The Use of venous thromboembolism prophylaxis in relatioN to patiEnt risk profiling Wave 3 study (TUNE IN Wave 3 study)

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine

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Dedication

I dedicate this research to my wife, Jeshika Bassett, for her endless support. I also acknowledge the many sacrifices we made in collecting and interpreting the data.

Presentations and publications arising from the research project

The Findings of the wave 3 were presented at the 21st annual Southern African Society of thrombosis and Haemostasis (SASTH) on the 3rd of November 2024. The Poster presentation won the best poster for the most promising junior researcher.

Acknowledgements

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I extend my appreciation to Dr. A. Essop for their contributions to data collection, which significantly enriched the study.

Furthermore, I am deeply grateful to all the participants involved in this research. Their willingness to contribute made this study possible, and their participation was fundamental to its success.

Thank you to everyone who played a role in the completion of this research.

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Abbreviations

American College of Chest Physicians	ACCP
Charlotte Maxeke Johannesburg Academic Hospital	CMJAH
Chief executive officer	CEO
Corona-Virus disease of 2019	COVID-19
Deep vein thrombosis	DVT
Direct oral anti-coagulants	DOACs
Glomerular filtration rate	GFR
Head of department	HOD
Human research ethics committee	HREC
Intensive care unit	ICU
International Medical Prevention Registry on Venous Thromboembolism	IMPROVE
International Medical Prevention Registry on Venous Thromboembolism	ENDORSE
Interquartile range	IQR
Low molecular weight heparin	LMWH
Pulmonary embolism	PE
Risk assessment model	RAM
Severe acute respiratory syndrome coronavirus 2	SARS-COV-2
South Africa	SA
Standard deviation	SD
Unfractionated Heparin	UFH
United States of America	USA
Upper limit of normal	ULN
Venous-thromboembolism	VTE

‘Submissable’ article

Title: The Use of venous thromboembolism prophylaxis in relatioN to patiEnt risk profiling Wave 3 study (TUNE IN Wave 3 study)

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Abstract

Background

Thromboprophylaxis significantly reduces the risk of venous thrombo-embolism (VTE) in hospitalised medical and surgical patients, nonetheless, the implementation of thromboprophylaxis in South Africa (SA) and worldwide is low.

Objective

The TUNE-IN (The Use of venous thromboembolism prophylaxis in relatioN to patiEnt risk profiling) Wave 3 study is an extension of TUNE-IN Wave 1 and 2. This prospective, cross-sectional study assessed the use of VTE thromboprophylaxis in hospitalised medical, surgical as well as orthopaedic patients.

Methods

Over a 9-month period 451 consenting patients > 18 years of age hospitalised at Charlotte Maxeke Johannesburg Academic Hospital in Gauteng, SA were included. Patients were assessed and risk stratified according to the IMPROVE (International Medical Prevention Registry on Venous Thromboembolism) bleeding risk and Caprini risk assessment tools. Data on the use of VTE thromboprophylaxis, agent and dose were collected from the hospital records.

Results

The study identified 180 (40%) medical, 198 (44%) surgical and 73 (16%) orthopaedic participants. VTE thromboprophylaxis was administered in 263 (58%) study participants. In accordance with the American College of Chest Physicians guidelines on VTE prevention,

adequate thromboprophylaxis was administered in 233 (52%). The most common thromboprophylaxis agent was low molecular weight heparin. Subsequently, the Caprini risk assessment tool identified 337 participants (75%) with a VTE risk score > 2, whereas the IMPROVE risk assessment tool identified 22 participants (5%) with a high bleeding risk score (≥7). According to the risk assessment tools, recommended thromboprophylaxis was administered in 68% of medical 59% of surgical and 79% of orthopaedic high risk participants ($p<0.012$). The proportion of medical and surgical participants at high VTE risk were similar in this study in comparison to the Wave 1 and/or 2 studies, however, the rates of VTE thromboprophylaxis in the current study were lower ($p=0.097$ for medical and $p< 0.001$ for surgical participants).

Conclusion

This study shows a significant gap between evidenced based thromboprophylaxis recommendations and clinical practice in a large sample of hospitalised medical, surgical and orthopaedic participants. It is recommended that an institutional VTE risk assessment tool be implemented to standardise risk evaluation and improve the administration of appropriate thromboprophylaxis for hospitalised patients.

Introduction

Venous thromboembolism (VTE) is an important cause of morbidity and mortality in hospitalised, medical and surgical patient populations [1]. In Africa, the incidence of deep vein thrombosis (DVT) has been reported to range from 2 % to 10% in surgical patients. In medical patients, the incidence of pulmonary embolism (PE), has been reported to range from 18% to 62% with mortality rates of 40% to 70% [1] Thromboprophylaxis significantly reduces the risk of VTE in hospitalised medical and surgical patients and is recommended by clinical practice guidelines[2-6]. The updated American College of Chest Physicians (ACCP) guideline for the prevention of VTE identifies medical and surgical patients at risk of VTE and provides recommendations for the type (mechanical and/or pharmacological), dose and duration of thromboprophylaxis [6,7]. It is also recommended to use risk stratification tools for VTE risk assessment in this setting. Several models including the Caprini, IMPROVE (International Medical Prevention Registry on Venous Thromboembolism), Kucher, Geneva, 4 elements and Padua model have been validated[6,7]. In particular, the Caprini score which is based on the ACCP guideline is a simple and comprehensive risk assessment model for surgical and medical hospitalised patients. The Caprini RAM incorporates a total of 39 risk factors, each assigned a specific scoring point. Moreover, it has been extensively validated in nearly 5 million patients and has garnered over 200 peer-reviewed publications [7] . Although these risk assessment models are associated with inherent limitations, these clinical tools help to stratify hospitalised patients according to thrombotic and bleeding risks. According to the ACCP, a Caprini score of 1–2 warrants mechanical prophylaxis with intermittent pneumatic compression (IPC) devices. A score of 3–4, indicating moderate risk, requires pharmacological prophylaxis with low molecular weight heparin, low-dose unfractionated heparin, or fondaparinux. For scores above 5, the modified Caprini score recommends

pharmacological prophylaxis as outlined above, in combination with mechanical prophylaxis where feasible [6,7].

Despite the presence of updated guidelines and risk assessment models, many hospitalised patients at risk for VTE either do not receive VTE prophylaxis or receive inadequate VTE prophylaxis. The earlier multi-national ENDORSE (Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting) study showed that 50% of hospitalised patients were at risk for VTE, yet only 58% of surgical and 40% of medical patients received recommended VTE prophylaxis according to guidelines [8]. Locally, in South Africa (SA), the thromboprophylaxis rates have been described in the TUNE-IN (The Use of VTE prophylaxis in relatioN to patiEnt risk profiling) Wave 1 and 2 studies, which compared favourably with worldwide trends [8]. Patients were stratified according to a modified Caprini risk score. In the Wave 1 study conducted among private hospitalised patients, adequate VTE prophylaxis was administered in 68% of surgical and 70% of medical patients whereas in the Wave 2 study in both the private and public sectors adequate VTE prophylaxis was only administered in 59% of surgical patients of whom all were at risk. The Wave 2 study however did not include an assessment of medical patients.

The aim of the current Wave 3 study was to assess the utilization of VTE thromboprophylaxis in hospitalised medical, surgical as well as orthopaedic patients within the public sector, risk stratified according to the IMPROVE bleeding risk and Caprini risk assessment tools. Moreover, the study aimed to compare the current utilization of VTE

thromboprophylaxis to the previous Wave 1 and 2 studies to identify changes in clinical practice.

Methods

Study design and population

In this cross-sectional study, consecutive medical surgical and orthopaedic patients hospitalised at CMJAH in Gauteng, SA were recruited over a 9-month period between July 2023 and April 2024. Consenting patients older than 18 years of age were included. CMJAH is a 1,080 bed facility. There are 330 beds for medicine inpatients and sub-specialist units include endocrinology, gastroenterology, rheumatology, neurology, cardiology, infectious diseases, pulmonology, nephrology, oncology and intensive care. There are 360 beds for surgical inpatients and sub-specialist units include acute care surgery, cardiothoracic surgery, vascular surgery, trauma care, hepatobiliary surgery and endocrine surgery. There are an additional 180 beds for orthopaedic inpatients. Written informed consent was obtained from all study participants, and the study protocol was approved by the University of Witwatersrand Human Ethics Research Committee (HREC) (M-230146).

Data collection

Data were collected from the hospital records and patient interviews. The following patient information was collected: demographics, the use of VTE thromboprophylaxis, pharmacological or mechanical agent and dose. Appropriate agents and dosing were determined in accordance with the American College of Chest Physicians (ACCP) guidelines on VTE prevention[4]. Patients were assessed and risk scores calculated with the Caprini risk assessment model and the IMPROVE bleeding risk assessment tool according to clinical signs and symptoms, relevant medical and surgical histories and laboratory investigations during the current admission. According to the Caprini risk assessment model patients were classified as low (0-1), middle (2), high (3-4), or super high risk (≥5) for VTE. Additionally,

according to the IMPROVE bleeding risk assessment tool, patients were classified as low (<7) or high risk (≥7) for bleeding.

