Assessment of venous thromboembolism prophylaxis in a South African private hospital group

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PREFACE

This mini dissertation is presented in an article format, where the results are discussed in Chapter 3.

Four chapters divide this mini dissertation:

- Chapter 1 provides a brief overview of the study as well as all ethical considerations required to successfully complete the study
- Chapter 2 comprises a detailed literature review that addresses all relevant topics. This includes venous thromboembolism (VTE) pathogenesis, VTE prophylaxis through individual mechanisms of action and associated side effects, patient VTE risk stratification, as well as prescriber adherence to published guidelines. The chapter summary finalises this section
- Chapter 3 provides answers to the empirical investigation with results of this study in article format, as set out in Chapter 1, section 1.3.2 of this mini dissertation. The manuscript, written according to the specific journal requirements, was submitted for peer review and possible publishing in the *South African Family Practice Journal* on 8 November 2019 (submission reference number 5022)
- Chapter 4 contains conclusions derived from the study. This includes study limitations, strengths and recommendations for possible further research.

References follow at the end of this mini dissertation.

The article co-authors are both the supervisor and co-supervisor. Both have read and approved the mini dissertation (which includes the manuscript). Acknowledgements follow in the next section.

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ABSTRACT

Title: Assessment of venous thromboembolism prophylaxis in a South African private hospital group

Background: Prophylactic venous thromboembolism (VTE) strategies have the greatest impact on patient outcomes. Both global and local guidelines support VTE prophylaxis for hospitalised patients. However, studies have reported that these measures are routinely under-prescribed. This study evaluated prescribing patterns of VTE prophylaxis in one of the largest South African (SA) private hospital groups.

Methods: A quantitative, retrospective analysis of the hospital group's patient database was conducted for patients admitted between 1 September 2015 and 31 August 2016. Those younger than 18 years, with trauma or suffering from contraindications to anticoagulation were excluded. Additionally, patients with warfarin billed were also excluded as they possibly required therapeutic anticoagulation. Included prophylactic measures were compared to published SA guidelines by abstracting prophylaxis type and dosing, according to corresponding individual patients' VTE risk rating.

Results: Among the 373 020 patients included as study population (with a mean age of 49.08 years and a 38:62 percent split between male and female), 77% required prophylaxis. Of these, 32.81% received some sort of prophylactic measure during their hospital stay. In patients where prophylaxis was indicated, only 24.56% complied with SA guidelines. The most commonly used prophylactic measures where enoxaparin (89.09%) and fondaparinux (2.68%). Prophylactic measures differed per geographical location and speciality - with the highest use in the Tshwane region and most compliant amongst intensivists.

Conclusions: Less than 24.56% of patients who required prophylaxis received guideline appropriate interventions. Further studies should focus on understanding differences in practice and to improve acceptance of guideline-driven care.

Keywords: venous thromboembolism prophylaxis, hospital, South Africa

LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
aPTT	Activated partial thromboplastin time
ANOVA	Analysis of variance
APCC	Activated prothrombin complex concentrate
BIU	Business Intelligence Unit
BMI	Body mass index
CDC	Centers for Disease Control
CG	Clinical Guideline
COPD	Chronic obstructive pulmonary disease
CPT	Current procedural terminology
CVC	Central venous catheter
DVT	Deep vein thrombosis
ECT	Ecarin clotting time
ENDORSE	Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting (study)
EU	European Union
FDA	United States Department of Health and Human Services Food and Drug Administration
FFP	Fresh frozen plasma
FP	Foot pump(s)
FV	Factor five (V)

List of abbreviations (continued)

FV R506Q	Factor five (V) Leiden
GFR	Glomerular filtration rate
GP	Glycoprotein
H_0	Null hypothesis
H_a	Alternate hypothesis
HIT	Heparin induced thrombocytopenia
HIV	Human immunodeficiency virus
HREC	Health Research Ethics Committee
IBD	Inflammatory bowel disease
ICAM	Intercellular adhesion molecule
ICU	Intensive care unit
IMPROVE	International Medical Prevention Registry on Venous Thromboembolism
INR	International normalised ratio
IPC	Intermittent pneumatic compression
IPCD	Intermittent pneumatic compression device
ITGAL	Integrin alpha L
IU	International units
LMWH	Low molecular weight heparin
mRNA	Messenger ribonucleic acid
MUSA	Medicine Usage in South Africa
NHS	The National Health Service

List of abbreviations (continued)

NOAC	Non-Vitamin K oral anticoagulant
NSAIDs	Non-steroidal anti-inflammatory drugs
NWU	North-West University
PAF	Platelet-activating factor
PE	Pulmonary embolus
PCC	Prothrombin complex concentrate
PICC	Peripherally inserted central catheter
PTT	Partial thromboplastin time
RAP	Risk assessment profile
Rx	Medical prescription
r-FVIIa	Recombinant activated factor VII
SAP®	Systems Applications and Products
SASTH	Southern African Society of Thrombosis and Haemostasis
SLE	Systemic lupus erythematosus
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
TB	Tuberculosis
TF	Tissue factor
TT	Thrombin time
TTO	To take out
TUNE-IN	The Use of VTE prophylaxis in relatioN to patiEnt risk profiling (TUNE-IN) Wave 2 study

List of abbreviations (continued)

UFH	Unfractionated heparin
USA	United States of America
VKA	Vitamin K antagonist
VKOR	Vitamin K 2.3-epoxide reductase enzyme
VTE	Venous thromboembolism

LIST OF DEFINITIONS

Abnormal lung function	Reduced mechanical function of the lung, chest wall, and respiratory muscles after performing validated tests on total volume of exhaled air after forced inhalation (Johnson & Theurer, 2014:359).
Ankle-brachial pressure index	The ratio of the ankle systolic blood pressure to that measured at the brachial artery (Aboyans *et al*., 2012:2890).
Anticoagulant	Medication used to inhibit thrombosis (Moake, 2018; Zehnder, 2012:601).
Child-Pugh score	Three existing categories used to describe hepatic function: "A" meaning good hepatic function, "B" meaning moderately impaired hepatic function and "C" denoting advanced hepatic dysfunction (Tsoris & Marlar, 2019).
Clinical speciality	A branch of medical practice, selected by a clinician in which they concentrate on or is an expert in (Macmillan Dictionary, 2009).
Chronic obstructive pulmonary disease	Enduring inflammatory lung disease resulting in decreased airflow from out the lungs (Devereux, 2006:1142).
Congestive heart failure	Enduring, progressive reduction of pumping ability of the heart muscles (Hallstrom *et al*., 1995:1257).
Current Procedural Terminology	A standardisation system describing the terminology and coding for medical services and procedures (AMA, 2016).
Day case	Day cases are defined as hospital cases where the patient was admitted and discharged from the hospital on the same calendar day (Ranchod *et al*., 2015:315).
Deep vein thrombosis	A blood clot that forms in one or more deep-seated veins of the human body (CDC, 2019).

List of definitions (continued)

Hypercoagulability	A predisposition to have thrombosis due to inherited disorders (Thomas, 2001:2433).
Miocardial infarction	Changes (such as cell death) occurring in the heart muscle because of a sudden deficiency of circulating blood (Thygesen, 2007).
Narrow therapeutic index	Medication where small changes in dosing or blood concentration may lead to serious adverse drug events, possibly resulting in patient harm or death (FDA, 2017).
Paget von Schrotter syndrome	An effort-induced thrombosis of the acillary and subclavian veins due to compression of the subclavian vein at the site of the thoracic outlet (Saleem & Baril, 2018).
Pneumonia	Inflammatory illness of lungs where patient has any of the following, absence of runny nose and presence of breathlessness, crackles and diminished breath sounds on auscultation, heart rate of more than 100 beats per minute and fever (Moore *et al*., 2017).
Prophylaxis	A measure taken to improve health and prevent a disease (Cambridge Dictionary, 2019).
Pulmonary embolism	A sudden blockage in a lung artery caused by a blood clot occurring in another part of the human body which dislodges and travels through the venous system to the lung (Weitz, 2011:620).
Sepsis	Lethal organ dysfunction due to a dysregulated host reaction to infection (Singer *et al*., 2016:809).
Thrombus	A blockage in an artery or vein caused by a blood clot (Chen, 2018).

List of definitions (continued)

Toxaemia	Condition of reduced perfusion of the pregnant uterus causing the formation of molecules able to damage the uterus and causing harm to both mother and fetus (Chappel & Bewley, 2005).
Venous thromboembolism	A disease that includes the development of deep vein thrombosis as well as pulmonary embolism (CDC, 2019; Ozaki & Bartholomew, 2012).
Varicose veins	Enlarged convoluted, superficial veins of the leg resulting due to poor valve function within veins (Tisi, 2011).

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CHAPTER 1: INTRODUCTION

1.1 Introduction and background to the study

Thrombus formation is a natural homeostatic response of the human body aimed at bleeding prevention caused by physiological trauma (Smeltzer *et al.*, 2010:653; Tang *et al*., 2016:49). The formation of thrombi results from the activation of the three Virchow triad factors (Ritter *et al*., 2008:204). The triad, essential to thrombosis, is blood stasis (secondary to immobility, congestive heart failure or compression of veins), alteration to a vein wall (secondary to previous thrombosis, vein inflammation/infection, direct vein wall trauma, varicose veins) and blood hypercoagulability (Illustrated Dictionary of Podiatry and Foot Science, 2009). These factors are responsible for the activation of immune system components and changes in the endothelial blood vessel lining that promotes clumping of red blood cells and fibrin, resulting in venous stasis and a state of hypercoagulability (Beers *et al*., 2006:754; Govindarajan *et al*., 2016:1869; Ritter *et al*., 2008:204). Complications occur when a segment of the formed thrombi separates and lodges in an artery, cutting off essential blood flow to the affected organ, which results in anoxia (deficient oxygen state) and cell death (Beers *et al*., 2006:755; CDC, 2018). Deep vein thrombosis (DVT) refers to venous system occlusion, most common in the lower extremities (Kaushal, 2016). This occlusion can detach from the vein wall and migrate throughout the body, leading to pulmonary vasculature cut-off, more commonly referred to as 'pulmonary embolism' (PE) (Ritter *et al*., 2008:204). Deep venous thromboembolism and PE can present either individually or as a combination of pathological manifestations known as a venous thromboembolic (VTE) syndrome (Beers *et al*., 2006:754; CDC, 2019).

Many ancillary pathological manifestations are associated with VTE formation and occur when formed thrombi migrate and occlude arteries at critical organ(s). Post-thrombotic syndrome, for instance, occurs when a clot remains in the femoral vein for an extended period, causing damage to the vein wall or valve(s) (Goldhaber, 2010:217; Hicks *et al*., 2016:1004; Smeltzer *et al.*, 2010:654). This can result in a backflow of blood in the leg with additional thrombus formation, which may compound the problem (Goldhaber, 2010:217). Thrombotic occlusion at the pulmonary arteries, however, may lead to chronic thromboembolic pulmonary hypertension (when partial) or even PE when a complete arterial occlusion occurs (Wilbur & Shian, 2017:295). Sadly, the first symptom in up to 25% of these patients suffering from PE is sudden death (CDC, 2018). The lack of specific symptoms associated with underlying emboli results in PE being responsible for 10% of all annual preventable deaths worldwide (Beers *et al*., 2006:754; Nielsen, 2013:29; Ritter *et al*., 2008:204). Other pathologic manifestations of VTE include renal vein thrombosis,

myocardial infarction and cerebrovascular occlusions (Goldhaber, 2010:217; Hicks *et al*., 2016:1004).

It is estimated that the prevalence rate of VTE was approximately 900 000 people in the United States of America (USA) and approximately one million in Europe (0.26% to 0.39% of the estimated population of 2012) (CDC, 2018). An annual DVT and PE prevalence growth of 2.4%, with or without DVT, was predicted for both the USA and Europe as far back as 2012 (Jha *et al*., 2013:809). Venous thromboembolism prevalence in the USA is estimated to increase from 0.95 million in 2006, to 1.82 million in 2050 (Deitelzweig *et al*., 2011:2019); while the USA incidence for VTE is predicted to rise from 3.17 per 1 000 persons in 2006 to 5.67 per 1 000 persons in 2050, hereby making VTE a substantial burden on healthcare systems (Jha *et al*., 2013:809). Latest figures show that between 5 and 8% of people living in the USA are genetically predisposed to an increased risk for thrombosis and VTE (CDC, 2018). The risk of VTE development in South African hospitalised patients admitted in Gauteng has been described to be as high as 74.6% (Riback & Wessels, 2012:85). According to Statistics South Africa (2016), thromboembolic disease is responsible for 20 000 deaths annually. However, since most VTE symptoms remain undetected (Kooiman *et al*., 2015; Luciani *et al*., 2001:655), the true incidence of the disease in South Africa remains unknown.

Screening of VTE is necessary as pre-warning symptoms mostly go unnoticed (Luciani *et al*., 2001:655). Literature has shown that risk assessment of patients' VTE propensity reduces mortality (Roberts *et al*., 2013:1276; Roswell & Noakes, 2017:5). It is, therefore, unacceptable to solely rely on early diagnosis while not performing VTE prophylactic screening, because many patients could die before treatment can be initiated (Smeltzer *et al*., 2010:655). Deep vein thrombosis risk assessments are developed to select only those patients where DVT prophylaxis benefits would outweigh its risk – namely patients with a medium or high VTE propensity (Caprini, 2005:70; Grant *et al*., 2016:533; Obi *et al*., 2015:941). Pharmacologic and mechanical prophylactic interventions have demonstrated to be effective in preventing VTE-related morbidities in up to 70% of these patients (Lau & Haut, 2014:190; Roswell & Noakes, 2017:5). It has also been shown, through study, that VTE prophylactic measures are being under-prescribed, as fewer than half of hospitalised patients receive these interventions (Riback & Wessels, 2012:85; Kahn *et al*., 2013:7). Venous thromboembolic-related complications due to poor prophylactic practices furthermore resulted in 64.4% of annual premature deaths in both Europe and the USA (Jha *et al*., 2013:809). Given that VTE is potentially fatal and costly to treat, strategies to prevent VTE in at-risk populations will possibly prove to be beneficial with regard to patient health outcomes (Roswell & Noakes, 2017:1; Smeltzer *et al*., 2010:655).

The National Institute for Health and Care Excellence (NICE) clinical guideline 92 (CG92) recommends that all patients be assessed for VTE risk on admission to enable prescribers to decide on appropriate prophylaxis (NICE, 2015; NICE, 2018). However, poor nursing VTE risk assessment compliance has been described (NHS UK, 2015:2; Wilson, 2015:2). This is often a significant limitation not reported in studies, aiming at determining whether the prescribing of VTE prophylaxis is in accordance to guidelines (Wilson, 2015:1). It is consequently in the interest of a developing, resource-constrained country such as South Africa to establish the patterns of VTE prophylactic prescribing in a part of the health sector not governed by protocols and where cost containment, which includes preventable risk management, is desirable (Donnelly, 2016).

The safety of hospitalised patients (Cayley, 2007:147) is of great importance, and therefore it is necessary to measure patterns of VTE prophylaxis against recommended guidelines of the 2013 – Southern African Society of Thrombosis and Haemostasis (SASTH) (Jacobson *et al*., 2013:261). This study aimed at interpreting these obscurities by investigating the prevalence of private hospitalised patients across South Africa who required VTE prophylaxis as well as the appropriateness of the prophylaxis received. The study data were collected over a large geographical area spanning all the provinces of South Africa and included various prescriber specialties.

1.2 Problem statement

The VTE development risk for hospitalised patients is described to be high, both globally and in South Africa (Riback & Wessels, 2012:85). It has been shown, through research, that VTE prophylactic measures are able to save countless patients' lives (Lau & Haut, 2014:190). However, uncertainty exists towards the extent of compliance to accepted South African VTE prophylactic guidelines (Riback & Wessels, 2012:85). With these problems at hand, the research questions formulated for this study were:

- What is the prevalence of hospitalised patients requiring mechanical and/or pharmacologic VTE prophylaxis as set out by local 2013 SASTH guidelines?

- Do prescribers follow SASTH guidelines for VTE prophylaxis in a South African healthcare setting where protocols and formularies do not dictate prescribing?

- What is the percentage of VTE prophylaxis compliance to SASTH guidelines between the different clinical specialities?

This research endeavoured to address gaps in the existing knowledge base. The study contributed to a new perspective about the risks of inappropriate VTE prophylaxis and the

prevalence of patients who required prophylaxis while being hospitalised in private institutions throughout South Africa. An increase in understanding of the quality of healthcare rendered to VTE risk-rated patients was achieved after study result analysis.

1.3 Research aims and objectives

The general aim of the study was to evaluate the risk of VTE development, based on individualised patient VTE risk scoring, and the appropriateness of VTE prophylaxis used in patients who have been admitted to a South African private hospital group, between 1 September 2015 and 31 August 2016.

The study aimed to collect information on the prevalence of patients requiring pharmacological VTE prophylaxis (i.e. those rated as having a medium and high risk for VTE development) and the appropriateness of the prophylaxis received according to accepted local SASTH guidelines.

The study consisted of a literature review and an empirical investigation, each made up of its own objectives.

1.3.1 Literature review

Specific objectives for the literature review included the following:

- Contextualisation of VTE in order to form a better understanding of the disease mechanism, risk factors for its development, as well as complications associated with VTE development.
- Description of VTE prophylaxis through its mechanism, the reasons for patients to require VTE prophylaxis, as well as the type of mechanical or pharmaceutical prophylaxis as suggested by literature or accepted guidelines.
- Explanation of methods used to grade patients as having a low, medium, or high risk for VTE development as well as the determination of VTE development prevalence in these hospitalised patients, rated medium to high risk, as reported both locally and internationally.
- Review of the adherence of prescribers, per clinical speciality, to published VTE prophylactic guidelines as reported by local and international research publications.

1.3.2 Empirical investigation

The study focused on the use of pharmacologic and/or mechanical prophylaxis compared to published local guidelines. The specific empirical objectives for this study were to:

- Determine the prevalence of admitted patients who were not risk-rated as well as those who were risk-rated (having a low-, medium-, or high risk for VTE development) during the study period, 1 September 2015 to 31 August 2016.
- Evaluate the compliance and non-compliance of VTE prophylaxis management according to the recommended SASTH guidelines for each risk-rated group.
- Determine the association between SASTH guideline compliance and clinical specialties by risk group, using inferential statistics.

1.4 Research methodology

The research consisted of a literature review and an empirical investigation. No intervention or modification of standard care was carried out during this study.

1.4.1 Study design

The proposed study design was a quantitative, observational, descriptive, retrospective study. This type of study is a subcategory of the non-experimental design (Brink, 2012:102).

According to Machin and colleagues (2007:150), quantitative research aims to determine the relationship between two types of variables in a study population, namely the dependent and independent variable. A study with a non-experimental design is where the researcher's aim is not to influence or to control the independent variable that has an effect on the dependent variable, but rather to describe the effect that the independent variable has on the dependent variable (Brink, 2010:102). For descriptive studies, the applicable risk factors and their occurrence in a population are described (Brink, 2010:102-103).

Data used for the proposed study were for patients admitted from 1 September 2015 to 31 August 2016, which are historic in nature and the study is therefore retrospective. Different dependent and independent variables were measured, and their occurrences described without the researcher intervening. This resulted in a quantitative, descriptive, observational study that was non-experimental in nature.

The literature review focused on the most recent publications regarding the prevalence of VTE in hospitalised patients and the VTE prophylaxis guidelines with specific reference to those applicable to South Africa.

English articles were reviewed and critiqued. Electronic searches were conducted both manually and by utilising online databases, with results used in the literature review. The researcher utilised scientifically accredited databases, which included the following:

- Google Scholar™, EMBASE®, Ovid MEDLINE®, Cochrane Database of Systematic Reviews®, EBSCOhost®, Springerlink®, Scopus®, Read by QxMD®, as well as pharmaceutical textbooks.

Scientific information was searched with filtered parenthesised phrases to ensure greater accuracy in search results. The following are examples of words and/or phrases that were used either in combination or individually:

- “VTE”, “DVT”, “deep vein thromboembolism”, “venous thromboembolism”, “prophylaxis”, “VTE prophylaxis”, “safety”, “high risk”, “hospitalized”, “hospitalised”, “medium risk”, “low risk”.

During the empirical investigation, an assessment of VTE risk and treatment at a private South African hospital group was carried out.

1.4.2 Study setting and data source

Study data were obtained from one of the largest South African private hospital groups’ in-patient database. The study setting was selected due to its large geographical representation across South Africa in order to possibly reach a more representative assessment on prescribing practices across different clinical specialties. A private hospital group was selected, as prescriber habits are not governed by health sector formularies and restrictions. The identity of the study hospital group may not be disclosed with the reporting of study results due to a confidentiality agreement (refer to Annexure A). The hospital group consisted of 56 hospitals and a registered bed count of 9 252 at the time of data collection. Data of patient admissions from 1 September 2015 to 31 August 2016 were used, because the utilisation of the modified Caprini risk assessment model was replaced with a doctor VTE risk management tool in September 2016. The uptake of the doctor risk management tool however, remained consistently low, resulting in poor data quality.

All electronic patient-charged data for the study setting were linked to individualised patient case numbers, which were centrally generated to prevent duplication and were available per hospital and date of admission.

Individualised VTE risk scoring using the Modified Caprini risk assessment model (Caprini, 2005:73) has to be performed on each patient across the hospital group by the admitting nurse (Jacobson *et al*., 2013:10; NICE, 2015). The assessed risk, classified by risk profiles such as low, medium- or high risk of VTE, is calculated by the admitting nurse, using the risk assessment model; then, a clinical case manager checks the scoring and captures the result on the electronic patient admission profile. This profile includes all information necessary for medical aid reimbursement (including all surgical and pharmaceutical items charged on the patient account).

Data fields used on the database included:

- Date of admission
- Hospital of admission
- Venous thromboembolism risk-rated profile
- Clinical specialty of prescriber under which the patient was admitted
- Current procedural terminology (CPT) code for comorbidity development during the hospital stay
- Generic name of pharmacological prophylaxis items billed
- Dose of pharmacological prophylaxis billed
- Name of mechanical prophylactic measure billed per patient.

1.4.3 Study risk assessment model

The thrombosis risk assessment model utilised at the study hospital group, and included in this study, is an adapted version of the Caprini risk assessment model (which can be accessed at http://williams.medicine.wisc.edu/caprini_score.pdf and located on page 5 of the document at the website). This is similar to that used by Jacobson and colleagues (2013:261). Table 1-1 provides a summary of the risks and their scoring as contained in the study hospital's risk assessment model.

Table 1:1 Modified risk assessment model of study hospital group

Study hospital group risk assessment model
Risk factors assigned 1 point (low DVT development risk)
• Body mass index (BMI) of > 25 • Swollen legs (current) • Varicose veins • Medical patient currently at bed rest • Planned minor surgery • Acute myocardial infarction (MI) • Abnormal pulmonary function/ chronic obstructive pulmonary disease (COPD) • History of inflammatory bowel disease • History of prior major surgery/in the last 30 days • Suffering from congestive heart failure in the last 30 days • Sepsis in the last 30 days • Age between 41 and 60 years • Different lung diseases including pneumonia in the last 30 days • Women who are pregnant or postpartum 30 days • Women who are taking oral contraceptives or hormone replacement therapy • Women with a history of unexplained stillborn babies, those with more than 3 recurrent spontaneous abortions, those with toxaemia resulting in premature births and those with an infant with slowed growth
Risk factors assigned 2 points
• Age between 61 and 74 years • Those with a central venous line • Present or previous malignancy • Those with an immobilising plaster cast in the last 30 days • Those undergoing arthroscopy • Patients who are immobile for 72 hours and longer • Any planned surgery lasting more than 44 minutes
Risk factors assigned 3 points
• Those older than 75 years • Those with a history of DVT and PE • A family history of thrombosis
Risk factors assigned 5 points
• Patients suffering multiple trauma in the last 30 days • Those with paralysis or acute spinal cord injuries during the last 30 days • Patients with pelvic or hip fractures during the last 30 days • Patients who will undergo planned arthoplastic replacement procedures of hip or knee

When administering the risk assessment, points are awarded according to the different risk factors and their scoring. A total risk factor score of between 0 and 1 would relay a low DVT development risk with a DVT development incidence risk of 10%. Medium DVT development risk is associated with a total risk factor score of 2 and a subsequent DVT developmental incidence of between 10 and 20%. Scores of 3 and more are associated with a high DVT risk level and an incidence of between 20 and 80% for DVT development.

Through comparison of the Caprini and the study risk assessment models, it was found that the layout of the study hospital group's version differed from the original Caprini risk assessment model in that the listing of the risk assessment questions was done from highest to lowest scoring and not grouped. Furthermore, three key differences were found:

- Obesity is classified as having a BMI of above 25 in the study risk assessment model, whereas Caprini listed a BMI of over 30 as obese.

- The study risk assessment model excludes prothrombin 20210A, factor V Leiden, elevated serum homocysteine, anticardiolipin antibody and Lupus anticoagulant tests. This, however, corresponds to the modified Caprini risk assessment model, which was used and verified in a study by Bilgi and colleagues (2016:69). The authors reported that the main reasons for exclusion was the expensive nature of the required tests and that results were often lacking in their study population.

- Contraindications to patients receiving pharmacological prophylaxis and/or intermittent pneumatic compression devices differed from that of the Caprini model in that creatinine clearance value (CrCl), or the ability of kidneys to filter substances (Barrett *et al.*, 2016:645) is not required.

Apart from the above-mentioned, the study hospital group's assessment model further corresponds to that of Caprini. Of note is that the study risk assessment model as well as the Caprini risk assessment model do not include screening for either human immunodeficiency virus (HIV) or tuberculosis (TB). These two risks are included in the SASTH guidelines and the fact that they are not explicitly included, may be a pitfall when administrating either the Caprini or study risk assessment in the South African setting. The study risk assessment model, however, does refer to "Various different lung diseases including pneumonia in the last 30 days" and "Medical patient currently at bed rest", which may broadly include TB and to a lesser extent HIV. A possible reason for not explicitly naming HIV and TB as risk factors in the study risk assessment is to protect patient confidentiality as this form may be accessible as it is contained in the patient's file at bedside.

It is worth saying that the hospital group's risk assessment form also relies on the manual calculation of BMI (as with all other risk assessment models described under section 2.6). This may result in incorrect patient risk ratings due to calculation errors or where values for height and weight are based on patient self-reporting. A study by Rothman (2008:eS56) has shown that this is often a great pitfall in BMI calculation and causes many incorrect risk ratings for patients. A discussion on the impact of manual BMI calculation follows in section 2.7 of this dissertation. Even though a danger does exist for over-stratification of patient risk, studies conclude that risk assessment (especially those based on Caprini) forms the basis for appropriate and safe prophylactic care (Grant *et al*., 2016:533; Obi *et al*., 2015:941).

1.5 Sampling

All-inclusive sampling was performed, as all patient data that met the inclusion criteria were used.

1.5.1 Target and study population

Patient data for those admitted to the study hospital group, either as day cases or patients staying in hospital longer than one day, between 1 September 2015 and 31 August 2016, were taken as target population.

1.5.2 Study population

The study population was those patients whose data were analysed for the purpose of this study. The study population was determined from the target population by means of using inclusion and exclusion criteria.

1.5.2.1 Inclusion criteria

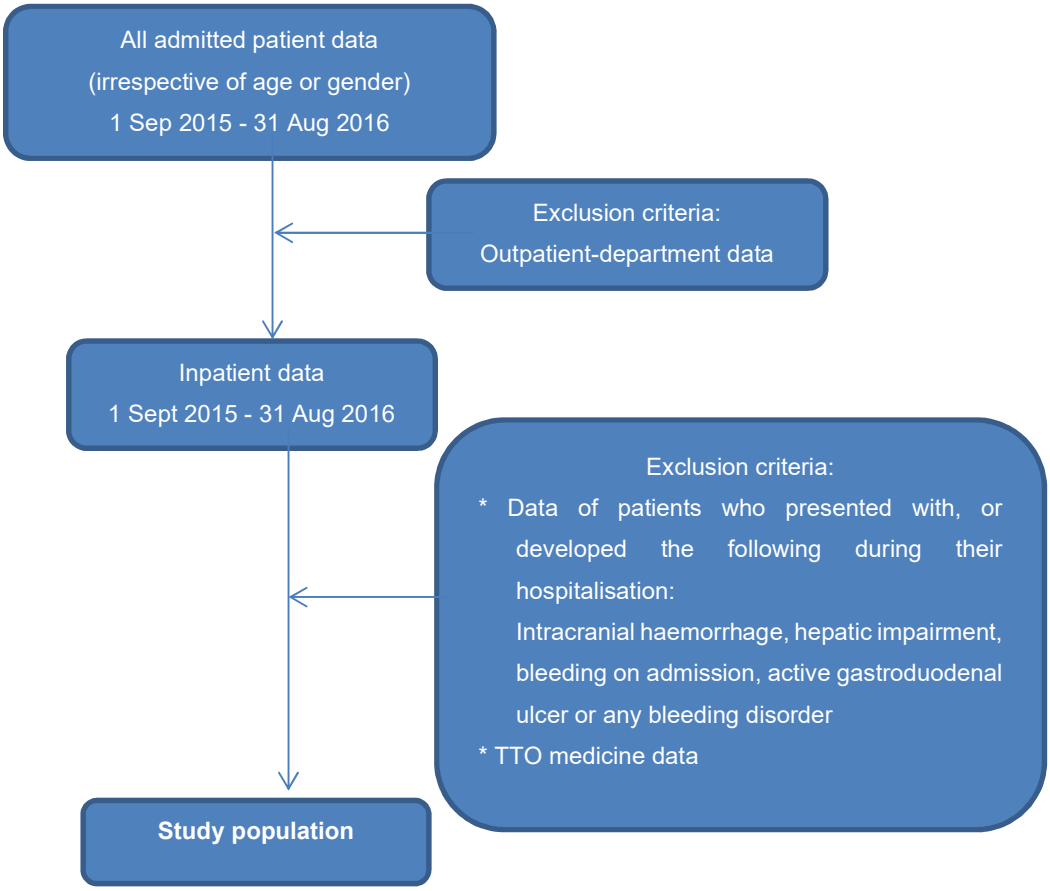
Data of all admitted patients (surgical day cases or longer stay admissions of all clinical specialities), irrespective of gender or age, from 1 September 2015 to 31 August 2016.

1.5.2.2 Exclusion criteria

Utilised exclusion criteria are bulleted below, with a diagrammatical representation of the study population selection method following on page 11:

- Data of patients treated in the outpatient department and not admitted to the hospital.
- Data of patients who presented with or developed during their hospitalisation, any of the following: intracranial haemorrhage, hepatic impairment, bleeding on admission, active gastroduodenal ulcer or any bleeding disorder.

- Data of pharmacologic prophylaxis or any medication prescribed to patients to take home once discharged were excluded due to the inability to determine compliance to the treatment.



TTO: "To take out" medicine, medicine prescribed to be taken home once patient is discharged.

Figure 1:1 Steps in selection of study population

1.6 Data analysis

The prevalence of medium- or high-risk VTE patients receiving pharmacological prophylaxis is an example of some of the variables that were analysed during the proposed study. For this study, several variables' prevalences were compared and their distribution described to answer the stipulated research questions and monitor trends. The prevalence of patients requiring VTE prophylaxis and the appropriateness of prophylactic measures used (according to SASTH guidelines) were studied from data obtained from the study hospital group.

1.6.1 Variables

Data received for analysis were of all patients admitted during the study period and included the following:

- All admitted hospital in-patients' VTE risk scores as determined on hospital admission by the admitting nurse (whether patient risk was documented or not). Venous thromboembolism risk scoring is done routinely for each patient admitted to all the facilities of the hospital group. The VTE risk scores are then checked for accuracy and captured on the study hospital group's Systems and Analysis Program (SAP®) by the clinical case managers for medical aid or private billing purposes. All captured VTE risk scores per patient were analysed to establish the prevalence of those requiring prophylaxis, i.e. patients rated as having a medium to high risk for VTE development on the risk assessment model.

- Billing data on the actual VTE prophylaxis (generic name and mechanical measure) and quantity for each patient were collected and compared to SASTH guidelines. This was done in order to establish the appropriateness of therapy used. Prophylaxis data were extracted from itemised, per patient billing data captured by pharmacy staff on the hospital group's electronic charging system SAP®. The researcher reviewed each patient's data according to VTE risk captured and prophylaxis received, against local SASTH guidelines. After review, the researcher then indicated on the spreadsheet those patients with correct prophylaxis as 'compliant' and others as 'not compliant'.

- Data on the clinical speciality under which the patient is admitted were also captured. All patients are admitted under a clinical specialty according to CPT codes retrieved from the admitting doctor's diagnosis. This was captured for each patient by the clinical case managers on SAP® and verified for accuracy by hospital file assessors (as standard procedure). This was done to determine the clinical speciality of the prescriber.

Current Procedural Terminology codes are generated according to the doctor's diagnosis and captured upon patient admission or during the patient's hospital stay. This was included in the data received in the database. In order to determine which patients were admitted with or developed comorbidities during their hospital stay, CPT codes for these comorbidities (intracranial haemorrhage, hepatic impairment, bleeding on admission, active gastroduodenal ulcer, or suffering from any bleeding disorder) were used to exclude data for the study (refer to section 1.5.2.2).

