approach was selected for use in this study.

An exploratory research approach is distinct in its effectiveness at investigating phenomena, where a substantial amount of uncertainty is evident. This includes phenomena which have not been thoroughly investigated, as well as instances where gaps in the literature are apparent (Jaeger & Halliday, 1998; Mainardes, Alves & Raposo, 2010; Colaço, 2018). Thus, this approach was employed in this study due to the apparent lack of information on the study topic as described in the literature.

Cross-sectional study designs have the capacity to allow for the collection of information concerning individual characteristics together with key outcomes. Therefore, cross-sectional study designs are considered to provide a 'snapshot' of an outcome and associated characteristics at a particular point in time (Levin, 2006; Aggarwal & Ranganathan, 2018; Wang & Cheng, 2020). A cross-sectional study design was selected as it offered several distinct advantages, including swift execution without significant expense, the ability to assess multiple outcomes and its usefulness in informing monitoring and evaluation as well as public health development planning. In addition, cross-sectional studies possess a unique practicality for determining optimal techniques for the identification of associations. Thus, cross-sectional studies typically serve as the foundation upon which more rigorous, in-depth studies, such as randomised controlled trials can be based (Grimes & Schulz, 2002; Mann, 2003; Thiese, 2014; Setia, 2016; Wang & Cheng, 2020). A cross-sectional design was used in the implementation of this study after considering the benefits associated with this type of design as well as its distinct ability to measure an outcome at a single point in time.

3.3 Study sites

The study was conducted at three public sector hospitals in the Cape Town Metropolitan health district in SA's Western Cape province. The SA public healthcare system, which includes hospitals and primary healthcare (PHC) facilities, is funded by the state and provides essential health services to the majority of the South African population at no cost (Coovadia *et al.*, 2009; Schellack *et al.*, 2011). The facilities included two district hospitals, which comprised Eerste River and Karl Bremer and a regional hospital, which comprised New Somerset Hospital. Figure 3.1 shows a map of the Cape Town Metropolitan health sub-districts and the public hospitals located in each sub-district.

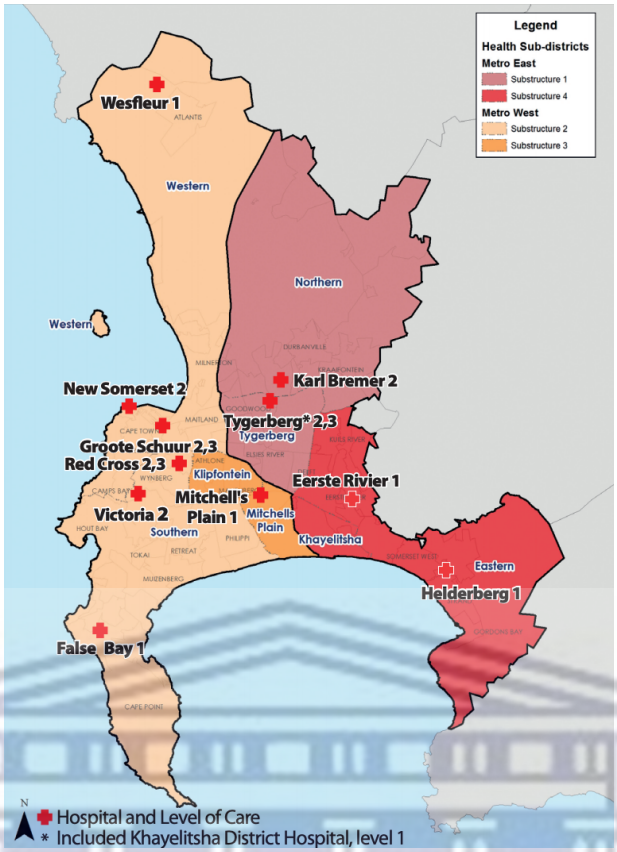

Figure 3.1: Map of public hospitals and health sub-districts in the Cape Town Metropolitan health district (Westwood, Levin & Hageman, 2012).

For the purpose of clarity, each of the participating hospitals are outlined according to their facility categories below.

District hospitals

Both Eerste River and Karl Bremer hospitals are categorised as 'district hospitals', which typically serve as primary-level referral hospitals (Jamison *et al.*, 2006; Madale *et al.*, 2011). The National Health Act 63 of 2003 stipulates that district hospitals must provide healthcare services to a defined population, which is located within a specific health district. Furthermore, district hospitals are required to provide support to and receive referrals from PHC facilities (Republic of South Africa, 2012).

Eerste River Hospital serves the Tygerberg Western Health sub-district of the City of Cape Town Metropolitan district (Madale *et al.*, 2011; Western Cape Government, 2020). The hospital, which contains 101 beds, can be considered a small district hospital in accordance with the classifications stipulated by Act 63 of 2003 (Madale *et al.*, 2011; Republic of South Africa, 2012).

Karl Bremer Hospital serves the Tygerberg Eastern Health sub-district of the City of Cape Town Metropolitan district (Bhikoo *et al.*, 2017; Western Cape Government, 2021a). The hospital

contains 310 beds; therefore, it is considered a medium-sized district hospital according to the classifications stipulated by Act 63 of 2003 (Madale *et al.*, 2011; Republic of South Africa, 2012).

Regional hospital

New Somerset Hospital is characterised as a regional hospital and can thus be regarded as secondary-level referral hospital (Jamison *et al.*, 2006; Western Cape Government, 2021b). Act 63 of 2003 specifies that regional hospitals must provide healthcare services, including specialised services to a defined regional drainage population in the relevant demarcated provincial boundaries. In addition, it is compulsory for regional hospitals to receive referrals from and support district hospitals (Republic of South Africa, 2012). New Somerset Hospital, which has approximately 330 beds, operates in the Cape Town Central district of the City of Cape Town Metropolitan district (Naidu, 2020).

The three participating hospitals were selected through the use of a convenience sampling approach. This sampling approach is characterised by the selection of a study sample on the basis of ease of access and convenience (Panacek & Thompson, 2007; Elfil & Negida, 2017; Turner, 2020). This sampling approach was employed in this study due to its association with low cost, rapid execution, and convenience. Thus, the first facilities to respond to the recruitment notice to participate in the study were selected due to availability and convenience.

3.4 Study population and sampling

This section provides an overview of the study population and the sampling approach used for population sampling in the study.

3.4.1 Study population

The study population included all adult medically ill inpatients (≥ 18 years) who were hospitalised in general medical wards in public sector hospitals in the SA's Western Cape province. The SA public healthcare sector typically serves patients from poor socioeconomic backgrounds who cannot afford private medical insurance. Moreover, the majority of these patients are black Africans that were historically disadvantaged due to spatial regulations established by the previous apartheid system (Naidoo, 2012; Maseko & Harris, 2018; Malakoane *et al.*, 2020). Further, a high dual burden of HIV and TB are reported to be prominent in this SA patient population (Coovadia *et al.*, 2009; Karim *et al.*, 2009).

3.4.2 Inclusion and exclusion criteria

The medical folders of these patients were only included in the retrospective review if they were admitted between 01 January and 31 July 2020. This allowed for the collection of data that could reflect contemporary trends in VTE risk assessment and prophylaxis practices during a set time period.

The aforementioned inclusion criteria, which stipulated that only adult patients (≥ 18 years) were to be included in the study were based on literature findings. These findings suggest that the risk of VTE in hospitalised paediatric patients is significantly lower than that of adults (Raffini *et al.*, 2011; Branchford *et al.*, 2012; Meier *et al.*, 2015; Rühle & Stoll, 2018). Thus, routine VTE prophylaxis, especially with pharmacologic therapy, is only recommended for use in specific high-risk paediatric individuals (Raffini *et al.*, 2011; Faustino & Raffini, 2017; Witmer & Takemoto, 2017; Newall, Branchford & Male, 2018; Jinks & Arana, 2019).

Patients requiring anticoagulation therapy for confirmed or suspected venous thromboembolic disease, atrial fibrillation, acute coronary syndromes, or any other indication besides VTE prophylaxis were excluded. The exclusion criteria were developed in accordance with the study's aim as well with standardised VTE thromboprophylaxis recommendations from the literature and various national and international guidelines (Jacobson *et al.*, 2013; Pai *et al.*, 2013; Liew *et al.*, 2017; Kahn *et al.*, 2018; Schünemann *et al.*, 2018; Brenner *et al.*, 2019; National Department of Health, 2019; National Institute for Health and Care Excellence., 2019; Yap *et al.*, 2019).

3.4.3 Sample selection

To achieve an adequate sample size for the study, a minimum of 377 medical folders needed to be reviewed retrospectively. This was based on a population proportion of 57.1% and a two-sided confidence interval of 95% with a ± 5% margin of error. The estimated risk of VTE in hospitalised medical patients in SA was reported to be 57.1%. This statistic was used as the population proportion as it simulated the risk of VTE in hospitalised medical patients in SA as described in the literature (Wessels and Riback, 2012).

To compensate for missing information, the sample size was increased by 15% per facility, which equated to a total of 434 medical folders for selection across the three facilities. Therefore, 145 medical folders were to be accessed at each of the three participating facilities and a minimum

of 126 needed to be included in the review to achieve an adequate sample size. Sample size was calculated using this equation:

$$n = \frac{Z^2 * P^2(1 - P^2)}{d^2}$$

Where *n* is the sample size, *Z* the statistic corresponding to confidence interval set (standard normal variate), *P* the population proportion, which is based on previous studies, and *d* the absolute error, which corresponds to the effect size.

This equation was selected as literature findings typically recommend its use in descriptive cross-sectional studies, which base their measurement on a pre-study population proportion (Eng, 2003; Charan & Biswas, 2013; Pourhoseingholi, Vahedi & Rahimzadeh, 2013; Wang & Ji, 2020).

3.4.4 Sample selection process

The initial step of the sampling process involved the acquisition of a list of patient admissions to medical wards at each participating facility during the pre-defined admission period, which was ranged from 01 January to 31 July 2020. This was achieved through accessing each facility's electronic Continuity of Care Record (eCCR) and generating a list of patient medical folder numbers from the admissions list. This step was preceded by the randomisation of the list of patient medical folder numbers using the randomisation or RAND function on Microsoft® Office Excel (Microsoft, US) 2016.

Following randomisation, a systematic random sampling approach was implemented, where medical folder numbers were selected at fixed, periodic intervals from the list. Systematic random sampling was employed due to its unique advantages, where the approach ensures that sampling is spread more uniformly across a study population and its association with a more pragmatic method of drawing a sample in comparison to a simple random sampling approach (Panacek & Thompson, 2007; Mostafa & Ahmad, 2018; Taherdoost, 2018a; Turner, 2020). Lastly, the selected medical folder numbers were used to access the corresponding physical folders from the records department at each participating hospital from which data was collected with a data collection tool.

3.5 Data collection tool

The data collection tool (Appendix A) utilised was developed for use in this specific study after a review of the available literature. The data collection tool was developed online using Google Forms® as the online platform as this would ease both the data collection and data capturing processes. The tool is comprised of four main sections: Demographics, VTE risk assessment, thromboprophylaxis use during admission and thromboprophylaxis-related safety considerations.