Data Analysis

A sample of 385 patients was estimated, assuming a 1.0% incidence of VTE, at a confidence interval (CI) of 95%. Statistical analysis was performed using Statistica Software version 13.2 (Statistica, Tulsa, USA). Normally distributed continuous data was presented as mean ± standard deviation (SD) and variables with non-Gaussian distribution as median [interquartile range (IQR)]. Categorical data was presented as frequencies and percentages. Comparisons between medical, surgical and orthopaedic participants were performed using chi-square test or Fisher's exact test when necessary. Comparisons between the Wave 1, 2 and 3 studies were performed using a one-way ANOVA. Statistical significance was set at a p value of <0.05.

Results

Characteristics

During the study period, 451 adult medical, surgical and orthopaedic participants were included (Figure 1). Table 1 shows the baseline characteristics of the study group. The mean ± SD age of the study group was 47 ± 16. There were a higher proportion of surgical male participants as compared to medical male participants ($p<0.010$). The median [IQR] hospital length of stay, which was recorded in 248 participants, was 7 [12] days.

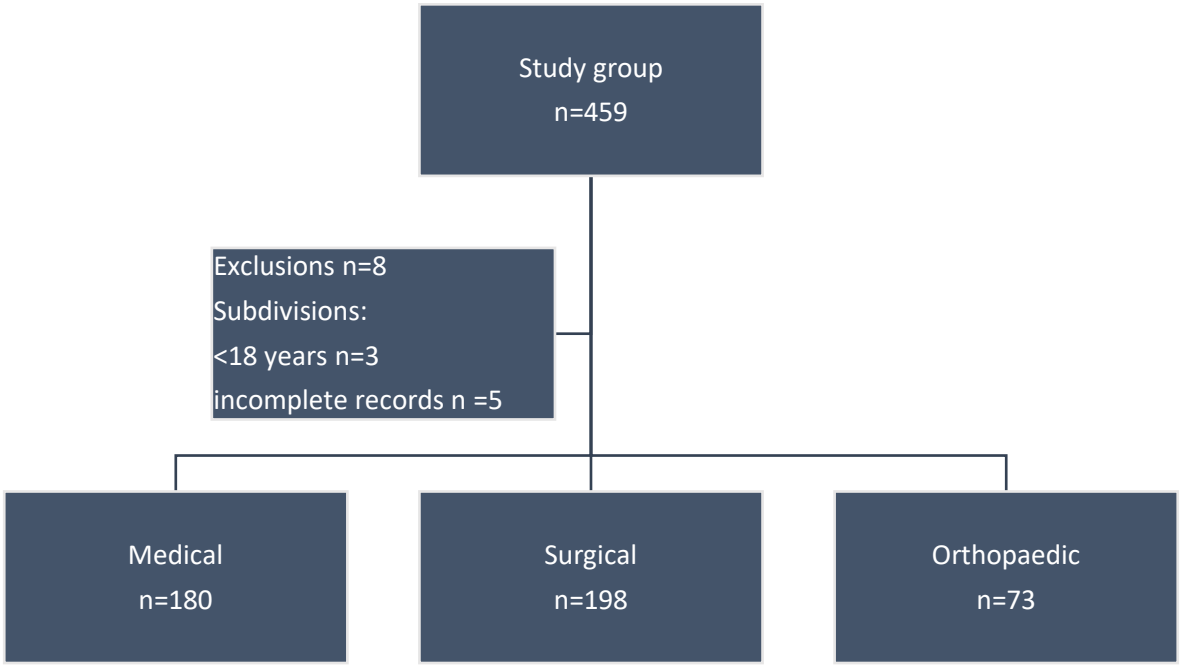

Figure 1: Flow of study participants

Table 1. Baseline characteristics according to hospital unit

Characteristics	Total n=451	Medical n=180 (40%)	Surgical n=198 (44%)	Orthopaedic n=73 (16%)	p value
Demographics					
Age at study entry (years)					0.660
18-40	178 (39.0%)	72 (40.0%)	77 (38.9%)	29 (39.7%)	
41-60	174 (38.6%)	65 (36.1%)	76 (38.4%)	33 (45.2%)	
61-75	81 (18.0%)	37 (20.3%)	35 (17.7%)	9 (12.3%)	
>75	18 (4.0%)	6 (3.3%)	10 (5.1%)	2 (2.7%)	
Sex (n,%)					0.035
Male	251 (55.6%)	88 (48.9%)	123 (62.1%)**	40 (54.8%)	
Female	207 (44.4%)	92 (51.1%)	75 (37.9%)	33 (45.2%)	
VTE thromboprophylaxis (n, %)	263 (58.3%)	105 (58.3%)	102 (51.0%)***	56 (76.7%)**	<0.001
Appropriate VTE thromboprophylaxis dose (n, %)	233 (51.7%)	90 (50.0%)***	90 (45.5%)***	53 (72.6%)	0.002
Key: VTE, venous thrombo-embolism ** p <0.01 versus medical; *** p <0.001 versus orthopaedic					

Scores

According to the Caprini risk assessment model, 337 (75%) participants had a VTE risk score >2 (Table 2.) The proportion of orthopaedic participants (n=71, 97%) with a VTE risk score >2 was higher, as compared to medical (n=120, 67%, p<0.001) and surgical participants (n=146, 74%, p<0.001). Figure 2. shows the frequency of VTE risk factors in the study group. In medical and surgical participants, the most common VTE risk factors were age (41-60 years) and sepsis. In orthopaedic participants the most common VTE risk factors were age (41-60 years) and pelvic/leg fracture within the last month.

Table 2. Caprini risk assessment model for study group, according to risk score

Risk	Total n=451	Medical n=180 (40%)	Surgical n=198 (44%)	Orthopaedic n=73 (16%)
Low (0-1) (n, %)	47 (10.4%)	29 (61.7%)	18 (38.3%)	0 (0.0%)
Middle (2) (n, %)	67 (14.9%)	31 (46.3%)	34 (50.7%)	2 (3.0%)
High (3-4) (n, %)	139 (30.8%)	63 (45.3%)	66 (47.5%)	10 (7.2%)
Super high risk (≥5) (n, %)	198 (43.9%)	57 (28.8%)	80 (40.4%)	61 (30.8%)

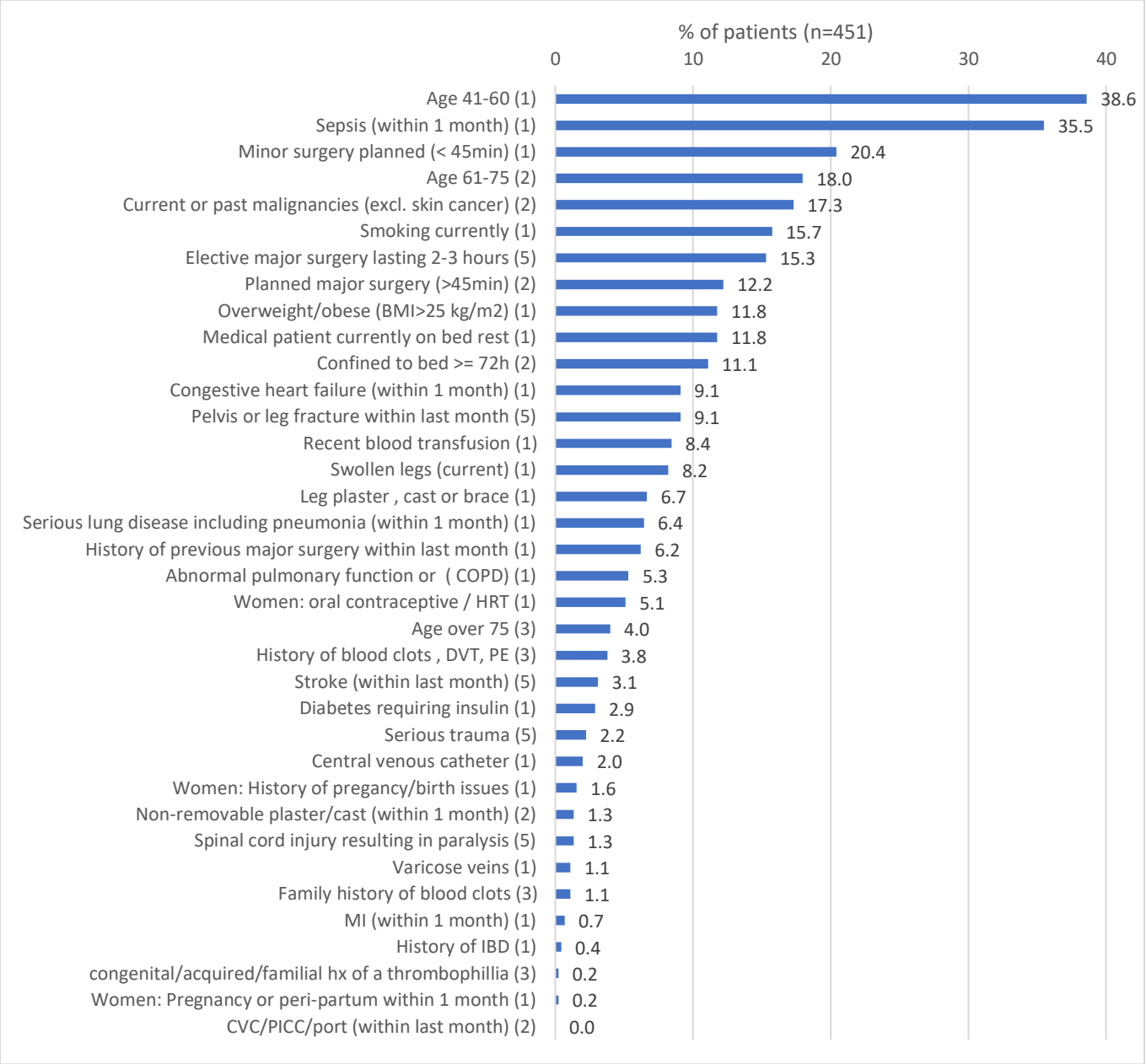

Figure 2. Frequency of VTE risk factors with the score of each associated risk factor bracketed (according to the Caprini risk assessment model) in study group (%).

