THE APPROPRIATENESS OF A RISK STRATIFICATION PROCEDURE FOR THROMBOEMBOLISM PROPHYLAXIS AFTER TOTAL KNEE REPLACEMENT SURGERIES

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by

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LIST OF ABBREVIATION

AAHKS	American Association of Hip and Knee Surgeons
AAOS	American Academy of Orthopedic Surgeon
ACCP	The American College of Chest Physicians
AHRQ	Agency for Healthcare Research and Quality
CKD	Chronic kidney disease
CVA	Cerebrovascular accidents
DHS	Dynamic hip screw
DM	Diabetes mellitus
DVT	Deep venous thrombosis
GA	General anesthesia
Hb	Hemoglobine
HFS	Hip fracture surgeries
HTN	Hypertension
ICD-9	International classification of diseases, ninth revision
ICF	Informed consent form
IHD	Ischemic heart disease
INR	International normalized ratio
IRB	Institutional Review Board
JUH	Jordan university hospital
KAAUH	King Abd Allah University Hospital
LMWH	Low molecular weight heparin
LOS	length of stay
mg	Milligram

MI	Myocardial infarction
NCHS	National Center for Health Statistics
NG89	NICE guideline update
NICE	National Institute for Health and Care Excellence
OA	Osteoarthritis
PE	Pulmonary embolism
Plt	Platelets
PSMMC	Prince Sultan Military Medical City
QALYs	Quality-adjusted life-years
QoL	Quality of life
RA	Rheumatoid arthritis
SD	Standard deviation
SIGN	The Scottish Intercollegiate Guidelines Network
SSIs	Surgical site infections
THR	Total hip replacement
TKR	Total knee replacement
TPHR	Total or partial hip replacement
UFH	Unfractionated heparin
VTE	Venous thromboembolism=thromboembolic

KESESUAIAN PROSEDUR STRATIFIKASI RISIKO UNTUK PROFILAKSIS TROMBOEMBOLISME SELEPAS PEMBEDAHAN PENGGANTIAN KESELURUHAN LUTUT

ABSTRAK

Penggantian keseluruhan lutut (total knee replacement-TKR) adalah salah satu pembedahan ortopedik utama, yang dianggap sebagai satu jalan penyelesaian bagi pesakit yang menghidapi penyakit sendi degeneratif. Pembedahan ini dianggap sebagai pembedahan yang berisiko tinggi menyebabkan tromboembolisme vena (venous thromboembolism-VTE). Mengelakkan kedua-dua kejadian VTE dan episod pendarahan adalah penting kerana pendarahan mempunyai kesan negatif terhadap hasil pembedahan. Oleh itu, antikoagulasi yang berlebihan harus dielakkan. Objektif primer untuk kajian ini adalah untuk menilai hasil klinikal penggunaan prosedur stratifikasi risiko VTE untuk memilih profilaksis VTE selepas pembedahan TKR. Sementara objektif sekunder pula boleh di simpulkan sebagai berikut: Menganalisis kesedaran dan amalan umum mengenai faktor risiko VTE dan profilaksis bagi pakar bedah dan ahli farmasi, penilaian kualiti kehidupan selepas pembedahan penggantian lutut , dan menilai pengurusan nyeri selepas pembedahan TKR. Untuk objektif yang utama kajian terkawal secara rawak dijalankan di dua buah pusat perubatan di Arab Saudi; Prince Sultan Military Medical City (PSMMC) dan King Abd Allah University Hospital (KAAUH) di Princess Noura University. Seramai dua ratus empat puluh dua orang pesakit didaftarkan dalam kajian ini selepas kemasukan melalui borang persetujuan termaklum, iaitu seramai seratus dua puluh satu orang pesakit didaftarkan dalam setiap kumpulan; kumpulan eksperimental (A) dan kumpulan kawalan (B). Perawakan dilakukan dengan menggunakan random permuted blocks. Kedua-dua

kumpulan ini diikuti selama 35 hari selepas pembedahan. Purata umur bagi semua peserta adalah 65.86 ± 8.67, majoriti adalah perempuan, iaitu seramai 137 orang (56.6%). Purata indeks jisim badan (BMI) peserta adalah 32.46 ± 5.51. Tiada perbezaan yang ketara antara kumpulan A dan kumpulan B dari segi umur, jantina, BMI, gaya hidup, penyakit, ubat-ubatan, faktor risiko VTE selain daripada pembedahan, skor caprine 2005 atau faktor risiko pendarahan, Prosedur Pembedahan, rawatan dan langkah-langkah pemulihan dari kemasukan hingga dibenarkan keluar. Perbezaan utama antara kedua-dua kumpulan ini adalah jenis pembedahan. Terdapat 69 kes TKR bilateral (28.5%) dalam kumpulan A, iaitu lebih banyak berbanding 40 kes (16.5%) dalam kumpulan B dengan nilai P yang signifikan pada 0.05. Sejumlah 15 orang peserta (6.2%) mengalami gejala DVT, dan seorang peserta, 1/242 (0.4%) mengalami gejala PE. Dari kelompok pesakit ini, diagnosis menunjukkan bahawa hanya 12/242 orang pesakit (4.95%) disahkan sebagai kes DVT tanpa sebarang kes PE yang sah. Hanya 1/121 (0.8%) kes DVT yang disahkan adalah dalam kumpulan A dan 11/121 yang selebihnya (9.1%) adalah dalam kumpulan B, dengan perbezaan yang signifikan antara kedua-dua kumpulan (nilai P <0.05). Tiada perbezaan yang ketara antara kedua-dua kumpulan dari segi pendarahan, jangkitan bahagian pembedahan (surgical site infection-SSI), atau kematian secara tiba-tiba selepas pembedahan TKR. Kadar pendarahan keseluruhan adalah 0.8% (2/242), kadar SSI keseluruhan adalah 0.8% (2/242), terdapat satu kes sahaja kematian secara tiba-tiba, dengan kadar 0.4% (1/242), tanpa perbezaan yang ketara antara dua kumpulan tersebut. Kadar kemasukan semula ke hospital untuk semua pesakit adalah 2.5% (6/242), semuanya daripada kumpulan B, dengan perbezaan yang ketara antara kedua-dua kumpulan, dan nilai P adalah <0.05. Jumlah kos bagi profilaksis VTE yang dilanjutkan untuk Kumpulan A adalah jauh lebih rendah daripada kumpulan B, iaitu $ 6020.11 dan $10503.36