The VTE risk assessment section was based on the validated 2013 version of the Caprini RAM described by Cronin *et al.* (2019). Further, the tool incorporates the same point-based risk scoring and risk categorisation strategy employed by the Caprini RAM (Cronin *et al.*, 2019).

Following the tool's development, an onsite medical practitioner/researcher employed at one of the participating facilities reviewed the tool for suitability and ease of use. After this step, both study supervisors reviewed the tool before the commencement of the pilot study.

The pilot study was conducted with the purpose of refining the data collection tool and providing insight into the feasibility of the study. The pilot study allowed for the evaluation of both the time taken to complete a medical folder review as well as the availability and location of various sets of pertinent information in the medical folders. The data collection tool was piloted at New Somerset Hospital over a one-day period, where a total of 10 medical folders were reviewed retrospectively. The data obtained from the pilot study was not included in the final sample as the medical folder numbers were excluded. Upon completing the pilot study, the data collection tool was amended as necessary in consultation with both study supervisors. This step was characterised by the final refinement of the data collection tool prior to the commencement of data collection. All amendments to the tool were finalised with the use of Google Forms®.

3.6 Validity and reliability of the data collection tool

To ensure robust results in research, consideration should be given to the rigor of data collection tools (Sullivan, 2011; Heale & Twycross, 2015). In quantitative research, adequate rigor of data collection tools can be achieved through optimisation of validity and reliability (Heale & Twycross, 2015). Heale & Twycross (2015) define validity broadly as "the extent to which a concept is accurately measured in a quantitative study". Whilst reliability is defined as the degree to which results obtained can be replicated (Taherdoost, 2018b).

Further, the broad term 'validity' can be further divided into internal validity and external validity (Bolarinwa, 2015). Internal validity refers to the extent to which observed results provide a true representation in the sample population and are not caused by methodological error. External validity describes how accurately the observed results from the study sample can be generalised to the study population (Bolarinwa, 2015; Patino & Ferreira, 2018). Several sub-categories of internal validity are described in the literature, including construct validity, content validity, face validity and criterion validity (Heale & Twycross, 2015).

Content validity describes the degree to which a data collection tool accurately measures all features of a variable (Heale & Twycross, 2015). In this study, content validity was optimised

through firm adherence to the overall study objectives. Only pertinent sections adhering to the criteria which they were intended to measure and those adapted from similar studies were included in the data collection tool (Lloyd *et al.*, 2012; Dentali *et al.*, 2014; Wallace *et al.*, 2017; Badinella Martini *et al.*, 2020; Frenette *et al.*, 2020). Moreover, the data collection tool included an adapted form of the validated 2013 Caprini RAM (Cronin *et al.*, 2019). Various studies have demonstrated and reported on the validity of the Caprini RAM, which has undergone external validation, in assessing VTE risk in medically ill inpatients (Liu *et al.*, 2016; Luo & Zhang, 2017; Chen *et al.*, 2018; Zhou *et al.*, 2018; Chamoun *et al.*, 2019; Cronin *et al.*, 2019; Wang *et al.*, 2019; Zhai *et al.*, 2019; Van der Merwe, Julyan and Du Plessis, 2020). Validation and follow-up reviews of the data collection tool were conducted in conjunction with study supervisors and an onsite medical practitioner/researcher at one of the participating facilities. Thus, content validity was established through firm adherence to study objectives, adaption of pertinent sections from the literature and expert validation (Sullivan, 2011; Taherdoost, 2018b).

Face validity refers to the subjective assessment of the operationalisation of a construct by experts (Sullivan, 2011; Taherdoost, 2018b). This form of validity was established through the piloting of the data collection tool on a small sample of study subjects that were representative of the study population. This allowed the data collection tool to be further refined prior to data collection. Only data obtained from the data collection tool was analysed and reported on; therefore, no external data was included in the analysis. To ensure accuracy, all data collected was reviewed by the investigator to detect errors. All errors identified were reviewed and discussed with study supervisors to ensure that they were ameliorated.

3.7 Data collection process

Data collection was undertaken by the researcher after ethics approval was granted and permission to conduct the study was attained from the relevant authorities. Data was collected over a period of five weeks between December 2020 and January 2021. Data was collected over a two-week period at both New Somerset and Karl Bremer hospitals, respectively. However, data collection occurred more rapidly at Eerste River Hospital in January 2021, where it took place over a one-week period. Potential explanations for this include the lack of public holidays and greater staff availability during the period in which data was collected at Eerste River Hospital.

The initial step of the data collection process involved consulting with each participating facility's medical records department to obtain the relevant eCCR records and allow for access to the pertinent medical folders. Following this step, data was collected retrospectively from the

relevant medical folders using the pre-designed and pre-piloted data collection tool. The data collection tool was completed via Google Forms® through the use of a mobile phone. Medical practitioner clinical notes, nursing care notes, inpatient prescription charts and other documents available in medical folders were reviewed to gather data. Only medical folders of patients who met inclusion criteria were included in the study.

3.8 Data entry and analysis

Data was captured online via the data collection tool, which was developed in Google Forms®. Captured data was transferred to Google Sheets® and then exported as a Microsoft® Office Excel (Microsoft, US) 2016 spreadsheet. The data set was reviewed and cleaned to ensure that no duplicate or missing data was evident. Following this step, the cleaned data was exported to IBM Statistical Package for Social Sciences (SPSS) Statistics version 23.0 for Windows (IBM Corp., 2015), from which statistical analysis were performed. As this study encompassed the collection of quantitative, descriptive observational data, all data was analysed using descriptive statistics. Categorical variables, such as VTE risk factors were expressed as percentages, proportions, and frequency counts. Continuous variables, including age were presented as means, standard deviations as well as minimum and maximum values. All data collected from this study was analysed using the program IBM SPSS Statistics version 23.0 for Windows (IBM Corp., 2015), while Microsoft® Office Excel 2016 was utilised to assist with data cleaning and general calculations.

3.9 Ethical considerations

This section presents the various ethical considerations as well as the funding information related to the study.

3.9.1 Permission

Permission to conduct the study was sought and obtained from the University of the Western Cape (UWC) Biomedical Research Ethics Committee (Appendix B, ref: BM20/5/9) and from the Health Research Committee from the Western Cape Government Health department (ref: WC_202007_013). Following this, permission to conduct the study was requested and obtained from each participating hospital's facility manager through the National Health Research Database (Appendices C, D and E).

In addition, the researcher ensured that this study was conducted in full conformity with the current revision of the Declaration of Helsinki, or with the International Conference for Harmonisation Good Clinical Practice regulations and guidelines, whichever afforded the greater level of protection to the study participant at the time (Vijayananthan & Nawawi, 2008; World Medical Association, 2013).

3.9.2 Informed consent

Informed consent from patients was not required for this study as data was gathered retrospectively from medical folders. Authorisation for access to medical folders was granted by the UWC Biomedical Research Ethics Committee (Appendix B, ref: BM20/5/9) and the Health Research Committee from the Western Cape Government Health department (ref: WC_202007_013).

3.9.3 Anonymity

Data collected from medical folders with the use of the data collection tool (see Appendix A) did not include any personal details nor identifiers of the patients or the facilities to which they were admitted. Therefore, it was not possible to link any extracted data to patient identity, nor disclose this information. This also ensured that no information could be traced to any of the participating facilities. Thus, patient and facility anonymity were ensured through the lack of collection of personal patient details and identifiers from medical folders. In addition, patient anonymity was safeguarded, in line with the National Health Act 61 of 2003 (Republic of South Africa, 2004).

3.9.4 Confidentiality

The confidentiality of information regarding patients whose medical folders were included in the retrospective review was ensured throughout data collection and analysis. The researcher ensured that the linkage of data to a specific patient's identify was not possible and that the data was unidentifiable following data collection. All electronically stored data from the medical folders was secured through password protection.

3.9.5 Funding

No sources of funding were used to finance this study.

3.10 Disseminating findings

Data and findings from this study could be converted to a format to allow for publication. A presentation could be given to the Western Cape Government health department, where study

findings and data may be shared with relevant stakeholders. In addition, data from this study could be further disseminated through presentations at both national and international conferences.

3.11 Summary

In this chapter the methodology and ethical considerations for this study were expanded upon. The chapter that follows will provide the results and key findings of the study in the form of a published manuscript.

CHAPTER 4: RESULTS

4.1 Introduction

This chapter presents the study's results in the form of a published manuscript. The manuscript was submitted to and accepted for publication in the *South African Medical Journal*, which is a peer-reviewed journal. Statements concerning the roles of the supervisor, co-supervisor, and investigator in the authoring of the manuscript as well as author guidelines from the pertinent journal are included as appendices (see Appendices F and G). Following the published manuscript, a note is presented concerning additional results of the study, which were not included in the published manuscript. A brief summary concludes the chapter.

4.2 Published manuscript

The manuscript presented in this section was prepared and submitted to the *South African Medical Journal* on 16 August 2021 (reference number: SAMJ16040). The manuscript was accepted for publication in the journal on 18 October 2021 (See Appendix H). References are included in the results section as part of the original accepted manuscript.

Venous Thromboembolism Risk Assessment and Prophylaxis in Hospitalised Medical Patients in the Cape Town Metropole, South Africa

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Background: Venous thromboembolism (VTE) is regarded as the most preventable cause of inpatient death in hospital settings globally. VTE can be prevented through the provision of non-pharmacological and/or pharmacological thromboprophylaxis following individualised risk screening. The Caprini risk assessment model (RAM) offers a validated and well-established approach for VTE risk assessment in medical inpatients. Literature findings describe a trend towards inappropriate and under-prescribing of thromboprophylaxis in this population. Together

with concerns regarding clinicians' perceived importance of VTE risk assessment, the need to clarify these aspects of practice is evident.

Objective: To describe VTE risk assessment and prophylaxis practices of medical practitioners in public sector hospitals in the Western Cape province of South Africa.

Methods: A retrospective, cross-sectional study design was employed in the medical wards of two district hospitals and one regional hospital in the Cape Town Metropole in the Western Cape province of South Africa. Medical folders of adult medical inpatients who were admitted between January 2020 and July 2020 were reviewed to assess VTE risk using the Caprini RAM. Thromboprophylaxis therapy prescribed and contraindications to chemoprophylaxis were also evaluated.

Results: Three-hundred and eighty patients were included in the review, of which 52% were female and the average age was 52 years (range 18 – 96). Twenty-one percent of patients had their weight recorded, whilst none had their height documented. Infectious disease was the predominant diagnosis (49.2%) detected in the sample. Common VTE risk factors identified included being at bed rest/ restricted mobility for <72 hours (76.3%) and serious infection (67.4%). A total of 97.1% (n=369) of patients were found to be at moderate or higher risk of VTE (Caprini score ≥2). Of this at-risk group, 24% were eligible to receive chemoprophylaxis, yet no prescription for thromboprophylaxis was identified. Seventy percent (n=266) of patients were prescribed chemoprophylaxis, with enoxaparin accounting for 98.5% of regimens. Contraindications to chemoprophylaxis were recorded in 13.4% of patients.