BMI= body mass index, COPD= chronic obstructive pulmonary disease, HRT, hormone replacement therapy, DVT, deep vein thrombosis, PE, pulmonary embolus, MI, myocardial infarction, IBD= Inflammatory bowel disease, CVC=central venous catheter, PICC=Peripherally inserted central catheter.

Of the study group, 22 (5%) participants had a high bleeding score (≥7) and were considered to have a contraindication to pharmacological prophylaxis. In these participants, dose reduced

low molecular weight heparin (LMWH) was administered. There was no significant difference in high and low bleeding scores between the medical, surgical and orthopaedic participants (Table 3.). The bleeding risk factors in the study group are listed in Figure 3 of which the most frequent risk factors were age 40-84 years and GFR 30-59 ml/min/m^2.

Table 3. IMPROVE bleeding risk assessment for study group

Risk	Total n=451	Medical n=180 (40%)	Surgical n=198 (44%)	Orthopaedic n=73 (16%)
Low (<7) (n, %)	286	119 (41.6%)	131 (45.8%)	36 (12.5%)
High (≥7) (n, %)	22	9 (40,9%)	13 (59.1%)	0 (0.0%)

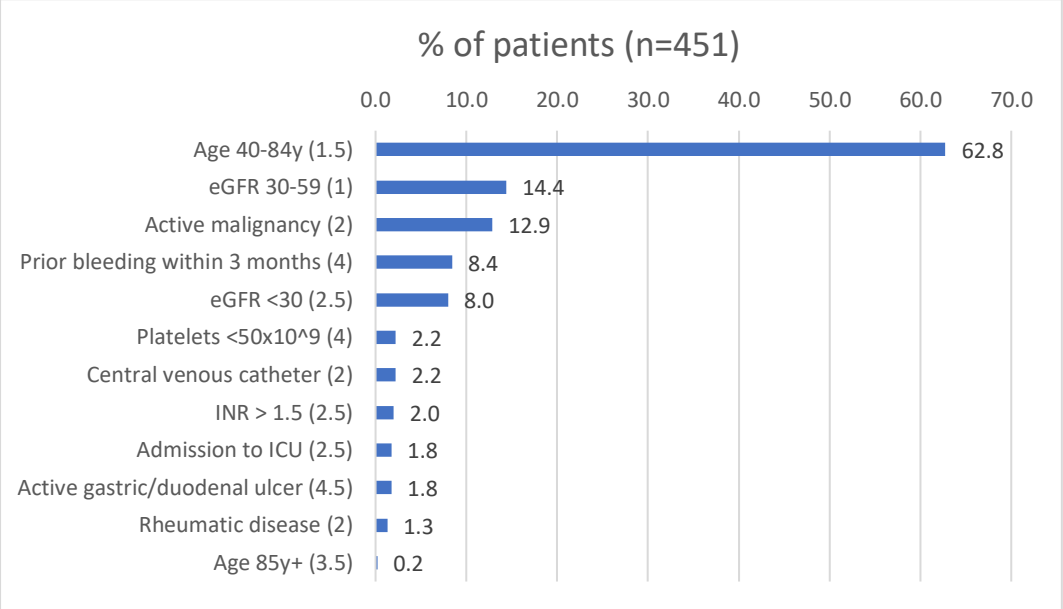

Figure 3. Frequency of Bleeding risk factors(with associated score) in the study group, according to the IMPROVE bleeding risk score (%).

eGFR= estimated glomerular filtration rate. INR= International normalised ratio, ICU= Intensive care unit

Thromboprophylaxis

VTE thromboprophylaxis was administered in 263 (58%) study participants. The most frequently used anticoagulant for VTE prophylaxis was LMWH in medical, surgical and orthopaedics participants (n=261, 99.7%). Only 1 (0.4%) participant received rivaroxaban. Among the orthopaedic participants, 56 (77%) received VTE thromboprophylaxis which was higher as compared to medical and surgical participants ($p<0.006$ and $p<0.001$ respectively). VTE thromboprophylaxis was administered at the appropriate dose in 233 (52%) participants. The administration of dose appropriate thromboprophylaxis was highest among orthopaedic participants (n=53, 73%) as compared to medical (n=90, 50%, $p<0.001$) and surgical participants (n=90, 46%, $p<0.001$). According to the Modified Caprini risk assessment model, 146 (73.7%) participants at high risk in the study group received thromboprophylaxis (Figure 4). Among orthopaedic, medical, and surgical participants at high risk (score >2), the use of recommended thromboprophylaxis was 79% (n=56), 68% (n=82), and 59% (n=86) respectively ($p<0.012$). (Figure 5-7). Thromboprophylaxis was increasingly administered in high-risk orthopaedic participants as compared to surgical participants ($p<0.004$).

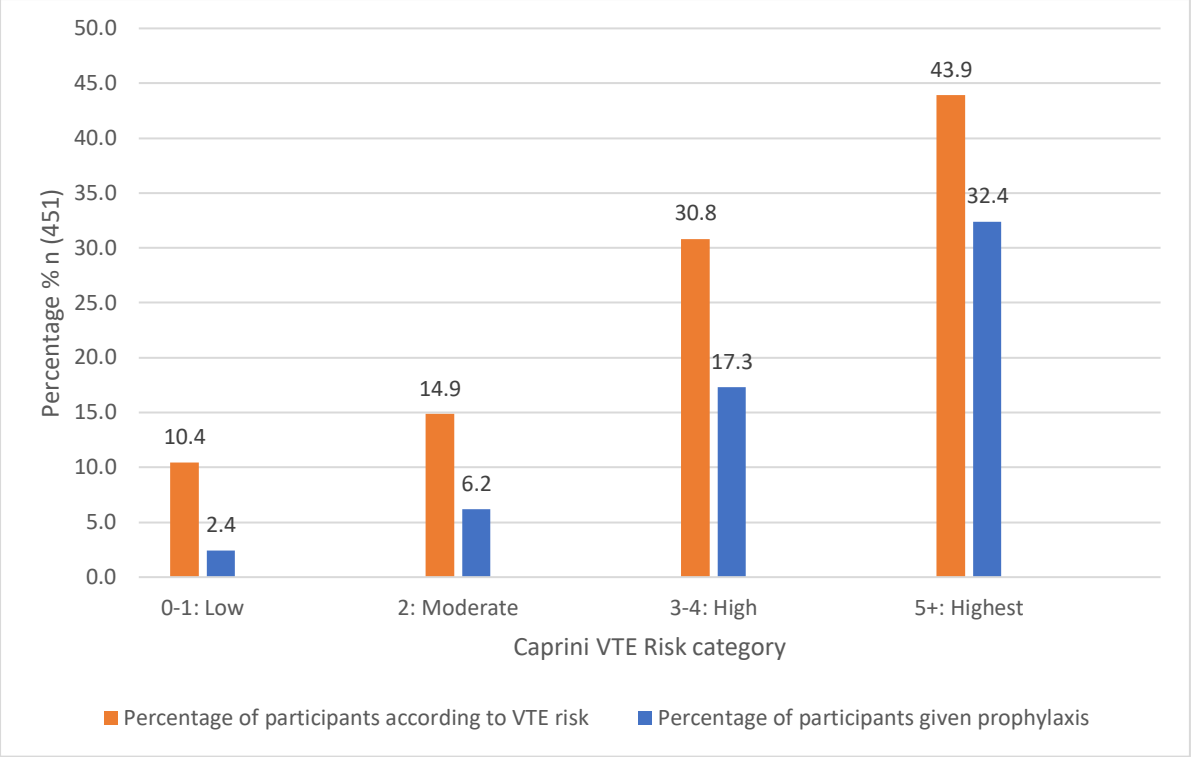

Figure 4. VTE prophylaxis administered in study group according to Caprini risk assessment.