1.6.2 Data analysis plan

In order to answer the stipulated research questions on the prevalence of patients who require VTE prophylaxis (those who were rated as having a medium- or high VTE development risk), the study population data were divided into two groups, namely patients who were not VTE risk-rated and those patients who were. The risk-rated group's data were further subdivided into that of "low risk", "medium risk" and "high risk", in order to classify patients on VTE risk development.

In order to enable the researcher to evaluate the prescribing compliance according to the SASTH guidelines, the prevalence of patients who were not risk-rated was calculated (not risk-rated patients are not in compliance to SASTH guidelines). Compliance to guidelines for those patients who were rated was calculated by comparing prophylaxis prescribed to the "medium risk-" and "high risk-" rated patients to that suggested by the SASTH guidelines for each type of VTE development risk-rated patient. This was done using descriptive statistics.

Inferential statistics were then utilised to determine the association between the different prescriber specialties' prescribing compliance to the SASTH guidelines.

The summarised process that was followed for data analysis is outlined in Figure1:2. The data analysis plan is outlined Table 1:2.

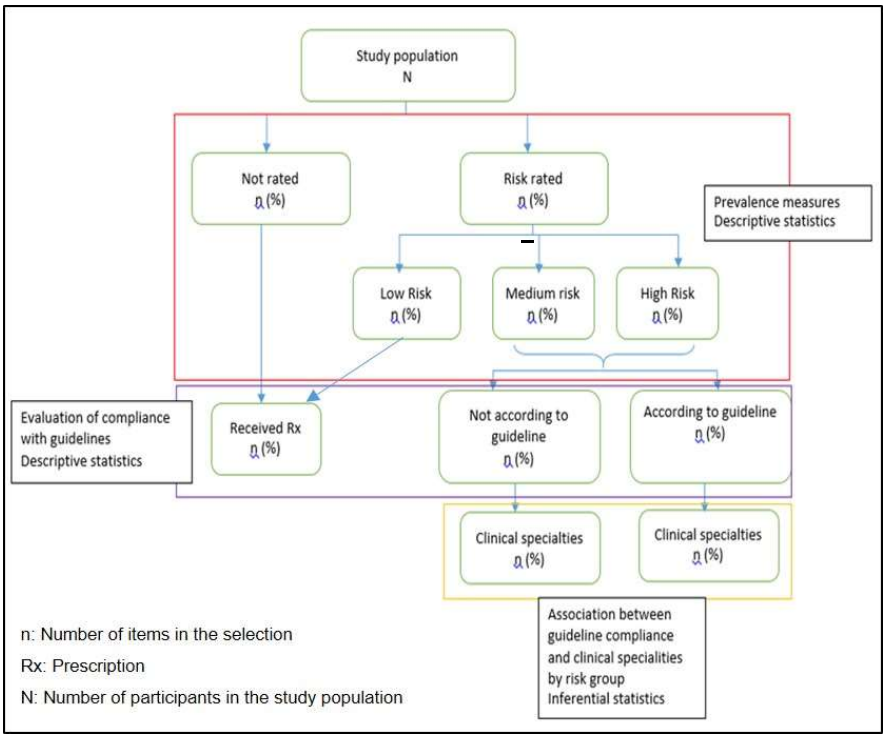


Figure 1:2 Steps of data analysis plan

Table 1:2 Data analysis plan

		Study variables	Proposed statistical techniques			
Objective	**Measurements**	**Dependent variable**	**Independent variable**	**Descriptive statistics**	**Inferential statistics**	**Effect sizes**
Determine the prevalence of admitted patients who were not risk-rated as well as those who were risk-rated (having a low, medium, or high risk for VTE development) during the study period 1 September 2015 to 31 August 2016.	Demographic profile of patients on database during study period Difference in age of patients by gender	Gender Age		Frequency (%) If normal distribution: Mean ± SD, 95% CI If skewed distribution: Median, IQR	Student t-test	Cohen's d
	Number of patients by risk rating	Risk rating (none, low, medium, high)	Number of patients	Frequency (%)		
	Association between demographic profile of patients and risk rating.	Risk rating (none, low, medium, high)	Gender Age group	Frequency (%)	Chi-square	Cramér's V

Table 1-2: Data analysis plan (continued)

		Study variables	Proposed statistical techniques			
Objective	**Measurements**	**Dependent variable**	**Independent variable**	**Descriptive statistics**	**Inferential statistics**	**Effect sizes**
Evaluate the compliance and non-compliance of VTE prophylaxis used (which includes generic name and mechanical measure with quantities used) and compared according to the recommended SASTH guidelines for each risk-rated group.	Determine compliance by risk rating	Compliance (yes/no)	Risk rating (none, low, medium, high)	Frequency (%	Chi-square	Cramér's V
Determine the association between SASTH guideline compliance and clinical speciality with the use of inferential statistics.		Clinical speciality	Compliance (yes/no)	Frequency (%)	Chi-square	Cramér's V

1.6.3 Validity and reliability of data

A test for the reliability of this scoring method was performed by Obi and colleagues in order to establish whether the method of risk scoring of VTE patients provides accurate data (2015:347). This was done in a population of 1 470 general surgery inpatients, whose VTE risk was prospectively assigned by physician assistants during patient history taking and then again during clinical physical assessment. The weighted kappa coefficient, comparing these approaches, was 0.572 (0.572-0.618, $p < 0.001$), indicating acceptable agreement (Obi *et al*., 2015:350). Therefore, valid and reliable data were generated for the purpose of conducting this study, by relying on a method where patients are scored on admission and where this data were analysed instead of utilising clinician notes.

It was important to ensure that all information was gathered from a reliable and accurate source to avoid the risk of reporting on data that were not valid or reliable. The research study was conducted assuming that all the data are accurate. However, precautions such as the performing of data checks by clinical case managers at each hospital site, to ensure correctness as well as the performing of data outlier checks by the researcher, were in place during statistical data analysis.

Another responsibility of the researcher was to ensure the validity and reliability of the research process. According to recommendations published by the United States Department of Health and Human Services Food and Drug Administration (FDA) (2013:4), the guidelines for reporting observational studies as described by Von Elm and colleagues (2008:346-347) should be used. This is because important information is often missing or unclear in observational research. The checklist designed to provide guidance on how to conduct proper research in epidemiological studies is referred to as “Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)”. The items from the checklist (Von Elm *et al*., 2008:346-347) relevant to this study are indicated in Table 1:3 and provided a guideline to ensure the validity and reliability of the research process.

Table 1:3 Applied STROBE checklist

Checklist consideration	Item in checklist	Approach followed in study
Title and abstract	The study's design should be indicated in the title and/or abstract with a commonly used term. The abstract should contain an informative and summarised version of what was done in the study as well as results found	A commonly used term was included in the title of the study ("assessment") to indicate that prescribing practices per medium or risk-rated patient of VTE prophylaxis, would be evaluated and compared to local guidelines A manuscript was included which summarised findings
Introduction: Background	The scientific background and rationale for the investigation being reported must be explained	A summary was included in the introduction, outlying the key features of the study
Objectives	The researcher must include specific objectives and hypotheses	The general research aim, including specific research objectives for both the literature and empiric phases, were included and described
Methods	Important elements of study design should be stated early in the paper	A data analysis plan as well as rationale for study design were included in Chapter 1
Setting	The study setting, locations and relevant dates, including periods of recruitment, exposure, follow-up and data collection must be clearly described	Both the study setting and data source as well as study time frame, inclusion and exclusion criteria were described in paragraphs 1.5.1 to 1.5.2.2
Variables and data source measurement	A clear definition of all outcomes, exposures, predictors, potential confounders and effect modifiers must be given	Definitions of data variables and measurements were given in paragraph 1.6 and its subsections
Bias	All efforts to address potential sources of bias must be described	A specific period was set for inclusion of data. Selection bias could not occur as all data matching inclusion criteria were used for the purpose of the study (refer to paragraphs 1.5.5 and 1.5.5.1)
Study size	An explanation should be given on how the sample size of the study was determined	A specified period of 1 year was used to account for variations in prescribing; therefore, no sample size had to be calculated
Results	The number of individual patient data should be reported at every study stage. Unadjusted estimates should be reported. All other analyses must be described	All data analyses and the number of individual patient data (as set out in paragraph 1.10) were reported and was set out in Chapter 3 of this mini dissertation

Table 1.3 : Applied STROBE checklist (continued)

Checklist consideration	Item in checklist	Approach followed in study
Discussion	Important results should be summarised and put into perspective with their study objective. Results should be interpreted and discussed All study limitations should be named and discussed	Results as obtained from this study were summarised, interpreted and discussed in a manuscript format (set out in Chapter 3 of this mini dissertation).

1.7 Statistical analysis of data

Statistical analysis on the data was performed using Statistical Analysis System®, SAS 9.3® (SAS Institute Inc., Cary, NC, USA) with the help of a statistician at the North-West University. To assist with the general computations, Microsoft Office Excel® 2010 was used.

The statistics used in this study can be classified into two categories, namely descriptive and inferential (Table 1-1). Descriptive statistics describe and summarise data (Brink *et al*., 2012:179). In other words, it is a method of arranging, organising, summarising and presenting data; this data presentation could be in the form of tables, charts or statistical measures. Inferential statistics use sample data to make an inference about the population of the study at hand from a smaller sample (Brink *et al*., 2012:179).

Descriptive statistics were used to describe the statistical data by summarising and then tabulating the aggregate data (using common descriptive statistical methods). These methods included: frequency or prevalence statistics such as count, mean or arithmetic average and standard deviation. When data are not distributed normally, the cause for this distribution should be determined and then an appropriate remedial action was implemented by the researcher with the help of a statistician (Ghasemi & Zahediasl, 2012:486). To ensure normally distributed data for statistical analysis during this study, data were represented in graphical form. Bimodal and/or multimodal data were stratified according to patient age, gender and prescriber speciality (McCluskey & Lalkhen, 2007:129). The size of data used was larger than 30 and the Shapiro-Wilk normality test was performed (Ghasemi & Zahediasl, 2012:488).

Inferential statistics make inferences and predictions about a population, based on a sample of data taken from the population. For this study, inferential statistics were used and included the Pearson's chi-square test.

The Pearson's chi-square test was performed to determine whether the deviation between the observed and expected counts was too large to be due to chance (Peat & Barton, 2005:219). For

this proposed study, the Pearson's chi-square test was used to determine whether the observed number of patients receiving prophylaxis and the expected prophylaxis according to SASTH guidelines (which should be zero) were too large to be attributed to chance.

The data obtained for this study are categorical, as results are obtained relating to "Compliant to the SASTH guideline" and "Non-compliant to the SASTH guideline" answers. The null hypothesis (H_0) would have stated that the prevalence of patients receiving prophylaxis calculated is only due to sampling error (Petrie & Sabin, 2000:42). The statistical difference would then be due to chance and insignificant. With regard to the alternate hypothesis (H_a), the calculation for prevalence of patients receiving prophylaxis is statistically significant and correlates to what is actually observed in the population (Petrie & Sabin, 2000:42).

Because statistically significant differences are more likely to occur with large sample sizes, effect sizes (or measures of association) are necessary to understand whether the differences are meaningful. Effect sizes reveal the practical or meaningful differences in data regardless of sample size. For Pearson's chi-square analyses (as was conducted in this study), the effect sizes could be calculated using Cramér's V (Cohen, 1988:25). Cramér's V defines a perfect relationship as one that is predictive and defines a null relationship as statistical independence (Cohen, 1988:25). Following recommendations from Cohen on the interpretation of effect size (1988, 25), examples of effect sizes that were used are 0.1 = small effect, 0.3 = medium effect and 0.5 = large effect. For this study, statistically significant measures with a small effect size or greater would indicate a meaningful difference.

1.8 Ethical considerations

Ethical considerations required for this study are laid out in the following sections.

1.8.1 Permission and informed consent

Since retrospective medical data were used for this study, a request to waive individual patient informed consent was made to the Health Research Ethics Committee (HREC) of the Faculty of Health Sciences of the North-West University (NWU).

The HREC granted ethical permission (NWU-00080-17-S1). The ethics approval letter is contained in Annexure D, and permission was then sought (in writing) and obtained from the study hospital group's Ethics in Research Committee. The study hospital group's Ethics in Research Committee permission letter is included in Annexure C.

1.8.2 Anonymity

On admission, a patient signs a patient admission form, which gives consent to the admitting facility to share their information with third parties such as clinical case managers who ensure accuracy of information before forwarding it to medical aid claims. The data for the proposed study were extracted after medical aid claims had been concluded and were anonymous in nature. Data used were depersonalised by automatic exclusion of patient admission numbers by the study hospital group's Business Intelligence Unit (BIU). These patient admission numbers were automatically replaced using numerical identifiers by BIU. It therefore was not possible to trace any numbers back to an individual patient. The received datasheet was the only copy available for data extraction and study purposes.

1.8.3 Confidentiality

Steps to safeguard the privacy of patients included the application of the private hospital group's policies and procedures that comply with the Protection of Personal Information Act (4 of 2013) by utilising depersonalised data for extraction and research.

All participating parties (study supervisor, co-supervisor and statistician) signed a confidentiality agreement (refer to Annexure A), which stated that the name of the hospital group may not be made public with the reporting of study results. A copy of these forms is kept in a locked cabinet in the office of Medicine Usage in South Africa (MUSA) and the originals, locked in the office of the participating hospital group's Ethics in Research Committee.

1.8.4 Justification of study participants

This investigation endeavoured to answer gaps in the local knowledge base on the routine VTE prophylaxis usage patterns for hospitalised patients. In order to best try and answer the research question, retrospective, electronic patient data were used for hospitalised patients. The study participants' data included were selected on the basis of specific criteria where VTE prophylaxis would have been indicated according to published guidelines for hospitalised patients. These participants were admitted through private facilities and were included because the study aimed to explore prescribing patterns of VTE prophylaxis in institutions not routinely governed by guidelines (Essential Drug List or hospital-specific treatment guidelines as is routine in the public health sector). Study participant data included were done to best mimic day-to-day hospital admissions encountered in these facilities, in order to ensure study generalisability.

1.8.5 Respect for study participants

Ethical research responsibilities to those studied (or in this case, those whose data are being analysed) must include methods to protect participants and bring no harm to them and the community they reside in.

In order to prevent inducing harm, identifiers of the patients whose data were studied were not included in the data received from the hospital group's BIU so that confidentiality was ensured. To render hospital group inclusivity, all results were summarised in a written report and submitted to their quality leadership manager after conclusion of the study.

Patients whose data were analysed did not endure harm, as the data used were retrospective in nature. Upon release of the findings of the study, both patients being treated and clinicians who will be treating them in the future would possibly gain information on current prescribing practices and where to possibly improve or maintain methods of prophylaxis.

Any misunderstandings that may occur due to the study had to be pre-empted by the researcher and counteracted. This was done by giving quarterly feedback to the hospital group's quality leadership manager on the study progress. This enabled the hospital group to voice concerns/request alterations and ensure reciprocity. Any alterations that may have been requested by the study hospital group would have been submitted for HREC approval before continuation of the study or result reporting. None were raised.

Data used for the purpose of this study would remain the intellectual property of the hospital group and were destroyed/deleted from any device belonging to the researcher, study supervisors or statistician when the study had been concluded.

1.8.6 Risk benefit ratio analysis

It is of great importance that the risk-to-benefit ratio of this study be balanced, with benefits outweighing the risks (Brink *et al*., 2012:39-40).

1.8.6.1 Anticipated benefits

In this study, the benefits outweighed the risks, with the benefits that the study holds outlined in the following sections.

1.8.6.1.1 Direct benefits

There was no direct benefit to individual patients as they could not be identified within the database to provide feedback to them.

1.8.6.1.2 Indirect benefits

- An improvement in preventive health measures may be reached as the results show that patients admitted to the private health sector of South Africa were generally receiving prophylaxis different to published guidelines.
- This may possibly lay the groundwork to draw attention to and improve the VTE prophylaxis in medium- to high-risk patients.

1.8.6.2 Anticipated risks and precautions

Explanations are furnished with regard to anticipated risk to the researcher and study patients in the following sections. These sections also include precautions taken by the researcher to minimise anticipated risks.

1.8.6.2.1 Anticipated risks to the participants and precautions taken

The proposed study was a minimal risk study since retrospective hospitalisation data were used. The potential risks for the hospital group, individual patients, medical schemes, provider, prescriber and the researcher were minimal, because none of their personal information was able to be identified from the data.

1.8.6.2.2 Anticipated risks to the researcher and precautions taken

The only risk of this study to the hospital group was the inappropriate or unauthorised use of, or access to their data; however, several precautions were taken to prevent this from happening (refer to paragraph 1.8.2). The researcher did not encounter any risks.

1.9 Data management

Retrospective data were required to perform this study. Data were received from the hospital group's BIU once an email by the researcher was sent to this department requesting data. The study inclusion and exclusion criteria were included in the email and it was requested that the data be received in an electronic Microsoft Office Excel® 2010 format file. A link to the electronic file was only made available to the researcher for downloading and was inactivated by the data assistant from the BIU once the download had been completed. Once the data had been downloaded, it was saved on an encrypted, password protected computer in the researcher's office. The researcher backed up data on a password protected electronic memory device, which was locked in a cupboard in the researcher's office. All software had an updated anti-virus

program installed. Only the researcher had access to both the computer as well as the electronic memory device.

Data were personally handed to the statistician at the NWU on a separate password protected electronic storage device for analysis. Only the researcher and the statistician knew the password to open and use this device.

All data will be kept by MUSA and then destroyed and/or deleted by the research assistant at MUSA after five years.

1.10 Dissemination of research results

Based on the employment contract between the researcher and the hospital group, feedback regarding all research projects using their data was given in the form of a written report. Feedback had been received and a final report would be furnished once the study reached full conclusion. The results of the project were also submitted for publishing in the form of a mini dissertation and manuscript.

1.11 Role and experience of the members in the research team

The researcher and study supervisors were responsible for ensuring that the study is conducted according to the research protocol and ethics principles. This was done to ensure that the rights and safety of all participants are protected, and that data verification and protection were applied.

The researcher is a qualified pharmacist with more than 12 years of experience in the correct use of medication in a hospital setting. All the study leaders have more than 30 years of combined experience in Pharmacy Practice and Clinical Pharmacy research as well as research methodology and biostatistics. All members of the research team had the appropriate clinical knowledge and research experience required for the proposed study (refer to individual curriculum vitae).

1.12 Conflict of interest

The researcher is employed at a hospital that forms part of the study hospital and received approval to conduct research from the Group’s clinical director. Written feedback to the request is attached in Annexure B of this mini dissertation.

Other members of the research team did not report any conflict of interest.

1.13 Monitoring of the research project

The MUSA scientific committee, in conjunction with the study supervisors, were accountable for the monitoring of the study process. This was done by abiding to the following guidelines:

- Adherence to all the confidentiality requirements of the study hospital group, who provided the data for this research project, and also protection of their rights as well as patient and prescriber anonymity.
- Monitoring of inputs was done by the study supervisors and the MUSA scientific committee in that the research proposal is consistent with the ethical research priorities of the NWU by obtaining ethical approval before commencement of the study.
- The study supervisors confirmed the monitoring of the research implementation process, by ensuring that a study timeline and budget were set. The extent of meeting the date deadlines and monetary targets was tracked by the researcher and reported to the study supervisors.
- The study supervisors, researcher and the statistician were responsible to ensure that the data were appropriately analysed according to the specified objectives.
- The study supervisors, researcher and research assistant of MUSA ensured that data were managed and stored according to the study proposal during and after the study.
- The study supervisor completed the ethics monitoring report every six months until the study had been completed.
- Research result outputs were monitored by the study supervisors by tracking the progress of the study.
- The MUSA scientific committee and research assistant will ensure that the data are destroyed after the five-year storage period.
- The researcher monitored the uptake of the research findings, which was done by tracking and reporting the adoption of information gained by the study hospital to the research supervisors.

1.14 Study limitations

The following limitations were applicable to this study:

- Even though data were collected from one of the largest private hospital groups in South Africa, private hospitals not belonging to the group's data were naturally not included and generalisation to the entire private hospital sector was therefore not possible.

- Since the public healthcare sector's data were not included in this study, generalisation to the entire South African healthcare sector is not possible.

- Data were not collected for items dispensed on patients to take out medication, because patient adherence to treatment cannot be accurately determined (the total length of prophylaxis cannot be determined and compared to the SASTH guidelines for compliance).

- In order to obtain reimbursement from medical aids for healthcare services rendered, it is necessary for accurate completion of certain data fields on risk-rating forms and electronic billing programmes, while it is possible to leave other fields incomplete. Since several individuals are able to enter data, substantial errors and variation may be present. For example, primary ICD10 codes are not always available on admission and require updates to be performed by hospital case managers. This may have led to uncertainty of whether a clinical diagnosis or medical treatment was recent, or whether the coded diagnosis was a complication or comorbid condition.

- While hospital case managers endeavour to accurately update data and rigorous audits are performed on patient billing files, a certain amount of over- and under billing of items may have been present in data sent to medical aids.

- The VTE risk assessment model utilised in the study did not include screening for either TB or HIV. This may have inadvertently excluded patients who would benefit from prophylaxis.

- Body mass index had to be manually calculated for the risk assessment model. This may have resulted in incorrect risk rating of patients by nursing staff.

1.15 Chapter summary

Chapter 1 served as the mini dissertation's introduction. The problem statement, research objectives, questions and methods as well as a division of chapters have been outlined. Methods used to reach objectives set in 1.3 were included in this chapter. Ethical approval to conduct the study was granted with ethics approval number: NWU-00080-17-S1. A literature review on VTE and its associated pathology as well as required prophylactic methods is provided in Chapter 2.

CHAPTER 2: LITERATURE REVIEW

2.1 Background to the problem

Venous thromboembolism (VTE) affects a considerable number of patients worldwide and may lead to acute or chronic complications and even death (Patel *et al*., 2017:1). Thrombosis can affect virtually any part of the venous circulatory system and is not a 'static disease' but a dynamic condition able to change rapidly (Heit, 2015:465; Karande *et al*., 2016:493). The constantly changing findings with respect to clinical, radiological, functional and laboratory results often increase the complexity of VTE as a disease and may, in part, explain the difficulties in establishing an initial diagnosis (Karande *et al*., 2016:493). The severity of the condition is determined by several factors, which include the presence of inherited risk factors, the origin and proportions of the formed thromboembolus, both the number and extent of the primary affected circulatory regions, the occurrence of recurrent thromboembolic events, the development of organ tissue necrosis, as well as the magnitude of organ infarction (Streiff *et al*, 2016:32).

Venous thromboembolism is categorised as a major contributor to patient mortality. It is estimated that the overall incidence rate of VTE was 107 per 100 000 person-years (Martinez, Cohen *et al*., 2014:255). In-hospital VTE development incidence has been reported to occur in 60 to 74% of all hospitalised adults (Jha *et al*., 2013:809; Riback & Wessels, 2012:85). The risk of VTE development among hospitalised patients can increase due to several risk factors. These risk factors include the type of surgery performed, any specific chronic conditions, inherited predispositions such as cancer, advanced age (those over 60 years of age), those suffering from immobility, as well as a history of prior VTE development. International VTE rates are reported to be higher in men than women (1.2:1 for male:female ratio); however, the pathological effects of thrombosis were found to be more extensive in women (Andreou *et al*., 2008:1713). Female gender was found to be an independent risk factor for DVT development as one in every 1 000 women of childbearing age are reported to be at risk of developing VTE mainly due to pregnancy or the use of oral contraceptives (Caprini, 2005:70; Pomp *et al*., 2008:632). It seems to appear that male or female gender as a risk factor for VTE development remains controversial.

Venous thromboembolic disease presents a high economic burden on a country's healthcare system due to the high cost of recurrent hospitalisation resulting from VTE-associated comorbid diseases (Jha *et al*., 2013:809; Ruppert *et al*., 2011:65). Fernandez and colleagues (2015:452) reported that recurrent hospitalisation due to VTE comorbidities may incur up to 48% higher costs than the initial admission for patients surveyed in the United States of America (USA). It is estimated that the highest cost is incurred during the first three days of hospitalisation in those

suffering from VTE-related comorbidities. The authors report that this might possibly be due to the higher level of care required to manage these patients. For instance, 24% of patients diagnosed with VTE initially need hospital intensive care unit (ICU) admission (Dasta *et al*., 2015:305). In 2014, VTE hospitalisations cost the USA healthcare system approximately $10 billion (Grosse *et al*., 2015). It was divulged to the researcher that, in 2017, over R195 000 000 was spent by one of South Africa's largest private hospital groups on pharmacological and mechanical VTE prophylactic measures alone (this figure does not include hospital stay, prescriber costs or laboratory tests).

Given that symptoms for VTE development are often non-specific or even undetectable and that untreated VTE can be debilitating or fatal, its prompt prophylaxis is vital for patient survival (Karande *et al*., 2016:493). Venous thromboembolism development has traditionally been attributed to patients already being hospitalised for a period; however, approximately 25 to 40% of non-hospitalised patients are also at risk for VTE development (Heit *et al*., 2016:4). For these reasons, patient risk stratification on admission is paramount to ensure that only at-risk patients are treated and that they receive the right type of prophylaxis without incurring additional harm (Caprini, 2005:77). Prophylactic medication use is also not without risk, as the critical mechanism of action of these medications requires the deactivation or dissolution of blood coagulation, which is central in the pathogenesis of VTE (Ritter *et al*., 2008:204). Due to the underlying mechanism of action for pharmaceutical prophylaxis, major bleeding may be induced and can be equally harmful to patients (Kearon *et al*., 2012: e480S). It is therefore important to avoid pharmaceutical prophylaxis when certain contra-indications exist in a patient (Caprini, 2005:77).

Venous thromboembolic-related complications due to poor prophylactic practices resulted in 64.4% of annual premature deaths in both Europe and the USA in 2012 (Jha *et al*., 2013:809). Great variance on adequate prophylaxis has been reported in patients receiving VTE prophylaxis worldwide (Bergmann *et al*., 2010:736; Cohen *et al*., 2008:1914; Schleyer *et al*., 2018:174). The Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting (ENDORSE) study (a large cross-sectional, multinational study) with 68 183 enrolled patients found that only 58.5% of at-risk surgical patients and 39.5% of at-risk medical patients received American College of Chest Physicians (ACCP)-recommended VTE prophylaxis (Cohen *et al*., 2008:1914). Similarly, appropriate VTE prophylaxis in patients from developing countries (which included South Africa) was reported to range between 22 and 79.9% (Bergmann *et al*., 2010:736; Geachan *et al*., 2016; Riback & Wessels, 2012:85). Studies reporting on adherence in the South African setting were found to either be specific to a certain surgical discipline (Jacobs *et al*., 2017:55; Snyman & Potgieter, 2016) or located in a single province (Awolesi *et al*., 2016; Riback & Wessels, 2012:85). All these studies,

however, mirrored international findings showing poor adherence to VTE prophylactic guidelines with guideline adherence of up to 74%. A study conducted by Wessels and colleagues (2012:87), for instance, found that, of the 608 surveyed patients across 29 different hospitals, only 67.9% of the highest risk patients received appropriate prophylaxis. Correct prophylaxis was prescribed in 77.2% of the highest risk-rated medical groups included in the survey (Riback & Wessels, 2012:87). This study did not report on the administration of correct prophylaxis for medium risk-rated patients – a category often overlooked in VTE prophylaxis compliance investigations. The study found that the main reason for the low prescribing of appropriate prophylaxis was the prescribers' perception of patients having a low risk for developing DVT (Riback & Wessels, 2012:87). The difference between patients clinically diagnosed as being at-risk for VTE development versus the actual at-risk patients after a risk assessment was completed, mirrored this finding (Riback & Wessels, 2012:87). A recent local study surveying thromboprophylactic methods in spinal surgery reports that 83% of participants indicated South African VTE incidence to be between 0 and 5% (Jacobs *et al*., 2017:55). A quarter of surgeons surveyed reported that they did not follow any protocol, whereas the remaining participants indicated that they based prophylaxis on their personal experience (Jacobs *et al*., 2017:55). Yet, VTE prophylaxis guideline implementation has been proven to be an important tier of improved patient VTE outcomes (Cardoso *et al.* 2016:491). It is therefore necessary to audit how the existing prescribing practices in the South African private healthcare sector correlate to published local guidelines. This may, in turn, lay the groundwork in improving patient outcomes over different medical specialties and possibly reduce future VTE-related mortality.

2.2 Definition of venous thrombosis

Venous thromboembolism can be defined as the formation of a clot or thrombus in the venous circulation of an extremity (Ozaki & Bartholomew, 2012). Thrombus formation can cause circulatory occlusion of vital organs resulting in residual damage and/or tissue necrosis (Wilbur & Shian, 2017:295). Deep vein thrombosis and pulmonary embolism (PE) are distinct but related aspects of the same dynamic disease process known collectively as VTE (Kroegel & Reissig, 2003:9). It must be noted, however, that thrombus formation can occur in both the venous as well as the arterial systems (Heit, 2015:465). For the purpose of this mini dissertation, emphasis will be placed on occlusion of the venous system.

2.3 Venous thrombosis incidence and prevalence

The incidence of venous thrombosis formation has been reported to be very high with an overall global incidence rate similar to that of stroke. Stroke has been described as the fifth leading cause of global mortality (Rothwell *et al*., 2004:1928). In the ENDORSE study, 51.8% of patients were believed to be at risk for VTE development. The ENDORSE study was performed in 32 countries around the world excluding sub-Saharan Africa (Cohen *et al*., 2008:371). The prevalence in sub-Saharan African countries was found to be 50.4% with the majority (62.3%) of at-risk patients classified as medical patients upon hospital admission with surgical patients making up 43.8% of the total study population (Kingue *et al*., 2014:161). In South Africa, the risk of VTE development in hospitalised patients admitted to private hospitals in Gauteng is estimated to be above 70% (Riback & Wessels, 2012:85). The authors found that over 84% of surgical patients were classified as having a high risk for DVT development (30.3% were classified as high risk and 54% classified as highest risk). They also reported that, in medical patients, 70.4% were classified as having a high to highest risk for VTE development.

Many studies have been conducted to investigate VTE prevalence and incidence based on the ethnicity and genetics of patients. For instance, the estimated average annual incidence rate of VTE among persons of European ancestry is reported to range from 71 to 132 cases per 100 000 patients per year (Zöller *et al*., 2014:296). A higher overall VTE incidence is reported in African-Americans (Hernandez *et al*., 2016:1923) with a lower incidence reported in Asians and Pacific Islanders (Liao *et al*., 2014:214). Interestingly, it was found that genetically, non-O blood type patients are at a higher risk to develop VTE; however, results were not statistically significant for those with provoked VTE (Dentali *et al*., 2012:535). Another risk factor was found to be that of having an increased height – the risk of VTE development was found to have increased by 40% for each 10 cm increase in height in patient of European ancestry (Roetker *et al*., 2017:1334).

Venous thromboembolism is, for the most part, a disease of older age for both men and women (Johnson *et al*., 2016:1869; Martinez, Cohen, *et al*., 2014:259). Venous thromboembolism risk, on the other hand, seems to be lower in adolescence (Biss *et al*., 2016:427; O'Brien, 2014:66). It must be noted that the risk of VTE in adolescence increases for those using oral contraception (O'Brien, 2014:66). Fewer studies are available for the paediatric population, although Takemoto and colleagues (2014:332) alongside Asfaw and colleagues (2016) reported on the prevalence of VTE to be between 0.3 and 0.5 per 100 paediatric admissions. Young adults (those aged between 18 and 21 years) and adolescents (those aged between 14 and 17 years) have a higher risk for VTE development compared to that in children (those aged between 2 and 9 years) (Takemoto *et al*., 2014:332). Incidence rates are somewhat higher in adult women during the childbearing years (Martinez, Cohen, *et al*., 2014:259), while the overall risk for VTE reoccurrence

is higher in men (Tagalakis *et al*., 2012:33). The risk of recurrence is highest within the first six to 12 months post-VTE development and never entirely dissipates (Martinez *et al*., 2014:259).

The incidence and prevalence of VTE development are both affected by patients' inherited and acquired risk factors and these risk factors are discussed further in paragraph 2.4.4.

2.4 Pathogenesis of venous thrombosis

Several innate (inherited) and acquired factors have been described, which are able to change the delicate homeostatic balance between coagulation and anticoagulation to an environment favouring thrombosis development (Shibeko *et al*., 2010:1; Violi & Ferro, 2013:426). Such factors that increase a patient's risk of VTE development are additive or synergistic in nature (meaning that the combined risk factors will have a greater impact on increasing a patient's VTE risk than their individual risk percentages simply added together) (Takemoto *et al*., 2014:332). These factors need to be understood to ensure proper patient risk stratification in order to guarantee appropriate and safe prophylactic interventions, while improving patient outcomes and reducing mortality. In order to better understand the factors responsible for increasing VTE formation risk, the mechanisms required for thrombus formation need to be described and are discussed under sections 2.4.1 and 2.4.2.

