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Examination of Venous Thromboembolism Prophylaxis in Patients Undergoing Total Knee Arthroplasty

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Arthroplasty

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TABLE OF CONTENTS

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Abstract

Elective total knee arthroplasty (TKA) is the most frequently performed inpatient surgical procedure in the United States (Kurtz, Ong, Lau, Mowat, & Halpern 2007). Complications of this procedure include deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE). Various pharmacological agents exist for VTE prophylaxis. Warfarin and low-molecular-weight heparin (LMWH) were commonly used for VTE prophylaxis in the past, but with the emergence of novel anticoagulants including factor Xa inhibitors and direct thrombin inhibitors (DTIs), warfarin is used far less frequently. Aspirin is also approved for VTE prophylaxis. The purpose of this study was to determine if a superior drug or combination of drugs exist for VTE prophylaxis based on patient outcomes, cost effectiveness, and risk profile. This review of literature analyzed studies from the past 10 years that compared aspirin, warfarin, Lovenox, and the novel anticoagulants for VTE prophylaxis in post-operative TKAs. Study outcomes included VTE prevention, bleeding risk, and cost. Reversal agents were also examined. Findings of this author's literature review demonstrated that currently, no one superior medication exists for prophylaxis of VTE events in patients undergoing TKA (Cafri et al., 2017). However, current research indicates that both factor Xa inhibitors and aspirin have emerged as the medications of choice. Of the two, aspirin is commonly favored as it does not require laboratory monitoring, it is cost effective, and it is available over the counter. It also has less risk of major bleeding compared to factor Xa inhibitors.

Keywords: TKA DVT prophylaxis, pharmacology, aspirin, Xa inhibitors, LMWH, warfarin, VTE prophylaxis cost TKA, diagnosing DVT

INTRODUCTION

Elective total knee arthroplasty (TKA) is the most frequently performed inpatient surgical procedure in the United States, with an estimated 700,000 TKAs performed in 2010 and a projected 3.48 million procedures per year by 2030 (Kurtz, Ong, Lau, Mowat, & Halpern, 2007). Well-known complications of this procedure include DVT and PE, collectively referred to as VTE. Without utilization of prophylactic measures, the reported risk of venographically documented DVT in patients undergoing TKA ranges from 41-85%. Since the implementation of VTE prophylaxis, a reduction in VTE events of 0.6-1% during hospitalization and 2-3% at three months postoperatively has been reported (Kakkar & Rushton-Smith, 2013). Various pharmacological agents exist for the purpose of VTE prophylaxis. Such agents include aspirin, clopidogrel, warfarin, LMWH, and novel anticoagulants including factor Xa inhibitors and DTIs. The American College of Chest Physicians (ACCP) and the American Academy of Orthopedic Surgeons (AAOS) initially had differing views regarding the superior VTE prophylaxis regimen for patients undergoing major orthopedic surgery, which includes TKA. However, as of 2012, the ACCP and AAOS have both approved of the sole use of aspirin as a means of VTE prophylaxis (Stewart & Freshour, 2013). The ACCP recommends use of LMWH, fondaparinux, dabigatran, apixaban, rivaroxaban, low-dose unfractionated heparin (UFH), vitamin K antagonists, or aspirin for a minimum of ten to fourteen days postoperatively (Falck-Ytter et al., 2012). The AAOS recommends using prophylaxis but does not currently endorse a single, superior medication (AAOS, 2011).

STATEMENT OF THE PROBLEM

Many potential pharmacologic options for VTE chemoprophylaxis exist, each with a unique profile of benefits, risks or side effects, and cost. These factors, along with patients' medical history, must be considered when determining the most suitable option for VTE chemoprophylaxis. To date, no singular "gold standard" therapy is recommended for VTE prophylaxis following TKA.

RESEARCH QUESTIONS

Among the current pharmacologic options for VTE prophylaxis following TKA, does a superior drug or combination of drugs exist based on patient outcomes?

Which of the current pharmacologic VTE prophylaxis options demonstrates the greatest cost effectiveness with the fewest risks?

METHODOLOGY

PubMed and Science Direct were utilized to find research articles regarding outcomes of different medications for VTE prophylaxis in patients undergoing TKAs. Because of the different functionality of the search engines, different MeSH terms were used to obtain the appropriate articles. MeSH terms that were utilized to obtain relevant articles in PubMed included the following: "Arthroplasty, Replacement, Knee, Venous Thrombosis/prevention and control" [Mesh] , "Aspirin"[Pharmacological Action], "Warfarin" [Pharmacological Action], " Factor Xa Inhibitors" [Pharmacological Action], "Lovenox," [Pharmacological Action], "Cost" [Mesh] and "Treatment Outcomes" [Mesh]. In Science Direct, search terms utilized included the following: "VTE prophylaxis TKA aspirin," "Aspirin AND Warfarin And Xa inhibitors AND VTE Prophylaxis," and "TKA AND Xa inhibitors AND enoxaparin." Lastly, "VTE prophylaxis for orthopedic surgery patients" was used to search for current guidelines in Dynamed Plus.

Publications examined for this literature review were peer reviewed articles published within the past ten years.

LITERATURE REVIEW

Review of the literature confirmed the existence of several pharmacologic options for VTE prophylaxis in post-operative management of patients undergoing TKA. The pharmacology of medications included in this literature review was obtained from various credible textbooks and research articles. Studies were included if the patient population underwent a TKA and did not have a preexisting condition requiring preoperative anticoagulation therapy. Only studies performed within the last 10 years were reviewed. Study participants were all adults.

DVT Pathophysiology, Risk Factors, and Diagnosis

The coagulation cascade is initiated by the release of tissue factor, which is stimulated by any tissue trauma and/or vascular injury. Once released, tissue factor forms a complex with factor VIIa which, in the presence of calcium, cleaves clotting factors IX and X to their activated forms, IXa and Xa (Adams, Anger, Greenwood, & Fanikos, 2013). The activation of these factors allows the prothrombinase complex to attach to a phospholipid membrane. This combination results in the breakdown of prothrombin to thrombin (Adams et al., 2013). Thrombin is one of the most potent activators of both primary (platelet mediated) and secondary (clotting factor mediated) hemostasis. Thrombin may also potentiate clot formation by fibrin polymerization, platelet receptor activation, endothelium activation, and activation of factors V, VIII, XI, and XIII (Adams et al., 2013). Anticoagulation agents work by alternating the various pathways within the coagulation cascade or by targeting thrombin directly, which ultimately interferes with clot formation. On the other hand, indirect inhibitors target and bind to naturally

occurring plasma cofactors, increasing their interaction with clotting factors to disrupt the cascade (Adams et al., 2013).

German physician Rudolf Virchow identified three major facets of thrombus formation; these include venous stasis, endothelial injury, and hypercoagulation and are known collectively as "Virchow's Triad." Patients undergoing TKAs typically meet all three components of the triad: venous stasis in the form of postoperative immobilization, endothelial and vascular injury as the result of surgical trauma, and postoperative release of tissue factor that renders a transient, low-level hypercoagulable state. Increased levels of plasminogen activator inhibitor 1 (PAI-1) are also associated with a decrease in fibrinolytic activity on the first postoperative day (Kneeper & Thomas, 2014).

