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ABSTRACT

OBJECTIVE
The objective of this selective EBM review is to determine whether or not the use of Apixaban or Enoxaparin is more effective in the prophylaxis of venous thromboembolism post-orthopedic surgery.

STUDY DESIGN
Review of three English language randomized, double-blind, placebo-controlled clinical trials from 2009-2010.

DATA SOURCES
Randomized, double-blind placebo controlled, clinical trials comparing the effectiveness of Apixaban and Enoxaparin in the prophylaxis of Venous Thromboembolism (VTE) post-orthopedic surgery were found using PubMed, the Cochrane Database of Randomized Controlled Trials, and the Cochrane Databases of Systematic Reviews.

OUTCOMED MEASURED
Development of venous thromboembolism (VTE) post-orthopedic surgery including Total Knee Replacement (TKR) and Total Hip Replacement (THR) compared to preoperative baseline was measured using four different modes of detection: Bilateral Venography, Ventilation Perfusion Scan, Spiral CT, Pulmonary Angiography, and bleeding during the treatment phase.

RESULTS
ADVANCE-1 (Apixaban Dose Orally vs. Anticoagulation with Enoxaparin) compared the efficacy of 2.5mg of Apixaban twice daily with that of Enoxaparin 30mg subcutaneous dosing twice daily post-TKR. Both regimens were initiated 12-24 hrs post surgery. No clear VTE rate reduction was evident with either drug, both exhibited similar results of 8.8% Enoxaparin, 9.0% Apixaban. However, reduced bleeding with Apixaban was observed. ADVANCE-2 focused on the two interventions, Apixaban 2.5mg twice daily initiated 12-24 hrs post surgery in comparison to Enoxaparin regimen of 40 mg subcutaneously 12 hrs prior and continued 10-14 days post-TKR. It was observed that Apixaban was superior to Enoxaparin post-TKR with a 9.3% relative reduction rate in VTE formation and 1% decline in bleeding episode. ADVANCE-3 evaluated the efficacy of Apixaban and Enoxaparin post-THR at the same dosage and administration as ADVANCE-2 TKR trial, however the treatment regimen was continued 35 days post-THR surgery. ADVANCE-3 trial concluded Apixaban was far more effective at VTE rate reduction with 1.4% compared with 3.9% of Enoxaparin use.

CONCLUSIONS
The use of Apixaban 2.5 mg orally twice daily is an appropriate, safe and effective alternative to the traditional Enoxaparin for thromboprophylaxis post-orthopedic surgery.

KEY WORDS
Venous Thromboembolism (VTE), Thromboprophylaxis Post-Orthopedic Surgery, Enoxaparin, Apixaban

INTRODUCTION

Venous Thromboembolism (VTE) is a major source of morbidity and mortality worldwide. It encompasses both Deep Venous Thrombosis (DVT) and Pulmonary Embolism.[1] This highly preventable medical condition affects over 1 million people each year and accounts for approximately 300,000 deaths/year.[2]

The aging population in the United States is on the rise with the influx of the baby boomer generation, which will yield a growth of degenerative diseases. As this population soars, it is of significant relevance to not only the patient but to the primary care giver whose role will be to ensure the safety of managing the pharmacotherapy and provide proper patient education.

As we age our joints become subject to deleterious effects of certain pathologic diseases such as Osteoarthritis and Rheumatoid Arthritis, which warrant the need for joint replacement.[3,4] By 2030, there will be an estimated 174% increase in total hip replacements and 673% increase in knee replacements.[3] One of the major complications of orthopedic surgery is venous thromboembolism. The economic burden of VTE in the United States incurs high health care costs of approximately $1.5 billion per year. Initial treatment and management of a single VTE event is approximately $3000-$9500. Total cost of VTE treatment over 3 months is $5000, six months, $10,000, and one year is estimated at $33,000.[5-7] The exorbitant cost can be attributed to long-term complications including Chronic Thromboembolic Pulmonary Hypertension (CTPH), Post-Thrombotic Syndrome (PTS), reoccurrence and follow-up treatment necessary when on anticoagulant therapy. Patients with VTE spend ten times as long in the Intensive Care Unit and more than twice as long hospitalized as those without a VTE.[5,7]

Venous thromboembolism is the third most common cardiovascular illness after acute coronary syndrome and stroke. Venous thromboembolism results from a combination of factors that contribute to the formation of a clot, hypercoaguable states, hereditary and acquired risk

factors, surgery, trauma, venous stasis, and vessel wall damage. Venous thrombi are formed from red blood cells, platelets, and leukocytes that are bound together by fibrin, where it adheres to a site of damaged vessel. Deep Venous Thrombosis is the most common form of VTE and forms in the distal calf veins where it propagates to the proximal veins and breaks free forming potentially lethal emboli to the pulmonary system resulting in a pulmonary embolus.[9] Therefore, patients undergoing orthopedic joint replacement surgery including total knee and hip replacements are at high risk of venous thromboembolism.[10]