2.4.1 Models describing blood coagulation

The human body's innate ability to maintain haemostatic equilibrium as part of an important host defence mechanism has been extensively studied. The link between thrombus formation and haemostasis was first recorded in 1720 by French surgeon Jean-Louis Petit (Owen, explained by Nichols & Bowie, 2001). The Swiss physician, Friedrich Hopff, noted that a then already well-known familial bleeding tendency in males was associated with increased hypocoagulability (higher propensity for blood clot formation) now known as X chromosome-linked haemophilia disorders (Owen, explained by Nichols & Bowie, 2001). The identification of coagulation abnormalities and their link with increased bleeding led to a rapid rise in research of this field. One of the most well-known theories relating to the explanation of factors initiating the coagulation process via thrombus formation was developed by German pathologist, Rudolf Virchow in 1856 (Virchow, 1856). Virchow's triad is still in use today almost 160 years after its first development. The theory of "Virchow's Triad" associates three conditions that are required for thrombogenesis (formation of thrombi), namely endothelial damage, a hypercoagulable state in the blood as well as blood stasis. Virchow's Triad theory, however, does not explain thrombogenesis completely and it was found that immunological influences are also required for this process to be initiated (Wang *et al*., 2015:19804). Complementary to Virchow's Triad was the discovery of coagulation

factors during the study of biochemical processes relating to blood coagulation in the 1940s by means of clotting factors. These models described each clotting factor as a pro-enzyme that could be sequentially converted to an active form resulting in a step-by-step response amplification process. The sequences of interaction of these pro-enzymes can be divided into an “intrinsic” and “extrinsic” pathway. Coagulation factors’ descriptions were designated using Roman numerals according to the sequence of their discovery. Several clotting factors had been described by 1957, namely: Von Willebrand factor (Von Willebrand, 1931), factor V (Owren, 1948), factor VII (Alexander *et al*., 1951), factor VIII (Patek & Taylor, 1937), factor IX or “plasma thromboplastin component” as it was originally named (Aggeler *et al*., 1952), factor XI or named “plasma thromboplastin antecedent” (Rosenthal *et al*., 1953) and factor X (Telfer *et al*., 1956; Hougie *et al*., 1957:494). The interaction of these coagulation factors was further described by means of a so-called enzymatic coagulation “cascade” (Macfarlane, 1964:498) or “waterfall” (Davie & Ratnoff, 1964) mechanism.

Several coagulation cascade models have been proposed describing the formation of a thrombus and include the intrinsic and extrinsic pathway models (Mackman *et al*., 2007:1687) as well as the cellular model described by Hoffman and Monroe (2001:958). The intrinsic and extrinsic pathway models divide the initiation of thrombus formation into two distinct pathways, namely thrombus formation initiation (extrinsic pathway) and thrombus amplification (intrinsic pathway) (Mackman *et al*., 2007:1687). The extrinsic pathway is thought to be responsible for the initial generation of activated factor X (factor Xa), while the intrinsic pathway leads to amplification of factor Xa generation (Mackman *et al*., 2007:1687). Although these two pathways are independently activated, cross talk exists between these pathways and both culminate in a final pathway known as the common pathway (Holy & Tanner, 2010:5). The cellular model, on the other hand, suggests that coagulation processes are better characterised to occur in four phases (Hoffman & Monroe, 2001:958). The four phases of the cellular model include: Thrombus initiation, amplification, propagation and termination (Hoffman & Monroe, 2007:2). The cell-based model includes the important interactions between cells directly involved in haemostasis (for example tissue factor (TF) secreting cells and its reaction with platelets) as well as the description of coagulation factor interactions (Chapin & Hajjar, 2015:19). These interactions are not included in the intrinsic and extrinsic pathway model descriptions. The cellular models, therefore, more accurately represent the interaction between cellular activity and coagulation proteins leading to thrombus formation and subsequent haemostasis (Hoffman & Monroe, 2007:8).

2.4.2 Aetiology of deep vein thrombus formation

Deep vein thrombus formation occurs when the body's normal haemostatic equilibrium is disturbed, and lysis of clots is prevented (Malone & Agutter, 2006:589). According to the ischaemic-hypoxic-hypothesis, a combination of factors that result in blood circulation becoming non-pulsatile in the deep veins of the lower limbs will result in haemodynamic imbalances (Malone & Agutter, 2006:588). These haemodynamic imbalances result in the activation of the intrinsic coagulation system as well as the release of inflammatory cytokines ending in local hypercoagulability or a prothrombotic state (Shibeko *et al*., 2010:11; Vaitla *et al*., 2013:A97). Thrombosis is a very complex process and involves a set of reactions requiring 30 different proteins (Colman *et al*., 2006:9; Holy & Tanner, 2010:5). These pro-thrombotic reactions eventually convert fibrinogen, a soluble protein circulating in the blood, to insoluble strands of fibrin (during the so-called initiation and amplification phases), which, together with platelets, form a stable thrombus or blood clot (propagation phase) (Colman *et al*., 2006:8; Vojacek, 2016:1). The phases of thrombus formation occur by means of highly interwoven physical, cellular and biochemical processes eventually contributing to normal haemostasis, or if not regulated, can lead to thrombus formation, embolisation and vein wall damage due to organisation. The regulation of thrombus formation is enabled by (1) the ability of blood to flow or be supressed, (2) intactness of the vein endothelium, as well as (3) inflammatory reactions (Wakefield *et al*., 2008:387; Farrell *et al*., 2016:623).

In a normal haemostatic equilibrium, plasminogen will be converted to plasmin, which, in turn, will cause lysis of the clot to prevent enlargement (Chapin & Hajjar, 2015:20). This occurs by means of the activation of plasminogen to plasmin (Hoffman & Monroe, 2007:8). Plasmin digests fibrin and also inactivates clotting factors V and VIII as well as fibrinogen. Circulating fibrinolysins such as protein C and S as well as antithrombin also play a role in regulating thrombolysis (Chapin & Hajjar, 2015:20). Protein C is a vitamin K-dependent plasma glycoprotein (GP), which, when activated, will inactivate both activated forms of factor V and factor VIII. The free form of protein S circulating in the blood further enhances the activity of protein C resulting in thrombolysis (Hoffman & Monroe, 2007:8). Normal, rapid blood flow therefore has an inhibitory effect on thrombus formation due to the dilution of activated clotting factors by the influx of regulatory or thrombus terminating substances (Hoffman & Monroe, 2007:8; Shibeko *et al*., 2010:1). Upon the disruption of normal haemostatic equilibrium, a hypercoagulable state occurs due to hypoxemia and a biochemical imbalance that occurs between circulating coagulation factors (Malone & Agutter, 2006:588; Shibeko *et al*., 2010:1). An increase in the endogenous thrombin forming potential ensues as a result of the hypoxic injury in the endothelium of the vein valve leaflets (Malone & Agutter, 2006:588). Circulation of blood in the veins is solely reliant on valve function

and if valves are impaired, further blood stasis with haemodynamic imbalances will occur (Malone & Agutter, 2006:588). In areas of decreased blood flow, oxygen supply declines with a subsequent increase in blood haematocrit and procoagulant factors (Hoffman & Monroe, 2007:8; Shibeko *et al*., 2010:1). The pockets next to vein valves are prominent locations for venous stasis and hypoxia. Here, antithrombotic proteins such as thrombomodulin and endothelial protein C are downregulated due to hypoxemia. The hypoxemia further increases the expression of P-selecting, attracting immunologic cells which are able to release TF or onto the bordering vein endothelium. These interactions result in a cascade of innate protease reactions (Vojacek, 2016:1), where the amplification phase ensues with eventual thrombus formation, adhesion to vein walls as well as vein wall or valve weakening.

Damage to the intima or endothelial layer of an affected blood vessel may be intrinsic (artherosclerotic plaque adhesions) or secondary in nature (external trauma) (Wakefield *et al*., 2008:387). When disturbances to the intact endothelial surface occur, be it due to vascular trauma or inflammation, the venous endothelial surface subsequently promotes a prothrombotic and vasocontricted state (Wakefield *et al*., 2008:387). Here, non-vascular, tissue-factor-expressing cells release TF into the circulating blood and react with circulating platelets, platelet activating factor, factor V and VII as well as endothelin-1 (Colman *et al*., 2006:9; Holy & Tanner, 2010:5). The interaction of blood with these damaged cells further releases GP complex 1, GP IIb/IIIa, TF III as well as serotonin, which eventually interact with clotting factor VII (Breitenstein *et al*., 2010:6). Tissue factor is a potent cellular receptor for factor VII and platelets (Colman *et al*., 2006:9), while endothelin-1 and platelet activating factor (PAF) causes vasoconstriction (Wakefield *et al*., 2008:387). Additionally, certain cell adhesion molecules such as P-selectin are secreted by the endothelium resulting in the activation of platelets as well as leukocytes able to amplify inflammation (Wakefield *et al*., 2008:387). The amplification of inflammation is through the endothelium's ability to express anticoagulants, procoagulants, cytokines, adhesion molecules as well as vasodilators or vasoconstrictors (Wakefield *et al*., 2008:387; Previtali *et al*., 2011:120). Activated platelets can secrete thromboxane, which acts as a potent vasoconstrictor and facilitator of platelet aggregation or adhesion. Platelet adhesion is achieved when thromboxane increases the expression of GP IIb/IIIa in platelets' cell membranes. The GP binds to circulating fibrinogen causing their adhesion. The reaction of TF III with factor VII forms an enzymatic complex, which will activate factor IX and factor X (Holy & Tanner, 2010:5). Activated factors IX and X (IXa and Xa) bind to factor VIIIa on the surfaces of membranes and form intrinsic tenase (Colman *et al*., 2006:9; Holy & Tanner, 2010:5). The interactions of activated clotting factor XII with TF are collectively known as the "intrinsic activator complex", and initiates the coagulation process (Aberg & Siegbahn, 2013:817). This occurs when the activated factor XII converts prekallikrein to kallikrein, which, in turn, accelerates the conversion of factor XII to its activated

form as part of a positive feedback mechanism or amplification reaction (Gailani & Renne, 2007:2507). The formed factor XII/TF complex further proteolytically cleaves factor IX to its activated form (Breitenstein *et al*., 2010:5). Activated factor XII reacts with activated factor X and thrombin, which then proteolytically cleave and activate factor VIII (Holy & Tanner, 2010:5). Activated factors VIII and IX further react and form a complex with circulating calcium atoms released from activated platelets and negatively charged phospholipids in the endothelium (Holy & Tanner, 2010:5). This formed complex is responsible for the activation of factor X, which, in turn, will react with activated factor V resulting in a formation with enzymatic activity. This enzymatically active formation is known as “prothrombinase” (Breitenstein *et al*., 2010:3; Mackman *et al*., 2007:1687). Prothrombinase is able to convert prothrombin to thrombin by enzymatically acting on fibrinogen to generate a fibrin monomer (Tshopanoglou *et al*., 2004:846). The formed fibrin monomer will also, in turn, convert fibrinogen to fibrin (Chapin & Hajjar, 2015:19; Furie, 2009:255; Krishnaswamy *et al*., 1993:261). The thrombin that has been generated from the initiation phase further activates factor VII and factor V (Palta *et al*., 2014:519). Activated factors V and VII serve as co-factors in the prothrombin complex and enhance the activation of other circulating factor II by factor Xa as well as the activation of factor Xa by factor IXa (Palta *et al*., 2014:519).

The substrates that interact with the formed fibrin clot cause an amplified increase in thrombin production and this interaction is called the “amplification phase” (Hoffman & Monroe, 2007:8). The amplification phase occurs when a stable matrix of the fibrin plug (also called the prothrombinase complex) is formed, comprising activated factor X as well as platelet bound factor V and calcium ions (Krishnaswamy *et al*., 1993:261; Palta *et al*., 2014:519). The purpose of the amplification phase is to generate sufficient amounts of thrombin by means of positive feedback loops between the reactions of thrombin and activated platelets (Palta *et al*., 2014:519).

The conversion of the soluble protein fibrinogen to insoluble fibrin strands by means of a series of protease reactions is called the propagation phase (Hoffman & Monroe, 2007:7). The thrombin produced during the initiation and amplification phases also activates factor XIII, which stabilises the thrombus by cross-linking it with fibrin strands. The resulting fibrin mesh traps and holds cellular components of the blood causing it to expand in size or, in other words, propagate (Hoffman & Monroe, 2007:8). The thrombus formation process completes in a matter of seconds and is required as a self-preservation mechanism during mechanical insults inflicted on the human body (Khurana, 2005:230). However, if these mechanisms are unregulated over a period of time, the formed venous plug subsequently is further infiltrated by inflammatory cells resulting in thrombus growth and eventually forming an artherosclerotic lesion (Myers *et al*., 2002:212). During the growth of the artherosclerotic lesion, cytokines are produced by leukocytes, which

stimulates the replication of smooth muscle cells in the vein wall (Myers *et al*., 2002:212). These cells can express enzymes that degrade elastin and collagen in response to the initiated inflammatory cascade (Gillitzer & Goebeler, 2001:515). This causes a fibro-elastic thickening and weakening of the intimal layer of the venous wall. Upon eventual rupture of the artherosclerotic plaque, the TF is yet again released and reacts with circulating blood cells (Myers *et al*., 2002:212). The cellular model of coagulation is reactivated, causing additional thrombus formations as well as further wall fibrosis and damage with subsequent vein occlusion (Gogalniceanu *et al*., 2009:192). Thrombi that form and attach in large blood vessels with rapid blood flow (such as the aorta) are called mural thrombi and typically restrict blood flow without complete occlusion (Khanna, 2016:79). Mural thrombi are grey-red in colour with bands of alternating fibrin containing trapped white and red blood cells that appear as light and dark lines, also known as “lines of Zahn” (named after their discoverer, pathologist Friedrich Wilhelm Zahn) (Khanna, 2016:78). An occlusive thrombus generally forms in small blood vessels with an embolus being the result if such a thrombus dislodges and migrates to occlude blood flow at a distant organ (Bělohlávek *et al*., 2013:129; Khanna, 2016:80).

The formation of an acute venous thrombus can also originate from processes other than unregulated intrinsic mechanisms. One such an example is the formation of thrombi due to immuno-inflammatory processes triggered by cells infected with foreign pathogenic microorganisms or due to the presence of malignant cells (Wang *et al*., 2015:19804). The circulation of endotoxins produced by bacteria (especially those located in the intestinal tract) has been reported to propagate thrombus formation (Violi & Ferro, 2013:426). Immune system disturbances such as with sepsis cause activation of integrins β2 and β3. These substances are situated on the membrane of the white blood cells and platelets and will combine with the fibrinogen ligand into a reversible, mesh-like structure or monomer (Wang, *et al*., 2015:19804). These fibrin monomers are stabilised and cross-linked by factor XIIIa (thrombin-activated transglutaminase) (Rijken *et al*., 2016:1458). Thrombin amplifies its own generation by feedback activation of factor V and factor VIII (Maas *et al*, 2010:9084; Yao *et al*., 2015). Thrombin is able to also activate factor XI, which will lead to further factor Xa generation (Maas *et al*, 2010:9084; Yao *et al*., 2015). Coagulation factors and cofactors assemble on the surface of platelets, which amplifies and increases the numbers of *platelets* adhering to the sub-endothelial matrix (Yao *et al*., 2015). Platelet granule proteins as well as pro-coagulant activity will enhance thrombin generation (Yao *et al*., 2015). Thymus originated lymphocyte (T cell) mediated immunity can be markedly reduced in septic patients or those suffering from malignancy, which, in turn, results in a loss of cytotoxic T cell functions (Wang *et al*., 2012:386). The cytotoxic T cell functions are responsible for normal thrombus resolution (Luther *et al*., 2016:1294). Additionally, a high messenger ribonucleic acid (mRNA) expression of L-selectin, integrin alpha L (ITGAL) and

intracellular adhesion molecule (ICAM)1 in these patients cause elevated adhesion of vascular endothelial cells, white blood cells and platelets that further propagate thrombus formation (Wang *et al*., 2012:386). Eventually the formed thrombus will occlude circulation locally resulting in DVT or, if the thrombus dislodges and migrates through the circulation, blood flow will be cut off at a critical organ in a different part of the body also known as embolisation (De Palo, 2017).

Figure 2-1 depicts a summary of the processes involved during thrombus formation and was adapted from De Caterina and colleagues (2012:1414). The illustration highlights the central role thrombin plays during fibrin stabilisation and the propagation of protease reactions.

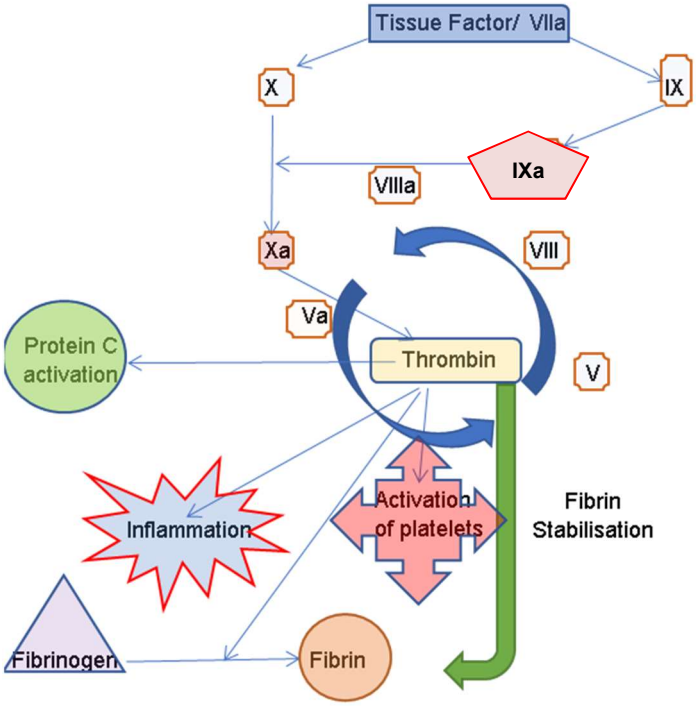


Figure 2:1 Summary of the thrombus formation cycle

2.4.3 Pathophysiology of venous thromboembolism

Signs and symptoms of superficial DVT's include local pain or tenderness, swelling, warmth, redness or discoloration, and distention of surface veins, although those suffering from a VTE in the deep vein circulatory system usually do not display any symptoms and often present to healthcare facilities with non-specific cardiogenic symptoms that often quickly complicate resulting in death if proper prophylactic measures are not administered (Johnson *et al*., 2016:1876). During the formation of venous thrombi in the body, such thrombi may propagate and dislodge due to proximal extension of the local vein (De Palo, 2017). Upon dislodging, some

complications may arise as a result of blood flow obstruction and include (Mennon & Hamilton, 2004:301; De Palo, 2017):

- Venous thromboembolism
- Venous insufficiency and post thrombotic syndrome
- Pulmonary embolism.

Complications listed are described in the bulleted paragraphs below:

- Venous thromboembolism

Most DVTs form in veins of the distal lower leg, particularly within the gastrocnemius and soleus muscles (Cohen *et al*., 2008:151; De Palo, 2017). They may also form in the posterior and anterior tibial veins or the peroneal veins (Utter, 2016). Schwarz and colleagues (2003:2759) reported a 2% incidence in DVT development of the peroneal veins in patients travelling on flights of eight hours and longer. Distal DVT is a very common complication not only in the relatively healthy population, but particularly after joint arthroplasty in non-anticoagulated patients (Falck-Ytter *et al*., 2012:278; Kim & Kim. 2002:569). Deep vein thromboembolism in these patients can occur in up to 30% of those who underwent hip replacement surgery (Falck-Ytter *et al*., 2012:278) and in up to 41% patients undergoing total knee replacement surgery (Kim & Kim, 2002:569). Although VTE is often associated with major surgery, medical patients constitute the majority of patients who suffer an episode of VTE (Stein & Matta, 2010: 611). Gene mutations of factor V and factor V Leiden (FV) R506Q, which result in an antithrombin deficiency state (Van Boven *et al*., 1996:417), are also associated with a more distal location of leg DVT formation. Many small, distally located DVTs can, however, remain localised to a muscle, but do not obstruct circulatory blood flow completely and may even resolve on their own, rendering them asymptomatic (Cohen *et al*., 2008:151). In approximately 15% of cases, however, these thrombi may extend into the proximal femoral venous system of the leg (Cohen *et al*., 2008:151). If the circumstances that initially caused the thrombus to develop persist, these thrombi can propagate into the larger proximal deep veins of the lower limb such as the popliteal veins resulting in blood supply occlusion (cut off) or embolisation (Cohen *et al*., 2008:151).

Upper extremity VTE normally results from endothelial injury, which can be caused by venous thrombosis of the subclavian vein in thoracic inlet syndrome or Paget-von Schrötter syndrome, clavicular fractures, hypertrophy of the scalenus muscle or due to insertion of central venous catheters (CVC), peripherally inserted central catheters (PICC) and/or cardiac pacemakers (Dep *et al*., 2013; Grant *et al*., 2012:105). Patients are at substantially greater risk of embolisation and mortality if formed DVTs are proximally situated in the body (“above the knee”) (Kucher,

2011:862). The two forms of upper-extremity DVTs are effort-induced thrombosis (Paget-von Schrötter syndrome) and secondary thrombosis due to injury (Mall *et al*., 2013:355). Paget-von Schrötter syndrome accounts for 10 to 20% of all DVT cases (Mall *et al*., 2013:355). In effort-induced thrombosis, an underlying chronic venous compressive abnormality caused by the musculoskeletal structures in the costoclavicular space is present at the thoracic inlet and/or outlet (Zucker *et al*., 2016:519). Secondary thrombosis due to injuries can be incurred upon injection drug use, pacemakers, central venous catheters, thoracic outlet syndrome or occasionally as part of superior vena cava syndrome causing hypercoagulable states (Zucker *et al*., 2016:519). Untreated proximal thrombi complicate more readily and represent a significant source of clinically significant PE, cardiogenic shock as well as right ventricular failure (Kucher, 2011:861).

- Venous insufficiency and post-thrombotic syndrome

Acutely formed DVTs that are large enough to cause obstruction in a vein can, over time, result in the formation of additional blood flow routes or collaterals as a method of the body to restore perfusion to the affected area (Dictionary.com, 2018; Meissner *et al*., 2000:51; Modarai *et al*., 2005:801). Collateral vessels are small branches similar to capillaries, which become enlarged and conjoined to adjacent vessels (Bashist *et al*., 1996:1450). These vessels may not be able to ensure the volume of venous flow required during times of increased exertion and may predispose a patient to strokes, brain abscesses as well as an increased cardiac output state – depending on the location of their formation (Bashist *et al*., 1996:1458). Upon thrombus formation, said thrombus will attach to the venous wall, causing damage. Damage of the venous wall will result in wall distention and venous reflux, which, in turn, will cause valvular damage with subsequent venous incompetence and blood pooling (Gogalniceanu *et al*., 2009:192). The residual damage caused to valves and the resulting venous insufficiency have been observed in some patients, months after thrombus resolution (De Palo, 2017). Another mechanism that contributes to venous incompetence is the natural healing process of the thrombotic vein. During the body's attempt to clear the thrombotic mass by inflammatory reaction and fibrinolysis (Gillitzer & Goebeler, 2001:515), the valves and venous wall are altered by organisation and ingrowth of smooth muscle cells and the production of neointima. This process leaves vein valves damaged and incompetent, predisposing the patient to chronic venous reflux also known as "venous insufficiency" (Gogalniceanu *et al*., 2009:193). The mural inflammatory reaction breaks down collagen and elastin, leaving a compromised venous wall where the damage may become irreversible. Haemodynamic venous insufficiency is the underlying pathology of post-thrombotic syndrome, also referred to as postphlebitic syndrome (Gogalniceanu *et al*., 2009:194; Shaydakov *et al*., 2016:161). Chronic oedema is a common recurring symptom resulting from valvular dysfunction in patients who have had a large DVT (Shaydakov *et al*., 2016:161) and can lead to post-thrombotic syndrome.

Post-thrombotic syndrome occurs in between 20 and 50% of patients suffering from acute symptomatic DVT (Winter *et al*., 2017:1531). Signs and symptoms of post-thrombotic syndrome include: pain, swelling and oedema, hyper-pigmentation, erythema, superficial varicose veins and recurring DVT (Kahn *et al*., 2008). Skin ulceration will develop in 5 to 10% of patients suffering from post-thrombotic syndrome (Kahn *et al*., 2008). The risk of VTE recurrence is 7% beyond one year, 14% at five years, 20% at 10 years and 27% at 20 years (Mohr *et al*., 2000:1249). Venous thromboembolism recurrence rates have been measured to be as high as 20% in those suffering from cancer and post-thrombotic syndrome (Prandoni *et al*., 2002:3484). Post-thrombotic syndrome is associated with a reduced quality of life and an increase in healthcare costs due to the resulting complications (Kahn *et al*., 2009:879; Mahan *et al*., 2016:130).

- Pulmonary embolism

Pulmonary embolism is defined as a condition when a thrombus, which formed in a deep vein, migrates through the circulatory system, causing partly or total occlusion of more than one of the pulmonary arteries (Piazza *et al*., 2015:1392). Pulmonary embolism is a life-threatening condition, which may lead to lung damage, cardiac arrest and/or death (Piazza *et al*., 2015:1392). It is estimated that up to 25% of all PE patients will present with sudden death without any pre-warning symptoms (Lucena *et al*., 2009:196). In the absence of anticoagulation, the risk of PE from an extensive and newly formed iliac vein thrombus is reported to be in the region of 70% with mortality risk increasing by 5% per day (Veller & Pillay, 2009:307). Pulmonary embolism occurs in approximately 10% of patients with acute DVT and can cause up to 10% of in-hospital deaths (Bělohlávek *et al*., 2013:129). The formation of DVTs in the lower extremities will cause PE in up to 10% of sufferers (Bělohlávek *et al*., 2013:129). Pulmonary embolisms can either present immediately after the formation and migration of the leg thrombus or days later. Multiple studies using various plasma-based assays indicate that PE is associated with altered fibrin clot properties, which include an impaired fibrinolytic capacity (Lami *et al*., 2014:738; Martinez, Cuker *et al*., 2014:L397; Zabczyk *et al*., 2017:365). Martinez, Cuker and colleagues (2014:L397) have reported that thrombi in acute isolated PE were characterised by faster clot lysis time and lower fibre density when compared with DVT alone. Perfusion defects in certain areas of the pulmonary arteries following PE have been shown to be the cause of fibrinolytic resistance (Lami *et al*., 2014:738). Massive PE is defined by haemodynamic instability, which signals a poor prognosis for survival (Bělohlávek *et al*., 2013:134). Haemodynamic instability depends on both the size of the embolus as well as underlying cardiopulmonary status (Bělohlávek *et al*., 2013:134). The diagnosis of massive PE requires (1) sustained hypotension (systolic blood pressure below 90 mmHg for at least 15 minutes or the need for inotropic support), (2) asystole or pulselessness, or (3) bradycardia or a slow heart rate (Jaff *et al*., 2011:1829; Nasrin *et al*., 2016:371). Any combination of angiographic obstruction as well as cardiopulmonary function resulting in

haemodynamic decompensation qualifies as a massive PE (Condliffe *et al*., 2014:178; Samaranayake *et al*., 2015). Sub-massive PE is characterised by a large clot burden as well as symptoms of right ventricular dysfunction or evidence of myocardial necrosis, but without haemodynamic instability (Condliffe *et al*., 2014:179). Sub-massive pulmonary embolism results in elevation of right ventricular afterload with a subsequent increase in right ventricular wall tension, which may lead to dilatation and cardiac myopathy (Condliffe *et al*., 2014:179). Right coronary artery flow decreases with resulting increased right ventricular myocardial oxygen demand. Ischemia subsequently occurs as left ventricle compression leads to decreased cardiac output and coronary perfusion (Samaranayake *et al*., 2015). Death eventually results from right ventricular failure. Saddle PE describes emboli that lodge in the bifurcation of the main pulmonary artery into the right and left pulmonary arteries and can be massive or sub-massive in nature (Rya *et al*., 2007:1537). The diagnosis of saddle PE signals an unstable, high clot burden in the pulmonary artery with the possibility of sudden haemodynamic collapse. Most PE patients (around 75%) will present as asymptomatic with diagnosis normally occurring on autopsy (Rya *et al*., 2007:1537). Symptoms for PE are non-specific and can include sudden cough, haemoptysis, rapid breathing or sudden shortness of breath and/or chest pain – which can range from sharp, stabbing, burning, aching, or dull. Symptoms can occur at rest or while a patient is performing normal daily functions such as coughing or eating (Piazza *et al*., 2015:29).

It is clear from the previous sections that venous thromboembolism occurrence is common, often resulting from various additive mechanisms. Even though VTE may occur in patients without any predisposing factors, certain patient- as well as environmental factors may increase thrombogenesis risk. A discussion on the risk factors that may increase a patient's propensity for VTE development follows in section 2.4.4.

2.4.4 Risk factors for thrombus formation

Various inherited as well as acquired factors additionally raise a patient's VTE development risk by causing changes in blood constitution and/or the vessel endothelium (Lijfering *et al*., 2010:830). Whether the development of VTE is provoked by an acquired or inherited risk factor, either transient or persistent, or whether the development risk is unprovoked, all have important implications on the prophylactic measures necessary to improve prognosis (Kearon *et al*., 2012:419S). Because of the implications of VTE recurrence, it is important to understand the risk factor aetiology classification, in order to separate it into that of unprovoked and provoked factors. Unprovoked risk factors are those not associated with an environmental initiating factor. Patients may have non-environmental risk factors such as hereditary thrombophilia, advanced age or male sex (Kearon *et al*., 2016:1482). Recent major surgery can be classified as a provoked transient risk factor (Kearon *et al*., 2016:1482).

The most significant independent risk factors in acutely ill medical patients for VTE development were the presence of an acute infectious disease (provoked), advanced age (older than 75 years) (unprovoked), malignancy (provoked) as well as a prior VTE history (provoked) (Kearon *et al*., 2016:1480; Samama *et al*., 1999:795). The placement of central venous catheters (provoked risk) accounts for 9% of VTE incidences in patients. High triglycerides (provoked or unprovoked), especially in post-menopausal (provoked) female patients, are shown to double VTE development risk. Van Deventer and colleagues (1990:2520) showed that the release of endotoxins by infectious organisms in septic patients led to the activation of the coagulation cascade by means of an up regulation in TF secretion (Moore *et al*., 1987:124). Violi and Ferro (2013:426) found that endotoxemia originating from the intestinal tract can also contribute to VTE formation, meaning that factors outside of the circulatory system can also affect thrombogenesis. The complete mechanism of pathogenesis is not completely understood for septic patients, however, multiple factors, including immobility and venous stasis, activation of inflammatory pathways as well as disseminated intravascular coagulation seem to increase a patient's risk for VTE development (Kaplan *et al*., 2015:1224). Acute respiratory distress syndrome and higher positive end expiratory pressure were associated with increased risk of VTE prophylaxis failure and patient mortality (Hanify *et al*., 2017:207) and are classified as provoked factors.

Active malignancy is noted as an independent and provoked VTE development risk factor in as many as 30% of medical patients (Ashrani *et al*., 2016:29; Chee *et al*., 2014:3972; Kearon *et al*., 2016:1481). Stage IV pancreatic cancer, brain cancer, myeloproliferative disorders, ovarian cancer, lung cancer and cancer stage progression were significant for VTE recurrence prediction (Chee *et al*., 2014:3983). The thrombogenic mechanisms involve abnormal coagulation (Falanga & Marchetti, 2009:4849), as evidenced by 90% of cancer patients having some abnormal coagulation factors (Kearon & Akl, 2014:1794). Chemotherapy may increase the risk of venous thrombosis by affecting the vascular endothelium, coagulation cascades as well as tumour cell lysis (Tempfer *et al*., 2017:3327). The incidence has been shown to increase in those patients undergoing longer courses of therapy for breast cancer, from 4.9% for 12 weeks of treatment to 8.8% for 36 weeks (Kearon & Akl, 2014:1794). Chemotherapeutic agents, especially thalidomide and tamoxifen, have been shown to increase VTE risk in patients (provoked risk factor) (Tempfer *et al*., 2017:3327).

Chronic inflammatory conditions such as inflammatory bowel disease, chronic infections as well as rheumatoid arthritis are described as persistent provoked risk factors for VTE disease (Kearon *et al*., 2016:1481). However, data describing the direct relationship of these inflammatory mechanisms in causing VTE are not statistically significant (Kearon *et al*., 2016:1482).

Persons travelling on flights for longer than four hours' VTE development risks have been found to be increased – this is referred to as the so-called "economic class syndrome" (Hughes, 2013:744). Risk factors contributing to their heightened risk are prolonged sitting in crowded conditions leading to venous stasis, hypoxia experienced in the cabin as well as dehydration (all of which are provoked risk factors) (Gavish & Brenner, 2011:113). Estimates show that the occurrence of VTE in flights over four hours is around one in 4 656, but increases to one in 200 for those travelling in flights lasting longer than eight hours (Kesteven, 2000:S32; Hughes, 2013:744).

Obesity appears to increase the risk of anticoagulation reversal failure for patients diagnosed with VTE (Parkin *et al*., 2012:1897). Ageno and colleagues (2003:I-10) showed that patients with a higher body mass index (BMI) suffering from symptomatic proximal DVT were more likely to develop post-thrombotic syndrome during a 12-month follow up. Previous DVT development (post-thrombotic syndrome) is described as an added provoked risk for VTE recurrence (Kearon *et al*., 2012:e493S). Sub-therapeutic anticoagulant levels and active cancer disease are described as provoked risk factors for recurrence (Shulman, 2017:3285). Another acquired risk factor for DVT and PE recurrence is superficial vein thrombosis (Farrell *et al*., 2016:624).