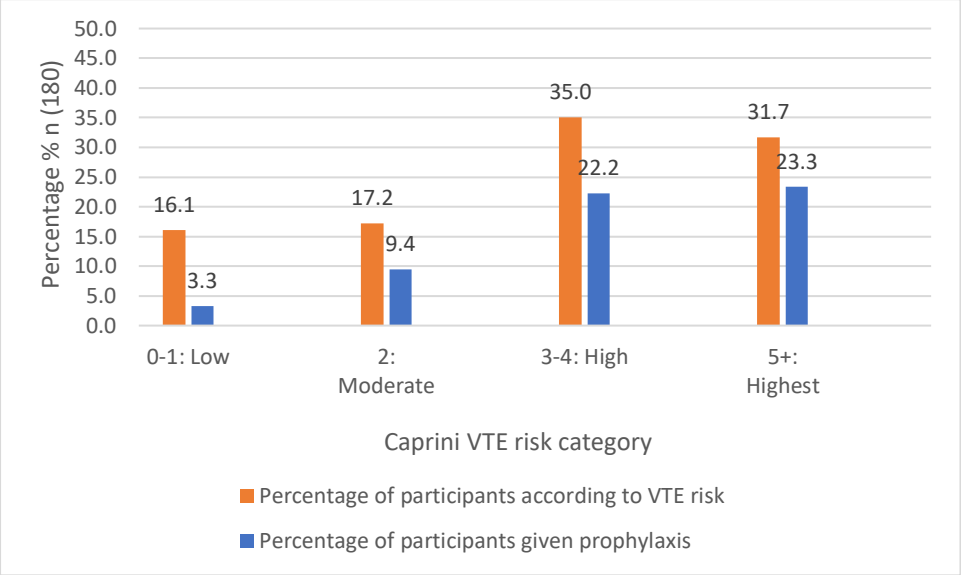

Figure 5. VTE prophylaxis administered in medical participants according to Caprini risk assessment.

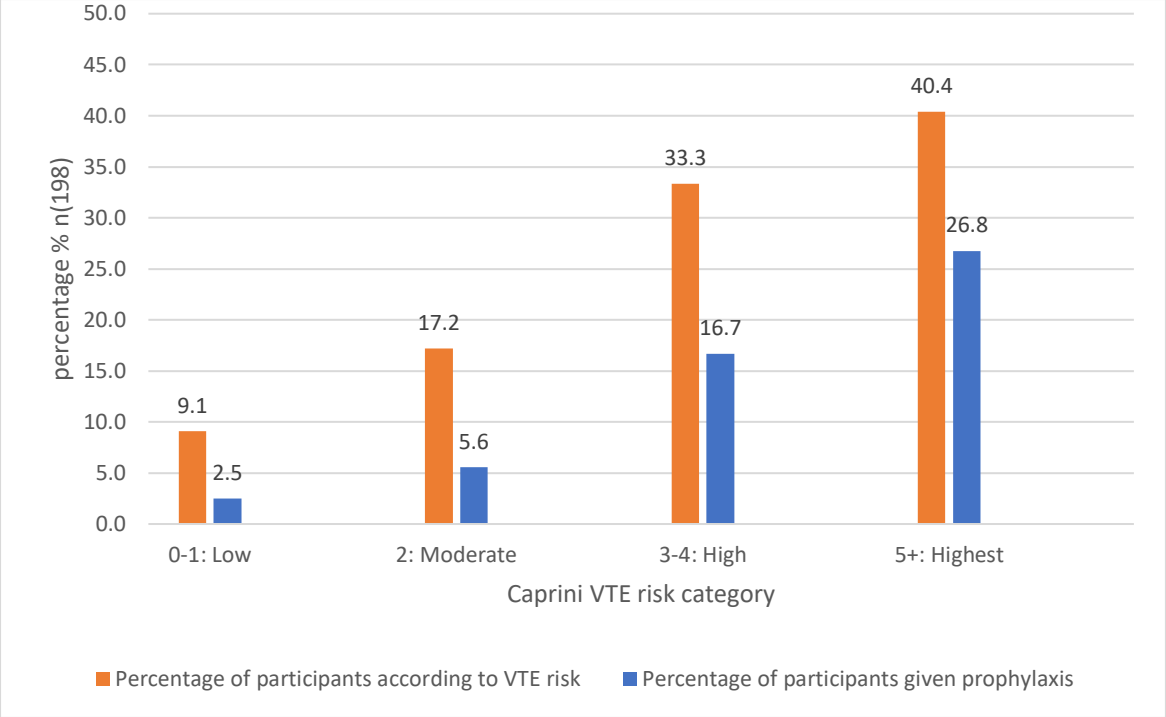

Figure 6. VTE prophylaxis administered in surgical participants according to Caprini risk assessment.

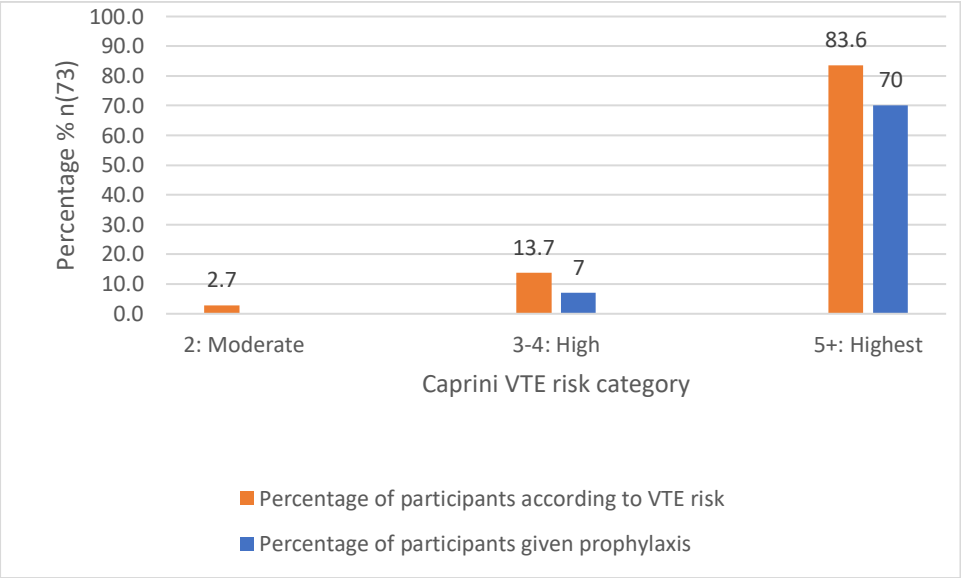

Figure 7. VTE prophylaxis administered in orthopaedic participants according to Caprini risk assessment

Recommended thromboprophylaxis was administered in 85% of participants with stroke or paralysis, 83% of participants with a history of elective major surgery (2-3 hours), 90% of

participants with serious trauma and 90% of participants with pelvis or leg fracture within the last month (Figure 8.).

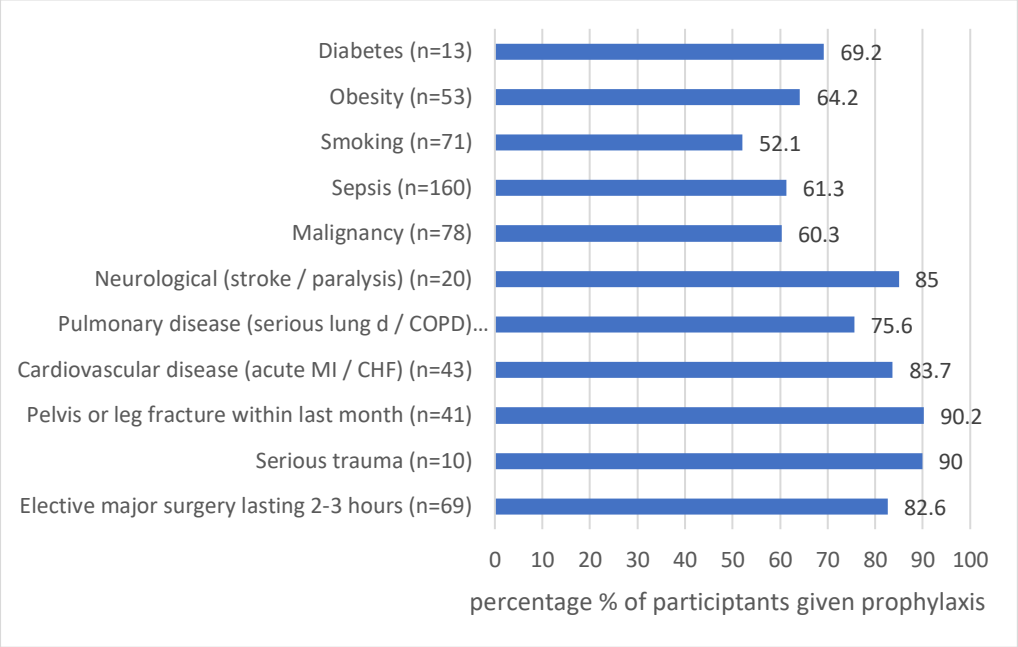

Figure 8. Thromboprophylaxis administered according to condition

Serious lung d=serious lung disease; COPD= Chronic obstructive pulmonary disease; MI= myocardial infarction; CHF= Congestive heart failure

Comparison with Wave 1 and 2 studies

The proportion of medical and surgical participants at high VTE risk were similar in this study in comparison to the Wave 1 and/or 2 studies (Table 4.). The proportion of medical participants receiving VTE prophylaxis was non-significantly lower in this study in comparison to the Wave 1 study. The proportion of surgical participants receiving VTE prophylaxis was lower in this study in comparison to the Wave 2 study ($p<0.001$).

Table 4. Comparison of thromboprophylaxis characteristics between Caprini high risk participants in the Wave 1, 2 and 3 studies (1,2).