Conclusion: Although rates of VTE prophylaxis in medical inpatients may be improving, thromboprophylaxis still remains critically underutilised in this population. This study highlighted a consequence of this trend, with inappropriate chemoprophylaxis prescribing becoming more evident. Mechanical prophylaxis prescribing in medical inpatients is lacking, despite the associated benefits. RAMs should be adapted for the South African setting, where infectious diseases are prevalent. Future research should assess RAM use by clinicians as this could provide insight into improving RAM uptake and thromboprophylaxis prescribing.

Background

Venous thromboembolism (VTE) is a preventable and potentially life-threatening disease that frequently complicates the admission of hospitalised patients. VTE can manifest as either deep vein thrombosis (DVT) and/or pulmonary embolism (PE), which are both associated with increased morbidity and mortality. PE as a complication of VTE, is the most preventable cause of

inpatient death across the globe.[1,2] VTE is linked to increased healthcare costs, intensive care unit (ICU) admission and longer hospital stay.[3]

Findings from the multinational ENDORSE (Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting) study revealed that more than half of all hospitalised patients were at risk for VTE, and 41.5% of these were medical inpatients.[4] A multinational, cross-sectional survey conducted across five countries in sub-Saharan Africa (SSA) found that a greater proportion of medical inpatients were at-risk for VTE (62.3%) as compared to 43.8% of surgical patients.[5]

In South Africa (SA), studies aimed at assessing VTE risk are limited, which has led to paucity of VTE-related data in the South African population.[6,7] This lack of data extends across both the private and public healthcare sectors.[2,3] The SA-based TUNE-IN (The Use of VTE prophylaxis in relation to patiEnt risk profiling) study aimed to assess VTE prophylaxis use in hospitalised patients in relation to their risk profile. The authors reported a 67.1% risk of VTE in medical inpatients admitted to private healthcare sector hospitals across the Gauteng province of SA.[8]

VTE can be prevented through the provision of appropriate non-pharmacological and/or pharmacological prophylaxis following individualised patient screening with a structured risk assessment model (RAM) or through clinical evaluation.[3,9] The Caprini RAM offers a simplistic and comprehensive approach to VTE risk assessment in both surgical and medical inpatients.[1-3] Further, it has undergone several modifications since its founding in 1991 and has been validated in more than 250 000 patients in over 100 trials worldwide.[1] The Caprini RAM's development was based upon the implementation of the American College of Chest Physicians (ACCP) thromboprophylaxis guidelines, which are one of the leading VTE prophylaxis guidelines worldwide.[3] The therapeutic practice guideline for VTE developed by the Southern African Society of Thrombosis and Haemostasis closely mirrors the ACCP guideline, which bases VTE risk assessment on the Caprini RAM.[2,9]

SA has one of the greatest dual burdens of Mycobacterium tuberculosis (TB) and HIV infection globally and both infections possess well-established relationships with VTE development.[7] In SA, TB was reported to be the leading cause of death in 2017 and disruptions in TB-related care due to the COVID-19 pandemic have been reported.[10] SA has the largest HIV epidemic globally, where 19% of all persons infected with virus reside in the country.[11] TB and HIV are prominent VTE risk factors that are frequently overlooked in the South African setting and their impact is not well known.[12] A prospective cohort study conducted at Charlotte Maxeke

Johannesburg Academic Hospital aimed to investigate VTE's association with TB and HIV. The authors found that 53.0% and 21.2% of patients presenting with DVT were infected with HIV and TB, respectively.[7]

Low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) have proven to be safe, effective and cost-effective agents for VTE prophylaxis in medical inpatients.[12] Mechanical thromboprophylaxis, including intermittent pneumatic compression (IPC) and graduated compression stockings (GCS), are advocated for use in patients who possess contraindications to anticoagulants. [9,13]

Despite growing evidence supporting VTE risk assessment and thromboprophylaxis in medical inpatients, inappropriate and under-prescribing of thromboprophylaxis is evident.[4,14] The multinational survey conducted by Kingue *et al*.[5] found that only 36.2% of medical inpatients who were at-risk for VTE received prophylaxis.[5] In SA, a study investigating thromboprophylaxis in a private hospital group, which included 373 020 patients, found that less than 25% of at-risk patients received guideline appropriate interventions.[3]

In SA's public healthcare sector, a lack of adequate data regarding VTE risk assessment and prophylaxis practices in medical inpatients has been reported.[6] This, together with the low rate of adherence to VTE clinical practice guidelines accentuates the need to clarify these aspects of practice.[4] Therefore, the objective of this study was to describe the VTE risk assessment and prophylaxis practices of medical practitioners in public sector hospitals in the Cape Town Metropole of South Africa.

Methods

A quantitative, observational, descriptive, exploratory cross-sectional design was employed in this study. Quantitative data was retrospectively retrieved from patient medical folders in the medical wards of three public sector hospitals (two district hospitals and one regional hospital) within the Cape Town Metropole.

Only folders of adult (≥18 years) medical inpatients who were admitted to medical wards between January 2020 and July 2020 were included in the study. Patients younger than 18 years, surgical patients and those who required therapeutic anticoagulation for confirmed or suspected VTE, atrial fibrillation, acute coronary syndromes, or any other reason besides VTE prophylaxis were excluded from the study.

The estimated proportion of medical inpatients with VTE in SA was reported to be 57.1%.[8] Using this proportion and a two-sided confidence interval of 95% with a ± 5% margin of error, a

minimum of 377 medical folders needed to be reviewed to achieve an adequate sample size. Length of hospital stay for each patient was calculated in units of 24 hours and reported in days.[15] Convenience sampling was used to recruit hospitals for inclusion in the study, where the first hospitals to respond to the recruitment notice were selected. Patient medical folders were selected using random systematic selection. This was achieved through the randomisation of a list of medical folder numbers obtained from each facility's electronic Continuity of Care Record (eCCR). Patient medical folder numbers were then selected at fixed, periodic intervals from this list, prior to being accessed at each participating hospital.

Data was manually extracted from medical folders with the use of a predesigned data collection tool, which included an updated version of the Caprini RAM.[1] Prior to data collection, the tool was piloted to further inform and refine its design. Patients' individual VTE risk factors were documented, followed by the calculation of their VTE risk score and subsequent VTE risk categorisation according to the Caprini RAM. Inpatient prescription charts were also evaluated to compare thromboprophylaxis prescribed with that recommended by the Caprini RAM. Additional data collected included basic demographic information. Data was then exported to a structured Microsoft Office Excel© (Microsoft, USA) spreadsheet, from which analyses were performed.

Descriptive statistics were used to summarise data in the form of percentages and proportions. The Student's *t*-test was used to draw comparisons between means for gender differences in terms age, weight, height and Caprini VTE risk scores. P-values <0.05 were regarded as significant.

Ethical considerations

Approval to conduct the study was granted by the University of the Western Cape's Biomedical Research Ethics Committee (BM20/5/9) and the Western Cape Government Health (WC_202007_013). Informed consent from patients were not required by the applicable ethics committees as the study was retrospective, lacked direct patient contact and data was anonymised prior to analysis.

Results

The review included 435 medical folders, which were randomly selected from 4884 medical admissions that were registered on the eCCR database during the 7-month data collection period. Of these, 380 were included in the final sample of the study. Forty-one medical folders were

excluded as they did not meet inclusion criteria and 14 folders were excluded due to missing information.

The patient sample consisted of more females (52%) than males (48%), with an overall mean age of 52 years (Table 1). No significant difference between the mean age of males and females was detected in the sample (p=0.25).

Table 1. Demographics of the study population (N=380)

Gender	Number of patients, n (%)	Age 18–30 years (%)	Age 31–40 years (%)	Age 41–60 years (%)	Age 61–74 years (%)	Age ≥ 75 (%)	Mean age, years	Standard deviation	Minimum age, years	Maximum age, years	Median age, years
Female	196 (52)	39 (10.3)	34 (8.9)	54 (14.2)	38 (10)	31 (8.2)	53.1	18.0	18	96	55
Male	184 (48)	19 (5)	42 (11.1)	69 (18.2)	43 (11.3)	11 (2.9)	51.0	15.3	19	84	52
Total	380 (100)	58 (15.3)	76 (20.0)	123 (32.4)	81 (21.3)	42 (11.1)	52.1	16.8	18	96	54

Only 81 patients (21%) had a documented weight, but not one record of patient height was documented, thus body mass index (BMI) could not be calculated. Out of these 81 patients, no statistically significant difference between the mean documented weights were detected between males and females (p=0.94). The average length of stay was calculated at 5.9 (range 1 - 35) days, with more than 80% of patients hospitalised for ≥3 days.

Approximately a quarter of the patients had been hospitalised within three months prior to admission (24%). Evidence of recent hospitalisation (≤ 90 days) is shown in Figure 1.

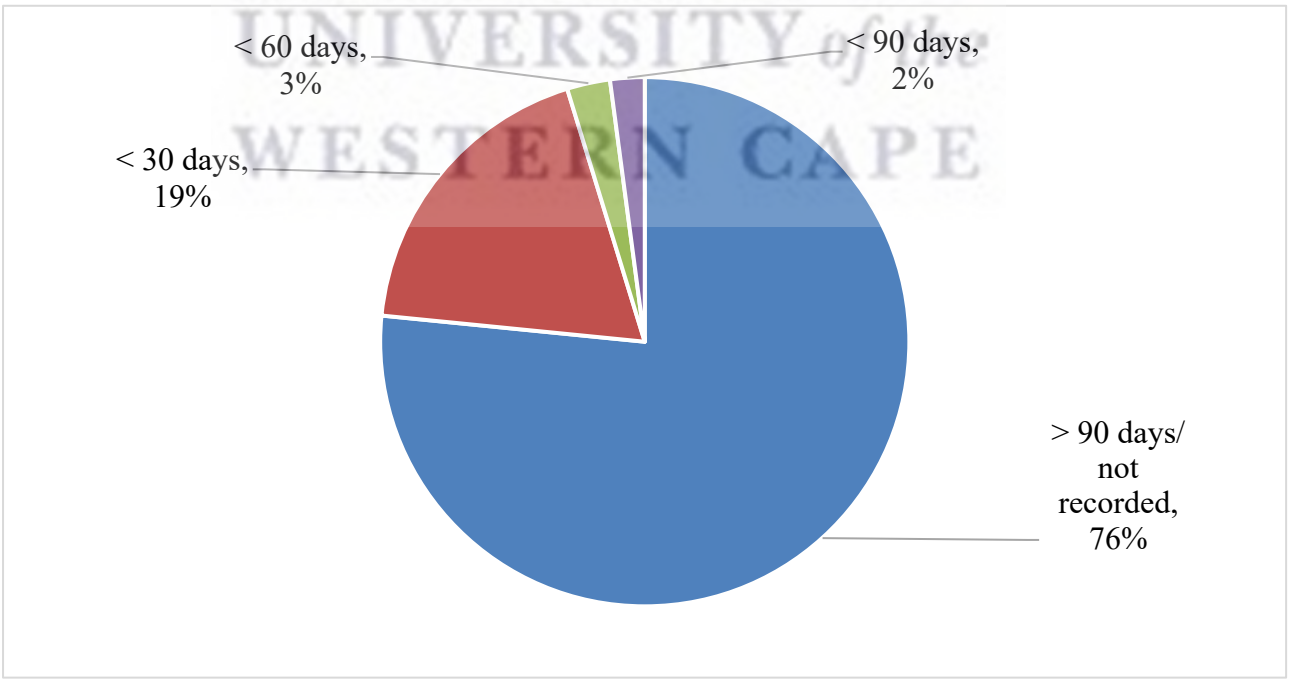

Fig. 1. Proportion of total sample by previous hospitalisation (N=380).