There is significant armamentarium of anticoagulant therapy used in the treatment and prophylaxis of VTE, which includes: Low-Dose Unfractionated Heparin, Low-Molecular Weight Heparin (Enoxaparin, Dalteparin), Factor Xa Inhibitor (Fondaparinux), and Vitamin K agonists (Warfarin). The benefit to the use of Warfarin has considerably decreased postoperative VTE, however there are several impediments to its use. Patient compliance is of great concern; there are several drug and food interactions, rigorous monitoring, and first and foremost the risk of bleeding during therapy. Low-Molecular Weight Heparins (LMWH) such as Enoxaparin has been the FDA approved therapy for prophylaxis of VTE. This drug class negates the need for constant monitoring, however it is administered subcutaneously, which may require home health assistance or significant patient compliance and education.[11]

Current pharmacologic treatment for prevention of VTE postoperative provides effective prophylaxis short-term, however a significant risk for VTE remains in those patients with THR and TKR. It has documented that subclinical venous thrombosis occurs in 15-20% of THR and 30-40% of patient who have undergone TKR.[12]

Optimal anticoagulant prophylaxis of VTE post-orthopedic surgery would prove to be a therapeutic agent that does not require monitoring, one that has easy patient compliance, limited

adverse reactions (i.e. bleeding) and have an antidote. Several new anticoagulants are currently being investigated in the prevention and treatment of VTE in orthopedic patients, one of which is Apixaban, a Factor Xa Inhibitor. This oral drug formulation has multiple routes for elimination, reaches peak levels after 3 hrs of dosing, a half-life estimated between 9-14 hrs., and no monitoring parameters.[13] The following randomized, double blind clinical trials, and placebo-controlled studies to be examined have compared Apixaban to Enoxaparin for the prophylaxis of VTE after THR and TKR.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not the use of Apixaban or Enoxaparin is more effective in the prophylaxis of venous thromboembolism post-orthopedic surgery.

METHODS

The criteria used for the selection of the three studies included: 1) the population patients involved in the study were females ages 60 and older post-orthopedic surgery THR and TKR, 2) the intervention measured was Apixaban, 2.5mg dose twice daily), 3) the comparison group evaluated at two different doses of Enoxaparin, 30mg and 40mg, twice and once daily, respectively, 4) the outcomes addressed were VTE prophylaxis 10-14 days post-TKR and THR, and 35 days post-THR. The three chosen studies to be analyzed: 1) ADVANCE-1 comparing Apixaban (2.5mg) with Enoxaparin (30mg) post-TKR, 2) ADVANCE-2 comparing Apixaban (2.5mg) with Enoxaparin (40mg) post-TKR, and THR comparing Apixaban (2.5mg) with Enoxaparin (40mg) post-THR.

Randomized, double-blind placebo controlled, clinical trials comparing the effectiveness of Apixaban and Enoxaparin in the prophylaxis of Venous Thromboembolism (VTE) post-

orthopedic surgery were found by the author using PubMed, the Cochrane Database of Randomized Controlled Trials, and the Cochrane Databases of Systematic Reviews from 2009-2010. Key words used: Venous Thromboembolism (VTE), Thromboprophylaxis Post-Orthopedic Surgery, Enoxaparin, and Apixaban. All trials were published in peer-reviewed journals in the English language, were selected based on the importance of outcomes to the patient (Patient Oriented Evidence that Matters, POEMS). Inclusion criteria consisted of studies that focused on treatment and prophylaxis with Apixaban, that were randomized placebo-controlled, double blind clinical trials that focused on patient oriented outcomes. Exclusion criteria included active bleeding or contraindication to anticoagulant treatment.

The statistics used in the study included p-values with confidence intervals (CI), numbers needed to treat (NNT), numbers needed to harm (NNH), relative risk (RR), relative risk reduction (RRR), relative risk increase (RRI) and absolute risk increase (ARI). The demographics and characteristics included in the studies are shown in Table 1.