masing-masing. Dalam kajian ini, kedua-dua kumpulan rawakan ini adalah sama dalam hampir semua aspek, walaupun jumlah kejadian VTE dalam kumpulan B adalah lebih tinggi daripada kumpulan A. Kajian ini membuktikan bahawa teknik stratifikasi risiko VTE mengurangkan kesulitan VTE serta kejadian kemasukan semula selepas pembedahan TKR. Selain itu, kajian ini mendedahkan bahawa prosedur stratifikasi risiko VTE mengurangkan jumlah kos untuk profilaksis VTE selepas pembedahan TKR. Untuk objektif sekunder , pakar bedah didapati telah mencapai tahap skor pengetahuan dan sikap di kedua dua buah pusat kajian. Untuk penilaian kualiti kehidupan, keputusan mengambarkan tahap kepuasan yang tinggi untuk pembedahan penggantian lutut di Arab Saudi. Selain itu, pesakit bedah penggantian lutut melaporkan skor kesihatan fizikal dan mental yang hampir sama dengan populasi Amerika yang sihat berusia 75 tahun ke atas. Untuk penilaian pengurusan nyeri selepas TKR di kedua-dua pusat perubatan mencapai tahap yang dapat diterima dan majoriti pesakit telah mendapat ubat rawatan nyeri yang mencukupi dalam operasi pasca TKR.

THE APPROPRIATENESS OF A RISK STRATIFICATION PROCEDURE FOR THROMBOEMBOLISM PROPHYLAXIS AFTER TOTAL KNEE REPLACEMENT SURGERIES

ABSTRACT

Total knee replacement (TKR) is one of the major orthopedic surgeries, which is considered one solution for patients with degenerative joint disease. These surgeries are considered high risk surgeries for the development of venous thromboembolism (VTE). Limiting both VTE events and bleeding episodes is essential; since the bleeding has a negative impact on the surgical outcomes, so, excessive anticoagulation should be avoided. The primary objective in this study is to evaluate the clinical outcomes for the use of a VTE risk stratification procedure for selecting the extended VTE prophylaxis post-TKR Surgeries. The secondary objectives for this study can be summarized as follows: Analyze the general awareness and practice regarding VTE risk factors and prophylaxis for both surgeons and pharmacists, assess quality of life post joint replacement surgeries, and assess pain management post TKR surgeries. For the main objective a Randomized controlled trial was conducted in two medical centres in Saudi Arabia; Prince Sultan Military Medical City **(**PSMMC) and King Abd Allah University Hospital (KAAUH) in Princess Noura University. Two hundred and forty-two patients were enrolled in this study after admittance the informed consent form, one hundred twenty-one patients were enrolled in each group; experimental group (A) and control group (B). For the experimental group (A) a VTE risk stratification procedure prepared by the author was used, while for control group (B), a Caprini risk assessment tool 2005 was used. Both groups were followed for 35 days post-operation. The mean age for all participants was 65.86±8.67, majority were

females 137 (56.6 %). BMI population mean was 32.46 ±5.51. There were no significant differences between group A and group B in age, gender, body mass index (BMI), lifestyle, medical illnesses, medications, VTE risk factors other than the surgery, Caprini score or bleeding risk factors, surgical procedure, treatment, and recovery measures from admission to discharge. The main difference between the two groups is surgery type, bilateral TKR 69 (28.5 %) in group A was higher than group B 40 (16.5 %) with a significant p-value < 0.05. A total of 15 participants (6.2 %) were experienced DVT symptoms, PE symptoms were seen in one case 1/242 (0.4 %), from these patients, the diagnosis has been confirmed for only 12/242 (4.95 %) patients as DVT cases without any confirmed PE cases. One (0.8 %) of the confirmed DVT cases was in group A and the rest 11 (9.1 %) are in group B, with a significant difference between the two groups (P-value <0.05). There were no significant differences between the two groups in bleeding, surgical site infection (SSI), or sudden death post TKR surgery; total bleeding rate was 0.8 % (2/242), total SSI rate was 0.8 % (2/242), sudden death happened for one case only in the control group, with a rate of 0.4 % (1/242), without a significant difference between the two groups. The readmission rate for all patients was 2.5 % (6/242), all were from group B with a significant difference between the two groups, p-value <0.05. The total cost for the extended VTE prophylaxis for Group A is significantly less than that of group B; $ 6020.11 and $ 10503.36 respectively. In this study, the two randomized groups were similar in almost all aspects, despite this number of VTE events in group B was higher than group A. This study has proven that the VTE risk stratification technique reduces the VTE complications, as well as the readmission events post TKR surgeries. Moreover, this study reveals that VTE risk stratification procedure reduces the total cost for the extended VTE prophylaxis medications post TKR surgeries. For the secondary

objectives; the surgeons have achieved a good knowledge and attitude scores in both medical centers. For quality of life assessment, the results indicated a high satisfaction rate for joint replacement surgeries in Saudi Arabia. Additionally, post joint replacement surgeries patients reported physical and mental health scores which is closely matched those of healthy American population aged 75 years and above. For pain management assessment post TKR in both medical centers achieved an acceptable level and majority of patients had received an adequate analgesia in post TKR surgeries.

CHAPTER 1

INTRODUCTION

1.1 Background

Major Orthopedic Surgeries are divided into 3 major categories: Total Hip replacement (THR), Total Knee Replacement (TKR), and Hip Fractures Surgeries (HFS). According to The American College of Chest Physicians (ACCP), these surgeries are considered high risk surgeries for the development of venous thromboembolism (VTE) and the subsequent complications (ACCP, 2012).