Some researchers have further investigated venous stasis in postoperative TKA patients. Sasaki et al., (2009) researched venous hemodynamic alterations in lower extremities following total joint arthroplasty, including TKA and total hip arthroplasty (THA). Utilizing Doppler ultrasonography, they measured preoperative and postoperative venous flow volumes. They found the mean venous flow velocities (MVFV) at three days postoperatively and at one week postoperatively were significantly lower than preoperative MVFV. However, at two or more weeks postoperatively, no significant difference from preoperative MVFV was noted. Because venous stasis has a fundamental role in thrombus formation, the results of this study demonstrated that the highest risk of developing a DVT is during the initial two-week postoperative period; after two weeks postoperatively, the risk decreases (Sasaki et al., 2009).

Physicians must carefully consider VTE risk factors prior to clearing patients for total joint arthroplasty. Researchers have found that older age (greater than 70 years), female sex, high BMI (greater than 30), malignancy, bilateral surgery, cemented fixation, and prolonged surgery

time (greater than two hours) place patients at higher risk for developing VTE (Zhang et al., 2015). Other VTE risk factors include history of VTE, diabetes mellitus, hypertension, varicose veins, general anesthesia, and hormone replacement therapy (Bauersachs, 2012). Protective and preventive factors include chemoprophylaxis and early mobilization. By identifying high-risk patients preoperatively, clinicians can plan for more intensive treatment and closer monitoring to better prevent DVT.

DVTs are difficult to diagnose with physical exam alone, and clinical diagnosis relies most heavily on the presence and analysis of risk factors. The most common symptoms associated with DVT include leg pain and swelling; however, most DVTs produce no symptoms. (Patel, 2017). Special physical examination testing includes Homan's sign, which signifies DVT if the patient exhibits calf pain with passive dorsiflexion of the foot. Objective evidence of DVT is found in fewer than 50 percent of patients with the aforementioned signs and symptoms (Patel, 2017). Clinical workup of a suspected DVT consists of a blood test called a D-dimer and/or a venous duplex ultrasound. The D-dimer is only helpful when negative, as a positive D-dimer can signify many other pathological and non-pathological events. The venous duplex ultrasound is the most practical diagnostic tool because it is noninvasive, easily repeatable, and inexpensive. The inability to visualize compressibility of a vein with real-time, B-mode Doppler ultrasound is more than 95 percent sensitive and specific for detecting proximal DVT (Kassai et al., 2004). However, the gold standard for DVT diagnosis is more invasive contrast venography, which demonstrates an intraluminal defect in the presence of a DVT (Kassai et al., 2004).

The majority of orthopedic patients with PE are also asymptomatic unless the embolism is large enough to increase pulmonary resistance, which results in right sided heart failure and hypoxemia (Bauersachs, 2012). Symptomatic patients most commonly present with chest pain

and sudden-onset shortness of breath. Physical exam findings associated with PE include tachypnea and pulmonary crackles (Bauersachs, 2012). The gold standard for PE diagnosis is pulmonary angiography; however, less invasive computed tomography (CT) angiography is more commonly used for diagnosis. If the embolism is large enough to impede all cardiopulmonary function, immediate death can ensue.

Pharmacology and Pharmacokinetics of Current Chemoprophylaxis Agents

Several VTE chemoprophylaxis options exist for patients undergoing TKAs. Clinicians must be aware of the pharmacology and pharmacokinetics of each agent so as to choose the most appropriate agent in light of each patient's co-morbidities, allergies, and risk factors. Knowledge of each agent's mechanism of actions, adverse side effects, potential drug interactions, and reversal agent is required.

Aspirin non-selectively and irreversibly inhibits cyclooxygenase, reducing prostaglandin and thromboxane A2 synthesis, ultimately inhibiting platelet aggregation (Fleisher, Roizen & Roizen, 2017). It is metabolized in the stomach and excreted in the urine. Because its metabolism occurs in the stomach, aspirin ingestion may irritate the stomach lining and potentiate gastric ulcer formation with chronic use. Other common side effects of aspirin include dyspepsia, nausea, vomiting, and bleeding (Fleisher et al., 2017). Common dosing for VTE prophylaxis is 81 milligrams (mg) twice daily for six weeks postoperatively following TKA. A reversal agent does exist in the case of overdose or excessive bleeding. To reverse any antiplatelet agent used in the last 24 hours, the patient should be given platelets (one pack or six units of donor platelets) and desmopressin (DDAVP) (0.3 micrograms(mcg)/kilogram(kg) DDAVP in 50 milliliters (mL) normal saline given over 15 to 30 minutes). DDAVP is a synthetic antidiuretic hormone

analogue and works by increasing plasma levels of factor VIII and von Willebrand factor, which are important in the coagulation cascade (DeLoughery, 2015).

Factor Xa inhibitors such as rivaroxaban and apixaban work by inhibiting the common pathway of the coagulation cascade. Clot formation is dependent upon the activation of factor X to factor Xa via the intrinsic and extrinsic pathways (Alquawaizani, Buckley, Adams, & Fanikos, 2013). Factor Xa inhibitors inhibit clot formation by selectively and reversibly blocking the active site of factor Xa. They also inhibit free and clot-bound factor Xa and prothrombinase activity (Alquawaizani et al., 2013). Uniquely, factor Xa inhibitors have a short half-life of five to twelve hours. Thus, in the case of accidental overdose, normal dosing can resume just one day following such an event (Alquawaizani et al., 2013). The dosing regimen for apixaban is 2.5 mg 12-24 hours after surgery followed by 2.5 mg twice daily for 12 days ("Apixaban," 2017). Currently, no Food and Drug Administration (FDA) approved reversal agent exists for factor Xa inhibitors; however, a promising drug is currently undergoing phase III trials (Husted, Verheugt, & Comuth, 2015). This drug, andexanet alfa, is designed to neutralize the anticoagulant effects of both direct and indirect factor Xa inhibitors. Andexanet is a recombinant modified human factor Xa decoy protein that is catalytically inactive but retains the ability to bind factor Xa inhibitors at the active site with high affinity and a 1:1 stoichiometric ratio (Husted et al., 2015). Andexanet binds and sequesters factor Xa inhibitors within the vascular space, thereby restoring the activity of endogenous factor Xa and reducing levels of anticoagulant activity (Husted et al., 2015).

Lovenox is a LMWHs that, like the novel factor Xa inhibitors, inhibit factor Xa in the common pathway of the coagulation cascade. Additionally, Lovenox works to inhibit thrombin by binding to and potentiating the effects of antithrombin III (Alquawaizani et al., 2013).

Lovenox prevents the propagation and growth of formed thrombi but does not dissolve existing clots. Like aspirin and factor Xa inhibitors, no monitoring is required; however, the medication must be injected subcutaneously. Heparin-induced thrombocytopenia (HIT) is a risk of any LMWH, though the risk is lower than that associated with unfractionated heparin (Alquawaizani et al., 2013). A reversal agent, protamine sulfate, is available. Protamine sulfate is given intravenously; upon contact with heparin, the drug forms salts that neutralize heparin's anticoagulant effects (Alquawaizani et al., 2013). If the last dose of Lovenox was fewer than eight hours ago, then one mg of protamine per one mg of enoxaparin should be administered. If the last dose was between eight and twelve hours ago, then 0.5 mg of protamine per one mg of enoxaparin should be administered. If over 12 hours have passed since the last dose, then protamine may not be required (Symthe et al., 2016).