	Wave 1 study	Wave 2 study	Wave 3 study	p value
Study participants	608	453	451	
Caprini high risk score (score >2)				
Medical participants (n, %)	154 (70.0%)	-	120 (67.0%)	0.923
Surgical participants (n, %)	328 (84.0%)*	372 (82.0%)	146 (74.0%)	0.086
Orthopaedic participants (n, %)	-	-	71 (97.0%)	-
VTE thromboprophylaxis (score >2)				
Medical participants (n, %)	119 (77.0%)	-	82 (68.0%)	0.097
Surgical participants (n, %)	223 (68.0%)	349 (94.0%)	86 (59.0%)	<0.001
Surgical participants, public sector (n, %)	-	95 (86.0%)**	86 (59.0%)	<0.001
Orthopaedic participants (n, %)	-	-	56 (79.0%)	-

*includes orthopaedic participants

** of 110 participants

Discussion

In this large, prospective study of the public sector, we observed low rates of VTE thromboprophylaxis (58%). Additionally, rates of recommended VTE thromboprophylaxis in accordance with the ACCP guidelines [9,10] were also low (52%). These findings are consistent with the earlier ENDORSE international study. The rates of recommended thromboprophylaxis in the present study were significantly higher for orthopaedic participants (73%), followed by medical (50%) and surgical participants (46%)[9-10]. Major orthopaedic surgeries including lower-limb fracture repair, total hip and knee arthroplasty are well recognised risk factors for VTE. It is noteworthy that, despite ongoing debates regarding the choice of preventive agents, LMWH was the most commonly used option in this setting [14]. In conjunction with reports in the literature, this study shows an ongoing, concern regarding the use of evidenced based thromboprophylaxis for hospitalised patients.
The Caprini risk assessment tool was applied to the study population. This revealed that a high proportion (75%) of the study population had a VTE risk score > 2.

Thromboprophylaxis rates, as recommended by the Caprini risk assessment tool [9], were significantly higher among orthopaedic participants (79%), followed by medical (68%) and surgical participants (59%). Specifically, in medical participants, recommended thromboprophylaxis was administered in >75 % with neurological conditions, including stroke or paralysis; pulmonary disease including, serious lung disease and chronic obstructive pulmonary disease; cardiovascular disease, including acute myocardial infarction and congestive heart failure. Among surgical participants, recommended thromboprophylaxis was administered in >80 % for elective major surgery (2-3 hours) and serious trauma. Among orthopaedic participants, recommended thromboprophylaxis was administered in >90 % for pelvis or leg fracture within the last month and serious trauma. A small proportion of

participants (5%) had a high bleeding risk score (≥7) based on the IMPROVE risk assessment tool, which suggests that bleeding risk was not the primary factor behind the low rates of thromboprophylaxis. This study observed lower rates of thromboprophylaxis among participants with the following risk factors: malignancy, obesity, smoking, sepsis, and diabetes requiring insulin. Nonetheless, these represent small numbers, which limit the statistical power for subgroup analysis. Further studies are warranted to validate these findings.

The findings of the Wave 3 study are consistent with the earlier Wave 1 and 2 studies [12,13]. Firstly, a similar proportion of medical and surgical participants at high VTE risk were observed as compared to the Wave 1 and 2 studies. In the wave 3 study medical participants at high risk accounted for 67.0%, surgical participants at high risk accounted for 74.0% and as expected orthopaedic participants at high risk accounted for 97.0%. The high proportion of at risk participants highlights the importance of conducting such a study. Secondly, we observed no significant difference in the proportion of medical participants at high risk who received VTE prophylaxis in comparison to the Wave 1 study. In the Wave 3 study, only 68% of high-risk medical participants received VTE prophylaxis, with a notable disparity observed in certain high-risk categories e.g. malignancy that were less likely to receive appropriate prophylactic measures. Of further concern, the proportion of surgical participants at high risk receiving VTE prophylaxis was significantly lower in this study in comparison to the Wave 2 study, in both the private and public sector. These findings suggest that VTE risk may be underestimated by surgeons in clinical practice in certain types of surgeries. Moreover, there may be hesitancy to administer prophylaxis post-operatively as a result of concerns about bleeding complications. Cases with multiple comorbidities add further complexity, as factors such as renal impairment, liver dysfunction, and abnormal platelet

counts can significantly influence bleeding risk. This highlights the importance of implementing standardised risk assessment tools such as the Caprini and IMPROVE models.

The observed decline in VTE prophylaxis rates may be attributed to limited awareness regarding the necessity of thromboprophylaxis, as further reflected in the inappropriate dosing practices noted. This underscores the need for continuous education on validated VTE risk assessment models, with particular attention to the appropriate initiation of prophylaxis and dose adjustments based on renal function, body mass index, and bleeding risk. A limitation of this study is the lack of clarity on whether surgical participants were evaluated in the preoperative phase where omission of prophylaxis may have been intentional or in the immediate postoperative period. These distinctions could have influenced the overall findings. Collectively, the results reinforce the critical importance of strict adherence to updated clinical guidelines.

There are several limitations to this study. Firstly, this was a cross-sectional study as such, the length of stay was only recorded in 45% of participants. While length of hospital stay is not included in the Caprini risk assessment model, future studies are warranted to correlate length of stay and the duration of in-hospital thromboprophylaxis. Furthermore, pre-operative surgical and orthopaedic participants were not routinely prescribed VTE prophylaxis, which may have underestimated the rates of thromboprophylaxis in the study group. Secondly, it was not possible to perform a bleeding risk assessment according to the IMPROVE bleeding risk score in 143 (32.0%) participants who did not have an INR test performed. In hospitalised patients at low risk of bleeding, routine INR testing as an assessment of liver function may negatively contribute to healthcare costs. Thirdly, medical participants from

ICU were underrepresented (n=8, 2.0%), despite the hospital ICU capacity of 55 beds. Critically ill ICU participants were unable to give informed consent to participate in the study. Orthopaedic participants were also underrepresented, owing to fewer hospital admissions during the study period. At CMJAH there are 330 medical and 360 surgical beds as compared to 180 orthopaedic beds. Lastly, data on HIV status were not collected for this study population, despite a high burden of infection. However, more recent updates to the Caprini RAM have included HIV as a risk factor[11]. This inclusion reflects increasing evidence that chronic inflammation, immune dysregulation, and endothelial activation associated with HIV infection predispose to thrombosis.

In conclusion, this study confirms the significant gap between evidenced based thromboprophylaxis recommendations and clinical practice in a large sample of hospitalised medical, surgical and orthopaedic participants. In this study a considerable proportion of participants were at high risk of VTE. Nonetheless, recommended VTE thromboprophylaxis was prescribed in approximately half of the participants at high risk of VTE. It is recommended that an institutional VTE risk assessment tool be implemented to standardise risk evaluation and improve the administration of adequate thromboprophylaxis for hospitalised patients.

Conflict of Interest

The author(s) declare that there is no conflict of interest regarding the publication of this paper.

Author Contributions

Dr. Bassett was responsible for study design, data collection and analysis and writing the manuscript. Prof. Schapkaitz contributed to study design, data analysis, and editing the final manuscript Prof. Jacobson conceptualized the study and contributed to study design, and editing of the final manuscript. Dr. A. Essop contributed to data collection.

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Appendices

Appendix A: Research Protocol

Literature Review

Epidemiology of Venous thromboembolism

Venous thromboembolism (VTE) is a pathological condition encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT primarily manifests in the lower extremities but can also occur in splanchnic, cerebral, and upper limb veins (1). While women face a higher risk of VTE during their reproductive years (20-40 years), the overall lifetime risk does not differ significantly between men and women [12]. The prevalence of VTE is significantly increased in high-income countries, being four times more frequent compared to lower income countries [12,13]. Possible reasons include improved healthcare access leading to enhanced recognition of VTE, a higher incidence of major surgical procedures associated with increased VTE risk, and the availability of advanced diagnostic tools for accurate diagnosis[12,14]

The development of VTE is influenced by a multitude of risk factors, and the likelihood of its occurrence increases in the presence of multiple risk factors. Virchow's triad, comprising stasis, hypercoagulability, and endothelial dysfunction, forms the basis of VTE risk assessment[131]VTE risk factors can be acquired or inherited. Major acquired risk factors for VTE include surgery, particularly orthopaedic pelvic surgery, which can result in VTE rates as high as 40-60% without thromboprophylaxis [13]. Traumatic hip fracture carries a 50% risk of VTE without prophylaxis[13]. Major general surgery poses a 10-40% risk of VTE without prophylaxis. Malignancy, multiple trauma, and spinal cord injury also confer a high risk of VTE. Medical conditions generally have a lower VTE risk compared to major trauma, malignancy, and surgery. However, certain medical conditions, such as stroke, heart failure, respiratory failure, or any condition requiring prolonged hospitalization or intensive care unit (ICU) care, are also associated with a higher risk of VTE [13].According to a systematic review of 21 studies performed in Africa, the prevalence of DVT in surgical patients ranged from 2.4% to 9.6% [14]. A single study reported a high prevalence of DVT (61.5%) in tuberculosis patients, but this finding needs further confirmation [14]. Regarding PE, the prevalence in medical patients ranged from 0.14% to 61.5%, with mortality rates of 40.0% to 69.5% [14]. These studies on VTE, nonetheless, have limitations, such as small sample sizes, poor data quality, and predominantly retrospective study designs [14].

Clinical presentation and diagnosis of venous thromboembolism

The clinical presentation of DVT includes leg swelling, pain and erythema[15,16]. Leg swelling or oedema is observed in 97% of cases, while pain is reported between 19-86% of the time, and erythema in 48-72%. Physical examination findings may include signs of underlying disease processes such as malignancy[16].