Patients undergoing high-risk orthopedic procedures, specifically, THR, TKR, and HFS, have a significantly increased risk of VTE, with rates historically estimated as high as 60% without appropriate prophylaxis (Geerts, *et al*., 2008). According to the American Academy of Orthopedic Surgeon (AAOS), DVT after a hip fracture has been reported to occur in 30% up to 60% of patients. Different studies indicate a significantly increased risk of VTE if the surgery for a hip fracture is delayed for 48 hours or longer (Pincus *et al.,* 2017). Fatal PE has been reported to be more common in hip-fracture patients than in patients with elective replacement procedures (AAOS, 2011). Patients are predisposed to venous thrombosis if they fulfill the elements of Virchow's triad discussed by Rudolf Virchow, a German pathologist, in 1856. These are venous stasis, endothelial injury, and hypercoagulability (Byrnes& Wolberg, 2017). Venous stasis occurs secondary to long periods of immobilization in the operating room and delayed, limited, or impaired postoperative ambulation. Endothelial injury can result from either a direct injury to the deep veins or the surrounding tissue of the lower extremities or indirectly by a hematoma or thermal

injury (Haake and Berkman, 1989). The annual incidence of VTE in the United State (US) is estimated to be 350,000- 900,000 of which approximately 100,000 die. Of those that survive, 30-50% will go on to develop post-thrombotic syndrome and as high as 30% will develop a second DVT within 5 years (Streiff, *et al*., 2014).

1.2 Problem Statement

Over the last decade, it is clear that limiting both VTE events and bleeding episodes is essential. Despite that efficacy is important, excessive anticoagulation should be avoided since bleeding can have a negative impact on the surgical outcome (Lieberman and Pensak, 2013). In the last ten years, there were major changes in the delivery of orthopedic surgeries (Jameson, *et al.,* 2014). The implementation of strategies such as day surgery admission and the use of spinal anesthesia resulted in a reduction in operating time also the proper analgesia which allows early mobilization and aggressive rehabilitation, resulting in a mean length of hospitalization of five days. These strategies contribute to decreasing the risk of death in the peri-operative period (Malviya, et al., 2011) and may reduce VTE since restricted movement and prolonged length of stay were common after joint replacement surgeries. Thus, the incidence of VTE after joint replacement would be smaller (Lieberman and Pensak, 2013). In the United Kingdom in 2011, the mortality within 90 days after elective hip and knee replacement have done due to osteoarthritis was 2.9 per 1000 (Jameson *et al*., 2014). Nowadays, patients routinely can walk using a walker within 24 hours of surgery (Khan *et al.,* 2014).

After conducting a study by Alamiri *et al.,* 2019**,** it is clear that the incidence of VTE post orthopedic surgeries in Jordanian patients is high, so as a solution for this problem risk stratification for each patient who is planned for a major orthopedic

surgery should be done, and this will help the physician to choose the suitable VTE prophylaxis according to patient-specific risk, and procedure-related risk factors (Alamiri *et al.,* 2019). For this, the researcher designed a novel risk stratification protocol for TKR surgery (See Appendix I) after reviewing all the related literature, it is suggested to be used by the physician and incorporated in the patients' files to ensure that each patient is receiving the tailored VTE prophylaxis agent. In this risk stratification tool, all surgical and patient-related factors that show significant associations with the incidence of VTE events are included (See chapter 2). Accordingly, risk stratification techniques will be both clinically and financially effective; since choosing the right VTE prophylactic agent for the right patient will save both patients' life and money spent to treat the VTE complications.

Since no anticoagulant has been proven to reduce mortality (NICE guidelines NG89, 2018) a question is raised about the cost-effectiveness of widespread (expensive) anti-coagulant use. The annual cost of potent anticoagulants in these joint replacement patients across England and Wales is approximately £13 million (For example Enoxaparin £3.03 per 40mg (daily) syringe, 14 days for 90 842 knee replacements and 35 days for 86 488 hip replacements, and this ignores community nurse fees to administer the drug to large numbers of patients (njrcentre.org.uk, 2014). In comparison between aspirin and low molecular weight heparins (LMWHs), the estimated cost of administering aspirin is around £110 000 per year less than 1% of the more expensive agents of LMWHs (Schousboe and Brown, 2013). In a Markov cohort cost-effectiveness analysis, the authors concluded that aspirin cost less and saved more quality-adjusted-life-years (QALYs) than warfarin in all age groups (Tabatabaee, *et al*., 2015).

Moreover, a Multimodal thromboprophylaxis study in which aspirin is administered to low-risk patients stated that aspirin is safe and effective following primary total joint replacement (Vulcano *et al*., 2012). Mistry *et al*., 2017 in his review article stated that aspirin represents a safe and effective option as VTE prophylactic agent. Regarding the optimum dose of Aspirin, several studies from the literature showed that high doses of aspirin (500 to 1500 mg/day) were no more effective than medium doses (160 to 325 mg/day) or low doses (75 to 150 mg/day) (Azboy *et al*., 2017).

Regarding the trend in Saudi Arabia, before the current study, they do not use aspirin as a VTE prophylaxis post TKR, rather they usually use anti-coagulant medications whether parenteral or oral choices as VTE prophylaxis post TKR surgeries (Al-Hameed et al., 2017).

VTE is a serious and underestimated potentially fatal disease with an effective prophylactic antithrombotic therapy that is usually underused (Abo-El-Nazar Essam & Al-Hameed, 2011). Surgeons' and pharmacists' knowledge, attitude and practice (KAP) can influence whether a patient under their care is receiving the optimal care or not (Al-Hameed et al., 2014). Moreover, another study that is done by Al-Hameed et al., 2017 in seven major hospitals in Kingdom Saudi Arabia (KSA), concluded that thromboprophylaxis was underutilized in major Saudi hospitals indicating a gap between guidelines and practice, they added that efforts to improve thromboprophylaxis utilization are warranted (Al-Hameed et al., 2017). So, in order to be able to know the weak and strong points regarding surgeons' and pharmacists' KAP, a cross-sectional study is needed to assess surgeons' and pharmacists' KAP in order to improve the weakness and emphasize the strength. Additionally, Al-Hameed et al., 2014 have elaborated the effective role for VTE prophylaxis educational

program in a tertiary-care hospital at KSA. They concluded that this educational program was associated with improvement in VTE prophylaxis utilization and VTE-associated mortality, they added that such programs are highly recommended (Al-Hameed et al., 2014).