The most frequently documented diagnosis was infectious disease (49.2%). This was followed by neurological disease, which accounted for 14.5% of the total sample. Various forms of TB as well as polymerase chain reaction (PCR) test positive and clinically diagnosed/ highly suspected COVID-19 infections accounted for 17.7% and 11.8% of the sample, respectively. Table 2 provides an overview of the diagnoses identified among sampled patients.

Table 2: Diagnosis (N=380).

Primary diagnosis	Number of patients (% of patients)
Infectious disease	**187 (49.2)**
Clinically diagnosed/ highly suspected COVID-19 infection*	7 (1.8)
Community acquired pneumonia	22 (5.8)
Disseminated TB	20 (5.3)
PCR test positive COVID-19 infection	38 (10.0)
Pulmonary TB	42 (11.1)
TB meningitis	5 (1.3)
Unspecified lower respiratory tract infection	5 (1.3)
Urinary tract infection	20 (5.3)
Other infectious diseases	28 (7.4)
Neurological disease	**55 (14.5)**
Epilepsy	9 (2.4)
Ischaemic stroke	21 (5.5)
Unspecified stroke	5 (1.3)
Other neurological diseases	20 (5.3)
Gastrointestinal/hepatobiliary disease	**35 (9.2)**
Acute gastroenteritis	20 (5.3)
Other gastrointestinal/ hepatobiliary diseases	15 (4.0)
Cardiovascular disease	**27 (7.1)**
Acute decompensated heart failure	22 (5.8)
Other cardiovascular diseases	5 (1.3)
Pulmonary disease	**26 (6.8)**
Acute exacerbation of COPD	20 (5.3)
Other pulmonary diseases	6 (1.6)
Endocrine/ metabolic disease	**17 (4.5)**
Diabetic ketoacidosis	10 (2.6)
Other endocrine/ metabolic diseases	7 (1.8)
Malignancy (active)/ haematological disease	**14 (3.7)**
Bronchogenic carcinoma	8 (2.1)
Other malignancies/ haematological diseases	6 (1.6)
Renal disease	**10 (2.6)**
Acute kidney injury	7 (1.8)
Other renal diseases	3 (0.8)
Psychiatric diseases	**7 (1.8)**
Drug overdose	6 (1.6)
Other psychiatric diseases	1 (0.3)
Other	**3 (0.8)**

TB = *Mycobacterium tuberculosis*; PCR = polymerase chain reaction; COPD = chronic obstructive pulmonary disease.

***** Clinically diagnosed or high suspicion of COVID-19 infection based on chest X-ray and clinical examination.

The most common VTE risk factors identified were:

- patients currently at bed rest/ restricted mobility for <72 hours (76.3%),
- serious infection that required hospitalisation and antibiotics (67.4%),
- age 41-60 years (32.9%),
- a personal or family history of genetic or acquired thrombophilia (27.6%).

Other notable risk factors identified among the sample included being non-ambulatory for >72 hours (20.8%) and age 61-74 years (20.3%). The distribution of VTE risk factors among sampled patients in relation to the Caprini RAM's risk scores is summarised in Table 3.

Table 3: Distribution of VTE risk factors among sampled patients in accordance with Caprini RAM [1] (N=380)*

VTE risk factors corresponding to 1 point on Caprini RAM	**Number of risk factors (% of risk factors)**
Age 41 – 60 years	125 (32.9)
Minor surgery planned (<45 min)	2 (0.5)
Past major surgery (>45 min) within last 30 days	4 (1.1)
Visible varicose veins	3 (0.8)
History of inflammatory bowel disease	0 (0)
Swollen legs (current)	56 (14.7)
BMI > 25 kg/m^2 †	47 (12.4)
Myocardial infarction	2 (0.5)
Congestive cardiac failure	39 (10.3)
Serious infection (requires hospitalisation and antibiotic(s))	256 (67.4)
Chronic respiratory disease e.g. COPD	60 (15.8)
Currently at bed rest or restricted mobility, including the use of removable leg brace for < 72 hours	290 (76.3)
Current use of birth control therapy or hormone replacement therapy	0 (0)
Pregnant or conceived within the last 30 days	3 (0.8)
History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxaemia or growth restricted infant	1 (0.3)
VTE risk factors corresponding to 2 points on Caprini RAM	
Age 61-74 years	78 (20.5)
Current or past malignancies (excluding skin cancer but including melanoma)	15 (3.9)
Planned major surgery lasting longer than 45 minutes (including laparoscopic and arthroscopic)	5 (1.3)
Nonremovable plaster cast that prevents leg movement within last 30 days	0 (0)
Tube in blood vessel in neck or chest that delivers blood or medicine directly to the heart within the last month (e.g., central venous access)	0 (0)
Confined to bed for 72 hours or more (unable to ambulate continuously for 30 feet)	79 (20.8)
VTE risk factors corresponding to 3 points on Caprini RAM	
≥Age 75	44 (11.6)
History of thrombosis, either deep vein thrombosis; pulmonary embolism or superficial venous thrombosis	9 (2.4)

Family history of thrombosis (up to third-degree relatives)	0 (0)
Personal or family history of genetic or acquired thrombophilia	105 (27.6)
VTE Risk factors corresponding to 5 points on Caprini RAM	
Elective major lower extremity arthroplasty	1 (0.3)
Hip, pelvis or leg fracture	1 (0.3)
Multiple trauma	1 (0.3)
Spinal cord injury with resultant paralysis	3 (0.8)
Stroke	29 (7.6)

VTE = venous thromboembolism; RAM = risk assessment model; BMI = body mass index; COPD = chronic obstructive pulmonary disease.

*Total number of risk factors identified in sample = 1258.

† BMI recorded as a risk factor when documented as being elevated in clinical notes.

Following the application of the Caprini RAM, 97.1% (n=369) of patients were identified to be at moderate or higher risk of VTE (Caprini score ≥2). No significant difference in Caprini VTE risk scores were detected between males and females (p=0.91). Of the 369 patients in the at-risk group, 71.0% were prescribed thromboprophylaxis. Out of the 239 patients in the highest risk group (Caprini score ≥5), 75.4% (n=180) were prescribed thromboprophylaxis. Of the 91 patients in the high-risk group (Caprini score 3-4), 65.9% (n=60) had thromboprophylaxis prescribed. Table 4 shows the number of patients categorised according to the Caprini RAM and those who had thromboprophylaxis prescribed. The number of patients in each Caprini risk score category and the rate of thromboprophylaxis prescription are show in Table 4.

Table 4: Risk stratification and thromboprophylaxis prescribed.

Caprini VTE risk score	Number of patients (%)	Number of patients who were prescribed thromboprophylaxis (%)
Low (0-1)	11 (2.9)	4 (1.5)
Moderate (2)	39 (10.3)	22 (8.3)
High (3-4)	91 (23.9)	60 (22.6)
Highest (≥5)	239 (62.9)	180 (67.7)
Total	380 (100)	266 (100)

VTE = venous thromboembolism.

A total of 266 (70%) patients were prescribed thromboprophylaxis, all of which were prescribed a subcutaneously administered anticoagulant. No prescription for any form of mechanical prophylaxis was documented. As shown in Table 5, enoxaparin was the most commonly prescribed thrombophylactic agent in 98.5% (n=262) of cases. Table 5 summarises the initial chemoprophylactic agents prescribed.

Table 5: Initial thromboprophylaxis prescribed (N=380)*

Agent	Dose	Frequency	Number (%)
Enoxaparin SC	20 mg	24-hourly	12 (4.5)
		48-hourly	1 (0.4)
	40 mg	24-hourly	210 (78.9)
		12-hourly	3 (1.1)
		48-hourly	1 (0.4)
	50 mg	24-hourly	1 (0.4)
	60 mg	24-hourly	12 (4.5)
		12-hourly	3 (1.1)
	80 mg	24-hourly	4 (1.5)
		12-hourly	13 (4.9)
	100 mg	12-hourly	2 (0.8)
UFH SC	5000 IU	8-hourly	4 (1.5)

SC = subcutaneous; UFH = unfractionated heparin.

* Total number of chemoprophylactic agents prescribed = 266.

Only 41 of the 266 patients who were prescribed thromboprophylaxis, had documented changes to their initial regimen. Twelve percent (n=32) of the sample who were prescribed thromboprophylaxis were switched to an alternative regimen, where the majority were switched to a lower dose of enoxaparin at 20 mg 24-hourly (n=8). Three percent (n=9) of those with documented changes had their thromboprophylaxis regimen discontinued entirely. Table 6 below displays the altered thromboprophylaxis regimens prescribed.

Table 6: Alternative thromboprophylaxis regimens prescribed (N=32).

Agent	Dose	Frequency	Number (%)
Enoxaparin SC	20 mg	24-hourly	8 (25)
	40 mg	24-hourly	6 (18.8)
		48-hourly	2 (6.3)
	60 mg	12-hourly	1 (3.1)
	80 mg	24-hourly	7 (21.8)
		12-hourly	5 (15.6)
	100 mg	12-hourly	1 (3.1)
UFH SC	5000 IU	8-hourly	2 (6.3)

SC = subcutaneous; UFH = unfractionated heparin.

Contraindications to chemoprophylaxis were recorded in 13.4% (n=51) of patients in the total sample. Active bleeding as a contraindication included any documented active haemoptysis, epistaxis, intracranial haemorrhage, including acute subarachnoid haemorrhage and hypertensive thalamic bleed and/or any form of gastrointestinal bleeding. The most prevalent contraindications were active bleeding during admission and hepatic impairment, which contributed 7.9% and 3.7% to the total sample. A total of 17 patients (4.5%) continued to receive chemoprophylaxis

throughout admission despite the presence of documented contraindications to these agents in their medical folders. Contraindications were only detected in 3 patients (0.8%) who were prescribed higher doses of enoxaparin (Table 7).

Table 7: Contraindications to chemoprophylaxis (N=380)*

Contraindication	Number (%)	Number of patients who received chemoprophylaxis throughout admission (%)	Number of patients who were prescribed high doses of enoxaparin † (%)
Active bleeding during admission	30 (7.9)	10 (2.6)	2 (0.5)
Thrombocytopenia (<100 × 10^9/L)	7 (1.8)	3 (0.8)	1 (0.3)
Hepatic impairment (INR > 1.5)	14 (3.7)	4 (1.1)	0 (0)

INR = international normalised ratio.