Imbalances in the coagulation system, such as with thrombophilia, result in VTE development in approximately one in three patients (Connors, 2017:1177). Thrombophilia can be classified as either inherited or acquired coagulation imbalances that lead to an increased risk of thrombosis due to mutations in factor V Leiden, prothrombin or factor II, proteins C and S as well as antithrombin genes (Connors, 2017:1178). Thrombophilia is typically diagnosed in patients who develop VTE with no apparent exposing or provoking risk factors such as in patients suffering from recurrent VTE, especially those aged younger than 45 years, those with a familial history of VTE development as well as women who experience multiple spontaneous abortions or stillbirths (Bates *et al*., 2012:e691S).

Additionally, DVT complicates in 29% of surgical procedures with risk increasing during neurosurgery, major orthopaedic surgery of the legs, thoracic, pelvic or abdominal surgery in cancer patients, renal transplantation as well as cardiovascular surgery (Jahmad, 2005:727; Kaye *et al*., 2015:243). Postoperative venous thrombosis varies depending on a multitude of patient factors, including the type of surgery undertaken (Jahmad, 2005:728; Kaye *et al*., 2015:243). The type of surgery undertaken predicts VTE risk due to the time that a patient is left immobile post operatively – surgery can be classified into four risk groups: low risk procedures (surgery duration of less than 30 minutes), moderate risk (arthroscopy or repair of fractures in lower leg, or procedures requiring a postoperative plaster cast), high risk (procedures requiring patient immobilisation of longer than 4 days) and high risk (hip or knee arthroscopy, hip fracture surgery,

major trauma, spinal cord surgery and procedures performed on multiple lower leg fractures) (Deitelzweig *et al*., 2008:S27; Falck-Ytter *et al*., 2012:e278S). Without prophylaxis, general surgery operations typically have an incidence of DVT around 20%, whereas orthopaedic hip surgery can occur in up to 50% of patients (Falck-Ytter *et al*., 2012: e278S). The nature of orthopaedic surgery, trauma and diseases predispose patients to the occurrence of VTE disease (Deitelzweig *et al*., 2008:S27; Falck-Ytter *et al*., 2012: e278S).

Venous thromboembolism is characterised by a tendency to re-occur and can therefore be considered a chronic disease (Fahrni *et al*., 2015:451). The presence of risk factors plays a prominent role in assessing the pre-test probability of DVT (Fahrni *et al*., 2015:451). Furthermore, transient or provoked risk factors require short-term anticoagulation prophylaxis, whereas idiopathic DVT or chronic risk factors warrant longer-term therapy (Kearon *et al.,* 2012:e422S; Kearon *et al*., 2016:1481). Transient as well as chronic factors that can contribute or enhance the risk of DVT development can be classified under genetic (idiopathic), acquired as well as environmental factors and are listed in Table 2-1. References used in Table 2-1 include Anderson and Spencer (2003:I-10), Bates and colleagues (2012:e691S), Gerhardt and colleagues (2016:2343) as well as Tempfer and colleagues (2017:3327).

Table 2:1 Hereditary and acquired risk factors for VTE development

Type of risk factor	Description
Genetic risk factors	Antithrombin deficiency Protein C deficiency Protein S deficiency Factor V Leiden Prothrombin gene mutation Non-O blood group Dysfibrinogenemia Elevated factor VIII Elevated factor IX Elevated factor XI Hyperhomocysteinemia (including homocystinuria)
Acquired risk factors	Increasing age Cancer or malignancy Antiphospholipid syndrome Human immunodeficiency virus (HIV), Sepsis Inflammatory disorders (systemic lupus erythematosus (SLE), irritable bowel disease (IBD), vasculitis) Nephrotic syndrome Obesity Smoking
Environmental	Surgery (major inpatient, ambulatory), Trauma, Immobilisation, Central venous catheter (CVC), Pregnancy/ post-partum period Hormonal therapy (includes oral, transcutaneous, vaginal ring contraceptive, depot progestin injections and hormone replacement therapy) Chemotherapy Travel

2.5 Venous thromboembolism prophylaxis

Venous thromboembolism prophylaxis is defined as methods that include pharmacological (anticoagulant) and non-pharmacologic (mechanical) interventions, which aim to reduce the risk of DVT and/or PE formation in susceptible patients (Flevas *et al*., 2018:138; Leme & Sguizzatto, 2015:686; Routhier *et al*., 2018). Pharmacological prophylaxis includes the administration of medication that promotes the lysis of formed thrombi and can be broadly grouped under the term “anticoagulants” (Waheed & Hotwagner, 2018:6). Mechanical methods on the other hand aim to

improve blood flow and reduce blood pooling by means of externally applied pressure to the muscles of the lower extremities to mimic pressure exerted during walking (Weinberger & Cipolle, 2016:36). Mechanical prophylactic approaches include external compression by means of graduated compression stockings, intermittent pneumatic compression devices, foot impulse devices or foot pumps as well as early mobilisation (Geerts *et al*., 2008:381s).

2.5.1 Pharmacological prophylaxis (anticoagulants)

Anticoagulants are medications that prevent or reduce the body's ability to form thrombi (Chen, 2018; Moake, 2018) and subsequently reduce the body's ability to form VTE (Flevas *et al*., 2018:138). The different properties for the available South African anticoagulants registered for VTE prophylaxis (Micromedex, 2018; Rossiter, 2016:100-109) are summarised in the below sections. For the purpose of this study, comparisons are described for each medication's prophylactic properties only.

2.5.1.1 Comparisons of anticoagulants

The anticoagulant class comprises (among others) warfarin, heparin, low weight molecular heparins (LMWHs) and the non-vitamin K oral anticoagulants (NOACs) such as dabigatran, rivaroxaban and apixaban (Micromedex; 2019; Rossiter, 2016:102; Yoshida *et al*., 2013). The heparins can further be subdivided into heparin or unfractionated heparin and the LMWHs (Hirsh *et al*., 2008; Rossiter, 2016:102). Heparin is a naturally occurring polysaccharide molecule from porcine intestine or bovine lungs and its effect is more unpredictable than the synthetised LMWH (The American Society of Health-System Pharmacists, 2016). Fondaparinux is an injectable, synthetic selective Factor Xa inhibitor with activity similar to LMWHs, however it does not exhibit thrombin inhibition (Vallerand *et al*., 2017c). The LMWH class of anticoagulants comprises molecules with short polysaccharide chains and exhibits a more predictable therapeutic effect profile (Hirsh *et al*., 2008; The American Society of Health-System Pharmacists, 2016). Molecules in this class are enoxaparin, dalteparin, nadroparin, tinzaparin and the newly South African registered bemiparin (Hirsh *et al*., 2008; Sánchez-Ferrer, 2010:19) which are included in Table 2-2.

Table 2:2 Anticoagulant formulations

Active ingredient	Available in South Africa	Registered South African trade name	Available formulations and concentrations
Apixaban	Yes (2017)	Eliquis®	2.5 mg and 5 mg tablet (Pfizer, 2015)
Betrixaban	No	Not applicable	Not applicable
Bemiparin	Yes (2018)	Hibor®	2500 I.U./ 0.2ml, 3500 I.U./ 0.2ml, 5000 I.U./ 0.2ml, 7500 I.U./ 0.3ml, 10 000 I.U./ 0.4ml (Litha Pharma, 2019)
Dabigatran	Yes	Pradaxa®	75 mg, 110 mg and 150 mg capsules (Boehringer Ingelheim, 2013; Rossiter, 2016:109).
Dalteparin	Yes	Fragmin®	Prefilled syringes for subcutaneous injection: 2500 I.U./ 0.2 ml, 5000 I.U./ 0.2 ml, 12500 I.U./ 0.5 ml, 15000 I.U./ 0.5 ml, 18000 I.U./ 0.72 ml (Rossiter, 2016:104).
Desirudin	No	Not applicable	Not applicable
Edoxaban	No	Not applicable	Not applicable
Enoxaparin	Yes	Clexane®	Prefilled syringe subcutaneous injections; 20 mg/ 0.2 ml, 40 mg/ 0.4 ml, 60 mg/ 0.6 ml, 80 mg/ 0.8 ml,100 mg/ 1 ml and multidose vial of 300 mg /3 ml (Sanofi-Aventis, 2012; Rossiter, 2016:104).
Fondaparinux	Yes	Arixtra®	Prefilled syringes for subcutaneous injection: 2.5 mg, 5 mg, 7.5 mg and 10 mg (Pharmacare Limited, 2012; Rossiter, 2016:109).
Heparin	Yes	Fresenius-Heparin®	1000 I.U./ml, 1ml; 5000 I.U./ml, 1 ml; 1000 I.U./ ml, 5 ml; 5000 I.U./ ml, 5 ml; 25000 I.U./ ml, 5ml (Fresenius Kabi, 2016; Rossiter, 2016:102).
Nadroparin	Yes	Fraxiparine®	Prefilled syringes for subcutaneous injection (each 1.0ml contains 9 500 IU nadroparin calcium): 0.2 ml, 0.3 ml, 0.4ml, 0.6ml, 0.8ml, 1 ml (Pharmacare Limited, 2002)

Table 2:2 Anticoagulant formulations (continued)

Active ingredient	Available in South Africa	Registered South African trade name	Available formulations and concentrations
Rivaroxaban	Yes	Xarelto®	Tablets: 10 mg, 15 mg, 20 mg (Bayer, 2013; Rossiter, 2016:109).
Tinzaparin	No	Not applicable	Not applicable
Warfarin	Yes	Aspen-Warfarin® Cipla-Warfarin®	Oral formulation only and is available as a 5mg tablet in South Africa (Pharmacare Limited, 1996; Cipla Medpro, 2007; Rossiter, 2016:102).

2.5.1.2 Pharmacological mechanisms of action

The mechanisms of action for anticoagulants differ between the various available medications, but all aim to prevent the ultimate conversion of fibrinogen to fibrin, which is required for thrombus formation (Vallerand *et al*., 2017f). Most anticoagulants, with the exception of warfarin, actively inhibit factor Xa either directly or via antithrombin III (Eriksson, 2011:41). Factor Xa neutralisation interrupts the blood coagulation cascade with the inhibition of thrombin and subsequent thrombus formation (Skidmore-Roth, 2018; Vallerand *et al*., 2017f). One molecule of factor Xa can generate more than 1 000 molecules of thrombin, thereby making the selective factor Xa inhibitors very useful in terminating the amplification of thrombin generation in the coagulation cascade (Mann *et al*., 2003:1508). A short summary of each South African registered anticoagulant's mechanism of action follows:

- ***Apixaban*** and ***rivaroxaban*** are molecules that competitively inhibit bound as well as circulating factor Xa, thereby inhibiting the activation of factor II (prothrombin) to factor Ia (thrombin) (Bayer, 2013; Vallerand *et al*., 2017e; Yoshida *et al*., 2013).

- ***Bemiparin*** is a 'second-generation' LMWH mostly because of its mean molecular weight of 3.6 kDa, which is lower than other LMWH. It furthermore has a narrow distribution of saccharide chain lengths, with most being less than 6 kDa in weight. It exhibits its activity by antagonising Xa and further increases the release and activity of TF pathway inhibitor from endothelial cells (Sánchez-Ferrer, 2010:19).

- ***Dabigatran*** is a competitive, reversible direct thrombin inhibitor that disrupts the conversion of fibrinogen into fibrin during the coagulation cascade (Boehringer Ingelheim, 2013; Ben Salem *et al*., 2014:11). Thrombus formation is subsequently prevented by inhibition of

fibrinogen formation on free circulating thrombin, fibrin bound thrombin as well as thrombin's influence on platelet aggregation (Boehringer Ingelheim, 2013; Ben Salem *et al*., 2014:11).

- ***Dalteparin*** exerts its activity through an indirect inhibitory effect on factor-Xa. This is achieved through binding to antithrombin III (Nutescu *et al.,* 2016:18).

- ***Enoxaparin*** binds to antithrombin III which results in the inhibition of coagulation factors Ia and Xa (Weitz, 2011:854; Vallerand *et al*., 2017b).

- ***Fondaparinux*** is a synthetic selective inhibitor of antithrombin III and potentiates the innate neutralisation of factor Xa by antithrombin by 300 times (Vallerand *et al*., 2017c).

- ***Heparin*** acts as a catalyst in the antithrombin-protease reaction by enhancing the inhibitory effects of antithrombin III (Weitz, 2011:854; Zehnder, 2012:604). This subsequently prevents the conversion of fibrinogen to fibrin and prothrombin to thrombin resulting in anticoagulation (Vallerand *et al*., 2017d; Weitz, 2011:854; Zehnder, 2012:604). High doses may interfere with platelet aggregation and extend bleeding time (Vallerand *et al*., 2017d; Weitz, 2011:855).

- ***Nadroparin*** exhibits a high binding affinity to anti-thrombin III which leads to an enhanced supression of factor Xa and to a lesser extent, factor IIa (Tiziani, 2017:226). Nadroparin has a factor Xa to factor IIa suppression ratio of 3.6:1 (Davis & Faulds, 1997:301). Additional mechanisms contributing to its antithrombotic activity include the release of tissue plasminogen activator from endothelial cells, the stimulation of TF pathway inhibitor, as well as it causing a decrease in blood viscosity and an increase of platelet and granulocyte membrane flexibility (Aspen Pharmacare Australia Pty Ltd, 2017; Davis & Faulds, 1997:302).

- ***Warfarin*** is administered as a racemic mixture of rectus (r) and sinister (s) stereoisomers (Tiuca, 2016:3; Vallerand *et al*., 2017f). S-warfarin is a 3 to 5 times more potent inhibitor of the vitamin K epoxide reductase complex than r-warfarin is (Tiuca, 2016:9; Vallerand *et al*., 2017f). Both these stereoisomers are metabolised by different phase 1 enzymes in the liver (Vallerand *et al*., 2017f). These stereoisomers actively antagonise vitamin K epoxide reductase (VKORC1), resulting in the inhibition of formation of vitamin K epoxide from vitamin K hydroquinone. This, in turn, prevents the conversion of clotting factors II, VII, IX and X to their active form as well as the formation of protein C and S by inhibition of the formation of gamma-glutamyl carboxylase containing proteins that are required for haemostasis (Pharmacare Limited, 1996; Vallerand *et al*., 2017f).

Figure 2-3 is a diagrammatic representation of anticoagulant mechanisms of action on the different coagulation molecules and their subsequent reactions. This diagram has been adapted from Eriksson (2011:41) and the Micromedex Drug Database (2018).

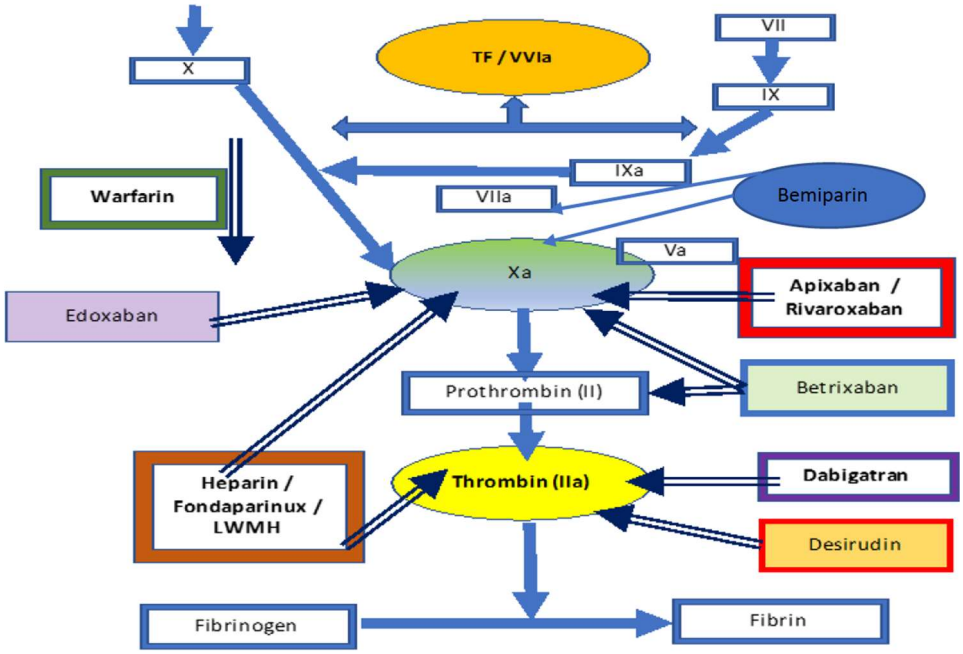


Figure 2:2 Pharmacologic mechanism of action for anticoagulants

2.5.1.3 Clinically important registration

Clinical registration for ***apixaban*** includes the prevention of VTE and PE in adult patients who have undergone arthoplastic surgery of the hip and/or knee. This registration is valid for both South Africa and the rest of the world (Agrawal & Manna, 2019; Yoshida *et al*., 2013).

Bemiparin exhibits the longest half-life of all LMWH and is registered in South Africa for the use of VTE prophylaxis as indicated in general surgery, abdominal surgery (in patients with a moderate risk of VTE development), after major orthopaedic surgery, prevention in non-surgical patients as well as clotting in the extracorporeal circuit after haemodialysis (Litha Pharma, 2019). It is further registered as an additional prophylactic agent in VTE recurrence in patients (with a transient high risk of VTE development) as well as the treatment of VTE (Ciccone *et al*., 2014:34; Litha Pharma, 2019).

Dabigatran and ***rivaroxaban*** registration include both treatment and prevention of acute VTE after hip and knee replacement procedures in South Africa, the US and European Union (EU) (Boehringer Ingelheim, 2013; Manucci & Franchini, 2011:116; Vallerand *et al*., 2017a). Venous

thromboembolism prophylaxis in hip and knee replacement surgery is registered for 30 or 14 days, respectively, in rivaroxaban (Vallerand *et al*., 2017e). However, dabigatran's current registered indication worldwide includes prophylaxis for hip surgery only (Micromedex, 2018). For rivaroxaban, registration status was expanded to include the reduction in DVT or PE recurrence risk (Vanassche & Verhamme, 2013: 589).

Dalteparin is registered in South Africa for DVT prevention in abdominal surgery, orthopaedic surgery (hip arthroplasty) as well as those diagnosed with malignancies (Rossiter, 2016:104).

Enoxaparin is registered for use worldwide in the prevention and treatment of VTE and PE in high-risk (immobile medical, surgical and orthopaedic patients) as well as moderate-risk patients (those undergoing abdominal surgery) (Manucci & Franchini, 2011:116; Sanofi-Aventis, 2012; Vallerand *et al*., 2017b; Weitz, 2011:858). Off-label uses (uses not registered with regulation authorities) include VTE prophylaxis in those suffering from cancer, those undergoing haemodialysis, patients undergoing percutaneous coronary intervention or travelling by air for extended periods of time (Micromedex, 2018).

Fondaparinux is registered both internationally as well as locally for VTE prophylaxis in patients undergoing major orthopaedic surgery (hip, leg and knee) or abdominal surgery (Pharmacare Limited, 2012; Skidmore-Roth, 2018). It is not registered in South Africa to be used in immobile, medically ill patients (Micromedex, 2018).

Heparin is registered in SA for subcutaneous administration in the prophylaxis for VTE following stroke, myocardial infarction, vascular surgery as well as other surgery (Fresenius Kabi Heparin Sodium injection®[package insert]:2016). Additional South African registration indications include the prevention of clot formation during dialysis as well as the treatment of VTE and prevention of thromboembolic phenomena in the coronary, retinal and cerebral venous systems (Fresenius Kabi, 2016; Vallerand *et al*., 2017d). In contrast, heparin is not registered to be used as prophylaxis in the US for percutaneous coronary intervention, patients suffering from cancer, carotid endarterectomy and thromboembolic disorder due to pregnancy (Micromedex, 2018).

Nadroparin is specifically registered in SA for the prophlaxis of DVT which may cause PE (Pharmacare Limited, 2002). Indications are for those undergoing hip or knee arthroplasty as well as at-risk patients undergoing abdominal surgery (Pharmacare Limited, 2002; Tiziani, 2017:226).

Warfarin is registered for the prevention and treatment of VTE and PE in South Africa (Pharmacare Limited, 1996), but not for those suffering from cancer (Micromedex, 2018; Pharmacare Limited, 1996).

2.5.1.4 Clinically registered dosing

Anticoagulant prophylactic doses differ from their therapeutic dosing recommendations. Table 2-3 provides a brief summary of the recommended South African prophylactic dosing as well as each's clinical anticoagulant characteristics.

Table 2:3 Clinical anticoagulant comparisons

Generic name	Recommended prophylactic dosage	Special warnings	Adverse effects
Apixaban	2.5 mg orally, taken 12 to 24 hours after surgery and continued twice daily (Agrawal & Manna, 2019).	Not indicated for those suffering from hepatic failure, patients with a high propensity for bleeding, recent brain or spinal injury and or surgery. Warnings exist for patients with vascular aneurysms, arteriovenous malformations and those taking other anticoagulants (Agrawal & Manna, 2019).	Brain aneurisms Haemorrhage of any organ of the body Hypotension Nausea Abnormal liver test results Haematuria Pruritus Alopecia Anaemia (Agrawal & Manna, 2019; Cohen *et al*., 2015).
Bemiparin	2 500 I.U. once daily for general surgery, 3 500 I.U. for orthopaedic surgery; give first dose 2 hours before or 6 hours after surgery. Continue for 7 to 10 days and until the patient is fully ambulant (Ciccone *et al*., 2014:34; Sánchez-Ferrer, 2010:19).	In epidural anaesthesia, 2 500 I.U. or 3 500 I.U. should be initiated 4 hours after removal of the catheter. The next dose should be given after completion of the surgery. Not recommended in children. Not enough evidence to recommend usage in pregnant or lactating women. (Fontcuberta, 2010:43).	Bleeding in the spinal area with nerve damage leading to a loss of strength or sensation in legs or lower body Increased liver transaminases Type 1 thrombocytopenia Bleeding Bruising (Miras-Parra *et al*., 2005:463).
Dabigatran	110 mg orally 1 to 4 hours postoperatively, then 220mg daily for 28 to 35 days (Rossiter, 2016:100-109; Wells *et al*., 2015:130-131).	Contraindicated with active haemorrhage, mechanical prosthetic heart valves and anaphylaxis. Precautions exist for epidural anaesthesia, renal impairment – CrCl less than 30 mL/min, the elderly (increases in GI bleeding risk for those 75 years and older) (Boehringer Ingelheim, 2013).	Oesophagitis Gastritis Gastrointestinal (GI) haemorrhage GI ulcer, Haemorrhage, Myocardial infarction, Anaphylaxis, Epidural Haematoma, Intracranial haemorrhage Alveolar haemorrhage (Micromedex, 2018; Cohen *et al*., 2015).

Table 2:3 Clinical anticoagulant comparisons (continued)

Generic name	Recommended prophylactic dosage	Special warnings	Adverse effects
Dalteparin	Dose in abdominal and gynaecological surgery: 2500 IU subcutaneously 1 – 2 hours pre-operatively and continued daily for 7 days (Micromedex, 2019c; Rossiter, 2016:102). Dose in orthopaedic surgery/ those suffering from malignancy: 5000 IU subcutaneously on evening prior to surgery, then 5000 IU daily for 7 days (Rossiter, 2016:103).	Even though data support safety in pregnancy, it is not recommended to be used in mothers who are breastfeeding. Dose adjustment is required in those suffering from severe renal failure (CrCl of less than 30ml/min) (Rossiter, 2016:103).	Alopecia Pruritis Cell-mediated immune response Erythema Hyperkalemia Thrombocytopenia Haemorrhage Paralysis (Micromedex, 2019c).
Enoxaparin	40mg once daily, within 12 to 24 hours after surgery; continue for 14 days (Wells *et al*., 2015:130). *see note	Prophylactic treatment in Paediatrics: Younger than 2 months, administer 0.75/kg subcutaneously 12 hourly Older than 2 months, administer 0.5mg/kg subcutaneously 12hourly (Clexane®[package insert]: 2012). Dosing reduction is require in patients suffering from severe renal failure (Pellizzari *et al*., 2018:605).	Diarrhoea Nausea Anaemia Fever Thrombocytopenia Skin necrosis Intracranial Haemorrhage Pneumonia (Micromedex, 2018).
Fondaparinux	Initiate with 2.5 mg subcutaneous daily, 6 to 8 hours after surgery and continued for 10 days in abdominal and 35 days in orthopaedic surgery (Wells *et al*., 2015:130; Skidmore-Roth, 2018).	In CrCl 30 to 50 ml/minute, use with caution as total clearance is 40% lower compared to patients with normal renal function (Pharmacare Limited, 2010; Pellizzari et al., 2018:605); Contra-indicated in CrCl of less than 30 ml/minute (Pharmacare Limited, 2010).	Injection site rash Fever Anaemia Haemorrhage Thrombocytopenia Anaphylaxis Intracranial haematoma Non-traumatic spinal subdural haematoma (Micromedex, 2018).
Heparin	DVT prophylaxis: Adults - 5000 I.U. subcutaneously every 8 to 12 hours (Zehnder, 2012:605).	Heparin cannot be used interchangeably unit for unit with LMWH's (Bara et al., 1985:634).	Thrombocytopenia Increased liver aminotransferase levels Haemorrhage

Table 2:3 Clinical anticoagulant comparisons (continued)

Generic name	Recommended prophylactic dosage	Special warnings	Adverse effects
Heparin (continued)			Hypersensitivity reaction Spinal haematoma (Micromedex, 2018).
Nadroparin	DVT prophylaxis: 0.3 ml administered subcutaneously 2 hours prior to abdominal surgery and repeated 8 hours post-operatively (Pharmacare Limited, 2002). Dosing in arthroplasty should be adjusted to patient weight (38 IU anti-Xa per kg for 3 days and 57 IU anti-Xa/kg thereafter) (Egger *et al.*, 2000:602).	Dosing according to anti-Xa activity must be individualised for nadroparin as it is not therapeutically interchangeable with other LMWH's (Pharmacare Limited, 2002; Tiziani, 2017:227).	Haemorrhage Thrombocytopenia Cutaneous necrosis Hypersensitivity reactions (Barradell & Buckley, 1992:858; Pharmacare Limited, 2002).
Rivaroxaban	Prophylactic dose is 10 mg orally once daily initiated 6 to 10 hours postoperatively. Duration of prophylaxis in hip arthroplasty is for 35 days with 12 days for knee arthroplasty (Skidmore-Roth, 2018).	Avoid use in CrCl of less than 30 ml/min. Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or hepatic disease associated with coagulopathy (Bayer, 2013).	Haemorrhage Syncope GI haemorrhage Haematoma Angioedema (Micromedex, 2018; Cohen *et al.*, 2015).
Warfarin	Prophylaxis should be initiated combining LMWH, fondaparinux or unfractionated heparin in from day 2 of prophylaxis, continued for 5 days with International Normalised Ratio (INR) kept at 3.5 (Wells *et al.*, 2015:131).	The INR may only show effects of dose changes after 5 to 7 days, dosages should not be change more frequently than every 3 days (Wells *et al.*, 2015:131).	Alopecia Cholesterol embolus syndrome Tissue necrosis Haemorrhage Hypersensitivity reaction, Compartment syndrome Intracranial or intraocular haemorrhage (Micromedex, 2018).

*Note: Interestingly, the FDA recommended prophylactic dose for enoxaparin in knee arthroplasty is 30mg subcutaneously, initiated 12 to 24 hours postoperatively and continued twice daily for 14 days. This does not correspond with South African guidelines.

2.5.1.5 Drug-drug interactions

Anticoagulants are not only administered as prophylaxis in hospitalised patients, but often also need to be administered to patients taking multiple chronic medications. Due to their high risk of haemorrhage, prescribers and patients need to be cognisant of possible drug-drug interactions.

Apixaban

- Apixaban is a direct factor Xa inhibitor, and, as with other factor Xa inhibitors, its concomitant use with medication increasing haemostasis such as antiplatelet drugs, concomitant use of drugs affecting haemostasis including antiplatelets, other anticoagulants, thrombolytic agents, antidepressants such as selective serotonin inhibitors (SSRIs) or selective noradrenaline receptor inhibitors (SNRIs) and nonsteroidal anti-inflammatory drugs (NSAIDs) should be done under close monitoring (Agrawal & Manna, 2019; Cohen *et al*., 2015).

Dabigatran

- Dabigatran is a substance for the PGP complex, a plasma membrane protein that is responsible for drug transport in or out of cells (Karim *at al.*, 2013). The bioavailability for dabigatran is lower than that of other direct oral anticoagulants, and small changes in its absorption and excretion may affect its blood concentration (Heidbuchel *et al*., 2013). P-glycoprotein IIb/IIIa inhibitors such as quinidine, verapamil and amiodarone as well as PGP substrates such as carbamazepine, rifampin and tipranovir will decrease dabigatran's effect (Boehringer Ingelheim, 2013; Heidbuchel *et al*., 2013).

- Unfractionated heparin, warfarin, LMWH and/or platelet inhibitors such as clopidogrel, acetylsalisylic acid and ticagrelor will potentiate bleeding side effects if taken concomitantly with dabigatran (Boehringer Ingelheim, 2013; Hirsh Raccah *et al*., 2018).

- Dabigatran primarily relies on renal excretion and nephrotoxic medication such as chemotherapeutics, NSAIDs (chronic treatment of high doses) and amphotericin B that will increase its anticoagulant effect (Boehringer Ingelheim, 2013; Ben Salem *et al*., 2014:15).

- An increase in bleeding has been reported when dabigatran is combined with St John's wort (Skidmore-Roth, 2018). This is due to St John's wort being an inducer of the PGP complex (Karim *at al.*, 2013).

Dalteparin

- Dalteparin exibits similar medicine interactions to that of the other LMWHs, in that its combined use with anticoagulants, platelet inhibitors, medicine that increase serum potassium

as well as intravenous nitroglycerine should be done with caution (Micromedex, 2019c). This is due to an enhanced bleeding as well as potassium sparing effect (Micromedex, 2019c).

Bemiparin

- Increased risk of bleeding is seen when bemiparin is combined with aspirin, ketorolac, other platelet inhibitors, systemic glucocorticoids, and diclofenac due to similar effects on thrombosis (Sánchez-Ferrer, 2010:19).

- Bemiparin levels may be decreased if combined with glyceryl trinitrate, possibly due to its heparin-like mechanism of action (Sánchez-Ferrer, 2010:19). This is because heparin-like agents and concomitant nitroglycerin (NG) administration result in decreased PTT (partial thromboplastin time), with an increase seen once the heparin-like agents are stopped (Sánchez-Ferrer, 2010:19).

- Bemiparin, like other LMWHs, may suppress adrenal secretion of aldosterone leading to hyperkalaemia and may result in drug interactions with agents also affecting aldosterone (Frosst Ibérica S.A, 2016:3,5).

Enoxaparin

- The metabolism of enoxaparin is primarily via hepatic depolymerisation to lower molecule weight fragments with reduced activity. These fragments (around 10%) are further excreted unchanged via the urinary system (Micromedex, 2019a). Drug interactions with enoxaparin primary occur due to concomitant reduction of platelet function (such as with abciximab, aspirin and clopidogrel), thrombolytics (such as alteplase and streptokinase and reteplase), other anticoagulants (warfarin and heparin), increased risk of GI mucosal injury (NSAIDs), potentiated antagonism of factor X (such as with other direct oral anticoagulants), alterations in excretion [such as with angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and canaglifozin] (Cohen *et al.*, 2019:464).

- Enoxaparin may increase the therapeutic effects of: Angiotensin converting enzyme inhibitors, aliskiren, angiotensin II receptor blockers, aspirin, ticlopidine, clopidogrel, ketorolac and diclofenac, canaglifozin, potassium salts, potassium-sparing diuretics and/or rivaroxaban (Sanofi Aventis, 2012; Micromedex, 2019b).

- The therapeutic effects of enoxaparin may be increased by the following (and are not all inclusive): Apixaban, argatroban, abciximab, bivalidrudin, dabigatran, NSAIDs, other anticoagulants, celecoxib, citalopram, clopidogrel, fluoxetine, sugammadex, tibolone and/or tipranavir (Cohen *et al.*, 2019:464; Micromedex, 2019b; Sanofi Aventis, 2012).

- Increased bleeding risk is reported with the combination of enoxaparin with garlic, ginger, gingko biloba, green tea, horse chestnut and/or feverfew (Micromedex, 2019b, Skidmore-Roth, 2018).

Fondaparinux

- Fondaparinux may increase the levels or therapeutic effects of other anticoagulants, rivaroxaban, iodine I-131 and/or tositumomab (Micromedex, 2018).

- The therapeutic anticoagulant effect of fondaparinux may be increased by agents with antiplatelet properties such as apixaban, dabigatran etexilate, dasatinib, ibrutinib, NSAIDs, omega-3 fatty acids, salicylates, sugammadex, thrombolytic agents, tibolone, tipranavir, urokinase and/or vitamin E (Micromedex, 2018).

- The therapeutic effect of fondaparinux may be decreased by oestrogen derivatives and/or progestins (Pharmacare Limited, 2012).

- Increases in anticoagulation have been reported with the combination of garlic, ginger, ginko biloba, feverfew and ginseng with a potential for dangerous haemorrhage due to additive mechanisms (Skidmore-Roth, 2018).