Historically, warfarin was the most popular agent for VTE prophylaxis following TKA. Currently other agents are preferred and prescribed, but warfarin remains the agent of choice for patients with mechanical heart valves. Warfarin works by inhibiting vitamin K-dependent coagulation factors, including factors II, VII, IX, and X, and proteins C and S (Alquawaizani et al., 2013). Patients taking warfarin are required to undergo frequent blood draws to assess the international normalized ratio (INR), which is used to determine whether the warfarin level is therapeutic. For DVT prophylaxis following TKA, the goal INR is two to three. Because warfarin inhibits a naturally occurring vitamin, foods containing vitamin K may counteract its effects; such foods include kale, spinach, and broccoli. Warfarin is also protein bound, so malnourished patients or postoperative patients consuming fewer calories due to nausea may demonstrate altered warfarin levels. Dosing is titrated or decreased based on INR results, and frequent dosage changes are often required. If the INR becomes supratherapeutic, various

reversal agents exist; the most appropriate agent depends on the severity and the urgency to reverse anticoagulation. Intravenous vitamin K works within 12-24 hours, fresh frozen plasma works within one to four hours, and prothrombin clotting complex (PCC) works immediately (Hatfield & Chen 2014). PCC contains factors II, VII, IX, and X and proteins C and S and is typically reserved for trauma patients requiring immediate surgical intervention (Alquawaizani et al., 2013).

Efficacy of Aspirin, Direct Factor Xa Inhibitors, Warfarin, and LMWH in VTE Prophylaxis in Patients Undergoing TKA

In a systematic review, Vincent, V. G., Phan, K., Yadin, L., & Warwick, B. (2009) examined the efficacy of aspirin in preventing VTE in patients undergoing THA or TKA. The researchers performed a systematic review and meta-analysis via electronic searches using Ovid Medline, PubMed, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), and the Database of Abstracts of Review of Effectiveness (DARE) during June 2015. The researchers only included studies involving arthroplasty patients given solely aspirin for VTE chemoprophylaxis. Researchers required that the studies reported both VTE and secondary outcomes related to chemoprophylaxis complications, such as major bleeding (gastrointestinal bleed, intracranial hemorrhage, and any bleeding requiring surgical intervention) and wound oozing during post-surgical follow-up. Of the 39 total studies included in the meta-analysis, 11 relevant studies qualified for inclusion. The overall rates of DVT and PE in the THA and TKA populations were 1.2% and 0.6%, respectively. The rate of major bleeding was 0.3%, and the pooled mortality rate was 0.2%. The researchers concluded that aspirin used both alone and in combination for thromboprophylaxis resulted in a low rate of VTE and major bleeding complications. This study demonstrated aspirin can be used as a sole means of VTE

prophylaxis in postoperative TKA patients. This conclusion is supported by the AAOS and ACCP.

Additionally, Wilson, Poole, Chauhan, & Rogers, (2016) performed a systematic review of 13 total studies investigating the efficacy of aspirin for DVT prophylaxis compared to warfarin, enoxaparin, factor Xa inhibitors, and direct thrombin inhibitors following THA and TKA. Of the 13 total studies, only a few were of acceptable quality (level 1), with most of the other studies demonstrating flaws and potential bias in their research methods and results. Evidence from one high quality randomized controlled trial (RCT) of 778 patients showed no difference in the rates of VTE in patients given aspirin or LMWH following TKA. A total of four RCTs investigated VTE prophylaxis in TKA alone. The first studied aspirin and LMWH groups in 778 patients. No significant difference was demonstrated between aspirin and LMWH in rates of VTE or wound problems, although a trend (p=0.091) toward increased wound complications with LMWH was observed. The second RCT had an unclear of bias and identified no significant difference in the rates of asymptomatic VTE with aspirin and pneumatic compression versus LMWH and pneumatic compression in 274 patients. An increased post-operative drain volume was seen with aspirin (p=0.03), but this was not associated with an increased requirement for transfusion. The third RCT had an unclear risk of bias and compared aspirin, LMWH, and rivaroxaban in 324 patients. The incidence of asymptomatic DVT was significantly higher in the aspirin group versus the rivaroxaban group (16.4% versus 2.9%, p=0.014), although no significant difference in rates of symptomatic DVT existed. Wound complications and average hidden blood loss, which represents all perioperative blood loss and is calculated by the change in pre- and postoperative total body red blood cell content, were both higher with rivaroxaban compared to aspirin (4.9% versus 1.8%, p=0.014, and 1.7 liters (L) versus 1.3 L, p=0.04). No

statistically significant difference existed between aspirin and LMWH in any outcome measure. The fourth RCT pertaining specifically to TKA compared aspirin and LMWH followed by rivaroxaban in 120 patients. This RCT demonstrated an unclear risk of bias and demonstrated no statistical difference in rates of asymptomatic DVT, but blood loss was higher in the LMWH and rivaroxaban groups (p≤0.05). One level III study had a serious risk of bias and compared aspirin with warfarin in THA and TKA in 696 patients. Overall, an increased rate of VTE was seen in the aspirin group. Subgroup analysis revealed this effect was limited to TKA.

A total of four RCTs compared aspirin with LMWH. One high quality RCT with 778 participants showed aspirin was non-inferior to LMWH (p≤0.001) for the prevention of VTE in TKA, with a trend toward increased wound complications with LMWH (p=0.09). Another showed no difference in rates of VTE in TKA in 274 patients but did show increased post-operative drain volume with aspirin (p=0.03). The third included 121 patients and showed an increased rate of DVT in patients taking LMWH compared with aspirin and pneumatic compression in TKA and THA (p=0.002). Subgroup analysis showed this effect was confined to THA. The final RCT reported no significant difference in rates of DVT or wound complications in 324 TKA patients among the aspirin and LMWH groups.

A total of three studies compared aspirin with dabigatran, all of which carried a moderate risk of bias. A paper examining 1728 patients demonstrated a decreased rate of symptomatic VTE, wound complications, and length of stay with aspirin compared to dabigatran in TKA and THA. All patients received LMWH as inpatients and aspirin or dabigatran as outpatients (Wilson et al., 2016). Another study showed decreased time to wound dryness (3.2 versus 6.4 days, p≤0.01) with aspirin in 110 patients undergoing THA and TKA (Wilson et al., 2016). A final study of 123 patients compared wound discharge and length of stay among postoperative THA

patients and demonstrated increased wound discharge and length of stay in the dabigatran group compared to the LMWH (for inpatient DVT prevention) and aspirin (for DVT prevention upon discharge) group. Rivaroxaban in TKA was evaluated by two RCTs. The first study with 120 patients showed no difference in asymptomatic DVT rate and no wound complications in either group but higher blood loss with rivaroxaban compared to aspirin, LMWH and dabigatran groups. The second trial, examining 324 patients, showed fewer asymptomatic DVTs with rivaroxaban but no difference in symptomatic DVTs and a significantly increased rate of wound complications and hidden blood loss with rivaroxaban. Wilson et al. (2016) concluded that insufficient evidence existed to establish one medication as superior and that each had a unique side effect profile to be considered on a case-by-case basis.