* Total number of contraindications = 51.

† Doses of enoxaparin exceeding the standard VTE prophylaxis dose and frequency of 40 mg 24-hourly.

Out of the 7 patients who experienced thrombocytopenia, 3 were prescribed enoxaparin 40 mg 24-hourly throughout admission and only one had their regimen altered, where they were switched to enoxaparin 80 mg 24-hourly. Of those who experienced hepatic impairment, three were prescribed enoxaparin 40 mg 24-hourly and one received enoxaparin 20 mg 24-hourly. Two out of the three patients who experienced intracranial haemorrhage during admission received enoxaparin 40 mg 24-hourly, whilst 10 of those who suffered from active bleeding during admission were prescribed enoxaparin 40 mg 24-hourly. Of these 10, two had their thromboprophylaxis regimen discontinued entirely and a further two were switched to enoxaparin 80 mg and 60 mg 24-hourly, respectively.

Significant renal impairment (creatinine clearance ≤ 30 mL/min) was noted in 11 patients (2.9%). Of these patients, 4 (1.1%) did not have any form of thromboprophylaxis prescribed, whilst 6 (1.6%) were prescribed 40 mg of enoxaparin 24-hourly and one (0.3%) had enoxaparin 60 mg 12-hourly prescribed. Two (0.5%) patients were switched from enoxaparin 40 mg 24-hourly to 20 mg 24-hourly and one (0.3%) was switched to 40 mg 48-hourly.

Discussion

Appraising VTE risk assessment and prophylaxis practices in medical inpatients is fundamental to understanding the evolution of VTE risks factors and limiting preventable adverse effects and costs associated with inappropriate thromboprophylaxis. Despite the significance of VTE risk

assessment and prophylaxis, a paucity of data describing these practices in medical inpatients is evident. Therefore, this study aimed to describe these practices in public sector hospitals in the Western Cape. To our knowledge, this study is unique in SA owing to its evaluation of VTE risk assessment and prophylaxis practices in medical inpatients across multiple public hospitals in the Cape Town Metropole. The use of the Caprini RAM to assess VTE risk, correlate risk with recommended thromboprophylaxis and draw comparisons to that prescribed was also unique in the study setting.

It has been reported that more than 75% of medical inpatients possess multiple risk factors for VTE, resulting in an 8-fold greater risk than that of the general population.[13] This concept is reflected in our findings, where the majority of our patient sample (97.1%) were determined to be at moderate or higher risk of VTE following objective risk assessment with the Caprini RAM. Similar findings were reported by Shah *et al*.[14] with 92.7% of patients found to be at a moderate or high risk of VTE, using the Caprini RAM. A Cameroonian study also reported similar findings, where 94.6% of medical inpatients were found to be at-risk using the Caprini RAM.[16] The South African TUNE-IN study compared clinical risk assessment, using clinician judgement with objective risk assessment, using the Caprini RAM. The authors reported a 13.3% shortfall in the number of patients identified to be at-risk for VTE when comparing clinical assessment with the Caprini RAM.[8] Together with our finding that most medical inpatients are at-risk for VTE, these findings accentuate the need to incorporate structured and validated RAMs into the package of care rendered to medical inpatients.

Obesity (BMI $\geq$ 30 kg/m^2) has been established as an independent risk factor for VTE development.[17] Numerous studies have demonstrated an approximate doubling in VTE risk in obese patients.[18] In our study, the lack of documented weight (21%) and height (0%) in medical folders was concerning in that BMI determination was excluded. Similar findings were reported in a prospective study at Chris Hani Baragwanath hospital in Johannesburg, where only 3 out of 352 patients had their weight and height measurements documented. After BMI measurement, the authors found that 16.2% of their sample were obese.[12] This is compounded by our finding that 12.4% of our sample had documented elevated BMI values that were >25 kg/m^2 , yet information required for BMI calculation was lacking. This lack of appreciation for BMI measurement is also evidenced by findings from the TUNE-IN study, where BMI was found to be one of the most overlooked VTE risk factors during risk assessments.[8] Dosing of LMWHs in certain populations is based on BMI and a paucity of information to calculate this presents various risks to optimal patient health outcomes, including increased bleeding and ineffectual VTE prophylaxis.[9,19]

Furthermore, pharmacokinetic studies indicate that a weight-based dosing regimen of enoxaparin could be more effective than a standard fixed-dosed regimen in morbidly obese medical inpatients.[20] The use of a standardised VTE RAM could serve to circumvent the lack of BMI measurement as structured RAMs could prompt clinicians to measure BMI as part of standard risk stratification.

Trends in SA hospital admission data have revealed a shift from infectious diseases as the primary diagnoses to non-communicable diseases.[15,21] In contrast to this, our study revealed that almost half (49.2%) of our sample had an infectious disease as the diagnosis. However, our finding may be confounded as the study period included the period during which the SARS-CoV-2 outbreak, and subsequent spread of the virus occurred in SA.[10] This postulation is supported by our findings, where > 10% of the diagnoses identified in our sample were PCR test positive and clinically diagnosed/highly suspected COVID-19 infections.

The recently published findings from the First National TB Prevalence Survey in SA demonstrated a high prevalence of the disease in the country at 737 per 100 000 persons.[22] Despite the high prevalence of TB in SA and its strong association with thrombosis, both the Caprini RAM and the South African VTE prophylactic and therapeutic guidelines do not include it as an independent risk factor.[1,9] Regarding TB infections, our finding (17.7%) was similar to that described by De Vries *et al.,* [23] who reported that 17.2% of their sample had active TB. Further, Hodkinson & Mahlangu[7] described TB as the predominant VTE risk factor in patients presenting with new onset DVT in their study. TB as a risk factor for VTE, is reported to be poorly understood, despite its known propensity to induce a hypercoagulable state.[24] The added VTE risk conferred by TB is theorised to be linked to prolonged exposure to systemic inflammation as compared to acute infections.[25] The causal relationship between TB and thrombosis has also been linked to the hypercoagulable state identified in patients initiating anti-TB treatment.[7] Although TB's association with VTE development is evidenced by the literature, various RAMs, including the Caprini RAM neglect to include it as an independent risk factor. This is mirrored by the South African VTE prophylactic and therapeutic guidelines, which only alludes to anti-TB treatment use as a VTE risk factor. Therefore, RAMs used in the South African setting should be adapted to include both TB and anti-TB treatment as VTE risk factors.

HIV infection possesses a well-established association with thrombosis and consequent VTE development.[7] In lieu of this concept, the South African VTE prophylactic and therapeutic guidelines includes HIV infection as a key risk factor, which is noted to confer a high level of VTE risk.[9] Similarly, the Caprini RAM classifies HIV infection under the "acquired thrombophilia"

section and infected patients are consequentially categorised as possessing a high VTE risk even in the absence of other risk factors.[1] In our study, acquired thrombophilia as a VTE risk factor was comprised of HIV infections only, thus indicating that 27.6% of our sample were HIV positive. Similar findings were reported by Du Plooy *et al*.,[21] who found a 29% prevalence of HIV in their sample. The extensive prevalence of HIV and other infectious diseases in SA should ratify VTE RAM adaption for use in this setting. A pragmatic approach would be to incorporate a separate HIV subsection into a structured RAM, thus improving its utility. Moreover, a conspicuous HIV subsection could lessen the risk of HIV being overlooked during RAM application.

Numerous studies have demonstrated the strong benefit associated with VTE prophylaxis use in at-risk medical inpatients.[14,26,27] However, thromboprophylaxis still remains underutilised in this patient population.[4,8,27] When considering this issue together with estimation that 75% of hospitalised patients who die from PE are medical inpatients, a need to improve thromboprophylaxis prescribing is necessitated.[28] Our findings showed that only 71% of patients found to be at moderate or higher risk of VTE with the Caprini RAM, were prescribed thromboprophylaxis. Similarly, the SA-based TUNE-IN study reported that 73.5% of medical inpatients in their sample received thromboprophylaxis.[8] Du Plessis *et al.*[12] detected comparable results, with 73.2% of those at-risk in their sample receiving thromboprophylaxis with a LMWH. In contrast, the ENDORSE study found that just less than half (48%) of medical inpatients in their sample received thromboprophylaxis.[4] Similar findings were reported in single-centre study in Israel, where 50% of the at-risk patients in the sample received thromboprophylaxis.[26] Yet, thromboprophylaxis prescription was markedly better in our study when compared to findings from the multicentre DISSOVLE-2 (Identification of Chinese Hospitalized Patients' Risk Profile for Venous thromboemboolis-2) study, which found that only 12.9% of medical inpatients received thromboprophylaxis.[27] Comparable results were described by Nkoke *et al.,*[16] where only 18.7% of high-risk medical inpatients received thromboprophylaxis across two Cameroonian hospitals. Despite our encouraging findings, 29% of at-risk patients in our sample did not have any form of thromboprophylaxis prescribed. Moreover, almost a quarter (24%) of at-risk patients failed to receive thromboprophylaxis despite their lack of contraindications to chemoprophylaxis. Based upon these findings, it may be construed that thromboprophylaxis prescribing in medical inpatients is expanding. However, a large number of at-risk patients are still overlooked, which may be attributed to a lack of objective RAM use in this setting.

Our finding that enoxaparin prescribed at 40 mg 24-hourly in 89% of our sample was anticipated as this represents the standard thromboprophylaxis regimen in most public healthcare sector hospitals in the Western Cape.[29,30] Dosing anomalies, where doses > 40 mg and frequencies differing from 24-hourly were detected in 15% of patients who were prescribed thromboprophylaxis. Du Plessis *et al.*[12] reported similar findings, where 17.5% of their sample were noted to have received the incorrect dose of a LMWH. These findings may be indicative of a new trend in VTE prophylaxis prescribing, where increased rates of thromboprophylaxis prescribing in medical inpatients are apparent, yet inappropriate dosing is increasing as a resultant consequence. This trend may be further complicated by the inappropriate prescribing of chemoprophylaxis in patients who possess contraindications as evidenced by the 4.5% of patients in our sample who received chemoprophylaxis throughout admission. Comparable findings were reported by Rocher *et al.,*[2] where 5.6% of patients in their sample were prescribed some form of chemoprophylaxis despite clear contraindications.

Mechanical thromboprophylaxis is a fundamental therapy when considering the prevention of VTE in patients with contraindications to anticoagulants, such as active bleeding.[4] The Caprini RAM recommends mechanical prophylaxis as an alternative to chemoprophylaxis in patients with a moderate VTE risk and as adjuvant therapy in those considered to be at high and highest risks.[31] No prescription for any form of mechanical thromboprophylaxis was identified in our study. Our finding was concordant with findings from other African studies, where a complete lack of mechanical thromboprophylaxis prescriptions were identified.[5,16] This paucity of mechanical thromboprophylaxis prescribing is worrisome, owing to the number of at-risk patients in our sample who possessed contraindications to chemoprophylaxis and would have benefitted from this form of prophylaxis (13.4%). This is further compounded by our finding that 39.2% of patients with documented contraindications to chemoprophylaxis still had anticoagulants prescribed. However, the possible lack of available mechanical thromboprophylaxis equipment for medical inpatient use may be a contributing factor to these findings. The use of IPC in resource-limited settings, such as in public healthcare sector hospitals is challenging as these devices require maintenance to ensure optimal functionality. However, GCS may offer a more feasible approach for use in medical inpatients and requires further consideration. The need to improve access to and awareness of mechanical thromboprophylaxis use in medical inpatients are evident from our findings.