OUTCOMES MEASURED

The primary outcomes measured by the three studies analyzed was the presence or absence of developing a VTE (DVT and PE) post-TKR and THR. Several means were used to access this outcome at the end of the anticoagulation treatment phase in all studies: bilateral venography to access for DVT and if pulmonary embolus was suspected then spiral CT or pulmonary angiography studies were conducted. ADVANCE-1 study evaluated the efficacy of two drugs, Apixaban 2.5 mg or Enoxaparin 30 mg subcutaneously, beginning 12-24 hrs post-

TABLE 1. Demographics and Characteristics of the Included Studies

STUDY	TYPE	# PTS	AGE (yrs)	Inclusion Criteria	Exclusion Criteria	W /D	Intervention
Advance 1 Lassen, et al., 2010	RCT (double-blind, phase III study)	3057	Age≥66	•Female •Elective unilateral TKR or same day bilateral TKR	•Active Bleeding •Requirement of ongoing prophylaxis with anticoagulant therapy • Uncontrolled HTN, ↓Renal Function, Heparin Allergy, Thrombocytopenia, Active Hepatobiliary Disease, Allergy to Radiocontrast Dye	0	• Apixaban 2.5mg twice orally + Enoxaparin placebo inj., once daily, 12-24hrs post surgery & continue10-14 days • Enoxaparin 30mg SC twice daily, 12 hrs prior to surgery & continued 10-14 days.
Advance 2 Lassen, et al., 2009	RCT (double-blind control study	3195	Age≥65	•Female •Elective unilateral or bilateral TKR •Or revision surgery of a previous joint replacement	•Same criteria as Lassen et al 2010	0	•Apixaban 2.5 mg PO BID + inj. of placebo Enoxaparin once daily, 12-24 hrs post surgery & continued 10-14 days • Enoxaparin, 40mg SC inj. once daily + placebo tablets, 12-24 hrs post surgery and continued 10-14 days
Advance 3 Lassen, et al., 2010	RCT (double blind control study	5407	Age≥60	Female •Elective THR •Or revision surgery of a previous joint replacement	Same criteria as Lassen et al 2010	0	Apixaban 2.5 mg PO BID + inj. of placebo Enoxaparin once daily, starting 12-24 hrs post surgery x 35 days • Enoxaparin, 40mg SC inj. once daily + placebo tablets, starting 12 hrs prior to surgery x 35 days

TKR surgery and continued for 10-14 days. Patients were followed-up at days 30 and 60, after cessation of anticoagulation.[12]

ADVANCE-2, phase 3, study focused on Apixaban 2.5 mg twice/daily beginning 12-24 hrs post-wound closure and Enoxaparin 40 mg subcutaneously once daily injections starting 12 hrs prior to TKR surgery. All medications were continued for 10-14 days and were evaluated at days 30 and 60 post-TKR.[14]

Lassen et al. conducted the ADVANCE-3 trial, which measured VTE formation post-THR. Apixaban 2.5 mg twice/daily and Enoxaparin 40 mg subcutaneously once/daily, were used starting 12 hrs prior to THR surgery. Treatment regimens were continued for 35 days. Patients were followed for an additional 65-95 days post-THR.[15]

All three studies included adverse affects to treatment, which included major and minor bleeding episodes that occurred during the treatment phase and within 2 days after stopping the medication, elevations in aminotransferase, bilirubin levels, stroke, and myocardial infarction were also analyzed during the treatment phase and follow-up periods. In each phase 3 trial the adverse affects were recorded for each treatment group.[12, 14,15]

RESULTS

ADVANCE-1 study evaluated 3195 female patients ages 65 years who underwent randomization for TKR. 1599 were treated with Apixaban 2.5 mg orally twice/daily plus placebo-Enoxaparin injections starting 12-24 hrs post-TKR. 1596 patients were administered 30 mg subcutaneous Enoxaparin twice/daily. Both medications were started 12-24 hrs postoperative and continued for 14 days. Patients were followed 60 days after cessation of anticoagulation.[12] It was observed that VTE developed in 9.0% patients in the Apixaban group with a 95%CI, 0.78-1.32 and ρ=0.06 in comparison with the Enoxaparin group 8.8% with a 95% CI, -2.22-2.44 and

$\rho<0.001$.[12] The percentage of VTE formation with the use of Apixaban was not significantly different from the Enoxaparin therapy post-TKR.[12]