Huang, Parvizi, Hozack, Chen & Austin (2016) compared the efficacy of aspirin to that of warfarin in patients undergoing a total joint arthroplasty (TJA). The researchers performed a retrospective study analyzing 30,270 patients who received aspirin or warfarin for VTE prophylaxis after primary or revision TJA between January 2000 and June 2014. The researchers compared the efficacy of aspirin versus warfarin in both low-risk and high-risk populations as well as the complication rates of both therapies. Patients were considered higher risk if they had a history of chronic obstructive pulmonary disease, active hypercoagulable disorder, history of VTE, active malignancy, pulmonary hypertension, or stroke. Patients were also considered higher risk if they had a combination of lesser risk factors that met a minimum cumulative threshold, including older age, anemia, CHF, peripheral vascular disease, and a history of myocardial infarction. The incidences of symptomatic VTE, acute periprosthetic joint infection (PJI), gastrointestinal complications, and mortality within 90 days of surgery were recorded. The results of the study revealed that the 90-day postoperative VTE rate and incidence of

postoperative complications were significantly lower in both lower- and higher-risk aspirin groups compared to warfarin groups. The incidence of VTE in the lower risk patients receiving aspirin was 0.2%; the risk was 0.6% in higher risk patients; this was significantly superior to warfarin, which resulted in a 1.8% incidence of VTE in the lower risk group and 3.2% in the higher risk group (p<0.001). The incidence of PE was 1.8% in the higher risk warfarin group and 0.1% in the higher risk aspirin group (p<0.001). The incidence of DVT was 1.7% in the higher risk warfarin group and 0.5% in the higher risk aspirin group (p=0.017). The incidence of DVT in the lower risk aspirin group was 0.1% in the lower risk group compared to 0.8%. Aspirin also demonstrated less risk of postoperative joint infection and gastrointestinal complication. The incidence of acute PJI was 1.7% in the higher risk VTE group receiving warfarin compared to 0.1% in the higher risk VTE group receiving aspirin (p=0.001). The gastrointestinal complication rate was 0.6% in the higher risk warfarin group compared to 0.0% in the higher risk aspirin group (p=0.054). The 90-day mortality rate was 1.1% in the higher risk warfarin group compared to 0.1% in the higher risk aspirin group (p=0.016).

Stewart and Freshour (2013) compared the 2011 AAOS guidelines for the use of aspirin to prevent VTE to recommendations from the ACCP. Also included in this study was a literature search to identify clinical trials that evaluated the use of aspirin as monotherapy or in combination with another method of prophylaxis (pneumatic compression devices) for prevention of VTE in high-risk patients. Researchers utilized only meta-analyses or RCTs from 1986 or after, published in English. After analysis, researchers were unable to conclude whether aspirin was a safe and effective option for VTE prophylaxis in high-risk patients undergoing THA, TKA, or hip fracture surgery. They concluded that enough validation existed for practitioners to use aspirin as the sole means of VTE prophylaxis, but not enough validation

existed to recommend a change to sole use of aspirin for practitioners who currently use a more potent anticoagulant.

Ma, Zhang, Wu, Wang & Ying (2015) performed a systematic literature search of multiple databases to identify studies that met their inclusion criteria comparing rivaroxaban or apixaban and enoxaparin. The authors performed a meta-analysis of six RCTs including 13,790 patients published between 2005 and 2010. Three of the six studies compared the outcomes of apixaban with enoxaparin regarding DVT, PE, and major bleeding, while the other three studies investigated rivaroxaban. Overall, the incidence of DVT was significantly decreased with the use of direct Xa inhibitors (twice daily dosing) other than enoxaparin (RR=0.68, 95% CI: 0.59-0.78, p<0.01). Subgroup analysis of three apixaban studies yielded similar results (RR=0.68, 95% CI: 0.59-0.79, p<0.01). However, further analysis stratified by the regimen of enoxaparin did not reveal a significant difference between apixaban and 30 mg twice daily enoxaparin (RR=0.85, 95% CI: 0.66-1.10, p<0.01.) Pooled analysis of three studies that used direct Xa inhibitors with once daily dosing demonstrated a significantly lower incidence of DVT compared to enoxaparin (RR=0.60, 95% CI: 0.50-0.73, p<0.01), and a similar result was obtained from the pooled analysis of two studies of rivaroxaban (RR=0.59, 95% CI: 0.48-0.72, p<0.01). No significant difference existed between direct Xa inhibitors (twice daily dosing) with enoxaparin regarding PE (RR=1.94, 95% CI: 0.96-3.92, p=0.06). Similar results were obtained with respect to the stratification analyses: apixaban and enoxaparin (RR=2.00, 95% CI: 0.97-4.12, p=0.06). The pooled analysis demonstrated no significant difference between direct factor Xa inhibitors and enoxaparin in terms of major bleeding.

A systematic review performed by Neuman et al. (2012) evaluated the risks and benefits of oral direct factor Xa inhibitors versus LMWH in patients undergoing TKA or THA. The

researchers utilized databases to find and analyze 22 RCTs. Of the 22 RCTs, 11 included patients

undergoing THA, and 10 included patients undergoing TKA. One study included patients

undergoing either procedure. In all trials, a mandatory venography was done within the last week

of prophylactic treatment to detect asymptomatic DVT. The results of the study revealed that,

when compared to LMWH, factor Xa inhibitors were associated with a reduced incidence of

symptomatic DVT (CI, 0.30-0.70). In the analysis that directly examined absolute differences,

researchers found a reduction of three DVT events (CI, 1-5 fewer events) per 1000 treated

patients over one to five weeks with factor Xa inhibitors. Using the baseline risk from an

observational study of 26 patients who underwent hip or knee replacement and received

thromboprophylaxis, researchers calculated that use of direct factor Xa inhibitors would result in

four fewer DVT events (CI, 3-6 fewer events) per 1000 patients treated. The pooled effect

estimate for nonfatal PE suggested no important difference between factor Xa inhibitors and

LMWH (CI, 0.65 to 1.73). The pooled effect estimate for major bleeding and bleeding leading to

reoperation was not statistically significant but suggested the possibility of a harmful effect. In

the analysis that directly examined absolute differences, researchers found an increase of two

major bleeding events (CI, 0-4 more events) per 1000 patients treated for one to five weeks.

Intracranial bleeding was assessed by twelve studies, and two events were reported (1

intracranial bleeding event in the control group in each study). Researchers found an association

between the dose used in the intervention group and the risk of major bleeding. Lower (CI, 0.70-

1.34) and intermediate (CI, 0.84-2.85) doses of factor Xa inhibitors failed to establish or refute

an increase in bleeding, but high doses increased the risk for major bleeding (CI, 1.38-4.53). The

same tendency was observed for the outcome of bleeding leading to reoperation, although the

test for interaction across the three doses was not significant (p=0.56). After adjusting for dose,

researchers found no association between drug and effect on thrombosis (p=0.98), effect on

bleeding (p=0.21), risk for bias, or length of treatment. Researchers also conducted a meta-

analysis on major bleeding. Moderate and high doses of factor Xa inhibitors caused more major

bleeding events than LMWH and low doses of factor Xa inhibitors. No difference was observed

between LMWH and low doses of factor Xa inhibitors.