Study limitations

The retrospective nature of this study is a key limitation since the quality of data obtained depends on the accuracy and quality of information documented in medical folders. The hospitals selected for this study were all located in the Cape Town Metropole and VTE risk assessment and prophylaxis practices may differ in rural facilities with limited access to specialist clinician consultations.

Conclusion

An improvement in the rate of thromboprophylaxis prescribing in medical inpatients is supported by our findings. Yet, a substantial portion of at-risk patients (29%) are still overlooked in practice, validating the need for extensive appropriation of structured RAMs in the South African public healthcare sector. Further, our study uncovered a resultant consequence of this improvement, where inappropriate dosing of anticoagulants is expanding. This is further complicated by the lack of mechanical prophylaxis prescribing as evidenced by our findings. The use of mechanical prophylaxis should be prioritised to bolster awareness around the benefits of use in patients with contraindications to anticoagulants. TB should be recognised as an independent risk factor for VTE, owing to its propensity to induce thrombosis and extensive prevalence in SA. Together with HIV, TB and anti-TB treatment use should be incorporated into structured RAMs for use in the South African setting. Demarcated subsections for HIV and TB should be incorporated within RAMs to improve utility and convenience of use. The Caprini RAM offers a validated, simplistic and effective approach to VTE risk assessment in medical inpatients. The Caprini RAM may be refined and adapted for specific use in public healthcare sector hospitals in the Cape Town Metropole. Novel research should explore reasons underpinning the lack of VTE prophylaxis prescribing and inappropriate prescribing of anticoagulants in medical inpatients.

Declaration

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Author contributions

AW: conceptualised and designed the study, performed data collection, analysis and drafted the manuscript. RC and JM: Supervised the study, aided in the design of the study and data collection tool and were major contributors to the final manuscript.

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Conflicts of interest

None.

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4.3 Additional results

Additional results obtained from the study, which were not included in the published manuscript are included as tables in Appendix I.

4.4 Summary

This chapter presented the results and key findings of this study in the form of a published manuscript. The chapter that follows presents a brief discussion of the additional results that were not included in the published manuscript in this chapter.

CHAPTER 5: DISCUSSION

5.1 Introduction

This chapter presents a brief discussion of findings that were not included and discussed in the published manuscript, which was presented in the previous chapter. The initial sections comprise brief discussions of the admitting diagnoses of study participants and the duration of chemoprophylaxis regimens prescribed. This is followed by an explanation concerning anti-factor Xa testing among the sample. A summary follows these sections and concludes the chapter.

5.2 Admitting diagnosis

Contemporary trends in hospitalisation statistics are indicative of a shift from infectious diseases as the primary reason for admission to non-communicable diseases in low-income countries worldwide. In SA, a dual increase in both non-communicable and infectious diseases have been reported in the literature (Mayosi *et al.*, 2009; Bulled & Singer, 2020). Similarly, this study revealed that the majority of patients in the sample (41.8%) were hospitalised with an infectious diagnosis as their admitting diagnosis. However, this finding could be confounded by the study period, which included the period during which the COVID-19 outbreak transpired in SA (Kaswa, Yogeswaran & Cawe, 2021). Furthermore, it may be construed that this postulation is supported by our findings, where the majority of infectious diagnoses detected in our sample were comprised of unspecified lower respiratory tract infections (12.6%) and suspected COVID-19 infections (8.5%). Despite the probability of this conjecture, McIntosh *et al.* (2021) reported similar findings in their observational cohort study, which examined reasons for referral to hospitals across 17 PHC facilities in SA's KwaZulu-Natal province. The authors reported that communicable diseases were the common reason for hospital admission following neonatal and/or maternal conditions (McIntosh *et al.*, 2021). In addition, our findings were synonymous with related findings reported by Stanley, Graham and Parrish (2008), who found that the most common disease category for re-admission to Cecilia Makiwane Hospital in SA's Eastern Cape province was infectious disease.

Etyang and Scott (2013) reported similar findings, when conducting a systematic review with the aim of describing the reasons for hospital admission in SSA. The authors included 30 articles comprising 86 307 hospital admissions and noted that the leading causes of admission were due to parasitic and other infectious diseases. Despite the congruency between these findings and those of this current study, the estimates reported were less than half (19.8%) of those detected in this study.

5.3 Duration of thromboprophylaxis regimens

The effectiveness of thromboprophylaxis regimens is reported to be dependent on the choice of modality or specific agent selected, dosing if applicable as well as the duration of therapy (Amin *et al.*, 2010; Stark & Smith, 2011). Therefore, the duration of thromboprophylaxis prescribed forms a fundamental component of the VTE prophylaxis continuum of care (Schünemann *et al.*, 2018; Rocher *et al.*, 2019). Furthermore, this concept is of particular import to thromboprophylaxis prescribing in medical inpatients, where data is reported to be lacking. Despite this apparent lack of data, previous trials have demonstrated that prophylaxis provided during the period of acute hospitalisation, which was previously 6 d to14 d for most medical patients, demonstrated the best effects in terms of safety and efficacy. However, recent concerns around the optimal duration of thromboprophylaxis in medical inpatients were raised due to a recent decline in the duration of hospital stay in this patient population (Stark & Smith, 2011; Amin *et al.*, 2012). A related finding concerning this concept was detected in this current study, where more than half of all chemoprophylaxis prescriptions (57.9% for initial regimens and 59.4% for alternate regimens) lacked a documented duration of therapy. This finding is concerning when considering the importance of appropriate duration of therapy to the VTE prophylaxis continuum of care. In addition, it is recommended that the anticipated duration of any therapy be furnished on the prescription to ensure optimal medication-related care (Aronson, 2004; Pollock, Bazaldua & Dobbie, 2007).

The most predominant duration of thromboprophylaxis identified in this current study was 14 d (36.8% for initial regimens and 31.3% for alternate regimens). However, Jacobson, Louw and Riback (2014) reported dissimilar findings in the TUNE-IN Wave 2 study, where the average duration of prophylaxis prescribed in public sector patients was noted to be 7 d. In addition, Amin *et al.* (2012) reported contrasting findings in their retrospective, observational study, where the investigators noted the average duration of thromboprophylaxis during admission to be 5 d. A plausible explanation for these incongruencies is that the investigators only recorded the duration of thromboprophylaxis up until patients were discharged and not what was initially furnished on prescriptions by prescribers.

5.4 Anti-factor Xa tests

No result for any anti-factor Xa tests were detected in this current study. However, this finding was anticipated as anti-factor Xa monitoring is not routinely recommended in patients receiving standard-dose thromboprophylaxis therapy with a LMWH. Although anti-factor Xa monitoring is

recommended in certain patient populations, including pregnant and morbidly obese patients, it is more frequently employed during the treatment of active VTE (Jacobson *et al.*, 2013; Louw *et al.*, 2021; Padayachee, Schoeman & Schellack, 2021). Therefore, patients included in the sample were not expected to have had anti-factor Xa tests conducted as those with active VTE were excluded from the study.

5.5 Summary

This chapter presented a brief discussion of the additional results obtained from the study, which were not included in the published manuscript. The chapter that follows will present the study's overall conclusions and limitations as well as recommendations arising from the study's findings.

CHAPTER 6: CONCLUSION, LIMITATIONS AND RECOMMENDATIONS

6.1 Introduction

This chapter presents an overview of the conclusions drawn from the study, which were conceptualised in accordance with the research question and objectives. The study's limitations are described thereafter. Recommendations for future research and practice-based recommendations, which were drawn from the study's findings conclude the chapter. This study aimed to describe the current VTE risk assessment and prophylaxis practices through investigating medical practitioner-led practices in this regard.

6.2 Conclusion

According to this study's findings, it can be concluded that the rate of thromboprophylaxis prescribing in at-risk medical inpatients is improving in this study setting. Despite detecting this favourable trend, a considerable number of patients who were at-risk of VTE did not receive any form of thromboprophylaxis. Together with synonymous findings from the literature, this constitutes both a global and local problem in healthcare. Furthermore, this study revealed a lack of appreciation for increased BMI as a risk factor for VTE as evidenced by the paucity of BMI measurement and documentation. This raises concern around the quality of the current VTE risk assessment and prophylaxis practices in public healthcare hospitals in SA's Western Cape province. In addition, these findings provide evidence for the need to explore the adoption and adaption of a standardised and validated VTE RAM, such as the Caprini RAM for specific use in the SA public healthcare setting. The findings of this current study highlight the need to accentuate prominent VTE risk factors in this setting, specifically HIV and TB infections in the adapted RAM. This would allow medical practitioners to conduct simple, objective, and extensive risk stratification of all medical inpatients under their care. Consequently, VTE prophylaxis prescribing would improve in this patient population, which in turn, would decrease VTE-related morbidity and mortality.

6.3 Limitations

The retrospective design employed in this study was a key limitation as the accuracy of the data gathered was dependent on the quality and accuracy of information documented in patient medical folders. Further, the data collected from medical folders was limited to the information documented in the folders, where missing information could have skewed the results. In addition,

information documented in patient medical folders was primarily comprised of handwritten clinical notes, which required a limited amount of interpretation; thus, resulting in possible information bias. Although the hospitals included in the study were located in various districts in the Cape Town Metropole, VTE risk assessment and prophylaxis practices could vary from those at rural hospitals as access to specialist medical practitioner consultations could be limited in these areas.

6.4 Recommendations

6.4.1 Recommendations for future research

To better understand the implications of this current study's findings, future studies could explore the reasons underpinning the lack of thromboprophylaxis prescribing in at-risk medical inpatients by medical practitioners. Moreover, this would allow for the exploration of barriers and solutions to the underutilisation of VTE RAMs and VTE prophylaxis in this patient population.

Another potential avenue for further research could be to investigate the effectiveness of interventions aimed at improving VTE RAM uptake and appropriate thromboprophylaxis prescribing. These interventions could include medical practitioner education around VTE prophylaxis, electronic alerts that serve as reminders for VTE prophylaxis and regular performance evaluations. Further, the findings of this research could inform strategic quality improvement plans by relevant stake holders, clinicians, and policymakers.

Studies validating adapted forms of standardised VTE RAMs for use in SA should also be considered. A key recommendation for this adaption would be to include separate, conspicuous sub-sections for TB infection, anti-TB treatment use and HIV infection. This would provide valuable evidence around the effectiveness, ease of use and feasibility of employing adapted RAMs in SA.