Osteoarthritis is a major cause of physical disability among elderly people, the pain and functional limitation over the joints of the lower limbs results in reduced quality of life (QoL) for these patients (Fransen et al., 2011). In patients with severely degenerative joints (end-stage osteoarthrosis), joint replacement surgeries represent an effective procedure to restore the functions of the joint and to relieve the pain (Hintermann et al., 2012). Joint replacement procedures have been considered as an attractive choice for most patients and this, in turn, increases the demand for such procedures (da Silva et al., 2014). So, there is a need to assess QoL and patients' satisfaction post total joint surgeries. To the best of authors knowledge, QoL assessment for patients who underwent TKR and THR in Saudi Arabia has not been studied before and local evidence is also poorly covered in the literature. Thus, this study aims to be the first study to evaluate the QoL of patients undergoing these procedures in Saudi Arabia.

Managing acute pain following joint replacement surgeries is very important due to the following reasons: First, studies have shown that poor control of acute pain after TKR is closely correlated with the development of chronic pain, which illustrates the importance of a good control of acute pain after TKR (McCartney & Nelligan, 2014). Second, joint replacement is one of the most widely used elective surgical procedures in the Middle East (Al-Taiar et al., 2013); in 1994, the number of TKR surgeries in Saudi Arabia was around 12 procedures per year (Ahlberg, 1994). The number of THR and TKR performed worldwide and in Saudi Arabia continued to

increase, according to Health Affairs of Ministry of National Guard in the Kingdom of Saudi Arabia 2018, about 5000 joint replacement procedures have been performed over the last 10 years with an average of 500 joint replacements annually. Third, joint replacement surgeries are primarily performed to relieve chronic joint pain (Hawker et al., 1998), and yet, some patients tend to experience chronic pain following joint replacement surgery, which refers to the failure of surgery for these patients. This therefore suggests that the use of effective acute pain management is crucial.

1.3 Research Objectives

Main objective:

Evaluate the clinical outcomes for the use of VTE risk stratification procedure post-TKR surgeries:

a. Measuring the incidence rate of *DVT* post TKR Surgeries.
b. Measuring the incidence rate of *PE* post TKR Surgeries.
c. Measuring the occurrence of *sudden death* post TKR Surgeries.
d. Measuring the incidence rate of *Bleeding* post TKR Surgeries.
e. Measuring the incidence rate of *surgical site infection* (SSIs) post-TKR Surgeries.

Secondary objectives:

1. Analyze general awareness and practice regarding VTE risk factors and prophylaxis.
    a) Analyze the surgeon awareness and practice regarding VTE risk factors and prophylaxis.

b) Analyze the pharmacist role and awareness regarding VTE risk factors and prophylaxis.

2. Evaluate acute pain management post TKR surgeries.
3. Assess the quality of life post-TKR and THR for patients having the procedure for 3 months and above.
4. Measure the extended VTE prophylaxis medications' cost for both experimental and control group.

1.4 Research Hypothesis

1. The use of a risk stratification tool for thromboembolism prophylaxis after TKR surgeries will avoid aggressive anticoagulation while achieving a low overall incidence of symptomatic VTE.
2. The use of a risk stratification tool for thromboembolism prophylaxis after TKR surgeries will reduce the bleeding events and accordingly will reduce the bleeding complications.
3. The use of a risk stratification tool for thromboembolism prophylaxis after TKR surgeries will be cost effective for the medical institution.
4. TKR and THR surgeries will improve the quality of life for targeted patients.
5. Acute pain post TKR will be managed perfectly in all the screened medical centers.
6. Surgeon and pharmacist will achieve a high level of awareness regarding VTE risk factors and the best choice for prophylaxis.

1.5 Importance of This Study

In 1994 the number of *TKR* surgeries in Saudi Arabia was around 12 procedures per year (Ahlberg, 1994). According to Health Affairs of Ministry of National Guard in the Kingdom of Saudi Arabia 2018, about 5000 joint replacement procedures have been performed over the last 10 years by a team of skilled Saudi surgeons with an average of 500 joint replacements annually. The number of THR and TKR performed worldwide and in Saudi Arabia continues to increase and the patients receiving these procedures seem to be sicker than in the past (Mcminn *et al*., 2012), therefore, the use of effective and safe prophylactic regimens is important. Over the last decade, it has become apparent that limiting both symptomatic events and bleeding episodes is essential. Although efficacy is important, patients should not have excessive anticoagulation.

1.6 Chapter Summary

This chapter introduced vital definitions for the most important terms, justified the reason for this study, and stated the study objectives, hypothesis, and importance. Next chapter (literature review) will discuss the most relevant studies.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

VTE is the formation of a clot inside the vein, most commonly in the veins of the legs causing DVT, or in lungs leading to PE (Blann and Lip, 2006). DVT and PE have serious complications. As reported, PE mortality rate is around 15% (Goldhaber & Bounameaux, 2012). Beside its acute symptoms, DVT can be complicated by PE, recurrent DVT and post thrombotic syndrome in one third of the patients, especially those with recurrent DVT (Kahn, 2016).

VTE is a common complication post-surgical procedure and it is the major cause of morbidity and mortality in hospitalized patients (Agnelli, 2004). The risk for VTE in surgical patients is determined by the combination of individual predisposing factors and the specific type of surgery (Geerts et al., 2004). Prophylaxis with mechanical and pharmacological methods has been shown to be effective and safe in most types of surgery and should be routinely implemented (ACCP, 2012). Patients undergoing major orthopedic surgeries, which include elective hip and knee replacement and surgery for hip fracture, are at particularly high risk for VTE (AAOS, 2011). Despite the use of prophylaxis, the rate of symptomatic VTE in these patients remains almost high (White et al., 2001). Venous thromboembolism is the most common cause for readmission to the hospital after hip replacement (Pellegrini et al., 2005). In this chapter an analysis for the related literature is presented.