King, Pow, Dickison, & Vale (2016) performed a retrospective analysis using a single

surgeon to compare the safety and efficacy of apixaban and enoxaparin in VTE prophylaxis

following TKA. The study included 506 patients from 2009 to 2015 that received either apixaban

or enoxaparin following TKA performed by one surgeon. The primary outcome researchers

assessed was total in-hospital VTE events; secondary outcomes measured included bleeding

complications, VTE mortality, and all-cause mortality. The authors hypothesized apixaban

would demonstrate superior safety and efficacy. Specific criteria regarding dosage and timing of

medication administration were required. Patients underwent Doppler ultrasonography between

days three and seven postoperatively. All tests were two-sided, and p-values ≤ 0.05 were

considered statistically significant. In the group of 506 patients, 253 (50%) received apixaban as

thromboprophylaxis, and 253 (50%) received enoxaparin. Thirteen lower limb Doppler

ultrasound results were missing and therefore were not included in the DVT analyses. One

record did not contain hemoglobin results and hence was not included in the analysis of

postoperative bleeding. Overall, of the thirty-three patients that developed VTE while in the

hospital, eleven of those were receiving apixaban, and 22 were receiving enoxaparin. Three of

the patients with a DVT suffered a subsequent PE; two in the enoxaparin group and one in the

apixaban group. Bleeding and fatality outcomes were also analyzed. Ten patients experienced a

postoperative drop in hemoglobin ≥20 g/L that either necessitated two or more units of blood,

caused hemodynamic instability, or both. This outcome was more common in the enoxaparin group, occurring in 9/253 (3.6%) compared to 1/252 (0.4%) in the apixaban group (p=0.020). There was no difference in this outcome between anticoagulant groups (4.7% vs 7.1%, p=0.254). Thirty-five patients experienced other bleeding events, with twenty-five (9.9%) in the enoxaparin group and ten (4.0%) in the apixaban group (p=0.009). There was one fatality in total; this was attributed to PE and occurred in the enoxaparin group.

Fuji et al. (2014) performed a RCT that was a phase three trial that compared the safety and efficacy of daily oral edoxaban beginning six to twenty-four hours postoperatively versus twice daily subcutaneous enoxaparin beginning twenty-four to thirty-six hours postoperatively for 11-14 days. Authors of the study assessed patients undergoing unilateral TKA. Authors excluded patients at high risk of complications, such as those with an increased risk of bleeding or VTE, severe renal impairment, hepatic dysfunction, pregnant or lactating women, and those with a body weight under 40 kg. The patients were randomly assigned to either the edoxaban or enoxaparin group. Researchers utilized a double-blind, double-dummy design to improve the validity of the study. They used venography of the operative extremity to detect DVT; this was performed within 24 hours of administration of the final dose of study medication or within 96 hours if it could not be obtained within 24 hours. Venography was repeated at 25-35 days following administration of the final dose of study drug. Primary outcome measures assessed included VTE events and safety endpoints including major bleeding, clinically relevant, non-major bleeding, all bleeding, and adverse events. Of 716 patients enrolled, 360 and 356 were randomized to receive edoxaban or enoxaparin, respectively. The primary efficacy outcome occurred in 22/299 (7.4%) in the edoxaban group and 41/295 (13.9%) patients in the enoxaparin group (relative risk reduction = 46.8%), indicating non-inferiority (p<0.001) and superiority

(p=0.010) of edoxaban versus enoxaparin. In the edoxaban group, major bleeding occurred in

4/354 (1.1%) compared to 1/349 (0.3%) in the enoxaparin group (p=0.373). Major and clinically

relevant, non-major bleeding occurred in 22/354 (6.2%) in the edoxaban group compared to

13/349 (3.7%) in the enoxaparin group (p=0.129).

Bala, Huddleston, Maloney & Amanatullah (2017) utilized Humana and Medicare

databases from 2007 to 2015 to gather and analyze TKA cases. The purpose of this study was to

determine whether differences in VTE incidence existed for patients undergoing primary TKAs

depending on whether they were administered aspirin, warfarin, enoxaparin, or factor Xa

inhibitors. The authors also sought to analyze the bleeding risk associated with each of the four

aforementioned agents. Finally, the authors assessed how the use of these agents has changed

with time. Researchers included 1,016 patients given aspirin, 6,096 given enoxaparin, 6,096

given warfarin, and 5,080 given factor Xa inhibitors. To determine whether patients experienced

a VTE, the authors searched for specific VTE diagnosis codes at two weeks, 30 days, six weeks,

and 90 days postoperatively. They also utilized the Charlson Comorbidity Indices and Elixhauser

Comorbidity Profile to establish criteria to determine high-risk patients. Study results revealed a

difference in the incidence of DVT at 90 days (p<0.01). Factor Xa inhibitors had the lowest

incidence of DVT (2.9%) followed by aspirin (3.0%), enoxaparin (3.5%), and warfarin (4.8%). A

difference in the incidence of PE at 90 days was also noted (p<0.01). Factor Xa inhibitors had

the lowest incidence of PE (0.9%) followed by enoxaparin (1.1%), aspirin (1.2%), and warfarin

(1.6%). A difference in the incidence of postoperative anemia at 90 days also existed (p<0.01).

Aspirin had the lowest incidence of postoperative anemia (19%) followed by warfarin (22%),

enoxaparin (23%), and factor Xa inhibitors (23%). Researchers also found a difference in the

incidence of blood transfusion at 90 days (p <0.01). Aspirin had the lowest incidence of a blood

transfusion (7%) followed by factor Xa inhibitors (9%), warfarin (12%), and enoxaparin (13%). No difference in bleeding-related complications existed among the groups (p = 0.81). Aspirin use increased at a compound annual growth rate of 30%, enoxaparin at 3%, and factor Xa inhibitors at 43%, while warfarin use decreased at a compound annual growth rate of -3%.

The authors concluded factor Xa inhibitors were associated with the lowest incidence of DVT and PE at 90 days. However, at two weeks and at 30 days, aspirin had the lowest DVT incidence. At six weeks, both aspirin and factor Xa inhibitors shared the lowest incidence of DVT. Warfarin, throughout the 90 days, was associated with the highest DVT incidence. Factor Xa inhibitors exhibited the lowest incidence of PE at 90 days. Aspirin was associated with the lowest incidence of postoperative anemia and need for blood transfusion but did not demonstrate statistically significant superiority regarding bleeding-related complications. Finally, the authors concluded that factor Xa inhibitors and aspirin exhibited the highest rates of growth in utilization from 2007 to 2015, at 43% and 30%, respectively.