A crucial step in the diagnostic process is assessing the pre-test probability of VTE by evaluating risk factors. The probability of DVT can be categorized into low, moderate, and high probability groups. This categorization is determined using the modified Wells score (Appendix (4)[16,17]. In patients with a low probability of DVT, a D-dimer screening test is recommended. If the D-dimer value falls within the normal range, further testing is not indicated. However, if the D-dimer is positive, further testing such as compression ultrasonography are indicated [16,17] In patients with a moderate pre-test probability, the algorithm recommends taking into consideration individual patient factors when deciding on further investigations. In [5,6]patients with a high pre-test probability compression ultrasonography is directly indicated[17].

PE exhibits a wide range of clinical presentations, ranging from chest pain to cough, and even sudden death[18]. The most prevalent symptoms include pleuritic chest pain (66%), dyspnea at rest or with exertion (73%), cough (37%), calf or thigh pain and/or swelling (44%), wheezing (21%), and haemoptysis (13%)[18]. Common clinical examination findings comprise tachypnea (54%), tachycardia (24%), rales (18%), decreased breath sounds (17%), an accentuated pulmonic component of the second heart sound (15%), jugular venous distension (14%), and fever mimicking pneumonia (3%)[18].

[8]To guide diagnostic decisions, the likelihood of PE is combined with established pre-test probability scores, such as the modified Wells score or the revised/simplified Geneva score[19]. When there's a low clinical suspicion of PE, the PE Rule-out Criteria (PERC)[20]. If the PERC are positive further testing is based on a D-dimer test and pre-test probability scores.[9] Confirmatory tests for the diagnosis of PE include Computed tomography(CT) Pulmonary Angiography or Magnetic Resonance Pulmonary Angiography. A filling defect in any of the branches of the pulmonary artery is indicative of PE[21]. This defect becomes evident after

contrast enhancement and is considered diagnostic[22]. A low radiation option is a Ventilation Perfusion (V/Q) Scan. A segmental or subsegmental perfusion defect with normal ventilation is diagnostic of a PE[23]. The images obtained can be interpreted as having high, intermediate, low probability, or as being normal. If the scan is normal or of low probability, and there's a low pre-test probability, then this is sufficient to exclude a PE[23]. A high probability V/Q scan, coupled with a high clinical suspicion, confirms the diagnosis of PE. Other combinations of scenarios are generally non-diagnostic for PE[23].Lastly, Echocardiography may guide therapy in patients who are haemodynamically unstable [24].

Morbidity and mortality associated with venous thromboembolism

VTE is associated with significant morbidity and mortality[1,2]. Conditions such as pulmonary hypertension, heart failure with chronic thromboembolic pulmonary hypertension, and chronic PE can have long-lasting effects. Additionally, chronic venous insufficiency may lead to persistent oedema and venous ulceration [12]. These sequelae impose a substantial burden on both patients and healthcare facilities in terms of morbidity and associated costs.

PE is a severe cause of mortality in both surgical and medical patients (15). A study conducted by Sandler et al in the late 1970s investigated the impact of PE on mortality. An autopsy series of 2857 patients from Hallamshire Hospital revealed significant PE in 239 patients, which contributed to their deaths. Of these 82% of these cases were not suspected clinically during the patients' hospitalization [25]. [26]Mortality trends indicate a decrease in PE-related deaths. In-hospital mortality decreased by 4.7% between 1999 and 2015 [25]. Mortality within 90 days also showed a decrease of 5% between 2004 and 2014 [25]. However, studies conducted in the USA have shown an increase in PE-related mortality among black men and women [25,27]. Racial and socioeconomic disparities in PE mortality persist globally, affecting access to newer medications like direct oral anticoagulants (DOACs) and diagnostic methods. Notably, there are downward mortality trends in the elderly population [25]. Multiple factors contribute to the decline in PE mortality, including improved CT angiogram techniques, standardized prophylaxis, scoring systems for risk stratification, increased awareness of PE, and greater utilization of post-discharge oral anticoagulation, particularly DOACs, in high-risk individuals [25]

Venous thrombo-embolism prophylaxis in medical and surgical patients

The implementation of prophylactic anticoagulation in the late 1970s resulted in a 12.4% reduction in PE detected during autopsies [28]. In the 1990s, Stein et al conducted a study on the incidence of PE in a general hospital. The prevalence of PE was found to be 0.3% among all deaths, with a higher prevalence of 1.6% observed in general surgery patients. Notably, autopsy confirmed PE in 14% of these cases, underscoring the existence of a significant number of undiagnosed patients [29]. Hospitalized patients have a more than 260-fold higher prevalence of VTE compared to the general population [30]. The prevalence of VTE increases proportionally with age [30]. With age and comorbidities, the risk of bleeding also increases. Thus, it is crucial to accurately calculate the risk to prevent morbidity and mortality.

Thromboprophylaxis in surgical patients has been shown to reduce mortality [31], while prophylaxis in medical patients reduces morbidity. Although the risk is higher for surgical patients, there is a larger number of admissions in the medical field [6]. Nonetheless, thromboprophylaxis in medical and surgical patients is underutilised.
The original TUNE-IN study was conducted in response to the ENDORSE study findings, which reported that 50% of hospitalized patients were at risk for VTE, yet only 58% of surgical and 40% of medical patients received adequate VTE prophylaxis[8,32]. The TUNE-IN study aimed to determine whether these results were applicable to the South African patient population. The study indeed identified similar VTE risk rates; however, it noted that 70% of patients received adequate prophylaxis.

The Wave 2 study examined the VTE risk of 453 surgical inpatients across the private and public sectors in Gauteng, South Africa (SA) in 2014 [26]. There were 269 (59.4%) patients who received thromboprophylaxis. However, when the Caprini VTE risk scoring model was applied, it revealed that all patients in this cohort were at risk of VTE, and only 59.4% would have been adequately covered with VTE prophylaxis [26].

Earlier randomized clinical trials have demonstrated the superiority of pharmacological thromboprophylaxis versus placebo in the prevention of VTE [33,34]. The following agents have

been evaluated; low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), fondaparinux and DOACs (Rivaroxiban, Edoxaban, Apixaban, Dabigatran)[24,25]

The American Society of Hematology (ASH) suggests the use of DOACs over LMWH in cases post total knee or hip replacement surgery[35]. The recommended dosages for DOACs are as follows:

- Rivaroxaban: 10 mg once daily, starting 6 to >10 hours after surgery.
- Apixaban: 2.5 mg twice daily, starting more than 12 hours after surgery.
- Dabigatran: 110 mg given 1 to 4 hours after surgery, followed by 220 mg daily thereafter.

Fondaparinux is an alternative to LMWH or unfractionated heparin (UFH)[35]. The recommended dosage for fondaparinux is 2.5 mg once daily, starting at least 6 to 8 hours postoperatively. For individuals with a creatinine clearance of 20-50 mL/min, a dose adjustment to 1.5 mg is suggested[35]. In acutely ill medical patients, the ASH guidelines recommend LMWH over DOACs. In surgical patients, there is no explicit preference between DOACs and LMWH; the choice should be based on individual cases and the quality of evidence[35]. Standard dosing for LMWH such as enoxaparin (which is the most common form of prophylaxis in state) is 40mg subcutaneously daily. The ASH guidelines allow the consideration of DOACs where there are contraindications to LMWH or based on patient preference.

Patients weighing over 100 kg should have a dalteparin dose increase by 50% or a dosing adjustment to 0.5 mg/kg daily for enoxaparin[35].

In patient subset where mechanical prophylaxis is used (high bleeding risk, contraindication to anticoagulation, or Caprini score of 2) guidelines suggest intermittent pneumatic compression devices over graduated compression stockings [35].

It is necessary to evaluate the bleeding risk in patients requiring thromboprophylaxis. The IMPROVE bleeding risk score was designed to estimate the risk of bleeding in acutely ill hospitalised patients in whom thromboprophylaxis is being considered. In the multicentre IMPROVE trial involving 15,156 patients from 12 different countries [27]the bleeding risk at 14 days of hospital stay was found to be 3.2%, with 1.2% of cases classified as major bleeding events [36]. This translated to 83 patients experiencing significant bleeding events.

The major sites of bleeding included the gastrointestinal tract in 29 patients, large hematomas in 12 patients, and intracranial haemorrhage in 10 patients. Among these 83 patients, 12 cases led to patient mortality [36]. The IMPROVE bleeding risk score includes factors such as age, gender, renal function, liver function, platelet count, admission to ICU, presence of a central venous catheter, active gastric or duodenal ulcer, prior bleeding within 3 months, and active malignancy. A cumulative score above 7 indicates an increased risk of bleeding [36]. The bleeding risk observed in this trial is consistent with the incidence reported in other large randomized trials [37]. Patients at higher risk for bleeding events often have a concomitant high risk for VTE. The literature suggests carefully balancing the potential benefits and risks and making individualized decisions regarding mechanical prophylaxis versus pharmacological prophylaxis
[36,38].

Venous thromboembolism in the COVID-19 Era

The COVID-19 pandemic in 2020 brought about a distinct change in the presentation of PE. The incidence of VTE was estimated to be as high as 7.4% in patients with severe illness, which is approximately nine times higher than the general non-COVID population [39]. Notably, PE in severe COVID-19 often manifested as smaller segmental and subsegmental PEs compared to non-COVID populations [39]. Leg symptoms and signs were less frequent in COVID-19 patients with PE [39]. In-hospital mortality for COVID-19 patients with PE was 16%, significantly higher than the 6.5% seen in non-COVID patients with PE [39]. The incidence of PE in COVID-19 was greater among individuals with more pronounced ground glass changes on lung imaging [39].