2.2 Pharmacological VTE Prophylaxis post Orthopedic surgeries

According to the last update for ACCP guidelines (9th edition) for VTE prophylaxis which is released in 2012 (despite that the 10th edition is released in February 2016, but in this new edition the VTE prophylaxis recommendations are the same as 2012, indeed there were some changes regarding VTE treatment protocols (Heffner, 2016)), prophylaxis methods are divided into mechanical and pharmacological. The former include mobilization, graduated compression stockings, intermittent pneumatic compression device (IPCD) (Grade 1C); the latter include the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis: low-molecular-weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted-dose vitamin K antagonist (VKA), aspirin (all Grade 1B). A controversy regarding the use of aspirin as a sole method of prophylaxis in total joint replacement and hip fracture surgeries is a concern between surgeons (Flevas et al., 2018). Accordingly, the coming discussion will be oriented toward aspirin use as VTE prophylaxis post orthopedic surgeries.

2.2.1 Aspirin as an Option for VTE Prophylaxis

Over the past three decades, there has been an interest in using aspirin as a prophylactic agent after total joint replacement and HFS. This is mainly because aspirin is an oral agent that requires no monitoring and is well tolerated by most patients (Lieberman and Hsu, 2005). According to American College of Cardiology Foundation (ACCF) 2009, cardiac-related deaths following surgery is more common, thus, giving an antiplatelet will reduce the peri-operative mortality (ACCF, 2009). With the introduction of routine aspirin as thromboprophylaxis, deaths from cardiovascular causes in a specific study dropped from 0.75% to zero (Malviya, *et al.*,

2011). Another study showed that LMWH had significantly increased wound drainage or hematoma compared to aspirin or coumadin (warfarin-sodium), and that each day of increased wound drainage significantly increased the risk of infection (Haas, *et al*., 2008). Comparing LMWH and aspirin in another study showed that patients on LMWH had more bleeding complications and a more difficult time gaining motion than those on aspirin (Keays, *et al*., 2003).

Before 2012, there was a controversy between AAOS and ACCP regarding the use of aspirin as VTE prophylaxis in total joint replacement and hip fracture surgeries. both of them (AAOS and ACCP) have developed evidence-based guidelines to prevent VTE in high-risk orthopedic surgery patients. Recent changes to these documents have brought them into agreement as to the inclusion of aspirin as an appropriate option for VTE prophylaxis in these patients' population. In addition, several studies have been shown that aspirin represents an effective choice post elective TKR or THR; a recent systemic review was done by Mistry, et al., 2017 has concluded that aspirin is an effective and safe prophylactic agent post elective arthroplasty.

According to a meta-analysis in 2016, although aspirin is a suitable therapy for the prevention of VTE in THR and TKR, as recommended by the ACCP, 2012 and AAOS, 2011, the evidence available is of limited quality and still remains unclear about the dosage and duration of administration of aspirin for VTE prophylaxis (An et al., 2016). Overall, it seems that the use of aspirin as a VTE prophylaxis agent in orthopedic patients remains controversial.

2.2.1(a) AAOS and ACCP Guidelines Controversy Regarding Aspirin

Guidelines have been developed by both the AAOS and ACCP to address the issue of prophylaxis in high-risk orthopedic surgery patients' population (Geerts, *et al*., 2008). Both documents were recently updated with significant changes (Flevas et al., 2018). In the past, the orthopedic community has had considerable concerns about the recommendations made by the ACCP which appeared to focus more on efficacy than safety due to the Grade 1A recommendation against aspirin use (Lachiewicz, *et al.*, 2009). Both AAOS and ACCP guideline statements are evidence-based; however, they differ in their methodology. The AAOS document still does not recognize DVT (symptomatic or asymptomatic) as an acceptable surrogate marker for potential complications associated with VTE. In spite of changing the title, it has a greater concern with the risk of bleeding from surgical wounds than ACCP does (AAOS, 2011). As appears in the recommendations set by each organization, the controversy is regarding the appropriateness of surrogate markers and the outcomes as well as the occurrence of adverse events; whether or not nonfatal and asymptomatic events are important outcomes to consider in clinical trials (Khatod, *et al*., 2012). ACCP 2008 recommended against the use of aspirin as an option for the prevention of fatal PE, while the AAOS recommends aspirin for patients with higher risk of adverse bleeding events (AAOS, 2011). Many studies comparing aspirin to another anticoagulant, concluded that aspirin was as effective as the comparator, however, statistical power was not achieved or reported (Stewart and Freshour, 2013). These studies failed to meet current standards of effective research, but both the AAOS and ACCP have developed strong statistical and analytical methods to overcome this problem through systematic reviews of the collective literature (Lachiewicz, 2009). Later in 2012,

ACCP has updated their recommendations by approving aspirin as one choice for VTE prophylaxis post orthopedic surgeries as Grade 1B recommendation (ACCP, 2012).

2.2.1(b) Aspirin in Other Guidelines

National Institute of Health and Care Excellence (NICE) guideline is different from ACCP and AAOS guidelines. NICE currently recommends extended VTE prophylaxis for all hip and knee replacement patients (between 10 and 14 days for knee replacement and 28 to 35 days for a hip replacement and HFS). The recommended drug is LMWH or newer oral agents. Aspirin is not recommended (NICE, 2010). According to recent update 2018 for NICE guidelines NG89, they listed Aspirin (75 or 150mg) for 14 days, as an option for VTE prophylaxis post TKR only, but they labeled this option as unlicensed medicines.

The Scottish Intercollegiate Guidelines Network (SIGN) and the Brazilian guidelines recommend aspirin as the sole measure of thromboprophylaxis (Grades B and A, respectively) (Struijk-Mulder *et al*., 2010). However, The SIGN guidelines (2010, updated in 2015) stated that aspirin is not recommended as the sole pharmacological agent for VTE prophylaxis in orthopedic patients (Flevas et al., 2018). The French guidelines, on the other hand, advise clearly against the use of aspirin as the sole method of thromboprophylaxis (Grade B) (Struijk-Mulder *et al*., 2010). In March 20, 2018, an updated version of NICE guidelines (NICE Pathways) specific for orthopedic surgeries, in which they included aspirin as a prophylactic choice post elective TKR and THR, but according to NICE Pathways, aspirin cannot be used directly post THR but it should follow the use of LMWH for a period of at least 10 days then aspirin (75 or 150 mg) for an another 28 days.