Heparin

- Drugs with antiplatelet activity, e.g. abciximab, aspirin, clopidogrel and dipyridamole may enhance the inhibition of platelets when given together with heparin (Fresenius Kabi, 2016; Harder & Klinkhardt, 2000:391; Tompkins *et al*., 2010:2380).

- Additive thrombolytic effects are seen when heparin is combined with other thrombolytics such as alteplase, reteplase and/or streptokinase (Harder & Klinkhardt, 2000:391).

- The simultaneous administration of heparin with potassium sparing agents (such as amiloride, hydrochlorothiazide, angiotensin converting enzyme inhibitors), in the presence of renal dysfunction may increase the risk of hyperkalaemia (Ben Salem *et al*., 2014:677). A possible mechanism has been reported being heparin's ability to suppress the enzymatic synthesis of aldosterone, causing hypoaldosteronism and subsequent hyperkalaemia (Ben Salem *et al*., 2014:677). This effect is potentiated during therapy in patients with impaired renal function and those receiving agents that increase potassium levels (Ben Salem *et al*., 2014:677).

- Increases in bleeding risk are reported to be seen with concomitant use of heparin with chamomile, clove, anise, arnica, dong quai, garlic, ginger, gingkobiloba, feverfew, horse chestnut and/or green tea (Skidmore-Roth, 2018).

Nadroparin

- As with other LMWH's, nadroparin should be cautiously used when combined with oral anticoagulants, antiplatelet agents as well as thrombolytic enzymes (streptokinase). This is due to their enhanced ability to cause bleeding (Pharmacare Limited, 2002; Tiziani, 2017:227).

- The anticoagulant effect of nadroparin may be prevented by tetracyclines, antihistamines, nicotine and digitalis (Pharmacare Limited, 2002).

- Patient potassium level monitoring should be conducted with concomitant nadroparin and systemic corticosteroid use, ACE inhibitors and NSAIDs due to an increased sparing effect (Tiziani, 2017:227).

- Partial thromboplastin time monitoring should be conducted with the co-administration of nadroparin and intravenous nitroglycerine (Pharmacare Limited, 2002).

Rivaroxaban

- This molecule is contraindicated in the concomitant use of human prothrombin complex concentrate (also known as factor X) as rivaroxaban is an antagonist for activated factor X (Milling & Ziebell, 2019).

- Serious drug-drug interactions occur between rivaroxaban and apixaban, clarithromycin, conivaptan, indinavir, ketoconazole and ritonavir and should be avoided. This is due to rivaroxaban being a substrate for cytochrome P450 isoenzyme 3A4 (CYP 3A4) and PGP. Ketoconazole, itraconazole, posaconazole, voriconazole (or azole antifungals), indinavir and ritonavir all strongly inhibit CYP 3A4 as well as PGP resulting in the decreased metabolism of rivaroxaban (Fralick *et al*., 2016:670; Janssen Pharmaceuticals Inc., 2016; Micromedex, 2019). Substances causing strong inhibition of PGP include cyclosporine, the azole antifungals and tacrolimus further increase the concentration of rivaroxaban, resulting in bleeding (Micromedex, 2019; Vazquez, 2018:2232).

- Drug therapy with the concomitant use of rivaroxaban and the following list of medication can possibly cause drug interactions where rivaroxaban concentrations may be increased between two and five fold: Amiodarone, clarithromycin, erythromycin, quinidine, verapamil and ticargrelor (Bayer, 2013; Hirsh Raccah *et al*., 2018; Vazquez, 2018:2233).

Warfarin

- Numerous drug-drug interactions are possible and the Micromedex® online drug reference has identified a total of 428 drug interactions with warfarin (Mircromedex, 2019). The effect of warfarin on albumin's displacement from its binding sites, warfarin's ability to cause changes in metabolism, absorption and/or its potentiating effects on other anticoagulants are mechanisms explaining its vast amount of drug-drug interactions (Pharmacare Limited, 1996).

- The following are contraindicated and may act as potentiators for warfarin action: Allopurinol, chloral hydrate, chloramphenicol, cimetidine, clofibrate, COX-2 selective inhibitors, dextrothyroxine, disulfiram, glucagon, heparin, HMG-CoA reductase inhibitors, indomethacin, isoniazid, mefenamic acid, cotrimoxazole, erythromycin, metronidazole, mifepristone, quinidine, quinolone antibiotics, SSRI's, steroids, fluconazole, isoniazid, metronidazole, and miconazole, amiodarone, clofibrate, propafenone, propranolol, and sulfinpyrazone; alcohol (only with concomitant liver disease), cimetidine; omeprazole, griseofulvin, rifampin and/or nafcillin. Warfarin also increases the toxicity of oral sulfonylureas and/or phenytoin (Bristol-Meyers Squibb, 2017:15-20; Micromedex, 2019; Patel *et al.*, 2019).

- Inhibitors of warfarin's antithrombotic action are: azathioprine, barbiturates, cholestyramine and other bile acid sequestrants, carbamazepine, oestrogens, oral contraceptives, factor IX/VIIa, griseofulvin, nafcillin, phenytoin, rifampin, sucralfate, sulfasalazine and/or vitamin K (Bristol-Meyers Squibb, 2017:15-20; Micromedex, 2019).

- Drug-food interactions listed show those with the most serious interactions possibly causing an increase in warfarin concentration, but are not all inclusive: leafy green vegetables containing vitamin K such as kale, spinach, Brussels sprouts and parsley, grape fruit, green tea and/or cranberry juice (Bristol-Meyers Squibb, 2017:23; Patel *et al.*, 2019; Vallerand *et al*., 2017f).

- Drug-herb interactions with the following effects are:

    - *Increased warfarin effect:* anise, basil, chamomile, chondroitin, dong quai, evening primrose, feverfew, garlic, ginger, ginko, ginseng, angelica, horse chestnut, liquorice, kava, melatonin, saw palmetto and/or red yeast rice (Bristol-Meyers Squibb, 2017:21-22; Skidmore-Roth, 2018; Vallerand *et al*., 2017f).
    - *Decreased warfarin effect:* St. John's wort and/or coenzyme Q10 (Bristol-Meyers Squibb, 2017:23; Skidmore-Roth, 2018; Vallerand *et al*., 2017f).

2.5.1.6 Drug-disease interactions

The anticoagulants may cause adverse effects when taken by patients suffering from certain chronic diseases. The following section summarises the most serious of adverse effects that may occur, as well as the disease state associated with the adverse effect:

Apixaban

- Apixaban is reliant on both renal and hepatic clearance and dosing reductions are advised for patients with a Child-Pugh score of A and/or suffering from mild renal impairment. Its use is not advocated in those with a Child-Pugh score of either B or C as well as patients suffering from end-stage renal disease (Agrawal & Manna, 2019).

- Apixaban should be avoided in those weighing less than 60 kg or older than 80 years (Agrawal & Manna, 2019).

Bemiparin

- An increased bleeding tendency is expected in patients with severe renal impairment and a dosage adjustment (2500 I.U. subcutaneously for VTE prophylaxis) is advised (Ciccone *et al*., 2014:35; Rico *et al*., 2014:1036).

- Age was not found to be a factor that affects the pharmacodynamics effects on patients (Rico *et al*., 2014:1036).

- Bemiparin was found to be able to significantly decrease angiogenesis and vasculogenesis as compared to fondaparinux and unfractionated heparin (UFH) (Da Pozzo *et al*. 2012).

- Favourable outcomes in terms of patient mortality were reported with bemiparin as VTE prophylaxis in cancer patients (Ciccone *et al*., 2014:35).

Dabigatran

- Liver impairment in patients with a Child-Pugh score of B or C, renal impairment (CrCl 30-50 mL/min), uncontrolled diabetes mellitus, those older than 75 years and those diagnosed with bleeding diatheses are at higher risk of bleeding (Boehringer Ingelheim, 2013; Samama *et al.*, 2016; Qamar *et al*., 2018:2167-2168). The use of dabigatran should be done with caution in these patients, as PTT tests are not reliable to determine risk of the patient to haemorrhage (Boehringer Ingelheim, 2013; Lindahl *et al*., 2011).

Dalteparin

- Dalteparin is metabolised in the liver via desulfation and/ or depolymerisation to lower molecular weight fragments (Nutescu *et al.*, 2016:18). These fragments exibit a reduced activity in the human body (Nutescu *et al.*, 2016:18).

- Dalteparin is however, also reliant on renal excretion as 3 % of active substrates are eliminated renally (Nutescu *et al.*, 2016:18).

- Patients suffering from renal and/ or hepatic impairment requires monitoring due to accumulation of active dalteparin substrates (Micromedex, 2019c).

Enoxaparin

- Haemorrhage may be potentiated with enoxaparin in active major bleeding, patients suffering from thrombocytopenia and receiving enoxaparin, those suffering from hypersensitivity to enoxaparin, concomitantly receiving heparin as well as those allergic to pork products or other components of the formulation, which may increase adverse effects (Crowther & Warkentin, 2008:4872,4873; Pellizzari *et al*., 2018:605; Sanofi-Aventis, 2012). The following patients may have an increased bleeding risk: patients with risk factors including congenital or acquired bleeding disorders, kidney failure, bacterial endocarditis, severe uncontrolled hypertension, haemorrhagic stroke, intracranial haemorrhage, used shortly after brain, spinal or ophthalmic surgery in patients treated concomitantly with platelet inhibitors or history of heparin-induced thrombocytopenia, severe liver disease, diabetic retinopathy, patients undergoing invasive procedures, active ulcerative or angiodysplastic diseases and/or recent GI bleeding or ulceration (Sanofi-Aventis, 2012).

- The use of enoxaparin in patients with current HIT with or without thrombosis is not generally recommended due to an increased cross-reactivity to heparin-platelet factor-4 antibody (LaMuraglia *et al.*, 2012:567; Sanofi-Aventis, 2012).

- Other disease-related concerns in conjunction with enoxaparin use include prosthetic heart valves due to insufficient evidence of efficacy and safety (Sanofi-Aventis, 2012). Enoxaparin should be used with caution in patients with severe renal failure as dosage adjustments are needed (American Geriatrics Society Beers Criteria Update Expert Panel, 2019:674; Sanofi-Aventis, 2012).

- A “Black Box Warning” (the strictest warning awarded to a drug by the FDA) was issued for enoxaparin use in conjunction with the following conditions: spinal or epidural haematomas, including subsequent paralysis, may occur with recent or anticipated neuraxial anaesthesia

(epidural or spinal anaesthesia) or spinal puncture in patients, anticoagulated with LMWHs or heparinoids (FDA, 2013; Sanofi-Aventis, 2012). The risk versus benefit should be considered prior to spinal procedures; risk is increased using concomitant agents that may alter haemostasis, the use of indwelling epidural and/or spinal punctures (Davies & Checketts, 2016:13; Sanofi-Aventis, 2012). Patients should be observed closely for bleeding and signs and symptoms of neurological impairment if therapy is administered during or immediately following diagnostic lumbar puncture, epidural anaesthesia and/or spinal anaesthesia (Davies & Checketts, 2016:13; FDA, 2013; Sanofi-Aventis, 2012).

- Factors increasing risk of epidural or spinal haematomas include (Davies & Checketts, 2016:13; FDA, 2013; Sanofi-Aventis, 2012):

1. Patients with indwelling epidural catheters

2. The concomitant use of other medication that can affect haemostasis (for example NSAIDs, platelet inhibitors, other anticoagulants)

3. Patients suffering from a history of traumatic or repeated epidural and/or spinal punctures

4. Patients who are suffering from a deformity of the spine or who have undergone prior spinal surgery

Fondaparinux

- Fondaparinux is contraindicated in severe renal failure (CrCl < 30 ml/minute), bacterial endocarditis, thrombocytopenia and those with a body weight of less than 50 kg (Metwali *et al*., 2016:131; Pharmacare Limited, 2012).

- Treatment or initiation thereof should also be avoided in patients suffering from haemorrhage, and special monitoring is required in patients diagnosed with severe hepatic impairment (Al-Shaer & Ibrahim, 2015:164; Pharmacare Limited, 2012).

Heparin

- Bacterial endocarditis, bleeding problems (haemophilia), hepatic impairment, major surgery, heavy/unusual menstrual bleeding, spinal anaesthesia, stomach/intestinal ulcer, bleeding, thrombocytopenia and pregnancy (especially those with comorbid conditions) are all conditions where the administration of heparin should be closely monitored as these may cause an increased bleeding tendency (Boonyawat *et al*., 2017:2603; Fresenius Kabi, 2016; Ginsberg *et al*., 1989:197).

- Resistance to heparin action will also be experienced in patients with acquired or familial antithrombin III deficiency (Bharadwaj *et al*., 2003). This is due to heparin not possessing a direct anticoagulant effect, but it being able to potentiate the activity of antithrombin, which is responsible for binding antithrombin (resulting in thrombosis) (Bharadwaj *et al*., 2003: 125; Spiess, 2008:2153).

- Heparin should be used with caution in patients suffering from severe hepatic disease, those with indwelling catheters as well as women over the age of 75 years (Fresenius Kabi, 2016). The reason for this being such patient populations are at an increased risk for haemorrhage (Micromedex, 2019; Robert-Ebadi & Righini, 2010:3543).

Nadroparin

- Nadroparin should be used with caution in patients suffering from diabetes, those suffering from metabolic acidosis or those with chronic renal failure. This is due to an increased risk of hyperkalaemia (Pharmacare Limited, 2002; Taziani, 2017:227).

- Patients should be monitored for haemorrhage when treated with nadroparin whilst suffering from kidney or liver insufficiency, severe arterial hypertension, those with a history of active peptic ulceration and those with an increased risk of bleeding – these include the postoperative period after eye, spinal or brain surgery and with infective endocarditis (Tiziani, 2017:227).

Rivaroxaban

- Rivaroxaban undergoes both renal and hepatic metabolism and requires dosage adjustments in moderate impairment (Kubitza *et al*., 2013:489).

- Prosthetic heart valves, moderate to severe hepatic impairment, coagulopathy associated hepatic disease, severe renal impairment (especially in those receiving concomitant CYP 3A4 inhibitors or PGP-substrate) as well as active major bleeding may interfere (enhance) with rivaroxaban anticoagulation (Kubitza *et al*., 2013:489).

- Caution in neuroaxial spinal anaesthesia or spinal puncture is also advised (Bayer, 2013). This is due to an increased risk of intraspinal haematoma formation (Horlocker *et al*., 2010:35:64).

Warfarin

- Warfarin has traditionally been the anticoagulant of choice for prophylaxis in patients suffering from liver disease. However, warfarin exhibits a narrow therapeutic index, particularly in

patients with liver disease due to these patients' reduced ability to produce protein S and C (Patel *et al*., 2019; Qamar *et al*., 2018:2165).

- Hepatic failure, active major bleeding and infective endocarditis may enhance patient response to warfarin (Patel *et al*., 2019).

- Patients suffering from severe kidney disease may require a dose reduction of up to 19% compared to healthy patients (Limdi *et al*., 2010:823).

- Recent case study reports, however, also indicate warfarin's ability to cause acute kidney injury in healthy as well as renally impaired patients (Mendonca *et al*., 2017:79).

- Nephropathy can occur via different mechanisms such as acute increases in serum creatinine within one week of initiation, interstitial nephritis, mesangial damage and arthero-embolism formation. It is therefore advised that dose escalation be done incrementally until therapeutic INR has been attained (Mendonca *et al*., 2017:80).

2.5.1.7 Special parameter monitoring

Close monitoring to confirm correct anticoagulant dosing as well as to reduce the risk of anticoagulant associated bleeding is required for patients receiving prophylaxis. Parameters requiring monitoring are listed per anticoagulant as follows.

Apixaban

- Due to apixaban's clearance routes, patients should be monitored for their renal and hepatic function (Agrawal & Manna, 2019).

- No specific anticoagulation assays are recommended in the use of apixaban in the general population (Agrawal & Manna, 2019).

Bemiparin

- Bemiparin dosing adjustment is not required in patients suffering from mild or moderate renal insufficiency (CrCl 30-80 ml/min); however, close monitoring is recommended with regard to patient renal function before commencement of therapy and daily thereafter for those requiring therapy of longer than seven days (Atiq *et al*., 2015:923).

- Creatinine clearance monitoring is only required in those with possible severe renal insufficiency (CrCl < 30 mL/min). A dose adjustment to 85 I.U. anti-Xa/kg once a day is advised (Atiq *et al*., 2015:923; Fontcuberta Boj, 2010:43).

- The measurement of peak anti-Xa levels at about four hours post-dose should be considered in patients diagnosed with severe renal impairment in order to establish therapeutic efficacy (Atiq *et al*, 2015:923).

Dabigatran

- Before commencing dabigatran anticoagulation, renal function should be monitored especially in patients where a decline is suspected possibly due to concomitantly ingested renally excreted medication, hypovolemic instances or where patients are prone to dehydration such as in the case with chemotherapy, those who may be non-compliant in taking medication and those on chronic NSAID treatment (Boehringer Ingelheim, 2013; Conway *et al*., 2017:236). Dabigatran use is not recommended for patients suffering from severe renal impairment with CrCl less than 30 ml/min (Boehringer Ingelheim, 2013).

- During treatment, thrombin time (TT), PTT and Ecarin clotting time (ECT) can be monitored to establish anticoagulation success. However, no single test can provide accurate measurements of the effects of dabigatran (Boehringer Ingelheim, 2013).

- Routine monitoring in most patients is not necessary and is only reserved for those suspected of suffering from severe renal dysfunction (Conway *et al*., 2017:236).

Dalteparin

- Dalteparin treatment monitoring through the measuring of trough anti-factorXa levels (levels taken prior to the following dose), is advised (Nutesco *et al*., 2016:18). This is especially helpful in patients suffering from renal impairment, those who are pregnant, patients who are morbidly obese, children and neonates as well as those with a high risk for haemorrhage (Micromedex, 2019c).

Enoxaparin

- Activated partial thromboplastin time (aPTT), platelets, prothrombin time, and haematocrit should preferably be monitored before commencing enoxaparin anticoagulation (Sanofi-Aventis, 2012). This should be done in order to establish a baseline in order to identify those patients where heparin-induced thrombocytopenia (HIT) may have occurred.

- Heparin-induced thrombocytopenia usually occurs between the 5th and 21st day after enoxaparin initiation in susceptible patients (Sanofi-Aventis, 2012). For these patients, it is advised that platelet counts are to be measured prior to initiation and regularly thereafter (Sanofi-Aventis, 2012). Decreases of 30 to 50% in platelet counts compared to pre-enoxaparin administration counts may signal heparin-induced thrombocytopenia. Here,

enoxaparin should be discontinued immediately, and alternative anticoagulation therapy started (Sanofi-Aventis, 2012).

- Renal function for those on therapy should be assessed to prevent an increased risk of bleeding (Atiq *et al.*, 2015:926; Pellizzari *et al.*, 2018:605).

Fondaparinux

- Renal function (measured as serum creatinine) should be assessed routinely as fondaparinux should be discontinued in patients who develop a CrCl of 30 ml/min or below during therapy. Patient weight should also be checked – total clearance is decreased by approximately 30% in those weighing less than 50 kg – therefore, the risk of bleeding is more pronounced in these patients and treatment is contraindicated (Ageno *et al.*, 2016:2293; Pharmacare Limited, 2012).

Heparin

- Patients, who may be allergic to heparin or bovine products, have a bleeding-related disease, have a low platelet counts, those on concomitant use of other anti-coagulants, pregnant patients, lactating patients, those suffering from stomach ulcers, liver disease, kidney disease or haematuria, should not be treated using heparin (Zehnder, 2012:605).

- Haematocrit and occult blood in stool tests need to be administered in patients on long-term therapy every three months. Partial prothrombin time as well as platelet count baselines should be taken in those who will receive heparin for seven days or longer (Zehnder, 2012:605).

- Activated partial thromboplastin time (aPTT) should be monitored and ranges should be kept at 1.5 to 2.5 times the control value during therapy (Zehnder, 2012:605).

- The aPTT should be taken six hours after heparin initiation as well as six hours after any dose adjustment. Platelet count should be done on days 2 to 3, as thrombocytopenia may occur on the fourth day of treatment (Zehnder, 2012:605). Hypersensitivity reactions in patients on heparin treatment will include fever, chills as well as an itchy rash.

- Heparin-induced thrombocytopenia: a 50% decrease (or < 150,000/mL) in platelet count compared to the pre-treatment value signals HIT (Weitz, 2011:859). This condition has been reported to occur in more females than males as well as in surgically treated patients (Weitz, 2011:859; Fresenius Kabi, 2016). This is a life-threatening condition that may present between five and 10 days after initiation of heparin treatment (Fresenius Kabi, 2016).

Nadroparin

- The renal function of patients should be established prior to nadroparin initiation. This is because the elimination of nadroparin relies primarily on kidney excretion and is not indicated in those with CrCl of less than 30 mL/min (Tiziani, 2017:227).

- Liver function should be checked in patients since these patients have a greater risk of haemorrhage – a symptom which may be enhanced when treated with nadroparin (Pharmacare Limited, 2012; Tiziani, 2017:277).

- Platelet counts should be monitored in those on long term prophylaxis. This should be done as a small risk of an immuno-allergic associated thrombocytopenia exists whereby symptoms normally present between days 5 to 21 of treatment (Pharmacare Limited, 2012).

Rivaroxaban

- Renal function should be established prior to initiation of rivaroxaban (Conway *et al*., 2017:237; Bayer, 2013). These tests should be conducted in order to establish the patient's ability to metabolise and excrete rivaroxaban. Dose adjustments are recommended for those suffering from moderate to severe renal dysfunction (Conway *et al.*, 2017:237).

- During treatment, patient blood pressure, haematocrit, PT, aPTT and liver function should be monitored (Bayer, 2013; Conway *et al*., 2017:236). This should be done as the use of rivaroxaban is contraindicated in those with severe hepatic impairment (Bayer, 2013).

- In the generally healthy population, however, routine monitoring is not required (Conway *et al*., 2017:236).

Warfarin

- Ideally, patients younger than 50 years should be tested for levels of antithrombin, protein C and S, factor V Leiden, prothrombin G20210A, lupus anticoagulant, anticardiolipin antibodies as well as factor VIII (Micromedex, 2018). These tests are used to establish the possible genetic reason for such a patient to present with VTE at such a young age, the patient's risk for adverse drug reaction development as well as to prevent the incorrect interpretation of misleading INR ranges. For instance, a hypercoagulable state resulting in a possible increased propensity for VTE development is found in patients with factor V Leiden and/or prothrombin G20210A gene mutations as well as those having elevated factor VIII levels (Nakashima & Rogers, 2014:87-89). Warfarin therapy ranges for patients suffering from these genetic predispositions, may be less in the therapeutic range, leaving such patients at risk for

thrombosis or bleeding (Nakashima & Rogers, 2014:91). In terms of adverse events, it was found that warfarin-induced skin necrosis (which usually presents within the first week of treatment) occurs at a higher rate in patients with protein C or S deficiencies (Patel *et al.*, 2019). Misleadingly elevated INR levels may be detected in patients with anticardiolipin and/or lupus antibodies. It is therefore advised that patients be screened for anticardiolipin and/or lupus antibodies prior to warfarin initiation as the use of INR to determine therapeutic range will not be safe (Crowl *et al.*, 2014:1482).

- During warfarin therapy, an important test to be conducted to establish therapeutic success is the INR test (Patel *et al.*, 2019). This is done because of warfarin's small therapeutic window (Crowther *et al.*, 1999; Horton *et al.*, 2000:635). Therapeutic range is between 2.0 and 3.0 (Dager *et al.*, 2000; Horton *et al.*, 2000:635; Patel *et al.*, 2019; Pharmacare Limited, 1996). If below 2.0, bridging therapy should be considered or an increase of 10 to 20% of the weekly dose should be initiated. For INR of 3.1 to 4.0, the weekly dose should be reduced by 10 to 20% (Pharmacare Limited, 1996). If the INR is between 4.1 and 6.0, one daily dose should be omitted and treatment restarted with a lower dose (Pharmacare Limited, 1996). Two doses should be omitted if the INR lies between 6.1 and 10.0 with the INR re-measured after 48 hours. For an INR of above 10.0, warfarin therapy should be stopped, and a dose of 2.5 mg vitamin K administered (Pharmacare Limited, 1996). The INR should be re-measured after 48 hours (Crowther *et al.*, 1999; Pharmacare Limited, 1996).

2.5.1.8 Management of anticoagulant induced bleeding

The use of the anticoagulant class is associated with a higher propensity for bleeding and can be ascribed to their mechanism of action (Dhakal *et al.*, 2017:410). It is therefore important to list the methods available to reduce and stop bleeding associated with anticoagulant administration.

Apixaban

- No reversal agent is currently registered in South Africa for factor Xa blockers; however, andexanet alfa was registered with the FDA in May 2018 (Agrawal & Manna, 2019; Bayer, 2010).

- Andexanet alfa is a modified recombinant derivative of factor Xa that has a higher affinity for factor Xa inhibitors than naturally occurring factor Xa. Its action in animal models shows the binding of andexanet alfa to the drug rather than to natural Xa and thereby reversal occurs (Agrawal & Manna, 2019).

Bemiparin

- Protamine sulphate administration at a dose of 1.4mg should be administered for each 100 I.U. anti-XA administration of bemiparin (Litha Pharma, 2019). However, it should be noted that only partial reversal of its anticoagulant effect will be seen, as bemiparin also affects factor VII (Sánchez-Ferrer, 2010:19).

Dabigatran

- Surgical haemostasis as well as blood volume replacement using fresh frozen plasma (FFP) or whole blood transfusion should be initiated (Boehringer Ingelheim, 2013). Factor VIIa and administration of activated prothrombin complexes may also be considered; however, the success of these agents in the clinical setting has not been conclusively demonstrated (Boehringer Ingelheim, 2013).

- Dabigatran is not highly protein bound and dialysis or increased diuresis procedures may be of value to enhance renal excretion (Boehringer Ingelheim, 2013).

- Idarucizumab or Praxbind® is indicated for reversal of dabigatran effect before emergency surgery or procedures as well as in life-threatening bleeding associated with dabigatran (Pollack *et al*., 2017:431; Van der Wal *et al*., 2018:748).

- Idarucizumab injection is administrated by using a 5 mg concentration of idarucizumab made up of two consecutive infusions of two 2.5 mg / 50 ml vials or can be administered as a bolus injection by injecting two 2.5 mg vials consecutively (Boehringer Ingelheim, 2015).

Dalteparin

- Treatment for dalteparin induced haemorrhage remains supportive and may include the slow administration of 1mg protamine for every 100 anti-Xa IU of dalteparin administered (Micromedex, 2019c). A second infusion of 0.5 mg protamine for every 100 anti-Xa IU of dalteparin received, may be required if the aPTT remains prolonged between 2 – 4 hours after initial infusion (Micromedex, 2019c).

Enoxaparin

- Protamine sulphate, at a dose of 1mg, will neutralise 1mg of administered enoxaparin (Sanofi-Aventis, 2012).

- During overdose situations, where enoxaparin has been administered in less than eight hours, protamine sulphate should be administered in a dose equal to the dose of the administered enoxaparin (Dhakal *et al.*, 2017:411; Sanofi-Aventis, 2012). For enoxaparin administered after

more than eight hours have elapsed or if it has been determined that a second dose of 0.5 mg protamine sulphate is required via infusion (e.g. if aPTT measured 2 to 4 hours after first dose remains prolonged or if bleeding continues) (Dhakal *et al*., 2017:412). No more than 50 mg of protamine sulphate should be administered at a time (Greinager *et al*., 2015:938; Sanofi-Aventis, 2012).

Fondaparinux

- No registered reversal agent is available to reverse fondaparinux effects (Pharmacare Limited, 2012).

- Haemodyalysis clears 20% of circulating active ingredient and may be implemented in the event of overdose to try and reduce circulatory dosage and reduce harm (Pharmacare Limited, 2012).

- Protamine sulphate is ineffective in bleeding associated with excessive fondaparinux dosing (Bijsterveld *et al*., 2002:2553).

- Recombinant activated factor VII (NovoSeven®) may partially reverse the effects of fondaparinux (Bijsterveld *et al*., 2002:2553).

Heparin

- Vitamin K can be administered under clinician supervision for reversal of bleeding; however, protamine sulphate is the agent of choice (Zehnder, 2012:605).

- Protamine sulphate 50 mg / 5 ml injection is indicated as 1 mg of protamine sulphate for each 100 I.U. of heparin given (Zehnder, 2012:607; Fresenius Kabi, 2016). Infusion of protamine sulphate should occur at a maximum rate of 50 mg over 10 minutes (Zehnder, 2012:607; Fresenius Kabi, 2016).

Nadroparin

- In the event of nadroparin related haemorrhage, limited clinical experience exist on the use of protamine sulfate (Pharmacare Limited, 2002), however 6 mg protamine sulfate can be given and should neutralise 950 IU of anti-Xa activity (Tiziani, 2017:227).

Rivaroxaban

- No specific antidote is registered for rivaroxaban in South Africa (Bayer, 2013). However, andexanet alpha was registered in 2018 in the USA (refer to apixaban) (Agrawal & Manna, 2019).

- Rivaroxaban is not expected to be dialysable due to its high plasma protein binding capacity (Bayer, 2013).

- In the event of bleeding complications, the next administration must be delayed or discontinue treatment as appropriate (half-life of rivaroxaban is between 5 and 13 hours) (Bayer, 2013). Management should be individualised depending on severity and location (Bayer, 2013).

- Administration of activated charcoal can be considered up to eight hours after the last dose of ingestion (Bayer, 2013). Symptomatic treatment can include mechanical compression, surgical haemostasis with bleeding control procedures, fluid replacement & haemodynamic support such as packed red cells, platelets or fresh frozen plasma depending on associated anaemia or coagulopathy (Bayer, 2013; Micromedex, 2018).

- If bleeding cannot be controlled with above measures, consideration should be given to using prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant factor VIIa (r-FVIIa) – but limited clinical experience exists with the use of these agents (Micromedex, 2018).

- Use of protamine sulphate, desmopressin, aprotinin, tranexamic acid, aminocaproic acid and vitamin K is not expected to affect anticoagulation effect of Xarelto® (Bayer, 2013).

Warfarin

- For asymptomatic non-therapeutic INR patients, or those with an INR greater than 4.5, warfarin dosing should be withheld. Further administration of Vitamin K should be initiated to reduce INR return time to normal (Wells *et al*., 2015:131). The next warfarin dose should also be withheld in patients with an INR of between 5 and 9. Patients exhibiting an INR above 10 and are not bleeding should also not receive their next warfarin dose. Oral phytonadion of 2.5mg should be administered in this group (Wells *et al*., 2015:131).

- In patients with elevated INRs and who are suffering from bleeding, warfarin therapy should be discontinued all together (Pharmacare Limited, 1996) for 24 to 48 hours. Here, a dose of 0.5 mg to 2mg vitamin K (by slow IV injection) or an oral dose of between 5 and 10 mg phytonadion should be initiated (Anderson, 2017:410). Vitamin K or phytonadion dosing may be repeated after eight to 12 hours (Anderson, 2017:410).

- Warfarin should be used with caution in those suffering from recurrent thromboembolism due to a possible INR overcorrection resulting in subsequent VTE formation (Wells *et al*., 2015:131).

- For life-threatening haemorrhages, an infusion of fresh frozen plasma with subsequent monitoring of the PT is recommended (Anderson, 2017:410; Pharmacare Limited, 1996). When required, a dose of 10 mg vitamin K (phytomenadione) should be administered with slow injection (Anderson, 2017:410). The therapeutic effect of vitamin K can take up to four to six hours to be experienced (Anderson, 2017:410).

2.5.1.9 Switching anticoagulants

Managing anticoagulant therapy is often complicated by a range of problems. For instance, LMWHs (such as bemiparin, dalteparin, enoxaparin and nadroparin) are administered via subcutaneous injection and may become problematic for patients having to administer doses themselves (Pandya & Bajorek, 2017:163). Often, patients who received subcutaneous or transfused therapy during their hospital stay would require oral therapy upon discharge because of the oral route's ease of administration. Adherence to anticoagulant therapy may also be hindered by drug-drug interactions (interactions between the newly prescribed anticoagulant and the patient's own chronic medication), high NOAC price or even the fact that certain oral agents (such as warfarin), which may be inexpensive, but require frequent follow-up parameter testing (Pandya & Bajorek, 2017:163). In these instances, switching between anticoagulant therapies may be required. Table 2-4 summarises strategies to follow for therapy changes (Agrawal & Manna, 2019; Boehringer Ingelheim, 2013; Micromedex, 2019a; Pfizer, 2015; Schulman & Crowther, 2012:3019; Tran *et al*., 2014:532).