VTE pathogenesis in COVID-19 involves complex interactions between inflammation and coagulation [12]. There is evidence suggesting that SARS-CoV-2 initiates endothelial damage by activating the alternative complement pathway [40–42]
SARS-CoV-2 infection is associated with various coagulation abnormalities. Coagulation markers such as fibrinogen, D-dimer, Factor VIII and von Willebrand factor antigen are increased in COVID-19 patients [42].[33]Studies also demonstrated the presence of a transient lupus anticoagulant in COVID-19 patients [43,44].

The COVID-19 pandemic highlighted the complex interplay between cytokines, coagulation factors, and thrombus formation, known as immunothrombosis [12]. Over the past decade, there has been a declining trend in VTE-related mortality [25]. The increased awareness of VTE during the pandemic may have a positive impact on reducing VTE-related mortality and morbidity in the post-pandemic period. [14]Additionally, there has been an inferred increase VTE diagnoses, which can be attributed to factors such as improved awareness, diagnostic techniques, and prophylaxis, however, the sources discuss trends and no direct causal link has been identified.

Risk Assessment Models

Several risk assessment models (RAMs) have been developed for evaluating the risk of VTE in hospitalized patients. The commonly used RAMs include the Padua, Kucher, Caprini, Geneva, IMPROVE, and 4 elements models. These tools assign a score to each identified risk factor in order to calculate a cumulative risk score for VTE. By utilizing these scoring systems, the probability of developing VTE during hospitalization can be estimated.

The Caprini risk assessment model

The Caprini RAM, initially reported in 1980, has undergone regular adaptations and refinements, resulting in a final model in 2013 [6]. This risk assessment model was developed by Professor Joseph Caprini, an Emeritus professor at NorthShore University. The Caprini score has been extensively validated in nearly 5 million patients and has garnered over 200 peer-reviewed publications [7]. The Caprini RAM incorporates a total of 39 risk factors. Notable high-scoring risk factors include major trauma, pelvic fractures, and spinal cord injury, which are assigned a score of 5 [6]. The cumulative VTE risk is determined by summing the scores of individual risk factors, categorizing patients as low risk (0-1), middle risk (2), high risk (3-4), or super high risk (≥5). A score of 5 or above exhibits a sensitivity of 95% in predicting a VTE event [6].

Other risk scoring venous thromboembolism models

The Kucher Model was designed to identify individuals at high risk for VTE using eight common risk factors[45]. Major risk factors including cancer, prior VTE, and

hypercoagulability are assigned a score of 3, while major surgery is assigned a score of 2. Minor risk factors, such as advanced age, obesity, bed rest, and hormone replacement therapy, receive a score of 1[4645]. A cumulative score of at least 4 indicates an increased VTE risk. Studies have shown that this model successfully increased the prescribing of prophylaxis and thereby reduced the incidence of VTE by 41% at 90 days, mainly among medical patients[46,45].

The subsequent RAM have been designed for medical patients. The Padua RAM built on the Kucher model with additional risk factors and scoring elements[47]. It includes 11 risk factors, with scores ranging from 1 to 3. A cumulative score above 4 indicates a high VTE risk[47]. The IMPROVE RAM, based on the IMPROVE trial, includes a D-dimer level as an additional risk factor[48,49]. It assigns scores from 0 to 3, with higher scores indicating higher VTE risk. [40]Lastly, the Geneva RAM utilizes a scoring system with 1 to 2 points assigned to various risk factors[50]. A cumulative score of 3 or higher indicates a high VTE risk. The ESTIMATE trial validated the Geneva RAM's performance, but there are limitations due to a relatively small study population and criteria derived from previous trials[50].

Predictive value of venous thromboembolism scores

The Caprini RAM has been validated in medical patients and shown to be more sensitive [6]. In a study by Liu et al, the data from 320 VTE and 320 non-VTE patients were reviewed in conjunction with the Caprini RAM and the Padau RAM. Using the Caprini model, 70.9% of the VTE patients were correctly classified into the high-superhigh VTE risk category, while the majority of non-VTE patients (73.4%) were classified as low-moderate risk for VTE. In contrast, the Padau RAM only correctly classified 23.4% of the VTE patients as high-risk. [21]Further validation of the other RAMs is needed to establish their sensitivity and specificity.

We are currently in the midst of a digital age where applications provide healthcare professionals with valuable tools to enhance their clinical decision-making processes. However, findings from the earlier TUNE-IN studies have highlighted that in clinical practice, thromboprophylaxis is underutilised in hospitalised patients [26].

Aim and Objectives

Aim

The TUNE-IN Wave 3 study serves as an extension of the original TUNE-IN and TUNE-IN Wave 2 studies. The aim is to assess the utilization of VTE prophylaxis in different patient risk profiles of hospitalised patients within the public sector.

Study Objectives:

1. To assess the utilization of VTE prophylaxis based on patient risk profiling with the Caprini RAM among medical and surgical hospital patients at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).
2. To assess the bleeding risk according to the IMPROVE risk assessment tool among medical and surgical hospital patients at CMJAH
3. To compare the utilization of VTE prophylaxis with the TUNE-IN and TUNE-IN Wave 2 studies

Methods

Study Design:

Prospective, single-site, cross-sectional study

Study Population:

The study will include medical and surgical, inpatients at CMJAH in Gauteng, SA. Patients will be recruited over a 6-12 month period between July 2023 and April 2024.

Inclusion Criteria:

- Medical inpatients aged 18 years and older.
- Surgical inpatients aged 18 years and older.
- Orthopaedic patients aged 18 years and older.
- Patients who have provided signed informed consent and data release consent form.

Exclusion Criteria:

- Patients who do not meet the inclusion criteria.
- Patients who are currently on anticoagulation for the treatment of VTE.

Study Procedures and Data Collection

CMJAH is a 1,080 bed facility. Data from patients in the medical, surgical and orthopaedic wards will be collected.

Medical Ward Arrangement:

Medical wards are located in Section/block 5 of the hospital. "5" signifies the section/block number within the hospital. The second number represents the floor, while the third number indicates the specific ward on that floor. For example ward 585, it is in the 5th section of CMJAH on floor 8 in ward number 5. Wards 586 and 587, specializing in psychiatry within

Section 5, are excluded from the study population. There are 230 potential candidate beds for the study within the medical wards.

Ward 565 functions as a combined Intensive Care Unit (ICU) with 18 beds available. Ward 566 serves as the cardiology ICU, offering 8 beds. Ward 575 operates as an endocrine and cardiology admission ward with 29 beds ready for use. Ward 576 is a multidisciplinary ICU with a capacity of 12 beds. Ward 585 is dedicated to cardiology, housing 31 beds. Ward 587 specializes in respiratory and infectious diseases, accommodating up to 31 patients. Ward 594 is reserved for oncology patients and provides 23 beds. Ward 595, dedicated to gastroenterology and haematology, can house 30 patients. Ward 596, serving radiation oncology and rheumatology, has 26 beds. Lastly, Ward 597 caters to nephrology patients.

Surgical Ward Arrangement:

The CMJAH surgical wards comprise various specialties with designated bed capacities. The ward for Breast Cancer, Hand Surgery, and Plastic Surgery, designated as Ward 494, accommodates 31 beds. The Colorectal and Endocrine Surgery ward, referred to as Ward 394, also holds 31 beds. The Vascular Surgery ward, known as Ward 395, provides 31 beds, matching the capacity of the Hepatobiliary Surgery ward, Ward 396. Ward 384, dedicated to Ear, Nose, and Throat Surgery along with Maxillofacial Surgery, has 28 beds available. Urology, in Ward 386, offers 31 beds, whereas the Cardiothoracic High Care unit, Ward 387, has 6 beds. The Adult Main Intensive Care Unit, identified as Ward 576, has a capacity of 12 beds. There are two Orthopaedic Surgery wards, Wards 474 and 375, with 30 and 31 beds respectively. The Cardiothoracic Intensive Care Unit, known as Ward 376, is equipped with 7 beds. The Acute Trauma General Ward, Ward 377, accommodates 26 beds. The Neurosurgery High Care and Intensive Care Unit, Ward 565, has 22 beds, which is consistent with the bed count in another adult main Intensive Care Unit, Ward 567. The Adult Trauma Intensive Care Unit, Ward 366, has 16 beds, and the Cardiothoracic Ward, Ward 369, has 20 beds. Collectively, the total bed capacity for all surgical wards amounts to 375 beds.

Data collection will be done via patient interview as well as review of the patient hospital records. The Caprini RAM will be utilized to evaluate the risk of VTE and patients will be classified into risk groups (low, medium, high risk) (Appendix 1 and 2). The following data

will be collected: demographics, relevant blood results will be obtained from the patient record. Additionally, the **IMPROVE** bleeding risk assessment tool (refer to Appendix 3) will be employed to evaluate the risk of bleeding. The following additional data will be collected: ICU/general ward, presence of a central venous catheter, active gastric or duodenal ulcers, prior bleeding episode within the last 3 months, rheumatic disease and active malignancy. Relevant blood results will be obtained from the patient record.