2.2.1(c) Summary for Aspirin Comparisons to other VTE Prophylaxis Agents

In this section a detailed discussion for studies that have compared aspirin as VTE prophylaxis post orthopedic surgeries to other VTE prophylaxis.

2.2.1(c)(i) Comparing Efficacy and Safety

The studies that assessed the use of aspirin in THR, TKR, and HFS in the 1970s and 1980s were of low quality and they used high dose aspirin that reached 3.8 gm per day (Flack-Ytter, *et al*., 2012). The PEP trial assessed the effect of 160 mg of aspirin given routinely for 35 days against placebo and allowed for additional antithrombotic intervention if seen necessary. In this trial (PEP trial), 13,356 patients with hip fracture were randomly assigned to receive 160 mg of aspirin or placebo for 35 days after surgery. About three-quarters of the patients also received another form of thromboprophylaxis (heparin or compression stockings). Patients who received aspirin had a significantly lower incidence of symptomatic DVT or pulmonary embolism (1.6 versus 2.5 percent). There was no benefit over aspirin in the subgroup who had received low molecular weight heparin. There was no difference in all-cause mortality for any group (Wolozinsky et al., 2005). Larger meta-analyses and other pooled analyses with tens of thousands of patients that compared aspirin to LMWH, and warfarin reported: No significant difference in major bleeding indices (Bozic, *et al*., 2010), increased rates of major bleeding with LMWH and warfarin (Dorr, *et al*., 2007), and increased operative site bleeding with LMWH and warfarin (Brown, 2009).

All patients in the single-center trial by Dorr, *et al*. (2007) received aspirin for the first 24–48 hours postoperatively regardless of the long-term prophylactic strategy (Dorr, *et al*., 2007). Accordingly, aspirin has the safest profile when compare it with LMWHs or warfarin.

In orthopedic surgery patients, the AAOS, 2011 has asserted strongly that bleeding risk is reduced with aspirin when compared to potent anticoagulants (warfarin and LMWH). When using DVT as an appropriate surrogate marker, the bleeding outcome also should be studied, since all surgeons are interested in preventing surgical site infection, and wound healing (Lachiewicz, 2009).

Another randomized control trial was done to compare aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty. In this trial 778 patients (who had elective unilateral THR between 2007 and 2010) were recruited from 12 tertiary care orthopedic referral centers in Canada. Patients were randomly assigned to 28 days of dalteparin (n = 400) or aspirin (n = 386) after an initial 10 days of dalteparin prophylaxis follow up elective THR. The objective was to compare aspirin and LMWH by measuring symptomatic VTE confirmed by objective testing (primary efficacy outcome) and bleeding. The primary outcome was development of symptomatic proximal DVT or PE during the 90 days after total hip replacement. The major limitation for this study that it was halted prematurely because of difficulty with patient recruitment. The researchers found that five of 398 patients (1.3%) randomly assigned to dalteparin and 1 of 380 (0.3%) randomly assigned to aspirin had VTE (absolute difference, 1.0 percentage point). Aspirin was noninferior ($P< 0.001$) but not superior ($P = 0.22$) to dalteparin. Significant bleeding episodes occurred in 5 patients (1.3%) receiving dalteparin and 2 (0.5%) receiving aspirin. The authors have concluded that extended prophylaxis for 28

days with aspirin was noninferior to and as safe as dalteparin for the prevention of VTE after THR in this group of patients. In addition to its low cost and oral route, aspirin may be an effective alternative for VTE prophylaxis (Anderson, *et al.*, 2013). So, according to this study aspirin has comparable efficacy to LMWHs and has a good safety profile.

Another Meta-analysis included 1,408 subjects, in which aspirin was compared with other anticoagulants for VTE prevention and bleeding after major lower extremity orthopedic surgeries. The primary outcome was the rate of proximal DVT. Anticoagulant classes included warfarin, heparin, LMWH and danaparoid. Treatment duration was seven to 21 days with a follow up period of six months. The results were reported as the following: The overall DVT risk didn't differ significantly between aspirin and anticoagulant; however, the risk of bleeding was lower with aspirin. In a balance of risk versus benefit according to the surgery type, there was a non-significant trend favoring anticoagulation for VTE prevention following hip fracture repair. No difference was found for knee/hip replacement. Rates of pulmonary embolism were too low in all the groups to provide reliable estimates (Harrison, *et al*., 2020).

2.2.1(c)(ii) Comparing Mortality Rate After Orthopedic Surgeries

A meta-analysis and systematic review of peer-reviewed publications was done by Sharrock *et al*., 2008. The objective was to determine whether the incidence of all-cause mortality and pulmonary embolism in patients undergoing total joint replacement differs with currently used thromboprophylaxis protocols. Twenty studies were reviewed; the following table 2.1 is a summary of this meta-analysis:

Table 2.1: Summary of Sharrock et al., 2008 Meta-Analysis

Criteria for inclusion	**Criteria for exclusion**
Published from 1998 to 2007	Specific cohort, for example, patients with cirrhosis, renal failure, bilateral procedures, or obesity.
English language publications	Expert opinion, communications between persons, and all studies that used DVT as a surrogate marker.
6 week or 3-month incidence of all-cause mortality, and symptomatic non-fatal PE Series with elective unilateral or bilateral THR and TKR, as well as revision surgeries	Patients with surgeries > 15 years ago
Limited to consecutive case series with documented patient follow-up and randomized trials	

Outcomes estimated were mortality and PE rates, as well as relative risk estimates for these rates.

The reviewed studies were separated into three groups:

Group A	**Group B**	**Group C**
15,839 patients	7,193 patients	5,006 patients
Receiving LMWH, ximelagatran, fondaparinux or rivaroxaban	Receiving regional anesthesia, pneumatic compression, and aspirin	Receiving warfarin alone

Studies belonging in the three categories were further divided into 6-week and 3-month follow-ups. The Variations in these study populations were as follows:

1. Group A: Included 36% (3785 of 10,437) of patients who received spinal or epidural anesthesia.
2. Group B: Included 8% (570 of 7193) of patients who received warfarin, either due to high risk of VTE or it being prescribed prior to surgery for other medical complications. Also included 6% (438 of 7193) of patients who received

general, rather than regional anesthesia; intra-operative heparin was used in one study for TKR.