Table 2:4 Switching between anticoagulants

Fondaparinux	LMWH	Heparin	Dabigatran	NOACs (Apixaban/ Rivaroxaban)	Warfarin
Switching from Fondaparinux to NOAC: Discontinue fondaparinux and start NOAC as soon as the next dose of fondaparinux would have been administered Switching from NOAC to fondaparinux: Discontinue NOAC and administer fondaparinux 12-24 hours after the last dose of NOAC (refer to half-life of the applicable NOAC).	Switching from LMWH to NOAC: Discontinue LMWH and start NOAC as soon as the next dose of LMWH would have been administered. Switching from NOAC to LMWH: Discontinue NOAC and administer LMWH 12-24 hours after the last dose of NOAC (refer to half-life of the applicable NOAC).	Converting from a continuous heparin infusion to NOAC: Discontinue heparin infusion and administer starting NOAC dose immediately. Converting from NOAC to unfractionated heparin: If patient CrCl is more than 30mL/min, NOAC (in this case dabigatran) should be discontinued and the unfractionated heparin started 12-24 hours after the last dabigatran dose. If patient CrCl is less than 30mL/min, dabigatran should be discontinued, and heparin started 48 hours after.	Switching from LMWH to NOAC: Discontinue LMWH and start NOAC as soon as the next dose of LMWH would have been administered Switching from NOAC to LMWH: Discontinue NOAC and administer LMWH, 12-24 hours after the last dose of NOAC (refer to half-life of the applicable NOAC) Switching from Dabigatran to Warfarin: Patients with normal CrCl (> 50 mL/min)-stop dabigatran for 3 days before initiating warfarin. Patients with CrCl between 31 to 50mL/min-discontinue dabigatran for 2 days before initiating warfarin.	Switching from Warfarin to NOAC: Discontinue Warfarin and start NOAC as soon as the INR is below 3.0 for Rivaroxaban and 2.0 for Apixaban. Switching from other anticoagulation to NOAC: Start Rivaroxaban 0-2 hours before the next subcutaneous scheduled evening dose of other anticoagulant (LMWH and other oral anticoagulants) and omit other agent. Apixaban can be started at the same time of next dose (LMWH and other oral anticoagulants). For unfractured heparin being administered as continuous infusion, stop infusion and start NOAC at the same time.	Switching from warfarin to LMWH – Prophylaxis for systemic embolism: Review thrombotic risk on a case-by-case basis and consider initiating prophylactic or treatment dose LMWH once INR < 2.0. Conversion from warfarin to rivaroxaban – discontinue warfarin and initiate rivaroxaban once INR is ≤ 2.5. Prevention of systemic embolism: Discontinue warfarin and initiate rivaroxaban once INR ≤ 3.0. Switching from warfarin to dabigatran – Discontinue warfarin and commence dabigatran as soon as INR is < 2.0.

Table 2.4: Switching between anticoagulants (continued)

Fondaparinux	LMWH	Heparin	Dabigatran	NOACs (Apixaban/ Rivaroxaban)	Warfarin
			Patients with CrCl between 15-30 mL/min – discontinue Dabigatran for 24 hours before initiating warfarin.	Switching from NOAC to other anticoagulant: Discontinue NOAC and give the first dose (parenteral or oral) at the time the next NOAC dose would have been taken.	

2.5.2 Non-pharmacological prophylaxis

Non-pharmacological methods of VTE prophylaxis work to combat venous stasis by exertion of intermittent pressure or pulsatile actions to increase venous outflow either mechanically or with exerted pressure (Geerts *et al*., 2008:381). Deep leg venous stasis causes a decrease in the mean flow and pulsatility of the venous blood system resulting in endothelial pooling and tearing with subsequent hypercoagulability of circulating blood (Masotti *et al*., 2014:4). Unlike pharmacological prophylaxis, none of the non-pharmacological methods are associated with an increased risk of bleeding and are recommended for use in patients with contraindications to pharmacological prophylaxis (Geerts *et al*., 2008:381; NICE NG89, 2018:11). Contraindications to the use of mechanical prophylactic methods include severe peripheral arterial disease, severe peripheral neuropathy, severe deformity of the leg as well as a recently received skin graft. Mechanical methods utilised for VTE prevention are (Geerts *et al*., 2008:38):

- Graduated compression stockings or anti-embolism stockings
- Intermittent pneumatic compression devices.

2.5.2.1 Graduated compression stockings

Graduated compression stockings are hosiery that, when worn on the leg, exerts a graded circumferential pressure from its distal to proximal regions, which, in turn, increases blood flow and promotes venous return (Masotti *et al*., 2014:4). In general, these stockings are commonly used, affordable and available in thigh, knee and ankle length (Masotti *et al*., 2014:4). The Sigel profile – which results in a graduated compression pressure profile of 18 mmHg at the ankle, 14 mmHg at the mid-calf, 8 mmHg at the knee (popliteal break), 10 mmHg at the lower thigh and 8 mmHg at the upper thigh – was found to increase deep venous flow velocity by 75% (NICE CG92, 2010; Sigel *et al*., 1973:40). The prevention of passive venous distension is thought to prevent the release and subsequent activation of clotting factors due to sub-endothelial tears resulting from venous pooling (Masotti *et al*., 2014:4). The use of graduated compression stockings is regarded as a passive mechanism of VTE prophylaxis and is recommended in use for post-surgical patients as well as immobilised medically ill patients (NICE NG89, 2018:11,15).

It is important that patients are fully assessed, and their legs carefully measured before stockings are fitted and that stocking use is monitored after application to enhance compliance (Naunton & Merrilees, 2012:395). Thigh length stockings, for instance, can be more difficult to fit and can roll down during wear creating a tourniquet effect, which is dangerous in patients suffering from an already compromised venous return (National Health and Medical Research Council, 2012).

Graduated compression stockings cannot be used indiscriminately and are contraindicated in patients suffering from: arteriosclerosis, peripheral arterial disease, severe peripheral neuropathy, massive leg oedema or pulmonary oedema, oedema secondary to congestive cardiac failure, local skin and soft tissue diseases such as cellulitis, having received a recent skin graft or suffering from dermatitis, extreme deformity of the leg, gangrenous limb and exhibiting an ankle-brachial pressure index of less than 0.8 (Aryana, 2018:3-4; National Health and Medical Research Council, 2012).

2.5.2.2 Intermittent pneumatic compression and foot impulse devices

Intermittent pneumatic compression devices (IPCD) and foot impulse devices, also known as foot pumps (FPs), are both "active" mechanisms for reducing VTE risk because these devices exert their haemodynamic effect by producing a pumping mechanism (Masotti *et al*., 2014:4).

Caprini (2010:670) proved that the pressures achieved with intermittent pneumatic compression devices (IPC) exerting a pressure of 16 to 22 mmHg, are preferred for improved venous return and reduction of VTE formation especially in surgical patients (NICE CG92, 2010; Sigel *et al*., 1973:40). Intermittent pneumatic compression devices are generally characterised by sleeves that are wrapped around the patient's legs or feet and intermittently inflated with air thereby exerting pressure and increasing venous return to the heart (NICE CG92, 2010). Foot pumps are designed to stimulate the venous return artificially by compressing the venous plexus and reducing stasis in immobilised patients by mimicking the haemodynamic processes that occur during normal walking (Corley *et al*., 2010:377). During walking, the venous plexus in the sole of the foot is rapidly emptied into the deep veins of the legs. The pulsatile flow produced by walking reduces the risk of thrombus formation and this is mimicked by the action produced from wearing foot pumps (Corley *et al*., 2010:377; NICE CG92, 2010). Intermittent pneumatic compression devices have been found to be more effective for high risk patients in combination with anticoagulants or used separately when anticoagulation is contraindicated (Naunton & Merrilees, 2012:395).

2.5.3 Guideline appropriate venous thromboembolism prophylaxis

The conventional pharmacological prophylactic method for VTE is initiated with an initial course of sub-cutaneous rapid-onset LMWH or fondaparinux (Kearon *et al*., 2012:e421S). Prophylactic therapy should continue for five to 10 days or until the patient is mobilised in moderate to high risk patients. Prophylaxis, however, should continue for up to 35 days in hip or knee arthroplasty patients (Kearon *et al*., 2012:e421S). Recently, NOACs have been developed and registered. These include direct factor Xa inhibitors such as rivaroxaban, apixaban and edoxaban, as well as

the direct thrombin inhibitor dabigatran (EINSTEIN Investigators, 2010:2499; Schulman *et al*., 2013:717). The NOACs have a reduced bleeding risk profile (as compared to warfarin), offer easier administration (these medications are only available as oral formulations) and do not require continued monitoring such as is required during warfarin therapy (EINSTEIN Investigators, 2010:2499; Schulman *et al*., 2013:718). In patients who are at risk of recurring VTE, treatment is suggested to be extended beyond six months or should even be continued lifelong in selected clinical circumstances (Kearon *et al*., 2012:e422S; Kearon *et al*., 2016:1481).

2.5.4 Venous thromboembolism prophylaxis guidelines in the South African setting

A succinct and user-friendly VTE prophylaxis guideline for use in both medical and surgical patients was developed by SASTH in 2009 (Jacobson *et al*., 2009:467). This guideline was subsequently reviewed in 2013 to also include NOACs (Jacobson *et al*., 2013:261). The SASTH VTE prophylaxis guideline is the only locally developed guideline and has been included in this study because it factored in the risk of human immunodeficiency virus (HIV) and tuberculosis (TB) (Jacobson *et al*., 2013:261). Human immunodeficiency virus infection causes a hypercoagulable state and the prevalence of VTE in the HIV-infected South African population is estimated to be as high as 18% (Awolesi *et al*., 2016). Of note is that most international VTE prophylaxis guidelines do not include TB or HIV as risk factors, nor are these included in risk screening models. It is, therefore, important to make use of guidelines that take the unique South African HIV/TB burden into account.

The updated 2013 SASTH guidelines also stipulate that individual patient risk assessments are essential, and a shortened and modified version of the Caprini risk assessment model is included in the guidelines. This makes sense as both Caprini's risk assessment model and the South African guideline are founded on the ACCP guidelines and in practice obtain the same endpoint (Jacobson *et al*., 2013:261). The SASTH guidelines rely on the identification of risk factors in both medical and surgical patients and also include the type of surgical procedure planned (according to low or higher procedural risk) to classify the individual patient's VTE development risk (Jacobson *et al*., 2013:261). Recommendations for thromboprophylaxis in pregnancy and gynaecological surgery as well as steps to follow when switching between anticoagulants were also included in both guidelines (Jacobson *et al*., 2009:467; Jacobson *et al*., 2013:265). Suggestions for management of non-therapeutic INRs, which includes patients suffering from sudden bleeding episodes, as well as VTE prophylaxis using two of the NOACs, were added to the 2013 version (Jacobson *et al*., 2013:266). At the time of the guideline's publication, only two NOACs were registered with the South African Medicines Control Council, namely dabigatran and rivaroxaban (Jacobson *et al*., 2013:266). Special recommendations are also included for patient monitoring when patients require prophylaxis after having undergone centro-neuroaxial blockade,

are pregnant or have undergone gynaecological procedures or require monitoring of effectiveness for the type of prophylaxis used (Jacobson *et al*., 2013:266).

2.5.4.1 Type of prophylaxis used in the South African Setting

The SASTH 2013 guidelines recommend the use of enoxaparin 40 mg (4000 anti-Xa units) subcutaneously or UFH 5000 I.U. subcutaneously three times per day in the use of medically ill patients as well as higher risk surgical patients without additional risk factors (Jacobson *et al*., 2013:263). The authors regard LMWH to be superior to UFH in VTE prophylaxis and recommend LMWH to be given to all immobile medically ill as well as patients undergoing surgical procedures (Jacobson *et al*., 2013:263,265). The guidelines propose that in patients at high risk of bleeding, the use of mechanical prophylaxis such as graduated compression stockings or IPC should be considered as an alternative if the risk of thrombosis is high (Jacobson *et al*., 2013:264). The prophylaxis recommended for surgical patients with added risk factors include enoxaparin (4000 anti-Xa units) subcutaneously daily or dalteparin (5000 anti-Xa units) subcutaneously daily or alternatively nadroparin (Jacobson *et al*., 2013:265). The identical dose for nadroparin is recommended for use in high risk surgical patients with or without additional risk factors (Jacobson *et al*., 2013:265). The dose recommended is 2850 anti-Xa units sub cutaneous two hours pre-operatively and eight hours after surgery in abdominal surgery, followed by 2850 anti-Xa units daily for seven days (Jacobson *et al*., 2013:265). The same dose is also recommended in major orthopaedic replacement surgery for both types of patients, i.e. a weight-adjusted dose of 38 anti-Xa units/kg subcutaneously 12 hours pre-operatively and repeated 12 hours after the surgery has concluded. Prophylaxis needs to continue with nadroparin daily on days 1 to 3, with 57 anti-Xa units/kg subcutaneously from day 4 for a minimum of 10 days (Jacobson *et al*., 2013:265-266; Pharmacare Limited, 2002). Fondaparinux is recommended (and registered) for orthopaedic hip and knee replacement and the dosage recommended by the guidelines is that of 2.5 mg subcutaneously daily, post-operatively (Jacobson *et al*., 2013:267-270). The inclusion of NOACs is added for patients undergoing either hip or knee replacement surgery (Jacobson *et al*., 2013:267). Rivaroxaban is recommended at 10 mg daily, initiated six hours after the end of the operation, while dabigatran is recommended to be dosed at 110 mg four hours post-surgery and continued at a dose of 220 mg daily (Jacobson *et al*., 2013:267). Dosage adjustment recommendations are included for the elderly, patients on concurrent amiodarone and those with moderate renal impairment (Jacobson *et al*., 2013:270).

2.5.4.2 Timing of prophylaxis

The SASTH guidelines recommend that pre-operative initiation of LMWH prophylaxis for major orthopaedic surgery should not commence before 12 hours or after 12 hours post-operatively (Jacobson *et al*., 2013:266-267). A study by Hull and colleagues (2001:1955), however, found that commencing LMWH within eight hours of surgery (hip-arthroplasty) had the best outcomes, while the American College of Chest Physicians (CHEST) (Falck-Ytter *et al*., 2012:e296S) recommends that LMWH be given to patients undergoing major orthopaedic procedures at least 12 hours either preoperatively or postoperatively. The duration of prophylactic LMWH in the SASTH guidelines is recommended to last at least between seven and 10 days (Jacobson *et al*., 2013:266), while the ACCP recommends minimum prophylactic duration of 10 to 14 days in major orthopaedic surgery (Falck-Ytter *et al*., 2012:e279S). Interestingly, Katsura and colleagues (2015:59) found that a duration of only three days to be sufficient for major surgery in patients with additional risk factors (cancer patients undergoing abdominal surgery) or very high-risk procedures (major orthopaedic surgery). It must be noted, however, that LMWH was combined with mechanical methods in both arms of the Katsura study (2015:59), while comparing outcomes after three to 10 days of respective prophylaxis. Extended duration thromboprophylaxis (28 days) was recommended in the CHEST guidelines for high-risk VTE patients undergoing abdominal or pelvic surgery for cancer (Grade 1B) (Kearon *et al*., 2016). In acutely ill hospitalised medical patients, the duration of prophylaxis is suggested to not be extended beyond the period of patient immobilisation or acute hospital stay. For patients undergoing major orthopaedic surgery, the authors recommend the use of one of the following antithrombotic prophylaxis: low-molecular-weight heparin; fondaparinux; dabigatran, apixaban, rivaroxaban (total hip arthroplasty or total knee arthroplasty but not hip fracture surgery); low-dose unfractionated heparin; adjusted-dose warfarin; aspirin (all Grade 1B); or an IPCD (Grade 1C) for a minimum of 10 to 14 days (Kearon *et al*., 2016). The addition of an Intermitted Pneumatic Compression Device to other prophylactic agents is recommended in those with extended hospital stay (Grade 2C) (Kearon *et al*., 2016). This is in line with 2013 SASTH guidelines (Jacobson *et al*., 2013:266).

The SASTH guidelines recommend that the initiation of the NOACs only be started postoperatively for surgical patients (Jacobson *et al*., 2013:266). Complementary to this is the RE-COVER II trial, which concluded that a fixed dose of dabigatran in the treatment of acute VTE is as effective as warfarin with similar safety outcomes (Schulman *et al*., 2011:709). One of the positive aspects about dabigatran use is the absence of laboratory monitoring required as is the case with warfarin. The EINSTEIN-DVT trial results were published in 2010 and reported similar effectiveness in prevention of VTE recurrence for oral rivaroxaban to patients receiving the standard therapy of LMW and warfarin (EINSTEIN Investigators, 2010).

2.5.4.3 Duration of prophylaxis

The SASTH guidelines recommend that prophylaxis be continued for five weeks in major cancer as well as hip replacement surgery (Jacobson *et al*., 2013:273). Prophylaxis for knee replacement surgery is stipulated to last for two weeks (Jacobson *et al*., 2013:273). The 2012 ACCP guidelines correspond with this SASTH recommendation in that a minimum of 10 to 14 days of prophylaxis in total hip and knee arthroplasty patients are recommended (Grade 2B evidence reported) (Falck-Ytter *et al*., 2012; Jacobson *et al*., 2013:273). Mention is made in the SASTH guidelines that prophylaxis needs to be continued in patients until they are fully mobile and for medical and surgical patients with additional risk factors or those undergoing major surgery (Jacobson *et al*., 2013:264). Recommended prophylactic duration in those at very VTE development high-risk due to surgical procedures is to last for at least seven to 10 days (Jacobson *et al*., 2013:265). The authors also mention that LMWH or warfarin prophylaxis of up to one month's duration has been shown to provide additional benefits (Jacobson *et al*., 2013:267). The 2012 ACCP guidelines recommend (Grade 2B evidence) extending thromboprophylaxis to 35 days post-operatively. Both the 2013 SASTH guidelines as well as the 2012 ACCP guidelines discourage the use of pharmacological prophylaxis in acutely ill medical patients who are mobile or in medical patients who have a high propensity for bleeding (Falck-Ytter *et al*., 2012; Jacobson *et al*., 2013:264). The extension of pharmacological prophylaxis in medically ill patients who have been discharged and are mobile are also not advocated in both SASTH and 2012 ACCP guidelines (Falck-Ytter *et al*., 2012; Jacobson *et al*., 2013:264).

Interestingly, De Caterina and colleagues (2012:13) found that patients mobilised within four hours post-operatively and given prophylaxis for duration of between one and four days, no DVT, PE, or mortality was reported. They also questioned the practice of extended prophylaxis when patients were mobilised early and mentioned that most studies on extended prophylaxis were partly sponsored by pharmaceutical companies. The fact that some authors were sponsored by clinical trials when compiling the pre-2012 ACCP guidelines (which recommended extended duration prophylaxis) was highlighted as one shortcoming by various authors (Kahn *et al*., 2012; Kearon *et al*., 2012:1698). This shortcoming was addressed when more than half the 2012 ACCP authors included did not report potential financial conflict of interests and new guidelines published. No conflicts of interest were reported with the SASTH guideline publication and no author was affiliated with any pharmaceutical company (Jacobson *et al*., 2013:261). The SASTH guidelines were reviewed by independent international external experts to avoid local bias and are also endorsed by the Critical Care Society of South Africa, the South African Society of Obstetricians and Gynaecologists, the South African Orthopaedic Association, the South African

Society of Cardiovascular Intervention and the Southern African Society of Thrombosis and Haemostasis (Jacobson *et al*., 2013:261).

2.5.4.4 General notes on anticoagulant type included in published guidelines

The inclusion of specific anticoagulants in published guidelines is centred on evidence-based therapeutic outcomes. In choosing the specific prophylactic anticoagulant to be included in guidelines, recommendations are that patient preference, ease of compliance, ease of administration as well as cost of anticoagulant should be considered. Warfarin's continued INR monitoring needs to be balanced against the higher costs of utilising the safer NOACs for prophylaxis. As mentioned in the preceding paragraphs, the only two NOACs that were registered with the then South African Medicines Control Council at the time of 2013 SASTH guideline publication were rivaroxaban and dabigatran (Jacobson *et al*., 2013:267). The latest American College of Chest Physicians guidelines now recommend the use of NOACs over warfarin or vitamin K antagonists as the first choice in prophylactic therapy due to their favourable side-effect profile (Bates *et al*., 2012). Both dabigatran and rivaroxaban (including other NOACs) are, however, relatively expensive in comparison to warfarin and are only registered for prophylactic use in hip and knee arthroplasty. Dabigatran proves problematic in patients with impaired renal clearance, while LMWHs require subcutaneous administration.

Wong and associates (2015:108) reported that 60.4% of patients in their study population (227 medical and surgical patients) preferred oral VTE prophylaxis to that of an injectable. Patients were asked to choose between the two administration methods after being told on each medication's efficacy. An aversion to needles (30.0%) and pain due to injection (27.7%) were reasons identified for patient decisions (Wong *et al*., 2015:108). Patients who chose subcutaneous injections (37.5%) were less likely to refuse prophylaxis than those choosing oral medication (51.3%), with the study's results being statistically significant. Interestingly, the authors found that those choosing the injectable formulation did so because they regarded its immediate bioavailability as an important aspect to effectiveness. In a different study by Haac and colleagues (2017), patients who chose the injectable route were those who knew they had a high risk for PE development and consequently death. These findings show the complex nature of patient preferences that should be individualised to ensure compliance to prophylaxis.

2.6 Risk assessment models for venous thromboembolism

To summarise section 2.5, the administration of VTE prophylaxis is not without serious risk. Because risk-adapted VTE prophylaxis can significantly reduce morbidity and mortality, the implementation of adequate risk assessment and its associated prophylaxis methods (which should be based on high-quality evidence) are both locally and internationally viewed as an important requirement for appropriate VTE reduction to enhance patient safety (Henke & Pannucci, 2010:230; Jacobson *et al*., 2013:261; Maynard, 2016; NHS UK, 2015:2). As described in earlier sections of this chapter, patient bleeding risk may be increased by surgery, medications, or inherent patient factors. It is therefore important for a VTE risk assessment model to include measures that exclude patients at risk of bleeding and those who may be harmed when VTE prophylaxis is indicated (Lau *et al*., 2018:1278). It is also preferable that risk assessment models can suggest alternative methods of VTE prophylactic measures in those who may be harmed (Lau *et al*., 2018:1278). A recent observational study by the Implementation of a Randomised Control Trial to improve Treatment With Oral anticoagulants (IMPROVE) investigators reported on aspects that were the strongest independent risk factors of in-hospital bleeding in medical patients (Spyropoulos *et al*., 2011:706). These risk factors included active gastro-duodenal ulcer, active bleeding within three months prior to admission and a platelet count of less than 50 000 (Spyropoulos *et al*., 2011:706). Advanced age (those older than 85 years), patients suffering from hepatic failure with an international normalised ratio (INR) > 1.5, those with impaired kidney function or glomerular filtration rate (GFR) < 30mL/min/m^2), patients with central venous catheter placement, those admitted to intensive care units, patients suffering from rheumatic disease, cancer as well as male gender were also found to predict for in-hospital bleeding (Spyropoulos *et al*., 2011:706). The Use of VTE prophylaxis in relatioN to patiEnt risk profiling (TUNE IN) study, as conducted in the private healthcare setting in South Africa, noted that with the use of a structured risk assessment model, a larger percentage of patients are found to be at risk compared to only relying on clinician evaluation (Riback & Wessels, 2012:85). The authors reported that the reason for this overestimation of patients requiring therapy is the calculation of BMI and the use of patient age as a risk factor upon completion of the risk assessment model (Riback & Wessels, 2012:88). This underestimation was postulated as a possible result of VTE risk over-diagnosis in patients at low- and moderate VTE development risk (Riback & Wessels, 2012:88). The authors also proposed that the reverse might occur for those who are rated as being at high risk for VTE development (Riback & Wessels, 2012:88). Literature is available, possibly showing a reduction of VTE-associated readmission and death with an increased VTE risk assessment uptake for admitted patients (Catterick & Hunt, 2014:575; NHS UK, 2015:2).

According to Lau and colleagues (2018:1281), as well as Grant and colleagues (2016:530-533), the ideal risk assessment model for VTE prediction should be able to:

1. Accurately detect all patients at risk of developing DVT
2. Reliably exclude patients who would be unlikely to develop DVT, minimising inappropriate over-prophylaxis in those of lower risk
3. Integrate into clinical practice results in a way that decreases hospital associated VTE without any increase in bleeding
4. Be simple to use in routine clinical practice, with minimal need for laboratory investigations or complex calculations
5. Have predictors of VTE risk available to ordering provider at the point of care
6. Externally be validated in the format of a quantitative point-based model.

(It must, however, be noted that a study by Beck and colleagues (2011:195) disputes the usefulness of a point-based scoring model, as the authors found only fair inter-rater reliability when utilising such models.)

Risk assessment models that are in use internationally, include (among others) the Brigham and Women's Hospital Model or the Kucher model (Kucher *et al*., 2005:969), the Padua VTE risk assessment model (Barbar *et al*., 2010:2450), the Autar risk assessment scale (Autar, 1996:763), the Risk Assessment Profile (RAP) scale (Greenfield *et al*., 1997:100), the Rogers risk assessment model (Rogers *et al*., 2007:1211), the Woller, also known as the Intermountain model (Woller *et al*., 2011:947), the IMPROVE VTE model (Spyropoulos *et al*., 2011:706) as well as the Premier VTE Risk model. These models are based on a system where the results rely on point-scoring for set criteria. Although these risk assessment models have a point-scoring method of risk calculation in common, they differ in the patient population on which they can be utilised. The Intermountain and IMPROVE VTE risk assessment models were all developed for medically ill patients (Spyropoulos *et al*., 2011:706; Woller *et al*., 2011:947), while the Rogers risk assessment model was developed for use on surgical patients (Rogers *et al*., 2007:1211). The Autar scale was developed in 1994 with results officially published in 1996, and was developed for use in orthopaedic, medical and surgical patients (Autar, 1996:763). The IMRPOVE model showed success in the re-evaluation of patient risk especially during long hospital stays (Spyropoulos *et al*., 2011:706). The largest oncological patient population that was included in risk assessment model development was during the development of the Intermountain model. It must be mentioned that oncology patients in general are regarded as having a high risk for VTE

development and some may be taking prophylaxis chronically (Khorana *et al*., 2007:632). During the development of the Intermountain model, however, no mention was made or criteria were included to assess how many of the included patients had already been taking VTE prophylaxis (Spyropoulos *et al*., 2011:706) – which, in turn, may have biased the results of the model.

The predictive ability of risk assessment models, however, requires outside validation to prove sensitivity and specificity (Desouky *et al*., 2010:48). A small validity and reliability assessment (35 patients) study was conducted using the Autar scale, by Desouky and colleagues (2010:48). The authors found that it achieved 60% sensitivity and 40% specificity in moderate VTE-risk-rated patients and 46.6% and 75% for the high-risk-VTE category, respectively. External validation and reports of demonstrated reduction in hospital acquired VTE are not available for any of the other models mentioned in the preceding paragraph.

Another important risk assessment model currently in use on a very large scale both internationally and locally is the Caprini VTE risk assessment model (Jacobson *et al*., 2013:261). The ACCP guidelines are generally regarded as the standard of care in VTE prophylaxis, and Caprini devised a risk-stratification system in order to render these guidelines more user-friendly (Caprini *et al*., 2001:12; Caprini, 2005:70; Guyatt *et al*., 2012). Caprini developed this individualised quantitative risk assessment model for surgical and medical patients, and it has subsequently been reviewed and refined many times by its developer. The Caprini VTE risk assessment model was also the first quantitative model to be externally validated for VTE risk predictability (Grant *et al*., 2016:533; Obi *et al*., 2015:941; Pannucci *et al*., 2011:105). One negative aspect of the Caprini model, however, is its relative complexity upon completion (Pannucci *et al*., 2011:109). Grant and colleagues (2016:533) investigated to what degree the Caprini risk assessment model can predict VTE development in hospitalised patients. Their large study showed a linear association between the Caprini risk assessment model and risk of VTE development. The subsequent administration of pharmacologic prophylaxis in these patients (after being risk rated by the Caprini model) resulted in a modest decrease in VTE risk (odds ratio = 0.85; with a 95% confidence interval of 0.72-0.99, p = 0.04) (Grant *et al*., 2016:533). An extremely low incidence of VTE events in non-ICU medical patients was, however, observed using the model and the authors concluded that the Caprini risk assessment model is not helpful in this type of patient (Grant *et al*., 2016:533). It must be noted that the Caprini risk assessment model is the only model for which a modest reduction in VTE prevalence was seen after patients (which included both surgical and medical ICU patients) had been screened and treatment indicated (Grant *et al*., 2016:533).

Several reviews of risk assessment models are available, and their results focus on the assessment model's ability to predict VTE development. However, it is worth mentioning that the prior described reviews do not report whether these assessment models are easy to implement and/or complete by nursing staff who are not specifically trained to complete them. Unfortunately, no consensus exists on the preferred VTE risk assessment model that should be used throughout the different types of hospitalised patients either locally or internationally (Maynard, 2016; Henke & Pannucci, 2010:230).

2.6.1 Risk stratification of patients by means of risk assessment models

Risk assessment models that are in use today, are designed to identify patients where the benefit of DVT prophylaxis would outweigh its risk. Many patient-specific thrombosis risk factors contribute to a patient's overall propensity to develop VTE or PE. These risk factors are complex in nature and have an additive effect to VTE development. Most risk assessment models are qualitative in nature and assign groups of patients to a risk category such as low, medium or high risk in DVT development. These risk categories are linked to appropriate prophylactic guidelines. Caprini based his risk assessment model on published data and assigned one point for risk factors that have shown a decreased propensity for VTE development. These include (among others) a patient between the ages of 41 and 60 years, those who will undergo a minor surgical procedure, medical patients who are required to undergo bedrest, women who are on oral contraceptives as well as those with a BMI of over 30 (Caprini, 2005:70). Two points were assigned to those between the ages of 60 and 74 years, those who have undergone a surgical procedure lasting for longer than one hour, those who have been diagnosed with previous cancer or malignancy, as well as those who are classified as being morbidly obese or having a BMI of over 40 (Caprini, 2005:70).

Factors conveying a higher risk were assigned three points. These include those older than 75 years of age, those who have undergone a surgical procedure lasting between two and three hours, those with a history or family history of DVT and/or PE, those suffering from HIT, and those who are undergoing present treatment for active cancer (Caprini, 2005:70). The highest point value (namely 5 points) was assigned to patients who are immobile and who have suffered a fracture of the hip or lower extremities, those with acute spinal cord injury, those who have undergone a surgical procedure lasting three hours or longer as well as those who have suffered a stroke (Caprini, 2005:70).

During the administration of the risk assessment model, a patient would be questioned on their medical history, height, weight as well as age, with points added for each positive risk factor obtained. Mostly, risk stratification is obtained by utilising a *point scoring method* where points

are assigned to each individual risk (Caprini, 2005:70). For the Caprini risk assessment model, a total risk factor score between 0 and 1 would signify a DVT development incidence of less than 10% (Caprini, 2005:70). These patients would then be grouped as having a “low risk level” for DVT development. A total risk factor score of 2 would indicate a DVT development incidence of between 10 and 20%, and regarded as a “medium risk level” (Caprini, 2005:70). Patients scoring between 3 and 4 would have a DVT development incidence of between 20 and 40% and are regarded as being at “high risk level” (Caprini, 2005:70). Caprini further classified those with five points or more on the risk factor score as having a 40 to 80% DVT development incidence, but also having a mortality risk of between 1 and 5%. These patients were classified as having the highest risk level (Caprini, 2005:70).

2.7 Chapter summary

The unsolved problem of efficient and safe VTE prophylaxis, encompassing accurate and consistent risk stratification, safe prophylactic measure implementation, as well as ultimate morbidity and mortality reduction, still results in suboptimal prophylactic VTE measure implementation in patients, who are oblivious to the danger they are in, even though first-class care should have been received. Fundamental disputes on when prophylaxis should be initiated as well as poor patient adherence (Gao *et al*., 2016) further lead to higher patient treatment costs, and therefore the demand for knowledge on VTE prophylactic prescribing in the South African private hospital setting emerged. The 2013 SASTH guidelines have set out a number of management points meant to improve quality of care within the framework of reliable healthcare provider systems. In the case of VTE prophylaxis, guided risk stratification and VTE prophylactic steps are available and should be followed to reassess the individual patient’s risk therapy. A disconnect, however, still exists in the administration of VTE prophylaxis as can be seen with current VTE and PE mortality rates. The key question therefore remains: “Are local evidence-based guidelines followed in a resourced setting?”

CHAPTER 3: ARTICLE MANUSCRIPT

3.1 Introduction

The results of this study are presented in the current chapter in article format. The manuscript follows in section 3.2 and the author guidelines are presented in section 3.2.1. Statements regarding the roles of the researcher, supervisor, co-supervisor and statistician can be found in section 3.2.2. The chapter summary follows in section 3.3.

3.2 Manuscript

The following section presents the prepared manuscript that was submitted to the South African Family Practice Journal (S Afr Fam Pract) on 8 November 2019 (submission reference number 5022).

Is guideline driven prophylaxis for venous thromboembolism common practice in the South African private hospital setting?

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Abstract

Background: Prophylactic venous thromboembolism (VTE) strategies have the greatest impact on patient outcomes. Both global and local guidelines support VTE prophylaxis for hospitalised patients. However, studies have reported that these measures are routinely under-prescribed. This study evaluated prescribing patterns of VTE prophylaxis in one of the largest South African (SA) private hospital groups.

Methods: A quantitative, retrospective analysis of the hospital group's patient database was conducted for patients admitted between 1 September 2015 and 31 August 2016. Those younger than 18 years, with trauma or suffering from contraindications to anticoagulation were excluded. Additionally, patients with warfarin billed were also excluded as they possibly required therapeutic anticoagulation. Included prophylactic measures were compared to published SA guidelines by abstracting prophylaxis type and dosing, according to corresponding individual patients' VTE risk rating.