Cafri et al. (2017) researched the comparative safety and efficacy of aspirin, LMWH, factor Xa inhibitors, and vitamin K antagonists for VTE prophylaxis following TKA. Researchers utilized data from the Kaiser Permanente Total Joint Replacement program, which included patients receiving unilateral TKA from May 2006 to December 31, 2013. Researchers reviewed all inpatient and outpatient records within 90 days of the TKA. The presence of a DVT required identification by duplex ultrasonography; pulmonary embolism (PE) presence required confirmation via CT scan of the chest or ventilation-perfusion (VQ) scan. The authors also reviewed safety outcomes including bleeding, infection, wound complication, and mortality. Specific dosages and frequencies of medication administration were required. Any deviation from the guidelines or addition of medications that could have influenced the outcomes excluded

patients from the study. The results of this study revealed that rates of VTEs were comparable among prophylaxis groups with the exception of warfarin, which exhibited a slightly higher risk of DVT, fondaparinux, which showed a slightly lower risk of PE, and aspirin, which had a slightly higher risk of PE. When considering the combined outcome of VTE, aspirin (1.14% incidence of VTE) and warfarin (1.12%) were somewhat higher than enoxaparin (1.02%) and fondaparinux (0.78%). The researchers concluded that a lack of evidence existed to indicate the superiority of any agent relative to aspirin.

Venker et al. (2017) focused on the safety and efficacy of the novel anticoagulants for the prevention of VTE following THA and TKA. Specifically, researchers assessed apixaban, fondaparinux, edoxaban, rivaroxaban, and dabigatran. The researchers used a meta-analysis of 18 double-blind RCTs and calculated the relative risk of each compared to enoxaparin. Of note, drug manufacturers sponsored all 18 trials included in the meta-analysis. Results of the apixaban studies revealed that 2.5 mg apixaban twice daily compared to 40 mg enoxaparin once daily demonstrated a reduction in VTE by 29%. However, no difference existed between apixaban at the aforementioned dose versus 30 mg enoxaparin twice daily. Clinically relevant bleeding rates were lower with apixaban, but no difference in major bleeding rates was noted. No difference in safety or efficacy was noted with dabigatran 150 mg versus 220 mg once daily. Dabigatran 150 mg daily was associated with a slightly increased risk of VTE compared to enoxaparin. The fondaparinux trials revealed that fondaparinux 2.5 mg daily significantly decreased VTE by 47%; however, an 11-fold increase in relative risk of major bleeding was noted. The four trials comparing rivaroxaban to enoxaparin demonstrated rivaroxaban 10 mg daily decreased VTE by 45%. Rivaroxaban also increased clinically relevant bleeds by 27% but did not significantly

increase major bleeds. The two trials comparing edoxaban and enoxaparin showed that edoxaban

30 mg daily decreased the risk of VTE by nearly 50% and did not increase the risk of bleeding.

Zou, Tian, Wang, & Sun (2014) compared the safety and efficacy of rivaroxaban,

LMWH, and aspirin for postoperative TKA VTE prophylaxis. They utilized a prospective RCT

that included patients undergoing primary unilateral TKA between July 2011 and July 2013.

Specific requirements regarding surgical technique, postoperative care, and medication dosages

existed for inclusion in this study. At 12 hours postoperatively, each group received an initial

dose of either aspirin, LMWH, or rivaroxaban, and all groups were treated with a single daily

dose of medication for 14 days. All patients were followed for four weeks postoperatively;

incision sites were assessed, and venous color Doppler ultrasonography was performed at two

and four weeks. The incidence of DVT was lower in the rivaroxaban group compared to the

other two groups 3 (2.94%) versus 14 (12.50%) ($p < 0.029$); 3 (2.94%) versus 18 (16.36%)

($p < 0.017$). However, hidden blood loss 1.71 (1.19–2.97) versus 1.18 (0.77–2.31), ($p < 0.009$);

1.71 (1.19–2.97) versus 1.30 (0.61–2.43), ($p < 0.004$) and wound complications, 5 (4.90) versus 3

(2.67), ($p < 0.027$); 5 (4.90) versus 2 (1.82), ($p < 0.014$) were more common in the rivaroxaban

group than in the other groups. No significant difference in DVT incidence existed between the

LMWH and aspirin groups, 14 (12.50%) vs. 18 (16.36%), ($p < 0.831$), hidden blood loss (1.18

(0.77–2.31) versus 1.30 (0.61–2.43), ($p < 0.327$) or wound complications, 3 (2.67) versus 2 (1.82),

($p < 0.209$). No significant difference in the incidence of limb swelling was found among the three

groups 38 (37.25%) versus 28 (25.00%) versus 24 (21.82%), ($p < 0.247$). The rivaroxaban group

demonstrated a higher incidence of subcutaneous ecchymosis in the affected extremity than the

aspirin group 74 (72.55%) versus 54 (49.09%), ($p < 0.039$), but no significant differences existed

between rivaroxaban and LMWH 74 (72.55%) versus 62 (55.36%), ($p < 0.193$) or between

LMWH and aspirin 62 (55.36%) versus 54 (49.09%), (p<0.427). Researchers concluded rivaroxaban had a positive anticoagulation effect but demonstrated an increased risk of both postoperative blood loss and wound complications. No significant difference in post-TKA DVT incidence was found between aspirin and LMWH, and the former can be used as part of a multimodal anticoagulation therapy approach.

Researchers concluded that rivaroxaban had the lowest incidence of DVT followed by LMWH, while aspirin had the highest incidence. Of these, only two patients in the aspirin group and one patient in the LMWH group had symptomatic DVTs. A higher incidence of occult blood loss, wound complications, and subcutaneous ecchymosis existed in the rivaroxaban group compared to the other groups. Researchers also concluded no statistically significant difference existed between LMWH and aspirin for post-TKA VTE prophylaxis.

Cost-Effectiveness Among VTE Prophylaxis Agents

Duran et al. (2012) completed research evaluating the cost-effectiveness of rivaroxaban versus enoxaparin for VTE prophylaxis in patients undergoing THA and TKA from a United States payer's perspective. Researchers utilized a decision-analytic model that was divided into the following three sub-modules according to the patient's anticoagulation: prophylaxis, post-prophylaxis, and long-term complications. The researchers considered the following costs: medication, medication administration, patient monitoring, diagnosis, and VTE treatment if required. They determined that patients undergoing TKA were hospitalized for an average of four days postoperatively, while THA patients were hospitalized for three days. This determination was made based on a US orthopedic surgery registry database. Medication costs were estimated using the medical care component of the Consumer Price Index; estimated costs of Medicare reimbursement rates for the diagnosis of VTE were based on a resource use report

by McGarry et al. (2004). Duran et al. (2012) also included direct year 2010 medical costs over one- and five- year time horizons. Results of the cost-effectiveness analysis were reported in terms of symptomatic VTE events avoided. The authors used the RECORD trials I, II, and III that compared rivaroxaban versus enoxaparin for VTE prophylaxis in patients undergoing TKA or THA. Record I and Record II trials compared rivaroxaban 10 mg daily for average of 35 days (31-39) with enoxaparin 40 mg daily for average of 35 days (31-39) (Record I) or 10 to 14 days (Record II) respectively in patients undergoing THA. The Record III trial compared 10 mg of rivaroxaban once daily for 10-14 days versus enoxaparin once daily for 10-14 days in patients undergoing TKA. The researchers found that rivaroxaban was associated with a cost savings of $465.74 per patient and prevented an average of 0.0193 symptomatic VTE events per patient. Sensitivity analysis demonstrated a cost savings ranging from $293.01 to $848.68.