3. Group C: Included 29% (397 of 1342) of patients who received spinal or epidural anesthesia.

The conclusions were as the following (Sharrock, *et al*., 2008):

1. Group A was associated with the highest all-cause mortality of the three modalities studied. All-cause mortality was higher in Group A than in Group B (0.41% vs. 0.19%).
2. Group B was associated with the lowest all-cause mortality after total joint replacement. The incidence of clinical non-fatal PE was higher in Group A than in Group B (0.60% vs. 0.35%).
3. All-cause mortality and non-fatal PE in Group C was similar to those in Group A (0.4% vs. 0.52%).

The findings of this meta-analysis and systematic review demonstrate clearly the effective and safe profile for aspirin when it is combined with spinal anesthesia, and this combination explains why the authors have chosen spinal anesthesia as one criteria for aspirin use, in the low high risk category in the proposed VTE risk assessment tool in the current study (Appendix 1).

Another study with a consecutive, nonselective clinical trial design, was conducted over a 10 years period. The study objective was to determine if aspirin is as effective as other thromboprophylaxis agents in preventing fatal and nonfatal PE or symptomatic DVT in the first 6 weeks after total knee replacement. Another endpoint was to determine if aspirin had a lower risk of major bleeding than other thromboprophylaxis agents. In this study three thousand and four hundred seventy-

seven patients were recruited, three thousand four hundred and two patients received aspirin 325 mg twice daily for 6 weeks. From the seventy-one patients who were not given aspirin, sixty-seven were given warfarin due to their medical history, and the rest of patient (four) had a history of PE or thrombophilia and were treated with a vena cava filter and LMWH or warfarin. Patients with a past history of DVT without PE were given aspirin alone. Outcomes included PE (both fatal and non-fatal), proximal DVT and bleeding. The author concluded that aspirin, if combined with early mobilization, spinal anesthesia, and pneumatic feet pumps is associated with a risk of fatal PE of approximately 0.1% in postoperative TKR patients (Lotke and Lonner, 2006). So, this study has a stipulated aspirin use, aspirin use should be combined with early mobilization, spinal anesthesia which represents the same listed criteria for low high category (Appendix 1) in the proposed VTE risk assessment tool in the current study. Another prospective study which was done; to determine the occurrence of fatal PE following elective primary joint replacement with the use of aspirin as VTE prophylaxis, has concluded that aspirin is safe with small complication rates, although there was a risk for GI bleeding and ulceration in some patients (Rounds, 2009). The design for this study was a prospective collection of data on 4253 consecutive patients with primary total hip or knee replacement. The study was performed between November 2002 and November 2007. The outcomes included PE, DVT, mortality and morbidity with aspirin used as thromboprophylaxis following THR or TKR.

2.2.1(d) Clinical Expert Opinions

In 2008 a Survey of American Association of Hip and Knee Surgeons (AAHKS) Membership was done to explore the preferred VTE prophylactic agent as well as the preferred guideline (Markel, *et al.,* 2009). Data collected was based on self-reported opinions and practices, and not on retrospective patient data. Anticoagulants were ranked for bleeding risk, wound drainage, ease of use and efficacy as the following:

a. Aspirin was ranked to be:
    1. The easiest to use, with the least risk of bleeding or wound drainage.
    2. The least effective of the six products (Aspirin, Enoxaparin, warfarin, fondaparinux, dalteparin, and Heparin) .
b. Enoxaparin was ranked as the most effective treatment and the second easiest to use.
c. Warfarin was ranked as the 5th easiest to use, but second behind aspirin as having the least risk of bleeding and wound drainage.

In the same survey they were comparing the guidelines & the results were as the following：

Comparing ACCP and AAOS guidelines:

1. 82% of surgeons agreed with AAOS guidelines compared with 19% of surgeons agreed with ACCP
2. 74% of surgeons did not believe ACCP guidelines were relevant to orthopedics.

Moreover, when surgeons were asked which of the guidelines were most relevant to their practice?

1. 3.1% believed ACCP guidelines were the most relevant.
2. 68% believed AAOS guidelines were the most relevant.
3. 27% believed elements of the ACCP and AAOS were both relevant.
4. 2.7% believed neither ACCP nor AAOS were relevant (Markel, *et al.*, 2009).

As it's clear from the results of this study that the general trend in 2008 was against the use of aspirin as VTE prophylaxis post orthopedic surgeries. But as known expert opinions studies have level C evidence, which is not strong enough to provide recommendations based on it.

Later in 2012, ACCP has updated their recommendations by approving aspirin as one choice for VTE prophylaxis post orthopedic surgeries as Grade 1B recommendation (ACCP, 2012). Moreover, several recent studies have proven the efficacy of aspirin as VTE prophylaxis post orthopedic surgeries (Azboy et al., 2017), which has a comparable efficacy as LMWHs with safer profile by having less bleeding events, as stated by Mistry, et al., 2017 in their recent systematic review.

2.2.1(e) Aspirin as VTE prophylaxis post HFS

Hip fracture is associated with increased mortality rates for both the short-term (3 to 6 months) and long-term 5 to 10 years (Hannan, *et al.*, 2001). A meta-analysis of prospective studies found the relative hazard for mortality during the first three months following a hip fracture to be 5.75 (95% CI 4.94-6.67) in older women and 7.95 (95% CI 6.13-10.30) in older men (Haentjens, *et al.*, 2010).

Hospital readmission rates after initial treatment for hip fracture range from 20 percent within 30 days of discharge (predominantly male) to 30 percent within six months (predominantly female; Katz, *et al*., 2012). Early readmission is associated with patients' comorbidities (Lenguerrand, *et al*., 2018).