Results: Among the 373 020 patients included as study population (with a mean age of 49.08 years and a 38:62 percent split between male and female), 77% required prophylaxis. Of these, 32.81% received some sort of prophylactic measure during their hospital stay. In patients where prophylaxis was indicated, only 24.56% complied with SA guidelines. The most commonly used prophylactic measures where enoxaparin (89.09%) and fondaparinux (2.68%). Prophylactic measures differed per geographical location and speciality - with the highest use in the Tshwane region and most compliant amongst intensivists.

Conclusions: Less than 24.56% of patients who required prophylaxis received guideline appropriate interventions. Further studies should focus on understanding differences in practice and to improve acceptance of guideline-driven care.

Keywords: venous thromboembolism prophylaxis, hospital, South Africa

Introduction

The global incidence of venous thromboembolism (VTE) formation has been reported to be exceptionally high with an annual overall prevalence rate similar to that of stroke, the fifth leading cause of death worldwide.[1] Sub-Saharan VTE prevalence was found to be at 50.4%, with the majority (62.3%) of at-risk patients classified under a medical specialty whilst surgical patients made up 43.8% of sufferers.[2] For South Africa, the risk of VTE development in hospitalised patients from parts of its Gauteng province was described to be at 74.6% with venous thromboembolic related deaths reported at around 20 000 persons annually.[3,4] However, since most VTE symptoms remain undetected, the true VTE incidence together with its possible impact on the South African private healthcare system largely remains unknown.[5,6]

Venous thromboembolic disease is not only debilitating, but presents a high economic burden on a country's healthcare system. This is mainly due to a 45% increased cost for recurrent hospitalisation with VTE-related comorbid diseases.[7] Recurring VTE-related hospitalisation often requires a 48% increased expenditure compared to the initial admission period.[8] It is estimated that the highest cost is suffered during the first three days after re-hospitalisation, possibly due to the higher level of care required.[9] Up to 24% of patients diagnosed with VTE will eventually require intensive care unit (ICU) re-admission.[9] Venous thromboembolic related hospitalisation cost the United States of America's (USA) healthcare system around $10 billion in 2014 and it was divulged to the researcher that in 2017, one of South Africa's largest private hospital groups spent over R195 000 000 on VTE prophylactic and treatment measures.[7] This may indicate VTE management being one of the most expensive medical strategies around.

Venous thromboembolic development has traditionally been attributed to patients already hospitalised for extended periods of time.[10] However, approximately 25 - 40% of non-hospitalised patients are at risk of VTE development.[10] Pharmacologic VTE prophylaxis is unfortunately not without risk, as its underlying mechanism may result in life threatening haemorrhage.[11] It is therefore important to avoid pharmaceutical prophylaxis when the benefit does not outweigh the risk.[12] For these reasons, patient risk stratification on admission is paramount in order to ensure that at-risk patients receive the correct type and dose of prophylaxis without incurring additional harm.[12] It has been proven that supplementary to risk stratification, implementation of VTE prophylactic guidelines result in improved patient outcomes.[13] Yet, VTE related complications due to poor prophylactic practices have given rise to 64.4% of all

premature deaths in Europe and the USA.[14] This may be attributed to variances in prophylaxis used on patients.[15-18] The South African arm of 'The Use of VTE prophylaxis in relatioN to patiEnt risk profiling' (TUNE-IN) study found that only 67.9% of patients rated as possessing a high risk for VTE development received appropriate prophylaxis.[3] Interestingly, it is reported that the main reason for resulting in reduced prophylactic prescribing are prescribers' perception that patients have a decreased risk for VTE development compared to available epidemiologic data.[3] A large discrepancy often exists in the perceived VTE development risk amongst patients clinically appraised versus those in whom a standardised Risk Assessment Model (RAM) was completed.[3] Risk Assessment Models are traditionally designed to select patients where VTE prophylaxis benefit would outweigh the risk.[3] Several reviews exist on the different available RAMs' ability to predict VTE development, however no consensus has been reached on a preferred model.[19-20] The American College of Chest Physicians' (ACCP) VTE prophylaxis guidelines are generally regarded as the gold standard to be followed, and Caprini devised a RAM to enable these guidelines to be easily implemented.[13] The Caprini RAM is founded on a point based scoring method where points are awarded to risk factors according to their propensity for VTE.[13] Based on the total calculated per patient, either a low, medium or high risk for VTE development is awarded.[13] The RAM by Caprini is also the only model which has been externally validated for its VTE prediction ability and can be used in medical as well as surgically ill patients.[22-24] A modest reduction was furthermore detected in VTE prevalence after patients were screened using the Caprini RAM and its suggested prophylaxis initiated.[22] This RAM possibly positions itself firmly as a tool to reduce VTE occurrence in patients, improve patient care and reduce medical related expenses.

Venous thromboembolism is considered one of the most expensive and common preventable causes of global mortality. Despite its implication, there are a scantiness of data available to describe VTE risk and prophylactic measures across the private hospital sector in South Africa (which is required to reduce healthcare costs). Local, peer reviewed VTE prophylactic guidelines have been published by the South African Society of Thrombosis and Haemostasis (SASH). These guidelines are based on those prescribed by the ACCP and are user friendly in their application. This study aimed at describing the VTE risk and prophylactic practices in the private sector across a large area of South Africa, by comparing practices to those prescribed by SASH guidelines. This may possibly lay the foundation for patient outcome improvement.

Methods

Study design

A quantitative, retrospective analysis was performed on in-patient data for those admitted over one year into one of the three largest private hospital groups in South Africa. Data were analysed by the Department of Statistics, Faculty of Health Sciences of the North-West University (NWU) of South Africa. Descriptive statistics comprised of percentages and frequencies (categorical variables) as well as means and standard deviations or medians and percentiles (numerical variables, depending on data distribution).

Setting

The study setting was selected due to its large representation of privately admitted hospital patients across South Africa. This enabled the researcher to include a larger study population in order to gain possible insight on local

prescribing practices in the private hospital setting. A private hospital group was selected as prescriber habits are not governed by health sector formularies or restrictions.

Data source

All admission and coding information, according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD10), could be cross-linked to in-hospital pharmacy billing data. This enabled the abstraction of the type of prophylactic use with its dosing and frequency compared to the principal diagnosis and VTE risk. Venous thromboembolism risk ratings were calculated by utilising a modified version of the Caprini RAM. Completion was conducted by nursing staff on patient admission, as is standard practice for the Group. A summary of each risk factor and score as contained in the modified Caprini RAM are presented in Table 1.

Table 1: Risk assessment model from study setting

Modified Caprini RAM
Low VTE development risk (Risk factors assigned 1 point each)
• Patients between 41 and 60 years of age • Body mass index (BMI) of > 25 • Patients currently suffering from swollen legs • Varicose veins • Medical patient currently at bed rest • Planned minor surgery • Myocardial infarction (MI) (acute) • Abnormal pulmonary function/ chronic obstructive pulmonary disease (COPD) • History of inflammatory bowel disease • History of prior major surgery/ in the last 30 days • Suffering from congestive heart failure in the last 30 days • Sepsis in the last 30 days • Different lung diseases including pneumonia in the last 30 days • Women who are pregnant or postpartum 30 days • Women who are taking oral contraceptives or hormone replacement therapy • Females with a history of unexplained stillborn babies, or having had more than 3 recurrent spontaneous abortions, toxaemia resulting in premature births or patients with an infant with slowed growth
Medium VTE development risk (Risk factors assigned 2 points each)
• Age between 61 and 74 years • Those with a central venous line • Current or prior malignancy • Immobilised patients with plaster cast in the last 30 days • Patients undergoing arthroscopy • Immobilised patients of 72 hours and longer • Planned surgery of longer than 44 minutes
High VTE development risk (Risk factors assigned 3 points each)
• Patients older than 75 years • Patient history of Deep Vein Thrombosis (DVT) and pulmonary embolism (PE) • Patient familial thrombosis history

High DVT development risk (Risk factors assigned 5 points each)
• Those suffering multiple trauma in the last 30 days • Patients suffering from paralysis or acute spinal cord injuries during the last 30 days • Those with pelvic or hip fractures during the last 30 days • Patients with planned hip or knee arthoplastic replacement

The modified Caprini RAM differed from the originator by classifying obesity as having a BMI of 25, whereas Caprini's classification included a BMI of over 30. Further differences included the exclusion of creatinine clearance (CrCl), factor V Leiden levels, prothrombin 20210A levels, serum homocysteine levels, anticoardiolipin antibody as well as Lupus antibody tests in the modified RAM. The modified Caprini RAM is useful and was verified for settings where it may be impractical to conduct tests such as Lupus antibody essays due to time or financial constraints.[25]

Data collection

Data consisted of all consecutive in-patient admissions from 1 September 2015 to 31 August 2016. The study population data were received in Microsoft Excel® format and consisted of anonymised admission data, respective billing data, VTE risk ratings, ICD10 coding as well as the primary prescriber's specialty. Only patient data of those admitted as "in-patients" were included, as these patients would be at greatest risk for reduced mobility. Patient data were excluded in those where anticoagulant use was contraindicated or not described by SASH guidelines. These included, patients younger than 18 years, those with hepatic failure, and any haemorrhagic linked condition, those admitted with traumatic brain injury or patients receiving therapeutic anticoagulation. All included patient billing data were compared to the "Venous Thromboembolism: prophylactic and therapeutic practice guideline" of the SASH, and compliancy to these guidelines were captured.[26]

Statistical analysis

The Statistical Analysis System®, SAS 9.3® (SAS Institute Inc., Cary, NC, USA) was used to analyse the data. Categorical variables were reported as frequencies and percentages. For this proposed study, the Pearson's chi-square test was used to determine the association between SASH guideline compliance and clinical speciality. Cohen's *d*-value was used to determine the practical significance of the results (with $d \geq 0.1$ defined as an effect with practical significance).

Results

There were 373 020 in-patient records that met the inclusion/exclusion criteria for the study period. A diagrammatical representation of the study population breakdown is contained in Figure 1. Patients were grouped together if they had undergone risk rating measures and further divided between those who would not require prophylaxis (Low VTE risk) and those who would (Medium or High VTE risk).

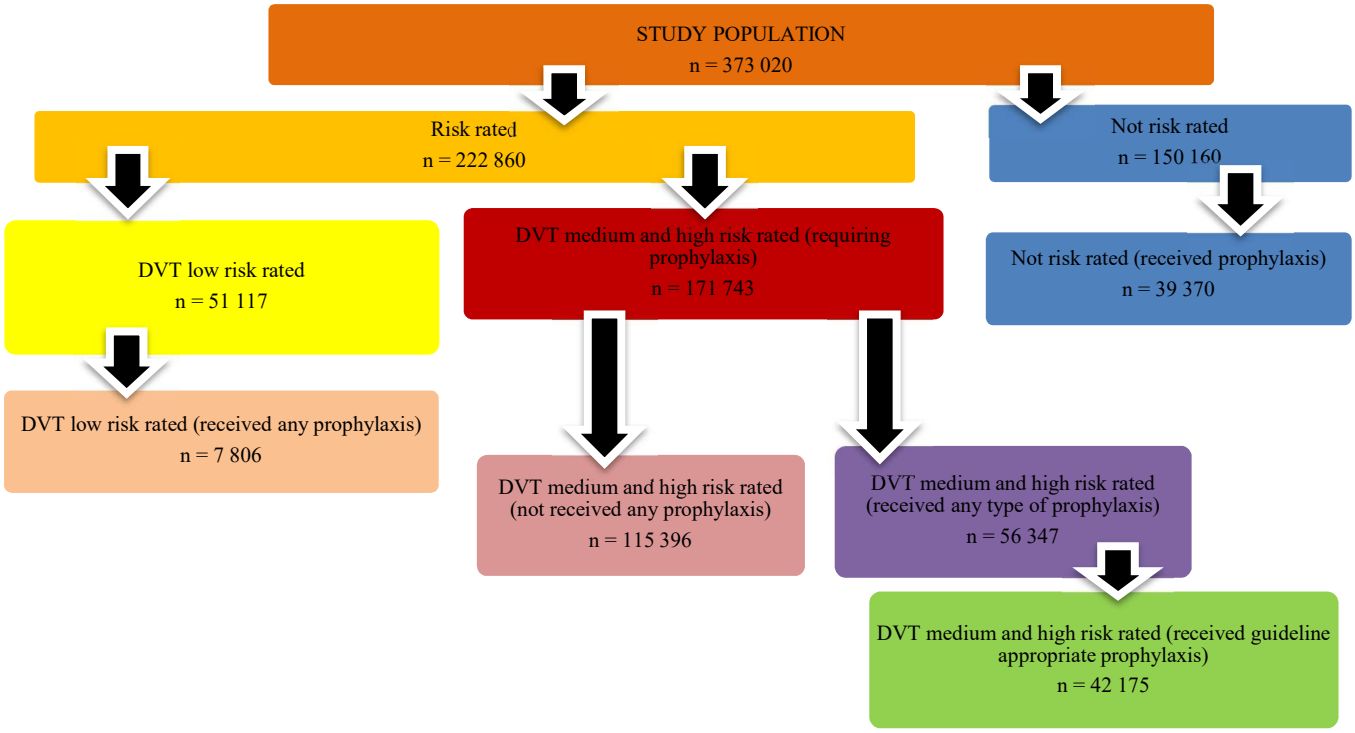

Figure 1: Risk-rated distribution of patients in study population

The mean age of the study population was 49.08 years (SD, 17.96) with a 38% to 62% male to female split. The modified Caprini RAM was applied to 59.74% of included patients, where 77% of risk assessed patients were found to exhibit a moderate (25.3%) to high (75.7%) propensity for VTE development and requiring prophylaxis.

A data summary for patients requiring prophylaxis was added in Table 2, with the mean age being 53.34 years (SD, 17.85) and the majority being female (61.89%). Admissions in this group of patients were higher for 'maternal care due to uterine scar' (4.46%), 'unstable angina' (3.26%) and 'pneumonia unspecified' (2.50%). Only 32.80% of those requiring prophylaxis, received some sort of preventative measure. Furthermore, only 24.56% of those requiring prophylaxis received guideline appropriate preventative measures. Patients who required and received prophylaxis were generally older (median, 54.55 years, $p < 0.01$), compared to those who required but did not receive. The most commonly used chemoprophylactic agents were a low molecular weight heparin (LMWH) such as enoxaparin (89.09%), factor Xa inhibitors as fondaparinux 2.5mg/ 0.5ml (2.68%) and novel oral anticoagulants (NOAC) as rivaroxaban 10mg (1.4%).

Table 2: Patient characteristics for those rated medium or high for VTE risk

Baseline Patient Demographics and Hospital Region Among Those Risk Rated and Requiring Prophylaxis: *Those Who Received and Those Who Did Not Receive Any Prophylactic Anticoagulation*				
Patient Demographics	*Received Any Prophylaxis n = 56 347*		*Did Not Receive Prophylaxis n = 115 396*	
Median Age (IQR)	54.9	(SD = 17.8)	51.7	(SD = 17.7)
Gender - Female	61.30%	(n = 34 558)	62.20%	(n = 71 734)
Gender - Male	38.70%	(n = 21 788)	37.80%	(n = 43 661)
Gender - Unknown	0.00%	(n = 1)	0.00%	(n = 1)
Primary admission coding				
Maternal care due to uterine scar	4.40%	(n = 2 490)	1.90%	(n = 2 141)
Unstable angina	3.00%	(n = 1 714)	1.40%	(n = 1 672)
Congestive heart failure	2.90%	(n = 1 632)	1.30%	(n = 1 528)
Pneumonia unspecified	2.80%	(n = 1 566)	1.60%	(n = 1 790)
Pulmonary embolism without mention of acute or chronic	1.70%	(n = 974)	0.00%	(n = 25)
Cellulitis of other parts of limb	1.20%	(n = 659)	0.00%	(n = 0)
Spontaneous vertex delivery	0.10%	(n = 38)	1.40%	(n = 1 650)
DVT Risk Rating				
High Risk	82.90%	(n = 46 716)	70.70%	(n = 81 548)
Medium Risk	17.10%	(n = 9 631)	29.30%	(n = 33 848)
Anticoagulant Received				
Enoxaparin	89.90%		0.00%	
Fondaparinux	2.60%		0.00%	
Rivaroxaban (10mg)	1.00%		0.00%	
Type of Prophylaxis Breakdown				
Chemoprophylaxis	98.80%		0.00%	
Mechanical Prophylaxis	1.20%		0.00%	
Hospital Region				
Gauteng - Johannesburg	34.60%	(n = 23 663)	65.40%	(n = 44 716)
Gauteng - Tshwane	42.60%	(n = 12 609)	57.40%	(n = 16 965)
Eastern Cape	25.10%	(n = 4 893)	74.90%	(n = 14 571)
Western Cape	31.00%	(n = 7 234)	69.00%	(n = 16 133)
Free State	17.10%	(n = 763)	82.90%	(n = 3 694)
Kwazulu-Natal	26.10%	(n = 5 814)	73.90%	(n = 16 488)
North-West**	32.60%	(n = 1 371)	67.40%	(n = 2 829)

Notes: North-West**; **Results representative of one hospital only

Characteristics for patients who received guideline appropriate prophylaxis are set out in Table 3. Admission codes were found to be highest for 'maternal care due to uterine scar from previous surgery' (5.01%), and 'unspecified viral hepatitis without hepatic coma' (1.49%) was found to be second most prevalent. Risk ratings in this subset of patient data favoured that of a high risk for VTE development (82.56%). Results revealed that high risk-rated patients most often received enoxaparin or fondaparinux as prophylaxis.

Table 3: Characteristics of patients who received SASH compliant prophylaxis

Population prophylaxis - compliant to SASH	**n = 42 175**	
Primary ICD Coding	**n =**	**Frequency %**
Maternal care due to uterine scar from previous surgery	2113	5.01
Unspecified viral hepatitis without hepatic coma	629	1.49
Unstable angina	629	1.49
Other primary gonathrosis	507	1.20
Spinal stenosis, lumbar region	488	1.16
Delivery by elective caesarean section	438	1.04
Adult hypertrophic pyloric stenosis	437	1.04
Adult respiratory distress syndrome	437	1.04
Stroke, notspecified as haemorrhagic	403	0.96
Bronchitis, not specified as acute or chronic	402	0.95
Bronchopneumonia, unspecified	402	0.95
Other and unspecified intestinal obstruction	393	0.93
Sepsis, unspecified	390	0.92
Insulin-dependent diabetes mellitus	368	0.87
Primary gonarthrosis, bilateral	351	0.83
Chronic obstructive pulmonary disease with acute exacerbation	350	0.83
Chronic obstructive pulmonary disease, unspecified	350	0.83
Gluteal tendinitis, pelvic region and thigh	325	0.77
Gonarthrosis, unspecified	325	0.77
Excessive and frequent menstruation with irregular cycle	302	0.72
Chronic kidney disease, stage 5	284	0.67
Malignant neoplasm of parotid gland	276	0.65
Malignant neoplasm of prostate	276	0.65
Acute renal failure, unspecified	268	0.64
Acute respiratory failure Type1 [hypoxemia]	268	0.64
Liver disorders in pregnancy, childbirth	262	0.62
Lobar pneumonia, unspecified	262	0.62
Lumbago with sciatica, site unspecified	256	0.61
Lumbar and other intervertebral disc disease	256	0.61
Gender		
Female	26 942	63.88
Male	15 233	36.12
Risk		
DVT High	34 820	82.56
DVT Medium	7 355	17.44
Mean age	**Std. Dev.**	
56.45	87.24	
Prophylaxis	**% use**	
Enoxaparin	87.24	
Fondaparinux	4.04	
UFH	3.59	
Rivaroxaban (10mg)	2.67	
Fraxiparine	1.2	
Nadroparin	0.27	
Dabigatran	0.27	
Mechanical prophylaxis	0.72	

By comparing the different molecules used as chemoprophylaxis in those who required prevention (Table 2), it was found that enoxaparin took the highest share (89.90%) of chemoprophylactic prescribing. It was mostly used at 40 mg subcutaneous every 24 hours. Fondaparinux was the second highest (2.60%) prescribed agent at 2.5 mg subcutaneous every 24 hours. Unfractionated heparin (UFH) (which had a higher use in those compliant to SASH guidelines, Table 3) was used at a dosing of 5000 I.U., every 8 to 12 hours. A dose of 10 mg rivaroxaban (NOAC) was more commonly used in orthopaedic surgery patients, however this was not limited to its registered indication for hip and knee arthroplasty. Prophylaxis used in surgery disciplines was highest for enoxaparin followed by dalteparin (NOAC). Prescribing of prophylaxis in medically ill patients favoured enoxaparin as a once in 24 hour administration, followed by dalteparin at 5000 I.U. subcutaneous every 24 hours. The recommended doses of LMWH, UFH and rivaroxaban appear to have been adhered to.

Whilst chemoprophylaxis formed the largest part of all types of prophylaxis used, mechanical prevention methods were utilised in 1.2% of patients (regardless SASH guideline compliancy measure). Graduated compression stockings were slightly more favoured (0.66%) as mechanical prevention method compared to the use of pneumatic compression sleeves (0.19%).

Using binomial analysis, the use of prophylactic measures varied by geographic region ($p < 0001$). Patients who received any type of prophylaxis, were more frequently found in hospitals located in Gauteng. The highest SASH compliant portion of patients were located in Tshwane-based hospitals compared to those in the Free State (40% vs. 14%; $p = 0.13$). The differences between available geographical groups were not statistically significant and was not found to influence prophylactic prescribing practices. The compliance of prophylactic prescribing by specialty varied amongst prescribers ($d > 0.1$ and $0.000 < p > 0.003$) (Figure 2). Intensivists ($d = 0.42$, $p < 0.003$), paediatricians and paediatric surgeons ($d = 0.2$, $p < 0.000$) generally were more likely to prescribe SASH guideline directed VTE prophylaxis (Figure 2).

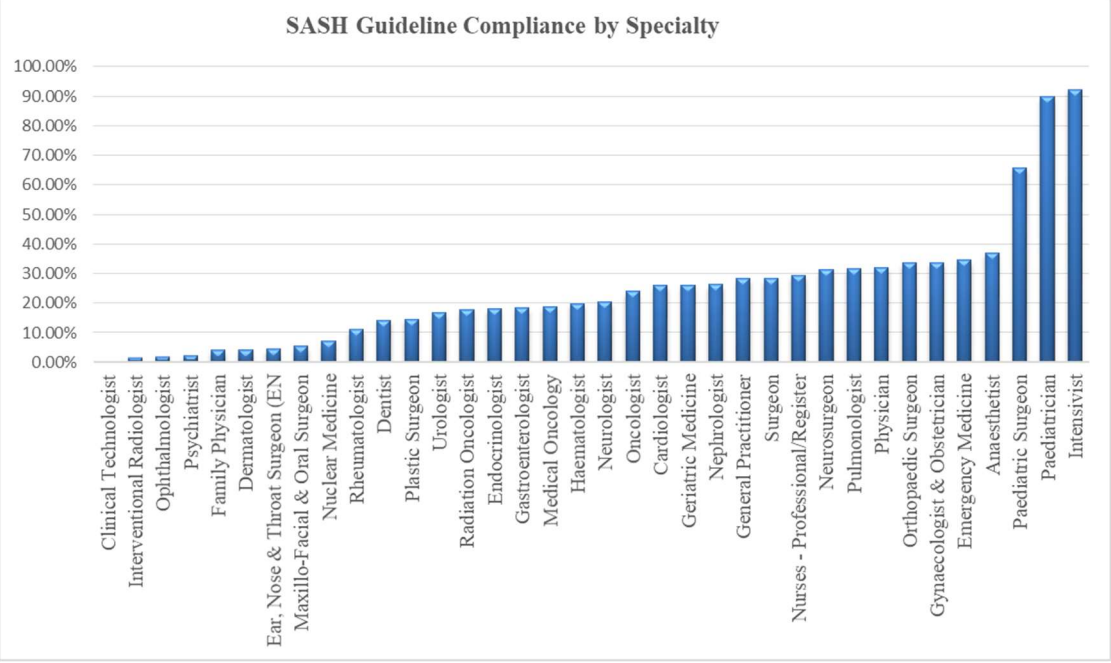

Figure 2: Distribution of SASH compliancy by doctor specialty

Discussion

In this single-year retrospective study, less than a quarter of patients requiring VTE prevention received guideline appropriate intervention. This is in contrast to the high VTE development risk found in over 77% of patients.

Mention should also be made of the reduced percentage of RAM application found in this study. Even though a risk of over classification of VTE prophylactic requirement in low-risk patients occurs with the use of a RAM, it has been proven to increase prescriber awareness of patients' VTE risk.[3] This is because it has been found that prescribers do not routinely risk assess patients and base prophylactic prescribing on their perceived patient VTE development risk.[3] The routine use of RAMs, on the other hand further prevents the underdiagnoses of patients at high risk for VTE in 20% of patients, as is recommended for use in the private sector of South Africa.[3] For this reason, only patients at medium to high risk for VTE development's prophylactic measures were evaluated.

The study population's mean age was found to be less than that reported in the TUNE-IN study but close to the mean age of 45.15 years as with the ENDORSE-Africa study.[3,2] The fact that this study population contained high gynaecological admission volumes as compared to other studies may explain the age differences. Female gender distribution was found to be similar to the South African arm of the TUNE-IN Wave 2 and ENDORSE-Africa (65.6%) studies.[20,2] This reported percentage of at risk patients is higher than the 74% average found in the TUNE-In Wave 2 study, but within the range of 44 - 80% for the ENDORSE study.[20,17] The rate of appropriate prophylaxis found, is much lower than rates from both the South African TUNE-IN Wave 2 (70.9%) and ENDORSE studies, but falls in line with the ENDORSE-Africa study of guideline compliance rates of between 22 and 80%.[20,17,2] A possible reason for the lower compliance in this study is that the study population for medically ill patients included all patients older than 18 years, risk-rated as either exhibiting a medium or high thrombosis risk. The ENDORSE methodology, (as followed in ENDORSE-Africa and TUNE-IN Wave 2 studies) however only included patients older than 40 years.[17,2,20] The SASH guidelines do not specifically mention age as a predictor of risk, but advocates RAMs to be used to determine VTE risk.[26] This resulted in adding RAM results and ICD10 coding as inclusion criteria. Upon comparing patient age amongst those requiring prophylaxis, findings revealed that older patients were more likely to have received prophylaxis compared to those who did not receive any form of prophylactic anticoagulation. A possible explanation for this finding is that 1.4% of patients, contained in the grouping which did not receive preventative measures, was admitted with 'spontaneous vertex delivery'. These patients theoretically are assumed to be of a younger age and here the use of prenatal anticoagulation is off-label. The SASH guidelines do recommend LMWH use prenatally in those where the benefit outweighs the risk, however this practice requires much caution.[26]

This study further found that in gynaecological surgery (such as in the case of the study population's highest admission portion), the use of enoxaparin 40 mg subcutaneous daily, starting between 6 - 8 hour post-procedure was prescribed. This is in compliance to SASH guidelines. The SASH guidelines suggest the use of dalteparin for patients undergoing high risk surgical procedures and is also registered as prophylaxis in patients at moderate risk of thrombosis (those undergoing abdominal and gynaecological surgery), as well as those presenting with a high risk of thrombosis (those undergoing orthopaedic surgery or suffering from an underlying malignancy). Study results reveal dalteparin use to be the second highest chemoprophylaxis molecule used in surgical procedures, which is in line with guidelines. The high overall use of enoxaparin (89.90%) is very similar to the TUNE-IN Wave 2 study (92%) and is in line with SASH

recommendations where LMWH is stipulated as being superior to unfractionated heparin for most prophylactic indications.[26,27] One possible reason for the low use of mechanical prophylaxis in our study population may be due to its recommended use in those at high risk of bleeding as well as the lower percentage of surgery related admissions (excluding gynaecological surgery) in the current study population. The use of mechanical prophylaxis (pneumatic stockings) was found to be used in less than 3% of patients in the TUNE-IN Wave 2 study which is however higher than our study (1.2%).[27]

While practices amongst specialties differed from published guidelines, no comment can be made on the appropriateness of prophylaxis used. This is because no clinical outcomes data for patients at risk of thrombosis development were available/ included in the study. One possible reason for the variance in prescriber prophylaxis may be due to the fact that the last review of SASH guidelines occurred in 2013 and newer anticoagulants have since been registered in SA. Another factor may be patients' bleeding risk (which may not have been ICD10 coded), as well as the risk of clinician litigation due to patient haemorrhage. It must be noted that this study's aim was not to critique prescribing practices but to illustrate occurring prophylaxis patterns as well as patient VTE risk spread.

Results for this study reveal that younger, female gynaecology patients make out the bulk of those who are at risk for VTE development. With such patient demographics existing in the private sector, and the fact that clinicians are relying more on their own diagnosis than results achieved from RAMs, a possibility exists that private hospital patients may require more prophylaxis than that traditionally prescribed.

Conclusions

This study confirms that most prescriber specialties do not prescribe VTE prophylaxis according to published local, consensus derived guidelines. It can further be concluded that patients are more likely to receive some form of VTE prophylaxis if they are at high VTE development risk. This is similar to other study findings where patients at medium risk for VTE development did not receive the required VTE prophylaxis as stipulated in the guidelines. Differences in prophylactic patterns were found between hospital geographical locations, however, the clinical implication of this effect remains unknown. The application of RAMs was found to have been used in just over half of admitted patients, possibly pointing to the fact that prophylactic prescribing is more reliant on clinician diagnosis than risk assessment. This is in contrast to guidelines suggesting that all admitted patients should be subjected to a RAM, together with a clinician review. The concern of bleeding risk in patients, and the costs associated with VTE prophylactic under prescribing should not be disregarded, therefor pointing to the importance of RAM outcomes to ensure only those at risk of thrombosis are treated.

Further review of VTE prophylaxis guidelines to include newly registered anticoagulants as well as methods to improve acceptance of RAMs may balance the current under- and overprescribing amongst the different VTE risk categories.

Limitations of this study

The study data set is similar to data utilised by medical aids in order for them to determine prescribers and/ or hospital disease risk profiling. As this was a retrospective study, dependent on claims information with linked pharmacy billings data, a potential for ICD10 case ascertainment and capturing errors as well as under-coding exist. Nevertheless, due to the availability of pharmacy data, a more detailed data set was available which enabled prescription details. A combination of inaccurate billing and VTE risk assessments may have contributed to the smaller percentage of patients found to have received prophylaxis in accordance to SASH guidelines. Primary ICD10 coding was used to select the study population – this may inadvertently have led to certain patients, where anticoagulation was contraindicated, to be included in the study.

Ethical Approval

The Health Research Ethics Committee (HREC) of the Faculty of Health Sciences of the NWU granted ethical approval (ethics number: NWU-00080-17-S1) and written permission was then obtained from the study hospital group's Ethics in Research committee.

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Conflict of interest – None.

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3.2.1 Author guidelines

The article manuscript was written according to the author guidelines of the *South African Family Practice Journal* and can be accessed at https://safpj.co.za/index.php/safpj/about/submissions.

3.2.2 Statements

The supervisor (Dr Jesslee du Plessis), co-supervisor (Dr Marlene Julyan) and statistician (Ms Marike Cockeran) of the mini dissertation also evaluated and supervised the writing of this manuscript. The mini dissertation and manuscript were both prepared by the researcher, Ms Melissa van der Merwe. Statistical analyses were generated by Ms Marike Cockeran.

3.3 Chapter summary

Results of the mini dissertation were presented and described in article format – as contained in Chapter 3. Conclusions and recommendations with regard to the outcome of this study are presented in Chapter 4.

CHAPTER 4: CONCLUSION

4.1 Introduction

Venous thromboembolism (VTE) is a serious life-threatening condition with more than half of hospitalised patients being at risk for VTE development (Kingue *et al*., 2014:161; Riback & Wessels, 2012:85). An estimated 43.8% of patients undergoing an elective general surgical procedure are at risk of some form of VTE as a postoperative complication, with the majority (62.3%) of at-risk patients classified under a medical specialty (Kingue *et al*., 2014:161). Literature describes the value of appropriate guideline-driven prophylaxis to prevent VTE-related morbidity and mortality (Cardoso *et al*., 2016:491). However, data from local, large-scale studies are scarce in order to establish South African risk profiling and thromboprophylaxis prescribing patterns.

The aim of the study was to evaluate the VTE developmental risk in patients, based on individualised patient risk assessment models, and the compliance to consensus based, local VTE prophylaxis guidelines. The focus was on the prescribing patterns of pharmacologic and/or mechanical prophylaxis compared to The SASTH guidelines in patients who have been admitted to a South African private hospital group, between 1 September 2015 and 31 August 2016. Conclusions and recommendations are set out in the sections below, as were derived from the aims and objectives set forth in section 1.3 of this mini dissertation.

4.2 Conclusions based on study objectives

The conclusions drawn are based on the study objectives contained in the literature review and that resulted from the empirical investigation. Each objective was successfully actioned and is presented in sections 4.2.1. and 4.2.2.

4.2.1 Literature review objectives

The following scientifically accredited databases and manual search engines were used to search for applicable English studies where results were analysed and included in this study: Google Scholar™, EMBASE®, Ovid MEDLINE®, Cochrane Database of Systematic Reviews®, EBSCOhost®, Springerlink®, Scopus®, Read by QxMD®, as well as pharmaceutical textbooks.