ADVANCE-2, phase 3 study focused on females ages 66-67 years undergoing TKR. 3057 patients were selected for the study. 1528 females were randomized to the Apixaban group, where 976 were selected completed the study through the follow-up period. N=552 were excluded because they either did not undergo venography or had venograms that could not be interpreted. 976 patients received Apixaban 2.5 mg twice/daily plus beginning 12-24 hrs post-wound closure plus placebo-Enoxaparin injections beginning 12 hrs prior to TKR surgery. 1529 females were randomized for the Enoxaparin group. Of the 1529 females, N=552 were excluded did not undergo venography or had uninterpretable results. 997 patients completed the trial, receiving Enoxaparin 40 mg subcutaneously once/daily injections starting 12 hrs prior to TKR surgery plus placebo-Apixaban tablets twice/daily starting 12-24 hrs post-wound closure. All medications were continued for 10-14 days and patients were evaluated at days 30 and 60 post-TKR.[14] Apixaban was found to be superior to Enoxaparin VTE events at 15% and 24% respectively, with a 95% CI, 0.51-0.74, $\rho<0.0001$. Furthermore, ADVANCE-2 confirmed VTE results with 75% of the suboptimum venograms able to be interpreted. In addition, 78% of the initial study population for the allocation of Apixaban and Enoxaparin groups could be assessed for VTE. The ADVANCE-3, phase 3 study, evaluated 5407 females, ages 60 years, undergoing THR. 2708 females were randomized to receive Apixaban. N=759 were excluded due to non-compliance with venography or uninterruptible venograms. 1949 patients received Apixaban 2.5 mg twice/daily plus placebo Enoxaparin beginning 12-24 hrs post-wound closure. 2699 patients were randomized into the Enoxaparin treatment group, n=782 patients were excluded from the study due to aforementioned exclusion criteria in the Apixaban group. 1917 females were treated

with 40 mg subcutaneously once daily starting 12 hrs prior to THR surgery plus placebo-Apixaban 12-24 hrs post-THR. Treatment regimens were continued for 35 days. Patients were followed for an additional 65-95 days post-THR.[15] It was observed that females undergoing hip replacement treated with Apixaban had a reduced rate of VTE formation of 1.9% and 3.9% of Enoxaparin. 95% CI, 0.22 to 0.54, 95% CI, 0.51-0.74, $\rho<0.001$. Again, Apixaban was superior to that of Enoxaparin at the dosage parameters set for this study.[15]

In the three studies analyzed, the participants involved did experience some adverse side effects. This data was reported as the number of patients that experienced adverse side effects of major bleeding defined as clinically overt bleeding, hemoglobin drop of greater than 20g/L in 24 hrs, bleeding at a critical site and transfusion of two or more units of packed red blood cells, minor bleeding episodes, stroke, myocardial infarction, elevation in aminotransferase and billirubin levels to as a result of the anticoagulant medication as represented in Table 2.[12, 14,15]

In the ADVANCE-1 trial the most common adverse side effect was major bleeding event. Apixaban was associated with a lower risk of bleeding, 0.7%, in comparison to 1.4% with Enoxaparin as demonstrated in Table 2. Least common adverse effects observed in both groups

TABLE 2. Adverse Side Effects Profile
ADVANCE-1 (N,%) ADVANCE-2 (N,%) ADVANCE-3 (N%)

	Apixa	*Enoxa*	*Apixa*	*Enoxa*	*Apixa*	*Enoxa*
Major Bleeding	11(0.7)	22(1.4)	9(0.6)	14(0.9)	22(0.8)	18(0.7)
Minor Bleeding	39(2.4)	40(2.5)	51(3.4)	54(3.6	184(6.9)	200(7.5)
MI	2(0.1)	5(0.3)	1(<1)	1(<1)	9(0.3)	4(0.2)
Stroke	0	2(0.1)	2(<1)	0	1(0.1)	5(0.2)
↑Aminotransferase	18(1.1)	27(1.7)	25(2)	23(2)	37(1.4)	46(1.8)
↑Bilirubin	2(0.1)	8(0.5)	15(<1)	8(<1)	27(1)	13(0.5)

Apixa=Apixaban, Enoxa=Enoxaparin, MI=Myocardial Infarction

were elevations in aminotransferase and billirubin levels, indicating a low risk for hepatotoxicity with use of Apixaban.[12] However, a total of 8 patients incurred a thromboembolic event in both groups, and 9 patients died during the study period. The ADVANCE-2 study observed no

difference in major bleeding episodes between the two groups. Other adverse side effects were MI, stroke, nausea, vomiting and constipation, which were found to be similar between the two groups in each conducted study (*see TABLE 2*). Four patients died during the study period.[14] The ADVANCE-3 trial also noted no elevated risk of bleeding episodes between the two groups as well as thromboembolic events.