Lastly, the feasibility of using mechanical thromboprophylaxis in resource-constrained settings warrants further investigation. In addition, it can be recommended that methods aimed at improving the availability of mechanical forms of thromboprophylaxis in resource-limited settings and general medical wards should be examined. The findings of which would be crucial for patient safety as a lack thereof would impede the care of patients who are at-risk of both VTE and bleeding.

6.4.2 Practice-based recommendations

Certain facility-driven interventions, such as electronic alerts and regular performance evaluations may be unfeasible in the SA public healthcare setting owing to a lack of adequate infrastructure. However, the incorporation of a prescription prompt for medical practitioners, where a section of inpatient prescription charts can be designated for VTE prophylaxis prescribing, may offer a more pragmatic solution. This prompt could serve as a reminder to all members of the multidisciplinary healthcare team of the need for VTE risk assessment and thromboprophylaxis. Moreover, this separate, designated VTE prophylaxis section would emphasise the role of VTE risk assessment and prophylaxis as part of the routine package of care offered to all medical inpatients. In addition, it can be recommended to include a standardised VTE RAM in clinical and/or nursing care notes in patient medical folders to encourage objective risk stratification. The completion of this RAM could serve as part of the routine admission bundle of all patients admitted to hospital and could offer a valuable means of improving the rate of thromboprophylaxis prescribing in at-risk medical inpatients.

Healthcare providers in all healthcare settings should consider creating a facility-driven and evidence-based VTE prophylaxis strategic plan. This strategy could encompass an enclosed prophylaxis policy by which evidence-based recommendations inform medical practitioners of the best VTE risk assessment and prophylaxis practices at the facility. Together with investing in clinician training around appropriate VTE prophylaxis, this would be beneficial in its capacity to optimise patient safety, function as a quality of inpatient care indicator, minimise VTE risk and prevent medicolegal litigation.

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APPENDICES

APPENDIX A: DATA COLLECTION TOOL

Venous Thromboembolism (VTE) Risk Assessment and Prophylaxis - Retrospective Folder Review

Please complete each section by following the relevant instructions.

Background and Demographics

Please tick the most appropriate tick-box below and fill in where required. Only select one option out of the those provided for each question.

Gender

☐ Male ☐ Female

Age (years): _____

Age range (years)

☐ 18–30 years ☐ 31–40 years ☐ 41–60 years

☐ 61–74 years ☐ ≥ 75 years

Weight on admission (if recorded): _____

Height (cm) (if recorded): _____

Length of hospital stay (days): _____

Admitting diagnosis (reason for admission):

☐ Ischaemic stroke ☐ Haemorrhagic stroke

☐ Unspecified stroke ☐ Unspecified lower respiratory tract infection

☐ Community acquired pneumonia ☐ Pneumocystis pneumonia

☐ Urinary tract infection

☐ Tuberculosis meningitis ☐ Fungal meningitis

☐ Cryptococcal meningitis ☐ Bacterial meningitis

☐ Acute gastroenteritis

☐ Pulmonary tuberculosis

☐ Acute exacerbation of chronic obstructive pulmonary disease

☐ Suspected COVID-19 infection ☐ PCR-confirmed COVID-19 infection

☐ Hospital acquired pneumonia

☐ Acute decompensated heart failure ☐ Acute kidney injury

☐ Diabetic ketoacidosis ☐ Epilepsy

☐ Status epilepticus ☐ Peptic ulcer disease

☐ Hypertensive emergency ☐ Hypertensive urgency

☐ Other: _____

Final primary diagnosis prior to discharge or demise:

☐ Ischaemic stroke ☐ Haemorrhagic stroke

☐ Unspecified stroke ☐ Unspecified lower respiratory tract infection

☐ Community acquired pneumonia ☐ Pneumocystis pneumonia

☐ Urinary tract infection

☐ Tuberculosis meningitis ☐ Fungal meningitis

☐ Cryptococcal meningitis ☐ Bacterial meningitis

☐ Acute gastroenteritis

☐ Pulmonary tuberculosis

☐ Acute exacerbation of chronic obstructive pulmonary disease

☐ Suspected COVID-19 infection ☐ PCR-confirmed COVID-19 infection

☐ Hospital acquired pneumonia

☐ Acute decompensated heart failure ☐ Acute kidney injury

☐ Diabetic ketoacidosis ☐ Epilepsy

☐ Status epilepticus ☐ Peptic ulcer disease

☐ Hypertensive emergency ☐ Hypertensive urgency

☐ Other: _____

Previous hospital admission:

☐ Within 30 days ☐ Within 60 days

☐ Within 90 days ☐ Not recorded

Modified Caprini Risk Assessment Tool

Adapted from the Updated 2013 Caprini Risk Assessment Model

Instructions for calculation of DVT risk score

a) Check all the tick-boxes that apply to the patient.

b) Tally up the score for sections A through D and record the value for each section in the designated area below each section.

c) Tally up the score from each section and record the value in the designated area below at the end of the tool.

Section A

Please tick the most appropriate tick-box(s) below. More than one option may be selected for each statement.

Add 1 point for each of the following criteria that apply to the patient (occurring currently or within past 30 days):

☐ Age 41 – 60 years

☐ Minor surgery planned (< 45 min)

☐ Past major surgery (> 45 min) within last 30 days

☐ Visible varicose veins

☐ History of inflammatory bowel disease

☐ Swollen legs (current)

☐ Body mass index > 25 kg/m^2

☐ Myocardial infarction

☐ Congestive cardiac failure

☐ Serious infection (requires hospitalisation and antibiotic(s)

☐ Chronic respiratory disease e.g., COPD

☐ Currently at bed rest or restricted mobility, including the use of removable leg brace for < 72 hours

Add 1 point for each of the following criteria that apply to the patient (For females only):

☐ Current use of birth control therapy or hormone replacement therapy (HRT)

☐ Pregnant or conceived within the last 30 days

☐ History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxaemia or growth restricted infant

Section A Score	

Section B

Please tick the most appropriate tick-box(s) below. More than one option may be selected for each statement.

Add 2 points for each of the following criteria that apply to the patient:

☐ Age 61–74 years

☐ Current or past malignancies (excluding skin cancer but including melanoma)

☐ Planned major surgery lasting longer than 45 minutes (including laparoscopic and arthroscopic)

☐ Nonremovable plaster cast that prevents leg movement within last 30 days

☐ Tube in blood vessel in neck or chest that delivers blood or medicine directly to the heart within the last month (e.g., central venous access, PICC line, port)

☐ Confined to bed for 72 hours or more (unable to ambulate continuously for 30 feet)

Section B Score	

Section C

Please tick the most appropriate tick-box(s) below. More than one option may be selected for each statement.

Add 3 points for each of the following criteria that apply to the patient:

☐ ≥Age 75

☐ History of thrombosis, either deep vein thrombosis; pulmonary embolism or superficial venous thrombosis

☐ Family history of thrombosis (up to third-degree relatives)

☐ Personal or family history of genetic or acquired thrombophilia

Section C Score	

Section D

Please tick the most appropriate tick-box(s) below. More than one option may be selected for each statement.

Add 5 points for each of the following criteria that apply to the patient now or within the last 30 days:

☐ Elective hip or knee joint replacement surgery

☐ Fractured hip, pelvis, or leg

☐ Serious trauma (e.g., multiple fractures due to a fall or motor vehicle accident)

☐ Spinal cord injury resulting in paralysis

☐ Stroke

Section D Score	

Total VTE risk score (Section A + Section B + Section C + Section D)	

VTE Prophylaxis during admission

Please tick the most appropriate tick-box(s) below.

VTE prophylaxis therapy used during admission

☐ Yes ☐ No

If yes, what form(s) of thromboprophylaxis was/were prescribed:

☐ Chemoprophylaxis ☐ Mechanical prophylaxis

☐ Other: _____

If chemoprophylaxis prescribed, select the specific agent prescribed:

☐ Unfractionated heparin ☐ Enoxaparin

☐ Dalteparin ☐ Fondaparinux

☐ Rivaroxaban ☐ Other: _____

If chemoprophylaxis prescribed, select the dose prescribed:

☐ 5 000 IU ☐ 8 000 IU ☐ 10 000 IU

☐ 2.5 mg ☐ 5 mg ☐ 7.5 mg

☐ 10 mg ☐ 15 mg ☐ 20 mg

☐ 30 mg ☐ 40 mg ☐ 60 mg

☐ 80 mg ☐ 100 mg ☐ 120 mg

☐ Other: _____

If chemoprophylaxis prescribed, select the route of administration prescribed:

☐ Subcutaneous (SC) ☐ Intravenous (IV)

☐ Oral (PO) ☐ Other: _____

If chemoprophylaxis prescribed, select the frequency of use prescribed:

☐ 24-hourly ☐ 12-hourly ☐ 8-hourly

☐ 6-hourly ☐ Other: _____

If chemoprophylaxis prescribed, select the duration of therapy prescribed:

☐ 3 days ☐ 5 days ☐ 7 days

☐ 10 days ☐ 14 days ☐ Other: _____

If mechanical thromboprophylaxis prescribed, select the specific alternative prescribed:

☐ Intermittent pneumatic compression

☐ Graduated compression stockings

☐ Other: _____

VTE prophylaxis discontinued and/or substituted during admission:

☐ Discontinued only

☐ Discontinued and switched to alternative therapy

☐ Other: _____

If switched to alternative thromboprophylaxis, select the form of prophylaxis prescribed:

☐ Chemoprophylaxis ☐ Mechanical prophylaxis

☐ Other: _____

If switched to alternative chemoprophylaxis, select the specific agent prescribed:

☐ Unfractionated heparin ☐ Enoxaparin

☐ Dalteparin ☐ Fondaparinux

☐ Rivaroxaban ☐ Other: _____

If switched to chemoprophylaxis, select the dose prescribed:

☐ 5 000 IU ☐ 8 000 IU ☐ 10 000 IU

☐ 2.5 mg ☐ 5 mg ☐ 7.5 mg

☐ 10 mg ☐ 15 mg ☐ 20 mg

☐ 30 mg ☐ 40 mg ☐ 60 mg

☐ 80 mg ☐ 100 mg ☐ 120 mg

☐ Other: _____

If switched to chemoprophylaxis, select the route of administration prescribed:

☐ Subcutaneous (SC) ☐ Intravenous (IV)

☐ Oral (PO) ☐ Other: _____

If switched to chemoprophylaxis, select the frequency of use prescribed:

☐ 24-hourly ☐ 12-hourly ☐ 8-hourly

☐ 6-hourly ☐ Other: _____

If switched to chemoprophylaxis, select the duration of therapy prescribed:

☐ 3 days ☐ 5 days ☐ 7 days

☐ 10 days ☐ 14 days ☐ Other: _____

If switched to alternative mechanical thromboprophylaxis, select the specific alternative prescribed:

☐ Intermittent pneumatic compression ☐ Graduated compression stockings

☐ Other: _____

VTE prophylaxis safety considerations

Please tick the most appropriate tick-box(s) below. More than one option may be selected for each statement.