Filters to databases were applied to be more productive and focused. Phrases and keywords mostly applied to narrow the search were:

“VTE”, “DVT”, “deep vein thromboembolism”, “venous thromboembolism”, “prophylaxis”, “VTE prophylaxis”, “safety”, “high risk”, “hospitalized”, “hospitalised”, “medium risk”, “low risk”.

Venous thromboembolism incorporates two vascular conditions, namely DVT and PE. Deep vein thrombosis and PE are divergent but related disease states stemming from the same haemodynamic process (Kroegel & Reissig, 2003:9). Deep vein thrombosis is a condition in which the clotting of venous blood occurs in a deep vein of an extremity due to dysregulation of the thrombotic mechanisms (Shibeko *et al*., 2010:1; Violi & Ferro, 2013:426). Thrombosis relies on various factors, namely changes in venous blood flow, damage to the vessel's tunica intima and the formation of a hypercoagulable state (Malone & Agutter, 2006:588; Virchow, 1856). These factors are described by Virchow and are colloquially known as "Virchow's triad". Even though "Virchow's triad" is used to mainly describe thrombosis, several other models exist and are essentially of use in describing initiation and resolution of thrombus formation on a cellular level (Hoffman & Monroe, 2001:958; Mackman *et al*., 2007:1687; Shibeko *et al*., 2010:1). Through literature it was found that all these models conclude that once the human body's normal haemostatic equilibrium is disturbed, thrombosis will be favoured, which may result in VTE (Figure 2-1).

It was determined that haemostatic equilibrium disruption risk can be predicted by certain innate or acquired patient factors. Literature studied revealed that patients suffering from cancer, those with advanced age (especially those older than 75 years), those who have had previous instances of VTE, those suffering from acute medical infections as well as immobile patients (due to illness or surgery) are all at greater risk for VTE development (Kaplan *et al*., 2015:1224; Kearon *et al*., 2016:1480,1482; Samama *et al*., 1999:795; Violi & Ferro, 2013:426). Other factors include thrombosis in especially proximal veins as well as the extent of thrombus propagation (Cohen *et al*., 2008:151; Kucher, 2011:861).

The literature review established that the possible complications of DVT include: VTE, PE, chronic venous insufficiency and subsequent post-thrombotic syndrome (Mennon & Hamilton, 2004:302; De Palo, 2017). Pulmonary embolism is the most common complication and is often fatal (Bělohlávek *et al*., 2013:134; Veller & Pillay, 2009:307). Embolisms essentially result from a blockage (which may be due to a DVT) that has dislodged and travelled through the circulatory system, cutting off blood flow to a critical organ. For PE, this blockage would occur in the pulmonary arterial circulation, resulting in partial or complete obstruction (Piazza *et al*., 2015:1392). This may or may not be symptomatic, making diagnosis difficult (Rya *et al*., 2007:1537). Post-thrombotic syndrome can occur in up to half of all patients suffering from a DVT and is mainly due to damage caused to venous valves (Gogalniceanu *et al*., 2009:193; Winter *et al*., 2017:1531). Valves are subsequently left incompetent, which results in retrograde blood flow or pooling. Many complications can follow due to the pooling of blood (Shaydakov *et al*., 2016:161) and VTE can recur in up to 27% of otherwise healthy patients after 20 years (Mohr *et*

al., 1249). Venous thromboembolism therefore is a syndrome able to cause patient morbidity and mortality which is associated with a heavy financial burden. It was found that preventative measures resulted in the best patient outcomes.

- **Description of VTE prophylaxis through its mechanism, the reasons for patients to require VTE prophylaxis, as well as the type of mechanical or pharmaceutical prophylaxis as suggested by literature or accepted guidelines**

Prophylactic measures implemented in medical and surgical patients were found to be effective in reducing the incidence of VTE occurrence. Mainly two prophylactic measures were revealed through literature and can be used individually or in combination. These measures are pharmaceutical or chemoprophylaxis as well as non-pharmacologic or mechanical prophylaxis (Flevas *et al*., 2018:138; Leme & Sguizzatto, 2015:686; Routhier *et al*., 2018).

Chemoprophylaxis mainly includes medication that directly (such as NOACs or indirectly (warfarin, heparin and LMWH) antagonises the formation of thrombin by means of activated factor X blockage (Eriksson, 2011:41; Vallerand *et al*., 2017f). Heparin, LMWH and fondaparinux are furthermore able to actively block thrombin, while dabigatran solely reversibly inactivates thrombin (Eriksson, 2011:41). Thrombin (or activated factor II) is the final enzyme that converts fibrinogen to insoluble fibrin, the main component of thrombi. A schematic adaptation of the different mechanisms of action of these molecules, known as anticoagulants (Eriksson, 2011:41; Micromedex, 2018), is presented in Figure 2-3 of this mini dissertation. It was established that the success of chemoprophylaxis lies in the fact that already formed thrombi are lysed and the additional formation, propagation and recurrence of other thrombi are prevented. The use of mechanical prophylaxis aims to increase blood flow by means of physical interventions. This is achieved by making use of pressure exertion by means of graduated compression stockings or intermittent pneumatic compression devices (IPC) (Geerts *et al*., 2008:381; Masotti *et al*., 2014:4). Unlike chemoprophylaxis, the use of mechanical methods does not increase the patient's risk of severe bleeding. However, mechanical prophylaxis is contraindicated in patients with arterial circulatory disorders, peripheral neuropathy, those without intact skin as well as those with limb deformities (Geerts *et al*., 2008:38; Aryana, 2018:3-4).

The reasons for prophylactic measure implementation are to reduce the risk of DVT recurrence as well as the resolution and prevention of DVT-related morbidity and mortality. Additionally, diagnosis of DVT is complicated as most patients are asymptomatic for the underlying problem (Karande *et al*., 2016:493; Lucena *et al*., 2009:196). After reviewing of literature, it is evident that efficient and safe prophylaxis are required to ensure patient survival (Jha *et al*., 2013:809; Karande *et al*., 2016:493).

Due to the distinctive risks associated with chemoprophylaxis, it is necessary to ensure that only those truly at risk of VTE development are treated. Several published guidelines are available worldwide, including South Africa, and are founded on best evidence-based outcomes (Bates *et al*., 2012; Jacobson *et al*., 2013:261). Locally developed guidelines were derived from principles of the 2009 ACCP international guidelines (Guyat *et al*., 2012) and require the risk rating of patients to ensure that only those at risk of thrombosis receive prophylaxis.

Many similarities are found between ACCP and SASTH guidelines and include:

- Patient risk rating
- Prophylaxis requirements in both medically ill and surgical (including orthopaedic) patients
- The superiority of LMWH over UFH
- The use of NOACs as prophylaxis
- Timing of pre-operative chemoprophylaxis (both SASTH and ACCP guidelines prefer initiation at 12 hours pre- or post-operatively)
- Combination of mechanical prophylaxis (such as IPC) with chemoprophylaxis in patients requiring an extended hospitalisation or who are at moderate risk for VTE development (and not at high risk for bleeding)
- Duration of chemoprophylaxis of 14 days in knee arthroplasty (ACCP suggests duration of minimum 10 to 14 days, while SASTH guidelines recommend 14 days)
- Discouraging the use of VTE prophylaxis in patients who are mobile
- Patient preference on administration and cost in order to ensure compliance is reported as an important aspect to keep into consideration
- The use of mechanical prophylaxis (IPC or foot pumps) in patients who are at a high risk for bleeding and require prophylaxis
- A duration of 35 days for prophylaxis in high VTE-risk patients (which includes those suffering from cancer)
- Both guidelines were peer reviewed and did not report any affiliation or sponsorship with pharmaceutical companies (ACCP 9th edition).

The differences between ACCP and SASTH guidelines include:

- Chemoprophylaxis duration of LMWH in major orthopaedic surgery – SASTH guidelines stipulate a duration of seven to 10 days, while ACCP recommends an increased duration of 10 to 14 days.

This objective concluded that local SASTH guidelines were based on well-researched recommendations centred on strong evidence-based studies. The basis of the SASTH guidelines relies on the use of a peer-reviewed risk assessment model proven to identify patients at risk of VTE development and results in a modest reduction of thrombosis. In comparison to other guidelines is the fact that SASTH guidelines include human immunodeficiency virus (HIV) as a risk factor for VTE development, making it appropriate for the South African context. Unlike ACCP guidelines, the layout of SASTH is concise and easy to follow. One possible drawback, however, is the fact that it has not been updated more recently (it is already 6 years old) to include the latest NOACs as well as a recent locally registered second-generation LMWH. However, the latest amendments in the 2016 ACCP guidelines (Kearon *et al*., 2016:315) only include options for VTE treatment, whereby prophylactic guideline principles have been kept the same as in the 2012 publication.

- **Explanation of methods used to grade patients as having a low, medium or high risk for VTE development as well as the determination of VTE development prevalence in these hospitalised patients, rated medium to high risk, as reported both locally and internationally**

A detailed analysis of available risk assessment models (RAM) as well as methods for risk stratification by means of these models was given in sections 2.7 and 2.7.1, respectively. The following paragraphs are a conclusion of VTE prevalence in the different risk-rated patients.

A study of literature revealed that, in South African patients rated as having a high VTE development risk, the prevalence for VTE development was 70.4% in medically ill patients and 84% in surgical patients, respectively (Riback & Wessels, 2012:85). This is similar to other sub-Saharan countries in terms of a higher prevalence for medical patients compared to those undergoing surgery (Kingue *et al*., 2014:159). A unique risk component for South Africa (and other sub-Saharan countries) is the high prevalence of HIV, which carries an 18% increase in VTE development (Awolesi *et al.*, 2016). This fact may explain the difference found in VTE prevalence of international high risk-rated patients. It was found that in these patients, more surgical patients are at high risk than those who are medically ill (Cohen *et al*., 2008:1914).

Lastly, this objective concluded that the use of a RAM to determine VTE risk is best practice. However, the training of those who are tasked to complete the assessment is desirable in order to reduce errors and possibly improve clinician acceptance.

- **Review of the adherence of prescribers, per clinical speciality, to published VTE prophylactic guidelines as reported by local and international research publications**

After a review of literature, a high variance between major clinical disciplines and their adherence to published guidelines was reported with adherence ranging from 5 to 74% (Bergmann *et al*., 2010:736; Cohen *et al*., 2008:1914; Geachan *et al*., 2016; Riback & Wessels, 2012:85). The different findings were described in sections 1.1. and 2.7. of this mini dissertation and all confirm that correct VTE prophylactic use in both global at-risk medical and surgical patients was suboptimal. Medically ill patients especially, were found to be at a greater risk for low VTE prophylactic prescribing. The scarcity of studies pertaining to VTE prophylaxis guideline adherence comparison per individualised clinical specialty deserves mentioning.

Reasons for the possible under-prescribing of VTE prophylaxis may include the risk of litigation due to bleeding complications or the perception of a lower VTE prevalence in patients by clinicians (Jacobs *et al*., 2017:56). This makes sense as patients would more readily identify bleeding tendencies because of chemoprophylaxis than being able to appreciate their DVT risk profile.

Lastly, it can be shown that guideline appropriate VTE prophylaxis is under-utilised globally, including in certain parts of South Africa. This leaves patients at an increased risk for disease and death. Furthermore, many reasons exist for reduced prophylactic use and include a possible lack of consensus on guidelines, which may even involve a push back on clinicians' part in terms of being prescribed to. However, in best practice, it begs the question – Are evidence-based, peer-reviewed guidelines not more appropriate than personal experience?

4.2.2 Empirical investigation objectives

The empirical investigation was done in article format (refer to Chapter 3) and its objectives were achieved by using the retrospective observational data as obtained in section 1.3.2. The specific objectives are described and listed in the following sections.

- **Determine the prevalence of admitted patients who were not risk-rated as well as those who were risk-rated (having a low-, medium- or high risk for VTE development) during the study period 1 September 2015 to 31 August 2016**

With regards to determining the prevalence for patient risk stratification in the retrospective study, it was found that 40.26% of the study population were not subjected to an assessment model. This is not in accordance to SASTH, ACCP or even National Institute for Health and Care Excellence (NICE) guidelines – where it is recommended that all patients be risk assessed upon admission (Cohen *et al*., 2008:1914; Jacobson *et al*., 2013:261; NICE, 2018). The high percentage of patients not risk assessed, however, is similar to international literature where ranges between 40 and 80% were reported, prior to implementation of quality improvement measures (NHS UK, 2015:4; Wilson, 2015:2).

The prevalence of at-risk patients (medium and high risk-rated) might seem extremely high (77%) and was found to be higher than other prevalence rates (see manuscript's "Discussion" section, Chapter 3). Possible reasons for the higher prevalence may be the fact that, unlike other locally conducted studies (Kingue *et al*., 2014:161; Riback & Wessels, 2012:86), no prior selection of participating hospitals was conducted and all patients (older than 18 years, regardless of surgical procedure or medical specialty) who did not present with a primary diagnosis where anticoagulation may be contraindicated were included in the study population. The possibility of an over-diagnosis for VTE risk development due to the application of a RAM may also have contributed to a higher VTE development risk prediction. However, this high prevalence may highlight the actual picture of VTE risk in South African private hospital patients.

It remains controversial whether compliance to risk assessment for all patients would, in fact, lead to better patient outcomes. However, data do support the value of risk assessments to be conducted in all hospitalised patients to enhance patient safety and possibly reduce readmission as well as costs due to undetected VTE risk (Catterick & Hunt, 2014:575; NHS UK, 2015:2). In summary, measures to improve the acceptance of clinicians to be alerted of at-risk patients by means of a risk assessment as well as increasing the percentage of risk assessed patients may possibly benefit healthcare settings.

- **Evaluate the compliance and non-compliance of VTE prophylaxis management, according to the recommended SASTH guidelines for each risk rated group**

Data analysis from the study revealed that 22% (*n* = 51 117) of risk-rated patients were deemed to be at a low risk for VTE development. According to SASTH guidelines, this population of patients do not require any form of prophylaxis apart from early mobilisation. However, the retrospective study found that 15.27% (*n* = 7 806) received some form of prophylaxis, which may be seen as over servicing. For patients who would have required prophylaxis (according to SASTH guidelines were rated as either medium or high risk, *n* = 171 743), a total of 67% (*n* = 115 396) received some form of prophylaxis. However, only 36.55% (*n* = 42 175) of these patients received SASTH appropriate prophylaxis. This figure is much lower than other local studies conducted (Riback & Wessels, 2012:85). One possible reason may be the fact that, unlike the TUNE-IN wave 2 study, all hospitals and their associated prescribers were included. The authors of the TUNE-IN wave 2 study did, however, mention this as a possible limitation, which may have resulted in biased results (Riback & Wessels, 2012:85).

Overall, it may be said that a lower use of appropriate prophylaxis exists in a part of the private hospital sector of South Africa. As this study was retrospective and quantitative in nature, no association between the low compliance and patient outcomes can be made. The low compliance to peer-reviewed, evidence-based guidelines is, however, concerning.

- **Determine the association between SASTH guideline compliance and clinical specialties, by risk group, using inferential statistics**

The study's compliance to SASTH prophylactic guidelines varied among the different clinical prescriber specialties ($d > 0.1$ was selected to show practical significance, with $p < 0.05$ denoting statistical significance). All specialties where associations were found to have practical significance (together with statistical significance), were offered in Table 4-1. A discussion on the findings was presented in Chapter 3 of this mini dissertation. In conclusion, a disconnect was found with regards to the prescribing prophylactic patterns of different clinical specialties to that of SASTH approved guidelines. Only three disciplines seem to be more inclined to prescribe guideline appropriate VTE prophylaxis in more than two thirds of their patients in need of thrombosis prevention. A very low compliance (less than 40%) of patients admitted to other disciplines received appropriate prophylaxis.

Table 4:1 Guideline compliance association to clinical specialty

Specialty	Compliance	p =	Effect size
Intensivist	92.31%	0.003	0.42
Paediatric Surgeon	70.20%	0.000	0.20
Anaesthetist	38.59%	0.000	0.11
Emergency Medicine	36.74%	0.000	0.13
Nurses - Professional/Register	36.73%	0.002	0.13
Gynaecologist & Obstetrician	36.62%	0.000	0.13
Orthopaedic Surgeon	34.53%	0.000	0.15
Physician	34.03%	0.000	0.16
Neurosurgeon	32.67%	0.000	0.17
Pulmonologist	32.49%	0.000	0.18
Surgeon	29.62%	0.000	0.20
General Practitioner	29.58%	0.000	0.20
Nephrologist	27.45%	0.000	0.23
Geriatric Medicine	26.19%	0.000	0.24
Oncologist	24.72%	0.000	0.25
Neurologist	21.32%	0.000	0.29
Haematologist	20.07%	0.000	0.30
Medical Oncology	18.84%	0.000	0.31
Gastroenterologist	18.73%	0.000	0.31
Endocrinologist	18.39%	0.000	0.32
Radiation Oncologist	17.96%	0.000	0.32
Plastic Surgeon	15.05%	0.000	0.35
Rheumatologist	11.12%	0.000	0.38
Nuclear Medicine	7.14%	0.000	0.43
Maxillo-Facial & Oral Surgeon	5.42%	0.000	0.45
Ear, Nose & Throat Surgeon	4.47%	0.000	0.45
Family Physician	4.12%	0.000	0.46
Psychiatrist	2.37%	0.000	0.48
Ophthalmologist	1.75%	0.000	0.48
Interventional Radiologist	1.47%	0.000	0.49

4.3 Recommendations

Due to the nature of the study, no conclusion can be made on the effect of SASTH guideline compliance and patient outcomes. Studies comparing guideline compliance to patient readmission rates may assist with this question. Additional to the above, no comment can be made on the reasons for low guideline approved prophylaxis use. Studies that focus on understanding the reasons for clinicians' low uptake on guidelines may prove to be beneficial in terms of understanding this phenomenon and possibly improving uptake. Lastly, quality improvement studies, focusing on appropriate RAM completion, may also prove to enhance patient care in the South African private sector.

4.4 Limitations

Due to reliance on electronically captured administrative data, certainty cannot be attained that the included cohort does not contain patient detail where contraindications to anticoagulants existed. An under-representation of prophylaxis used may have occurred due to the possible inclusion of patients not suitable for prophylaxis. Another limitation may have been that capturing errors could have been included in the analysed data, resulting in skewed data reporting.

4.5 Strengths

The use of a large nationwide dataset with linked pharmacy data enhances estimations on the usage patterns of thromboprophylaxis with a relatively high level of accuracy. It is worth mentioning that the data used in this retrospective study is similar to that used by medical aids to determine doctor risk profiling. Secondly, because of the large sample size, the ability to assess prescribing patterns across South Africa may have been enhanced.

4.6 Summary

This chapter highlighted the aim of the study and has drawn conclusions from literature and empirical objectives. Study limitations and strengths were addressed, and recommendations followed to complete this chapter.

4.7 Reflection of the study

This study was done in retrospect to investigate the prevalence of patients deemed to require thrombosis prevention, as well as the prescriber uptake of local published guidelines. The true prevalence of at-risk patients for VTE development for the South African population is not known. This study has found a guideline compliance prevalence that was much lower compared to other local and international studies. This was in conjunction with a higher frequency of patients deemed

at risk of thrombosis. These findings should alert prescribers to vigorously assess patients for VTE risk and ensure adequate prophylaxis.

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ANNEXURE A: CONFIDENTIALITY UNDERTAKING

CONFIDENTIALITY UNDERTAKING

entered into between:

I, the undersigned

~~Prof / Dr / Mr~~ / Ms Melissa van der Merwe

Identity Number: 8008 03 0007 087

Address: 33 Casa Toscana

hereby undertake in favor of [redacted]
Ltd., a private health institution [redacted]

Address: [redacted] Street corner [redacted]
[redacted]
South Africa

[redacted]

1 Interpretation and definitions

1.1 In this undertaking, unless inconsistent with, or otherwise indicated by the context:

1.1.1 "Confidential Information" shall include all information that is confidential in its nature or marked as confidential and shall include any existing and new information obtained by me after the Commencement Date, including but not be limited in its interpretation to, research data, information concerning research participants, all secret knowledge, technical information and specifications, manufacturing techniques, designs, diagrams, instruction manuals, blueprints, electronic artwork, samples, devices, demonstrations, formulae, know-how, intellectual property, information concerning materials, marketing and business information generally, financial information that may include remuneration detail, pay slips, information relating to human capital and employment contract, employment conditions, ledgers, income and expenditures and other materials of whatever description in which [redacted] has an interest in being kept confidential; and

1.1.2 "Commencement Date" means the date of signature of this undertaking by myself.

1.2 The headings of clauses are intended for convenience only and shall not affect the interpretation of this undertaking.

1

2 Preamble

2.1 In performing research duties, I will have access to certain Confidential Information provided by the [redacted] group in order to perform the said duties and I agree that it must be kept confidential.

2.2 [redacted] has agreed to disclose certain of this Confidential Information and other information to me subject to me agreeing to the terms of confidentiality set out herein.

3 Title to the Confidential Information

I hereby acknowledge that all right, title and interest in and to the Confidential Information vests with [redacted] and that I will have no claim of any nature in and to the Confidential Information.

4 Period of confidentiality

The provisions of this undertaking shall begin on the Commencement Date and remain in force indefinitely.

5 Non-disclosure and undertakings

I undertake:

5.1 to maintain the confidentiality of any Confidential Information to which I shall be allowed access by [redacted] whether before or after the Commencement Date of this undertaking. I will not divulge or permit to be divulged to any person any aspect of such Confidential Information otherwise than may be allowed in terms of this undertaking;

5.2 to take all such steps as may be necessary to prevent the Confidential Information falling into the hands of an unauthorised third party;

5.3 not to make use of any of the Confidential Information in the development, manufacture, marketing and/or sale of any goods;

5.4 not to use any research data for publication purposes;

5.5 not to use or disclose or attempt to use or disclose the Confidential Information for any purpose other than performing research purposes only and includes questionnaires, interviews with participants, data gathering, data analysis and personal information of participants/research subjects;

5.6 not to use or attempt to use the Confidential Information in any manner which will cause or be likely to cause injury or loss to a research participant [redacted] or the NWU; and

5.7 that all documentation furnished to me by [redacted] pursuant to this undertaking will remain the property of [redacted] and upon the reque[redacted] will be returned t[redacted] I shall not make copies [redacted] such documentation withou[redacted] r written consent o[redacted]

6 Exception

The above undertakings by myself shall not apply to Confidential Information which I am compelled to disclose in terms of a court order.

7 Jurisdiction

This undertaking shall be governed by South African law be subject to the jurisdiction of South African courts in respect of any dispute flowing from this undertaking.

8 Whole agreement

8.1 This document constitutes the whole of this undertaking to the exclusion of all else.

8.2 No amendment, alteration, addition, variation or consensual cancellation of this undertaking will be valid unless in writing and signed by me and a [redacted] representative.

Dated at ~~Polokwane~~ this 31 January 2017.

Witnesses:

1 .....

2 .....

(*Signatures of witnesses*)

.....

(*Signature*)

ANNEXURE B: GOOD WILL PERMISSION

Melissa Van Der Merwe

From: [redacted]
Sent: Monday, September 18, 2017 9:27 AM
To: Melissa Van Der Merwe
Cc: [redacted]
Subject: RE: Request to use depersonalised data for M.Pharm study purposes - Approval

Dear Melissa

We have discussed your protocol and are happy for you to continue with this study. Kindly ensure that you have received ethics approval from the University, and that patient & doctor confidentiality is maintained at all times.

As discussed, [redacted] to ensure that the study's findings is still "valid" for future research.

We appreciate you sharing your findings with us, especially as this is an important focus area for [redacted]

We are happy to assist further, if required, and wish you all the very best with your research studies.

Kind Regards
[redacted]

From: Melissa Van Der Merwe
Sent: 18 July 2017 04:59 PM
To: [redacted]
Subject: FW: Request to use depersonalised data for M.Pharm study purposes
Importance: High

Dear [redacted]

I am aiming to conduct a study on the prescribing patterns of venous thromboembolic (VTE) prophylaxis for privately admitted patients during a specified timeframe. The study forms part of the partial fulfillment for requirements of completion of a Masters in Pharmacy (Advanced Clinical Practice) through the North West University. I have attached the approval letter from [redacted] awarding me a bursary to complete the degree.

Due to [redacted] large footprint throughout South Africa and with prescribers practicing not only in its facilities but also other private competitor institutions an overall picture of prescribing patterns in private institutions throughout South Africa will be formed. It also is in the interest of a developing resource constraint country such as South Africa, to establish the prescribing patterns of VTE prophylaxis in a part of the health sector not governed by protocols or formularies and where cost containment, which includes preventable risk management, is desirable (Donnelly, 2016). I am therefor requesting goodwill permission to use depersonalised data on VTE prophylaxis charged between 1 September 2015 to 31 August 2016.

Background and problem statement

Venous thromboembolic-related complications due to poor prophylactic practices result in 64.4% of annual premature deaths in both Europe and the United States of America (Jha *et al.*, 2013:809). In South Africa, the risk of VTE development in hospitalised patients admitted in parts of its Gauteng province has been described to be as high as 74.6% (Wessels & Riback, 2012:85). According to Statistics South Africa (2011), thromboembolic disease is responsible for 20 000 deaths annually. Since most VTE symptoms remain undetected (Luciani *et al.*, 2001:655; Kooiman *et al.*, 2015), the true incidence of the disease in South Africa is unknown. The prevalence of privately hospitalised patients requiring VTE prophylaxis as set out by the 2013 South African society of thrombosis and haemostasis (SASH) guidelines, is unknown. It is also not known if prescribers follow these guidelines.

1

Research aim and objective

The general aim of the proposed study will be to evaluate the patterns of VTE prophylaxis used in patients admitted in a South African private hospital setting between 1 September 2015 and 31 August 2016 according to SASH guidelines.

Methodology

A quantitative, retrospective, analysis of inpatient data will be performed during the proposed study.

Anonymity and confidentiality

During the study and upon possible writing of the dissertation, NO mention will be made of;

1. The Hospital Group [redacted]
2. The prescribing doctor
3. The patient on whose account said medication was charged
4. The admitting facility
5. Any other information that might allow for tracing identification of any party which may have been involved during the specified time period.

Steps to safeguard privacy will include the application of [redacted] policies applicable to the Protection of Personal Information Act (4 of 2013) and all parties such as study co-ordinators, statisticians as well as the researcher having access to the study data will sign a confidentiality agreement from [redacted] to ensure anonymity is adhered to. The research will be conducted according to ethical regulations stipulated by the Health Research Ethics Committee (HREC) of the Faculty of Health Science of the North-West University as well as the [redacted] in Research committee. Only once approval is received from the Netcare Ethics in Research committee will the study commence. To ensure inclusivity, the researcher (myself) will forward the completed dissertation to yourselves and whomever is deemed necessary before any submission to the North West University will be made. This will be done to allow for amendments / deletions such as [redacted] feels appropriate prior to submission.

Thank you for taking time to consider my request. Please forward any questions, problems or concerns with regards to the proposed study to myself or the study supervisor, Dr. Jesslee du Plessis at 018 299 2204 or alternatively email jesslee.duplessis@nwu.co.za

Your response is appreciated.

Kind regards

Melissa van der Merwe

ANNEXURE C: STUDY HOSPITAL GROUP RESEARCH COMMITTEE APPROVAL

RESEARCH OPERATIONS COMMITTEE FINAL APPROVAL OF RESEARCH

Approval number: UNIV-2017-0046

E mail: Melissa.VanDerMerwe[redacted]

RE: ASSESSMENT OF VENOUS THROMBOEBOLISM PROPHYLAXIS IN A SOUTH AFRICAN PRIVATE HOSPITAL GROUP

Dear Ms Van Der Merwe

The above-mentioned research was reviewed by the Research Operations Committee's delegated members and it is with pleasure that we inform you that your application to conduct this research at the Pharmacies within the private Hospital Division has been approved, subject to the following:

i) Research may now commence with this FINAL APPROVAL from the Research Operations Committee.

ii) All information regarding The Company will be treated as legally privileged and confidential.

iii) The Company's name will not be mentioned without written consent from the Research Operations Committee.

iv) All legal requirements regarding patient / participant's rights and confidentiality will be complied with.

v) All data extracted may only be used in an anonymised, aggregated format and for the purposes of this specific study as specified in the proposal. The data may under no circumstances be used for any other purpose whatsoever.

vi) The research will be conducted in compliance with the GUIDELINES FOR GOOD CLINICAL PRACTICE IN HUMAN PARTICIPANTS IN SOUTH AFRICA (2016).

vii) The Company must be furnished with a STATUS REPORT on the progress of the study at least annually on 30th September irrespective of the date of approval from the Research Operations Committee as well as a FINAL REPORT with reference to intention to publish and probable journals for publication, on completion of the study.

viii) The Company has the right to implement any recommendations from the research.

ix) The Company reserves the right to withdraw the approval for research at any time during the process, should the research prove to be detrimental to the subjects/ Company or should the researcher not comply with the conditions of approval.

x) APPROVAL IS VALID FOR A PERIOD OF 36 MONTHS FROM DATE OF THIS LETTER OR COMPLETION OR DISCONTINUATION OF THE TRIAL, WHICHEVER IS THE FIRST.

We wish you success in your research.

Yours faithfully

22/10/17

Prof Dion du Plessis
Full member: Research Operations Committee & Medical Practitioner evaluating research applications as per Management and Governance Policy

[redacted]
Chairperson: Research Operations Committee
Date: 11/12/2017

This letter has been anonymised to ensure confidentiality in the research report. The original letter is available with author of research

ANNEXURE D: HEALTH RESEARCH ETHICAL COMMITTEE APPROVAL, NWU

Private Bag X6001, Potchefstroom
South Africa 2520

Tel: 018 299-1111/2222
Web: http://www.nwu.ac.za

Health Sciences Ethics Office for Research, Training and Support

Health Research Ethics Committee (HREC)
Tel: 018-285 2291
Email: Wayne.Towers@nwu.ac.za

Dr JM du Plessis
Clinical Pharmacy
MUSA

10 October 2018

Dear Prof du Plessis

APPROVAL OF YOUR AMENDMENT REQUEST BY THE HEALTH RESEARCH ETHICS COMMITTEE (HREC) OF THE FACULTY OF HEALTH SCIENCES

Ethics number: NWU-00080-17-A1

Kindly use the ethics reference number provided above in all future correspondence or documents submitted to the administrative assistant of the Health Research Ethics Committee (HREC) secretariat.

Study title: Assessment of venous thromboembolism prophylaxis in a South African private hospital group

Study leader/Researcher: Dr JM du Plessis

Student: M van der Merwe-11952628

You are kindly informed that your amendment request (Change in time period of files to be investigated) to the aforementioned project has been approved. Any future amendments to the proposal or other associated documentation must be submitted to the HREC, Faculty of Health Sciences, North-West University, prior to implementing these changes. These requests should be electronically submitted to Ethics-HRECApply@nwu.ac.za, for review BEFORE approval can be provided, with a cover letter with a specific subject title indicating, "Amendment request: NWU-XXXXX-XX-XX". The letter should include the title of the approved study, the names of the researchers involved, the nature of the amendment/s being made (indicating what changes have been made as well as where they have been made), which documents have been attached and any further explanation to clarify the amendment request being submitted. The amendments made should be indicated in yellow highlight in the amended documents. The *e-mail*, to which you attach the documents that you send, should have a *specific subject line* indicating that it is an amendment request e.g. "Amendment request: NWU-XXXXX-XX-XX". This e-mail should indicate the nature of the amendment. This submission will be handled via the expedited process.

We wish you the best as you conduct your research. If you have any questions or need further assistance, please contact the Faculty of Health Sciences Ethics Office for Research, Training and Support at Ethics-HRECApply@nwu.ac.za.

Yours sincerely

Prof Wayne Towers
HREC Chairperson

Prof Minrie Greeff
Ethics Office Head

Current details: (23239522) G:\My Drive\9. Research and Postgraduate Education\9.1.5.3 Letters Templates\9.1.5.4.1_Approval_letter_Amend_Req_HREC.docm
30 April 2018

File reference: 9.1.5.4.1

ANNEXURE E: LANGUAGE EDITING

To whom it may concern

Cecile van Zyl
Language editing and translation
Cell: 072 389 3450
Email: Cecile.vanZyl@nwu.ac.za

7 November 2019

Dear Mr / Ms

Re: Language editing of dissertation (Assessment of venous thromboembolism prophylaxis in a South African private hospital group)

I hereby declare that I language edited the above-mentioned dissertation by Ms Melissa van der Merwe (student number: 11952628).

Please feel free to contact me should you have any enquiries.

Kind regards

Cecile van Zyl

Language practitioner

BA (PU for CHE); BA honours (NWU); MA (NWU)
SATI number: 1002391

ANNEXURE F: TECHNICAL EDITING

Excellentia Edit & Transcribe

Physical address:
72 Eland Street
Miederpark
Potchefstroom
2531
Contact:
Email: excellentia.edit.transcribe@gmail.com
Phone: 0834755363

4 November 2019

TO WHOM IT MAY CONCERN

I hereby declare that the dissertation titled:

Assessment of venous thromboembolism phophylaxis in a South African private hospital group

by

Ms M van der Merwe

11952628

has been technically edited by myself, which includes all tables and figures as well as the layout of the document's contents.

E Oosthuizen

November 2019