Table 3 shows the adverse event rates in the control group (CER, control event rate) and the experimental event rate (EER). The CER depicts those who received Enoxaparin and developed VTE and the EER was determined as those who were administered Apixaban who experienced a VTE. The ADVANCE-1 study observed a negative relative risk (RRI) that depicts that an adverse reaction is less likely to occur in the experimental verses the control group. The absolute risk increase (ARI) demonstrates the difference in risk between both the control and experimental groups. In the ADVANCE-3 study the ARI is 0.2%, which means there is an absolute relative increase in bleeding with the use of Apixaban. Number Needed to Harm (NNH) was calculated to determine the number of people exposed to treatment to cause one person harm. In the ADVANCE-2 trial, for every 100 patients treated one person will experience an adverse event such as an MI, stroke, major/minor bleeding, or elevation in bilirubin or aminotransferase, compared to control.

TABLE 3 Analysis of Outcomes and Numbers Needed to Harm in Patients Prophylaxed with Apixaban and Enoxaparin Post-Orthopedic Surgery

STUDY	*# PATIENTS COMPLETED STUDY*	*CER*	*EER*	*RRI*	*ARI*	*NNH*
ADVANCE-1	3195	4.3%	2.9%	-33.5%	-1.4%	72
ADVANCE-2	3057	4%	5%	25%	1%	100
ADVANCE-3	5407	4.8%	5%	4.2%	0.2%	5

Table 4 depicts the amount of patients that needed to be treated to prevent adverse effects. The ADVANCE-2 study had the most significant data demonstrating that in order to prevent one bad outcome from occurring in this study, 12 patients would need to be treated to prevent a harm of one VTE post-TKR.

TABLE 4 Analysis of Outcomes and Numbers Needed to Treat in Patients Prophylaxed with Apixaban and Enoxaparin Post-Orthopedic Surgery

STUDY	*# PATIENTS COMPLETED STUDY*	*CER*	*EER*	*RRR*	*ARR*	*NNT*
ADVANCE-1	3195	8.8%	9%	2.27%	0.2%	5
ADVANCE-2	3057	24%	15%	37.5%	9%	12
ADVANCE-3	5407	1.4%	3.9%	1.78%	2.5%	1

DISCUSSION

Two of the three studies addressed in this paper demonstrate that Apixaban administered 2.5 mg orally twice/daily is superior to current standard therapy, Enoxaparin, 40mg subcutaneously once/daily in the prevention of VTE post-orthopedic surgery. [14,15] This novel drug has many additional benefits compared to the standard therapy such as: no routine monitoring, oral dosing, short half-life, and limited food interactions, which may be attractive for patient compliance. One of the major risks of post-orthopedic surgery is bleeding, as a safety measure this is of relative importance. It has been shown that treatment with Apixaban is associated with lower rates of bleeding episodes than traditional therapy, 4.8% and 5.0% of patients in the Apixaban and Enoxaparin groups, respectively (P=0.72).[15] However, there is no reversal for this agent, drug interaction data is not available and foremost Apixaban has only been recently FDA approved for the treatment of stroke and systemic emboli in patients suffering from atrial fibrillation in the US.[16] Apixaban (Eliquis®) is currently being used in Europe as a prophylactic measures against VTE post knee and hip surgery.[17]

The present analysis has several limitations that could have contributed to the results. Lack of information regarding the patient's health status or co-morbidities prior to surgery, such as total cholesterol levels, organ function, cancer, diabetes, and physical therapy sessions post surgery which all can contribute to the recovery phase.

All three studies also focused primarily on women. It has been documented that arthritis affects an estimated 46.4 million adults in the U.S., of whom 61 percent (28.3 million) are women.[18] However, degenerative joint disease, which is a leading cause of joint replacement surgery, affects both sexes. Although, the men make up a smaller percentage of the arthritic population, they should be accounted for in future studies when evaluating VTE prophylaxis post orthopedic surgery.

CONCLUSION

Apixaban offers a safe and effective alternative for the prophylaxis of VTE post-orthopedic surgery. This was proved by both the ADVANCE-2 and ADVANCE-3 trials, where the administration of 2.5 mg Apixaban orally twice/daily led to significant risk reduction of VTE, without increased incidence of bleeding events.[14,15]

The ADVANCE-1 study showed Apixaban was inferior to Enoxaparin for VTE prevention; however, it did demonstrate lower major bleeding rates, proving Apixaban may be an attractive option for orthopedic surgeons concerned with bleeding post-TKR and THR, which can predispose the patient to infections that can lead to destruction of the prosthesis.[12] In summary, the use of Apixaban in post orthopedic surgery is supported by lower rates of VTE and no further increase in bleeding episodes. Its relative ease of use, rapid onset of action and pharmacokinetic properties prove to be a novel anticoagulant alternative at the forefront of clinical medicine that will transform patient care and compliance.

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