Please tick the most appropriate tick-box(s) below (tick all that apply):

☐ Active bleeding during admission

☐ History of heparin-induced thrombocytopenia

☐ Hepatic impairment (INR > 1.5)

☐ Blood platelet count < 100 x 10^9/L

☐ Elevated serum creatinine > 106 μmol/L

☐ Other: _____

Please list the relevant laboratory values in the spaces provided:

Blood platelet count value (if < 100 x 10^9/L) of initial measurement: _____

Date of initial blood platelet count (if < 100 x 10^9/L) measurement: _____

Blood platelet count value (if < 100 x 10^9/L) of midpoint measurement: _____

Date of midpoint blood platelet count (if < 100 x 10^9/L) measurement: _____

Blood platelet count value (if < 100 x 10^9/L) of final measurement: _____

Date of final blood platelet count (if < 100 x 10^9/L) measurement: _____

Serum creatinine value (if > 106 μmol/L) of initial measurement: _____

Date of initial serum creatinine (if > 106 μmol/L) measurement: _____

Serum creatinine value (if > 106 μmol/L) of midpoint measurement: _____

Date of midpoint serum creatinine (if > 106 μmol/L) measurement: _____

Serum creatinine value (if > 106 μmol/L) of final measurement: _____

Date of final serum creatinine (if > 106 μmol/L) measurement: _____

Anti-Xa level of initial measurement: _____

Date of initial anti-Xa level measurement: _____

Anti-Xa level of midpoint measurement: _____

Date of midpoint anti-Xa level measurement: _____

Anti-Xa level of final measurement: _____

Date of final anti-Xa level measurement: _____

APPENDIX B: THE UNIVERSITY OF THE WESTERN CAPE BIOMEDICAL AND RESEARCH ETHICS COMMITTEE – ETHICS APPROVAL

UNIVERSITY of the WESTERN CAPE

60 YEARS of hope, action & knowledge

07 July 2020

Mr A Wehmeyer
School of Pharmacy
Faculty of Natural Sciences

Ethics Reference Number: BM20/5/9

Project Title: Perceptions and practices of medical practitioner led venous thromboembolism risk assessment and prophylaxis in public sector hospitals

Approval Period: 12 June 2020 – 12 June 2023

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report annually by 30 November for the duration of the project.

Permission to conduct the study must be submitted to BMREC for record-keeping.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

Director: Research Development
University of the Western Cape
Private Bag X 17
Bellville 7535
Republic of South Africa
Tel: +27 21 959 4111
Email: research-ethics@uwc.ac.za

NHREC Registration Number: BMREC-130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE.

APPENDIX C: NEW SOMERSET HOSPITAL APPROVAL LETTER

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 0866: fax: +27 21 483 6058
5th Floor, Norton Rose House,, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: WC_202007_013
ENQUIRIES: Dr Sabela Petros

Private Bag X 17
Bellville
7535
Republic of South Africa

For attention: Mr Alexander Wehmeyer, Prof Renier Coetzee, Dr Jane Mccartney

Re: Perceptions and practices of medical practitioner led venous thromboembolism risk assessment and prophylaxis in public sector hospitals

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.

Please contact the following people to assist you with any further enquiries in accessing the following sites:

Khayelitsha Hospital	**Kitesh Moodley**	**021 360 4500**
Somerset Hospital	**Jacques Hendricks**	**021 402 6180**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
3. In the event where the research project goes beyond the *estimated completion* date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
4. The reference number above should be quoted in all future correspondence.

Yours sincerely

DR M MOODLEY
DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE: 14/11/2020
CC

APPENDIX D: KARL BREMER HOSPITAL APPROVAL LETTER

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 0866: fax: +27 21 483 6058
5th Floor, Norton Rose House,, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: WC_202007_013
ENQUIRIES: Dr Sabela Petros

Private Bag X 17
Bellville
7535
Republic of South Africa

For attention: Mr Alexander Wehmeyer, Prof Renier Coetzee, Dr Jane Mccartney

Re: Perceptions and practices of medical practitioner led venous thromboembolism risk assessment and prophylaxis in public sector hospitals

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.
Please contact the following people to assist you with any further enquiries in accessing the following sites:

Karl Bremer Hospital	**De Vries Basson**	**021 918 1205**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
3. In the event where the research project goes beyond the *estimated completion* date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
4. The reference number above should be quoted in all future correspondence.

Yours sincerely

DR M MOODLEY
DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE: 22/10/2020
CC

APPENDIX E: EERSTE RIVER HOSPITAL APPROVAL LETTER

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 0866: fax: +27 21 483 6058
5th Floor, Norton Rose House,, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: WC_202007_013
ENQUIRIES: Dr Sabela Petros

Private Bag X 17
Bellville
7535
Republic of South Africa

For attention: Mr Alexander Wehmeyer, Prof Renier Coetzee, Dr Jane Mccartney

Re: Perceptions and practices of medical practitioner led venous thromboembolism risk assessment and prophylaxis in public sector hospitals

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.

Please contact the following people to assist you with any further enquiries in accessing the following sites:

Eerste River Hospital	**Dr Adele Anthony**	**021 902 8019**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
3. In the event where the research project goes beyond the *estimated completion* date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
4. The reference number above should be quoted in all future correspondence.

Yours sincerely

DR M MOODLEY
DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE: 22/10/2020
CC

APPENDIX F: *SOUTH AFRICAN MEDICAL JOURNAL* AUTHOR GUIDELINES

The manuscript was written in accordance with the author guidelines set out by the *South African Medical Journal*. The guidelines can be accessed at: http://www.samj.org.za/index.php/samj/about/submissions#authorGuidelines.

APPENDIX G: AUTHOR STATEMENTS

The supervisor (Professor Renier Coetzee) and co-supervisor (Doctor Jane McCartney) of this mini-thesis dissertation also supervised and evaluated the writing of the manuscript. The researcher (Alexander Stefan Wehmeyer) prepared and wrote both the mini-thesis dissertation and the manuscript.

APPENDIX H: JOURNAL ACCEPTANCE LETTER

Date: Oct 18, 2021
To: "Alexander Stefan Wehmeyer" 3470695@myuwc.ac.za
cc: "Renier Coetzee" recoetzee@uwc.ac.za, "Jane McCartney" jmccartney@uwc.ac.za
From: "SAMJ" submissions@hmpg.co.za
Subject: Your Submission
Attachment(s): SAMJ Page fees - 16040.pdf

Ref.: SAMJ16040
Venous Thromboembolism Risk Assessment and Prophylaxis in Hospitalised Medical Patients in the Cape Town Metropole, South Africa
South African Medical Journal

Dear Mr Wehmeyer,

We are pleased to tell you that your work has now been accepted for publication in South African Medical Journal.

Please find payment form attached herewith. As soon as proof of payment and the completed form have been received, we will send your article into production. (Please note that we are unable to process American Express card payments). Please send proof of payment to claudian@samedical.org

Thank you for submitting your work to the journal.

Best wishes

Bridget Farham, PhD
Editor
South African Medical Journal

APPENDIX I: ADDITIONAL RESULTS

Diagnosis on admission (n = 380)

Admitting diagnosis	Number of patients	Percentage of patients
Infectious disease	**159**	**41.8%**
Unspecified lower respiratory tract infection	48	12.6%
Suspected COVID-19 infection*	32	8.4%
Urinary tract infection	23	6.1%
Unspecified meningitis	11	2.9%
PCR test positive COVID-19 infection	9	2.4%
Pulmonary TB	9	2.4%
Community acquired pneumonia	8	2.1%
Disseminated TB	5	1.3%
Other infectious diseases	14	3.7%
Neurological disease	**53**	**13.9%**
Unspecified stroke	21	5.5%
Delirium	12	3.2%
Epilepsy	8	2.1%
Other neurological diseases	12	3.2%
Gastrointestinal/hepatobiliary disease	**35**	**9.2%**
Acute gastroenteritis	29	7.6%
Other gastrointestinal/hepatobiliary diseases	6	1.6%
Cardiovascular disease	**34**	**8.9%**
Acute decompensated heart failure	28	7.4%
Other cardiovascular diseases	6	1.6%
Pulmonary disease	**27**	**7.1%**
Acute exacerbation of COPD	18	4.7%
Pleural effusion	6	1.6%
Other pulmonary diseases	3	0.8%
Endocrine/metabolic disease	**19**	**5%**
Diabetic ketoacidosis	12	3.2%
Other endocrine/metabolic diseases	7	1.8%
Malignancy (active)/haematological disease	**14**	**3.7%**
Bronchogenic carcinoma	6	1.6%
Other malignancies/haematological diseases	8	2.1%
Renal disease	**10**	**2.6%**
Acute kidney injury	5	1.3%
Other renal diseases	5	1.3%
Psychiatric diseases	**10**	**2.6%**
Drug overdose	5	1.3%
Psychosis	5	1.3%
Other	**19**	**5%**

COVID-19: Coronavirus disease 2019; TB: *Mycobacterium tuberculosis;* PCR: Polymerase chain reaction; COPD: Chronic obstructive pulmonary disease

Duration of initial thromboprophylaxis regimens prescribed (n = 266)

Agent	Duration	Number of patients	Percentage of patients
Enoxaparin SC	3 d	1	0.4%
	5 d	2	0.8%
	7 d	11	4.1%
	14 d	94	35.3%
	Not specified	154	57.9%
UFH SC	14 d	4	1.5%

SC: Subcutaneous; UFH: Unfractionated heparin

Duration of alternate thromboprophylaxis regimens prescribed (n = 32)

Agent	Duration	Number of patients	Percentage of patients
Enoxaparin SC	7 d	3	9.40%
	14 d	8	25.00%
	Not specified	19	59.40%
UFH SC	14 d	2	6.30%

SC: Subcutaneous; UFH: Unfractionated heparin

APPENDIX J: EDITORIAL CERTIFICATE

strikethrough professional
Editing & Language Services

Proof of Edit

UWC/2021/04

2021/11/15

To whom it may concern,

Declaration

With this I certify that I, Louise Jean Keuler, was paid as freelance editor to edit Alexander Stefan Wehmeyer's mini-thesis (*Venous Thromboembolism Risk Assessment and Prophylaxis in Selected Public Sector Hospitals in the Cape Town Metropole*) for submission to the School of Pharmacy at the University of the Western Cape. It should be noted that as Mr Wehmeyer's editor, I did not contribute to the content or research of the article. The work is entirely his own and my contribution to it was merely for the sake of clarity and readability.

Services rendered

Editing

- Followed British English spelling, grammar and language conventions.
- Implemented Plain Language guidelines for ease of reading and word recognition.
- Prepared the document for distribution or publication through the following:
  - clarifying meaning,
  - polishing language by editing for grammar, usage, spelling and punctuation;
  - checking for consistency of mechanics and for internal consistency of facts; and
  - editing tables, figures and lists.

DESCRIPTION	EDITING OF MASTERS' DEGREE MINITHESIS
CHARGED TO	A.S. WEHMEYER
RECEIVED BY	LJ KEULER
TOTAL AMOUNT	R4 900.00

If you have any questions concerning this proof of edit please feel free to contact:
Louise Keuler at louise.jean.greyling@gmail.com or on 072 263 6805

LKeuler