The use of pharmacological and/or mechanical thromboprophylaxis and details pertaining to its use (name, dose, duration) will be collected.
Outcomes-bleeding/thrombosis.

Data collection will proceed on a bed-by-bed basis to determine patient eligibility for the study. The starting point will be Ward 597, located on the top floor, marking the commencement of data gathering. Following the completion of screening in Ward 597, the data collector will advance to the subsequent ward on the same floor. The data collector will proceed sequentially to the lower floors after all wards on the current level have been assessed. The sequence of wards for the data collection process will be as follows: 597 → 596 → 595 → 594 → 587 → 585 → 576 → 575 → 566 → 565 → 563. A similar approach will be implemented in the surgical block. This strategy is designed to avoid overrepresentation of a specific patient demographic in the study, ensuring that the data reflects a fair representation of the hospital population.

Data Analysis

Sample Size

The sample size for the TUNE-IN study and Wave 2 study will be similar, aiming for a sample size of 453 based on the original study to facilitate result comparison.
Sample size estimation was based on the key research question, in this case the estimation of the percentage of patients who received adequate VTE prophylaxis. Based on an estimate of 70%, 5% precision and the 95% confidence level, a minimum sample size of 323 was required. A number of 451 patients enrolled was achieved.

Sample size for prevalence was determined using the formula:

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

where n = sample size,

Z = Z-statistic for the chosen level of confidence,

P = expected prevalence or proportion

d = precision

Statistical Analysis

A sample of 385 patients was estimated, assuming a 1.0% incidence of VTE, at a confidence interval (CI) of 95%. Statistical analysis was performed using Statistica Software version 13.2 (Statistica, Tulsa, USA). Normally distributed continuous data was presented as mean ± standard deviation (SD) and variables with non-Gaussian distribution as median [interquartile range (IQR)]. Categorical data was presented as frequencies and percentages. Comparisons between medical, surgical and orthopaedic participants were performed using chi-square test or Fisher's exact test when necessary. Comparisons between the Wave 1, 2 and 3 studies were performed using a one-way ANOVA. Statistical significance was set at a p value of <0.05.

Ethics

Permission to conduct the study has been granted by the Chief Executive Officer (CEO) of CMJAH, the Head of Department (HOD) of Internal Medicine. Ethical approval has been obtained from the University of Witwatersrand (WITS) Human Ethics Research Committee (HREC) (M230146).

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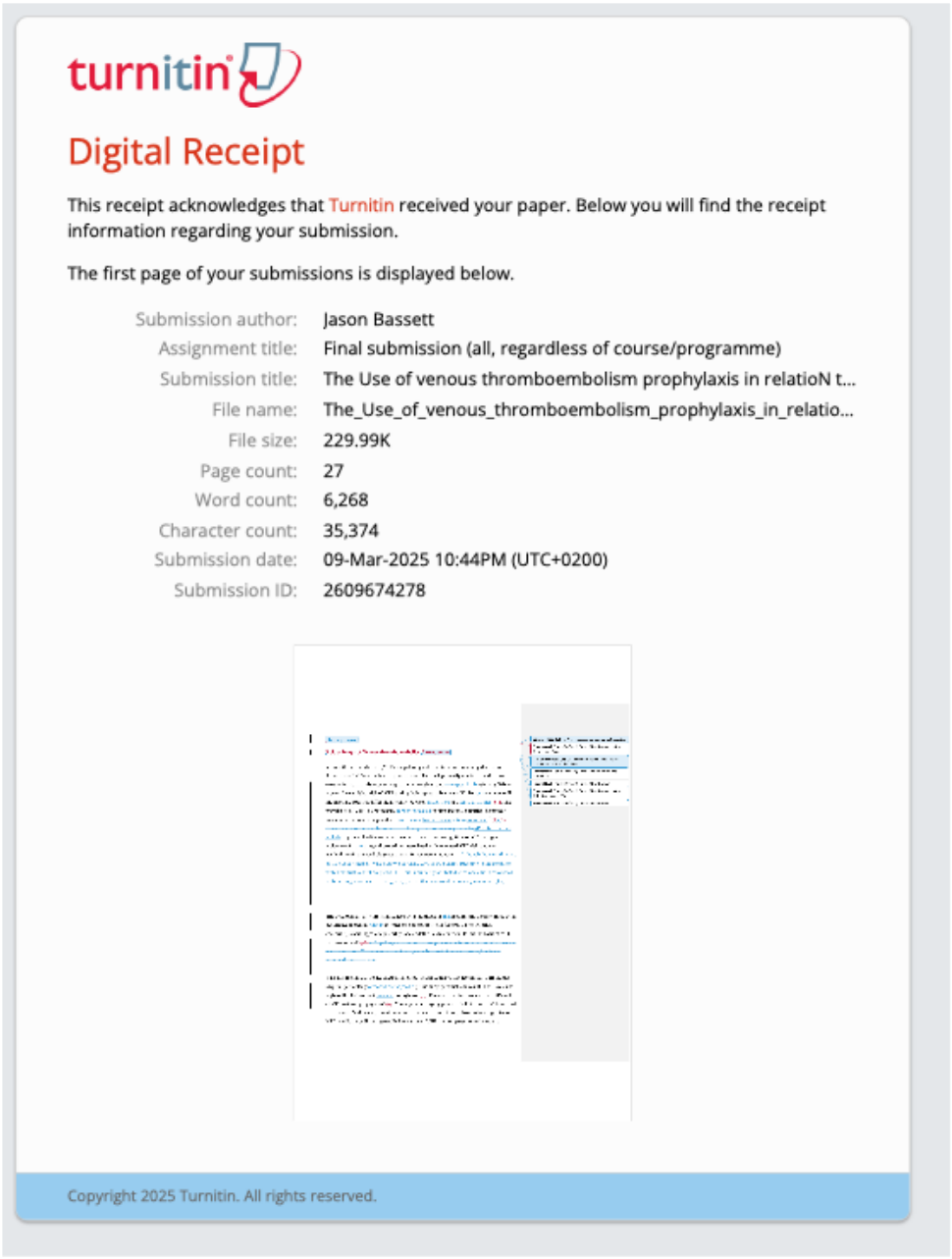
Appendix B: Journal Guidelines

The *South African Medical Journal* (SAMJ) is a monthly, peer reviewed, general medical journal publishing leading research impacting clinical care in southern Africa. We do not consider submissions outside Southern Africa.

All submissions must meet the following requirements.

- Please ensure you have submitted a regular version of the manuscript i.e. full text with author details and an anonymised version (author details remove). Failure to do so will result in your manuscript being returned to you.
- The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).
- The submission file is in Microsoft Word document file format.
- The text is single-spaced; uses a 12-point font; employs italics, rather than underlining (except with URL addresses); and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.
- Guideline word limit: 4 000 words
- The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below).
- Structured abstract-this should be 250-400 words

Appendix C : Turnitin digital receipt



turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	Jason Bassett
Assignment title:	Final submission (all, regardless of course/programme)
Submission title:	The Use of venous thromboembolism prophylaxis in relatioN t...
File name:	The_Use_of_venous_thromboembolism_prophylaxis_in_relatio...
File size:	229.99K
Page count:	27
Word count:	6,268
Character count:	35,374
Submission date:	09-Mar-2025 10:44PM (UTC+0200)
Submission ID:	2609674278

Appendix D: Ethics Amendments

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2 April 2024

Dr J Basett
School of Clinical Medicine
Department of Medicine
Division of Internal Medicine
Charlotte Maxeke Johannesburg Academic Hospital

Sent by e-mail to: jaybass4@gmail.com

Dear Dr Bassett

Protocol Ref No: M230146
Protocol Title: *The use of venous thromboembolism prophylaxis in relation to patient risk profiling (Wave 3)*
Principal Investigator: Dr J Basett

Thank you for your e-mail of 13 March 2024.

I confirm that we have noted and approve of your proposed changes to the data collection sheet.

Thank you for keeping us informed.

Yours Sincerely

Mr I Burns, for the Human Research Ethics Committee (Medical)

cc Professor M Kawonga

Appendix E: Human Research Ethics Committee Clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Jason Bassett

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M230146 MED23-01-011

NAME: (Principal Investigator)	Dr Jason Bassett
DEPARTMENT:	Internal medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	*The use of venous thromboembolism prophylaxis in relation to patient risk profiling (Wave 3)*
DATE CONSIDERED:	27/01/2023
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/05/2023 **EXPIRY DATE:** 29/05/2028

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **January** and will therefore be due in the month of **January** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

1/08/2023
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix F: Contribution to the research and writing of the submissible paper

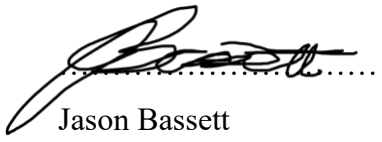
RE: JASON BASSETT'S CONTRIBUTION TO THE RESEARCH AND WRITING OF THE "SUBMISSIBLE" PAPER

To whom it may concern,

This letter serves to confirm that the co-authors of the "submissible" research paper have agreed to its use by Jason Bassett, student number 549681, as part of his MMed research report. Jason Bassett made a substantial contribution to conducting the research study and writing the manuscript.

Yours sincerely,

Professor Elise Schapkaitz
PhD (Wits)
Primary Supervisor



Jason Bassett
MMed Candidate