Mostafavi, Rasouli, Maltenfort, & Parvizi (2015) examined the cost-effectiveness of aspirin compared to warfarin in both THA and TKA. Only TKA results will be discussed. The researchers used a Markov cohort cost-effectiveness analysis that compared the costs, health benefits, and the costs per quality adjusted life year (QALY) for patients 55 to 85 years of age. The Markov model is utilized when a treatment decision involves consideration of continuous risk, the timing of events is necessary, and important events may occur more than once a year. The results of their analysis revealed aspirin was more cost-effective than warfarin in the majority of patients undergoing TKAs. In patients with a high probability of VTE and a low probability of bleeding, however, warfarin was more cost-effective. However, the reduced QALY for patients using warfarin was very small compared to those using aspirin, and the extra cost of using warfarin was no more than $4000 per patient. By increasing age in the TKA group, cost per TKA was $15,117.20 at age 55 to 60 and $24,458.10 by age 85. Two-way sensitivity

analysis was performed separately for the 65 to 70 age TKA group. In this analysis, warfarin demonstrated the highest VTE risk when risk of major bleeding was assumed to be extremely low.

DISCUSSION

Multiple medication options exist for postoperative DVT prophylaxis following TKA. Each option possesses a unique mechanism of action and side effect profile; further, variable efficacy and associated cost must be considered in analyzing the utility of each option in each patient case. Among the agents, aspirin and factor Xa inhibitors have demonstrated the most growth in utilization for DVT prophylaxis following TKA; they have demonstrated adequate efficacy as well. Factor Xa inhibitors are associated with an increased cost and risk of bleeding, but they also exhibit a slightly decreased risk of VTE compared to aspirin. Aspirin demonstrates comparable outcomes, with only a slightly increased risk of VTE as noted above and are available for a fraction of the cost of factor Xa inhibitors. Warfarin continues to be the drug of choice in patients with mechanical heart valves requiring chemoprophylaxis.

Among the current pharmacologic options for VTE prophylaxis following TKA, does a superior drug or combination of drugs exist based on patient outcomes?

Vincent et al. (2009) performed a systematic review to determine the efficacy of aspirin in preventing VTE in patients undergoing a TKA or THA. The researchers concluded that aspirin used both alone and in combination for thromboprophylaxis resulted in a low rate of VTE and major bleeding complications. This study demonstrated aspirin can be used as a sole means of VTE prophylaxis in postoperative TKA patients. This conclusion is supported by the AAOS and ACCP; however, limitations of this study must be considered. Aspirin dosages varied among the

studies, differences in study design existed, and user-specific differences existed in the interpretation of ultrasound to detect DVT.

In another systematic review performed by Wilson et al. (2016), researchers investigated the efficacy of aspirin for DVT prophylaxis compared to other agents following THA and TKA. They utilized studies that compared aspirin to warfarin, enoxaparin, factor Xa inhibitors, and DTIs. The researchers concluded that insufficient evidence existed to establish one medication as superior, and each had a unique side effect profile to be considered on a case-by-case basis. This particular article illustrated the importance of individualizing treatments for each patient or similar patient groups. The conclusion correlated with statements from the AAOS and ACCP, reporting that many options exist for VTE prophylaxis following TKA without a single, definitively recommended therapy.

Stewart et al. (2013) evaluated the suitability of aspirin in prevention of VTE in high-risk orthopedic surgery patients. After analysis, researchers were unable to conclude whether aspirin was a safe and effective option for VTE prophylaxis in high-risk patients undergoing THA, TKA, or hip fracture surgery. They concluded that enough validation existed for practitioners to use aspirin as the sole means of VTE prophylaxis, but not enough validation existed to recommend a change to sole use of aspirin for practitioners who currently use a more potent anticoagulant. This article supported the systematic review and meta-analysis performed by Vincent et al. (2016). but also demonstrated the diverse options for VTE chemoprophylaxis following orthopedic surgery. Thus, practitioners are afforded a variety of options for VTE chemoprophylaxis depending on the patient profile.

Another study conducted by Huang et al. (2016) compared the efficacy of aspirin to that of warfarin in patients undergoing TJA. The researchers compared the efficacy of aspirin versus

warfarin in both low-risk and high-risk populations as well as the complication rates of both therapies. The results of the study revealed that at 90 days postoperatively, VTE rate and incidence of postoperative complications were significantly lower in both lower- and higher-risk aspirin groups compared to warfarin groups. This article echoed the results of Vincent et al. (2016) and Stewart et al. (2013) articles regarding the benefits of using aspirin as the sole means of VTE prophylaxis. This article also revealed the benefits of aspirin compared to warfarin. Limitations of this study included differing dosages in aspirin groups (81 mg versus 325 mg), lack of randomization, and the sizes of the groups included in the studies. Only 18% of the low-risk and 11% of the high-risk groups received aspirin, while the remaining subjects received warfarin.

Ma et al. (2015) performed a systematic literature search of multiple databases to identify studies that met their inclusion criteria comparing rivaroxaban or apixaban to enoxaparin. The results of their study revealed the overall incidence of DVT was significantly decreased with the use of factor Xa inhibitors versus enoxaparin. However, when comparing apixaban and enoxaparin at 30 mg twice daily, no statistically significant difference was noted. No significant difference existed between factor Xa inhibitors (twice daily regimen) and enoxaparin regarding incidence of PE and major bleeding. This study was significant because it compared enoxaparin to two different factor Xa inhibitors. Interestingly, enoxaparin also has indirect inhibitory effects on factor Xa, inhibiting antithrombin. This study established that the new factor Xa inhibitors, acting directly on factor Xa, demonstrate improved VTE prevention.

Neumann et al. (2012) evaluated the risks and benefits of oral direct factor Xa inhibitors versus LMWH in patients undergoing TKA or THA. The results of the study revealed no significant difference existed regarding all-cause mortality at the time of anticoagulant therapy

cessation. The factor Xa inhibitors did show a significant reduction in symptomatic DVTs compared to enoxaparin. The researchers found three to four fewer symptomatic DVT events per 1,000 treated patients over five weeks in the factor Xa inhibitor group. This study illustrated findings similar to those of Ma et al. (2015), demonstrating a distinct advantage of factor Xa inhibitors over enoxaparin. The authors concluded that, when comparing low-to-medium dose to high-dose factor Xa inhibitors, higher dosages increased the risk of bleeding. Thus, practitioners must consider dosage regimens in addition to the risks and benefits of each individual agent when prescribing VTE chemoprophylaxis.

King et al. (2016) revealed outcomes similar to those described by Neumann et al. (2012) and Ma et al. (2015). Apixaban, a factor Xa inhibitor, showed VTE prophylaxis results superior to those of enoxaparin. The bleeding and mortality outcomes also favored apixaban. The authors concluded that apixaban was safer and more effective than enoxaparin. Numerous limitations existed in this study. Authors included both unilateral and bilateral TKA patients. The enoxaparin group included more bilateral TKA patients, who typically achieve postoperative mobilization later than unilateral TKA patients, thus increasing baseline risk of DVT. Further, the inclusion criteria were not specific; no screenings were performed for additional risk factors such as age, gender, prior VTE, prior cerebral vascular accident, or atrial fibrillation. Another potential limitation was that more patients in the apixaban group received tranexamic acid, which facilitates coagulation. This could have influenced bleeding-related complications in the apixaban group.