A meta-analysis of 10 orthopedic trauma trials found that aspirin significantly reduces the rate of DVT, and PE compared with placebo, but this reduction was significantly less than for other agents (Antiplatelet Trialists' Collaboration, 1994)**.** In a one double-blind randomized controlled trial, having 251 hip fracture patients, administration of low molecular weight heparin resulted in a relative risk reduction of 37 percent compared with aspirin (Anderson et al., 2013). In the largest trial (PEP trial), 13,356 patients with hip fracture were randomly assigned to receive 160 mg of aspirin or placebo for 35 days after surgery, about three quarters of the patients also received another form of thromboprophylaxis (heparin or compression stockings). Patients who received aspirin had a significantly lower incidence of symptomatic DVT or pulmonary embolism (1.6 versus 2.5 percent). There was no benefit over aspirin in the subgroup who had received low molecular weight heparin. There was no difference in all-cause mortality for any group (Cohen & Quinlan, 2000).

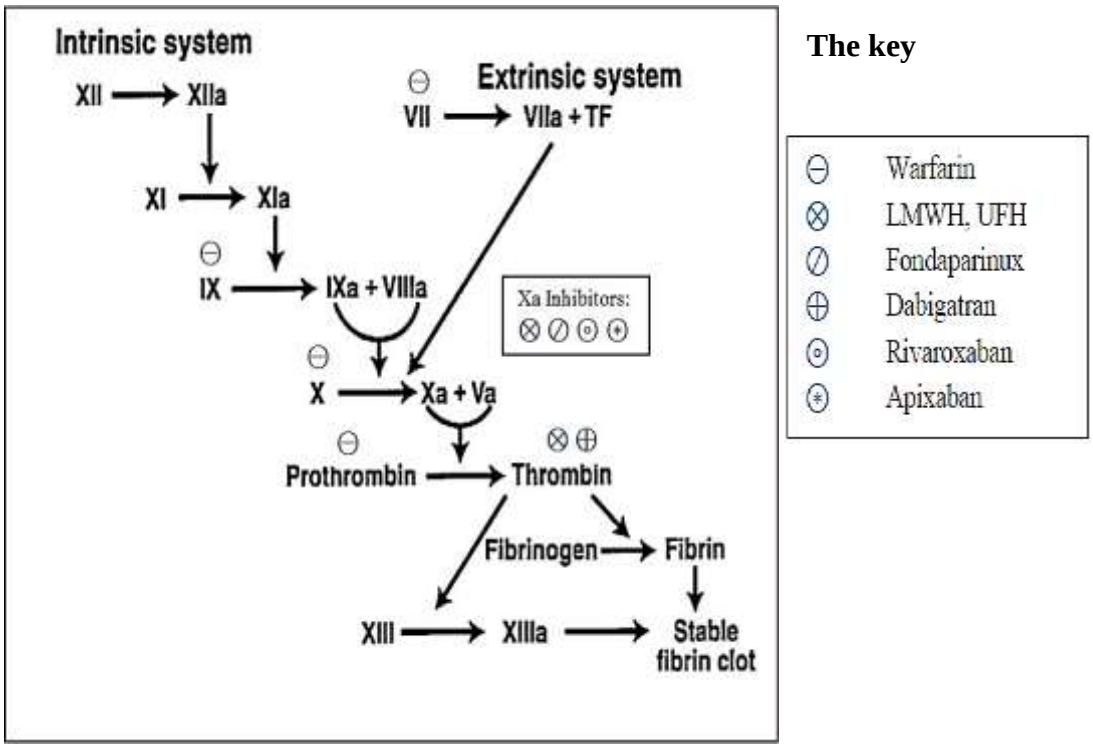
2.2.1(f) Aspirin as a Potential Anticoagulant

A professor from the Department of Biochemistry at the University of Vermont said: "The primary effect of aspirin as an anticoagulant is thought to involve platelet function; however, aspirin is also an anti-inflammatory." (Undas, *et al.,* 2006). The anti-inflammatory effect of chronic aspirin administration also probably down-regulates tissue factor presentation by inflammatory cells in the blood circulation. It also potentially alters tissue factor presentation by the vascular endothelial cells

(Undas, *et al.*, 2006). In a review article published in Blood, they presented an overview of other possible antithrombotic properties of aspirin, but still, mechanisms by which aspirin acts as an anticoagulant is not clear. Aspirin at higher doses (75 mg and 300 mg) will decrease the concentration of thrombin markers similarly, this effect was found in both healthy individuals and patients with high risk of coronary artery disease (Undas, *et al.*, 2014). Additionally, Azboy, *et al.*, 2017 stated that aspirin action is not limited to arteries rather it works in the venous circulation, in addition to its role in suppression platelet aggregation, it also decreases the production of thrombin by the acetylation of antithrombin III and prothrombin, reducing tissue factor expression on monocytes and macrophages.

2.2.2 Anticoagulants for VTE Prophylaxis Post Major Orthopedic Surgeries

Patients undergoing hip and knee operation or with hip fracture or major lower extremity injuries are at significantly high risk for VTE, and therefore the routine use of thromboprophylaxis has been standard-of-care for several years (ACCP, 2012). Before thromboprophylaxis was widely used, DVT, that is usually clinically silent, occurred in 40-60% of these patients, PE occurred in 5-10% of patients, and fatal embolism was one among the foremost common causes of death (Yang et al., 2019). The use of evidence-based thromboprophylaxis has been shown to scale back the risk of DVT by a minimum of fiftieth and, as a result, major and fatal VTE are currently terribly uncommon (ACCP, 2012). Actually, huge numbers of clinical trials have evaluated many various thromboprophylaxis modalities for VTE prophylaxis post major orthopedic surgeries (see figure 2.1); a brief summary for these options will be followed.



Reproduced with permission from: Sander GE, Giles TD. "Ximelagatran: light at the end of the tunnel or the next tunnel". Am J Geriatr Cardiol. 2004;13(4):221-224.

Figure 2.1: Anticoagulant and site of action summary

2.2.2(a) Oral Anticoagulant

Several oral options are available and approved to be used as VTE prophylaxis post major orthopedic surgeries (ACCP, 2012), vitamin K antagonists (Warfarin) factor Xa inhibitors like rivaroxaban and apixaban, and direct thrombin inhibitors like dabigatran. Table 2.2 shows a summary for these oral agents.