Fuji et al. (2014) performed the STARS E-3 trial comparing the safety and efficacy of once daily oral edoxaban beginning six to 24 hours postoperatively versus twice daily subcutaneous enoxaparin beginning 24-36 hours postoperatively for 11 to 14 days. The results of

this study paralleled the findings of studies performed by King et al. (2016), Ma et al. (2015), and Neumann et al. (2012), revealing that a factor Xa inhibitor, specifically edoxaban, was more effective than enoxaparin in reducing the incidence of symptomatic PE and symptomatic and asymptomatic DVT. Further, edoxaban did not demonstrate an increased incidence of bleeding or adverse events compared to enoxaparin. Some limitations of this study existed. Venography was performed only on the surgical leg, meaning asymptomatic DVT of the contralateral leg may have been missed. Further, the study had a relatively small sample size.

Bala et al. (2017) performed a study utilizing Humana and Medicare databases from 2007 to 2015 to gather and analyze TKA cases. The purpose of this study was to determine whether differences in VTE incidence existed for patients undergoing primary TKAs depending on whether they were administered aspirin, warfarin, enoxaparin, or factor Xa inhibitors. The authors concluded factor Xa inhibitors were associated with the lowest incidence of DVT and PE at 90 days. However, at two weeks and at 30 days, aspirin had the lowest DVT incidence. At six weeks, both aspirin and factor Xa inhibitors shared the lowest incidence of DVT. Warfarin, throughout the 90 days, was associated with the highest DVT incidence. Factor Xa inhibitors exhibited the lowest incidence of PE at 90 days. Aspirin was associated with the lowest incidence of postoperative anemia and need for blood transfusion but did not demonstrate statistically significant superiority regarding bleeding-related complications. Finally, the authors concluded that factor Xa inhibitors and aspirin exhibited the highest rates of growth in utilization from 2007 to 2015, 43% and 30%, respectively. This study demonstrated outcomes similar to those previously described, delineating factor Xa inhibitors and aspirin as superior selections for VTE prophylaxis. It also validated the importance of tailoring chemoprophylaxis to each patient based on the side effect profiles of the drugs and patients' past medical history.

Cafri et al. (2017) evaluated the comparative safety and efficacy of aspirin, LMWH, factor Xa inhibitors, and vitamin K antagonists for VTE prophylaxis following TKA. Researchers utilized data from the Kaiser Permanente Total Joint Replacement program, which included patients receiving unilateral TKA from May 2006 to December 31, 2013. The results of their study revealed that rates of VTEs were comparable among prophylaxis groups with the exception of warfarin, which exhibited a slightly higher risk of DVT, fondaparinux, which showed a slightly lower risk of PE, and aspirin, which had a slightly higher risk of PE. The researchers concluded that a lack of evidence existed to indicate the superiority of any agent relative to aspirin. The conclusion of this study did oppose the outcome of a study by Zou et al. (2014), which revealed an advantage of the novel anticoagulants over aspirin. It did, however, correlate closely with studies by Vincent et al. (2016), Stewart et al. (2013), and Huang et al. (2016).

Venker et al. (2017) conducted a study focusing on the safety and efficacy of the novel anticoagulants for the prevention of VTE following TKA and THA. Specifically, researchers assessed apixaban, fondaparinux, edoxaban, rivaroxaban, and dabigatran. Overall, this meta-analysis showed four of the five novel anticoagulants reduced the rate of VTE compared to enoxaparin after TJA. However, the reduced risk of VTE was offset by an increased risk of bleeding.

Zou et al. (2014) compared the safety and efficacy of rivaroxaban, LMWH, and aspirin for postoperative TKA VTE prophylaxis. They utilized a prospective RCT that included patients undergoing primary unilateral TKA between July 2011 and July 2013. Researchers concluded that rivaroxaban had the lowest incidence of DVT followed by LMWH; aspirin had the highest incidence. Of these, only two patients in the aspirin group and one patient in the LMWH group

had symptomatic DVTs. A higher incidence of occult blood loss, wound complications, and

subcutaneous ecchymosis existed in the rivaroxaban group compared to the other groups.

Researchers also concluded no statistically significant difference existed between LMWH and

aspirin for post-TKA VTE prophylaxis. This study was relevant because it compared aspirin,

which, based on other studies, is an effective sole therapy for thromboprophylaxis, to one of the

novel anticoagulants. The results demonstrated one of the novel anticoagulants displayed

superiority over more traditional options; however, an increased risk of bleeding was also

associated with the agent.

  In this author's opinion based on the literature reviewed, no single superior

chemoprophylactic agent exists to prevent VTE following TKA. Aspirin and factor Xa inhibitors

such as apixaban have recently become the two most commonly utilized agents for this purpose.

Each possesses a specific mechanism of action and side effect profile. Neither aspirin nor factor

Xa inhibitors require monitoring. Currently, no FDA approved reversal agent exists for factor Xa

inhibitors; however, a reversal agent is currently in phase III trials and shows promising data.

Which of the current pharmacologic VTE prophylaxis options demonstrates the greatest

cost effectiveness with the fewest risks?

  Medication cost incurred by the patient is difficult to determine due to varying insurance

coverage and out of pocket expenses. A website (www.goodrx.com) was utilized to obtain

average cost of each medication. The following costs do not include any insurance coverage. The

cost of 365 aspirin (81 mg tablets) was $5.70. The cost of 60 apixaban (5 mg tablets) was $454.

The cost of 30 warfarin (5 mg tablets) was $18.25. Finally, the cost of a 30-day supply of

enoxaparin (40 mg/0.4mL syringes) was $929.65. Clearly aspirin is the most inexpensive option.

Duran et al. (2012) evaluated the cost effectiveness of rivaroxaban versus enoxaparin for VTE prophylaxis in patients undergoing THA and TKA from a United States payer's perspective. Researchers utilized a decision-analytic model that was divided into the following three sub-modules according to the patient's anticoagulation: prophylaxis, post-prophylaxis, and long-term complications. The researchers considered the following costs: medication, medication administration, patient monitoring, diagnosis, and VTE treatment if required. They determined that patients undergoing TKA were hospitalized for an average of four days postoperatively, while THA patients were hospitalized for three days. This determination was made based on a US orthopedic surgery registry database. Medication costs were estimated using the medical care component of the Consumer Price Index; estimated costs of Medicare reimbursement rates for the diagnosis of VTE were based on a resource use report by McGarry et al (2014). The authors used the RECORD trials I, II, and III that compared rivaroxaban versus enoxaparin for VTE prophylaxis in patients undergoing TKA or THA.

This particular study conducted by Duran et al. (2012) also revealed that rivaroxaban, a factor Xa inhibitor, is more cost effective than enoxaparin. However, many limitations must be considered regarding this study. Authors allowed for patients to change from enoxaparin to warfarin therapy in the study. Further, many assumptions were made to generalize findings from the available data.

Mostafavi et al. (2015) examined the cost effectiveness of aspirin compared to warfarin in TKAs. The researchers used a Markov cohort cost effectiveness analysis that compared the costs, health benefits, and the costs per quality adjusted life year (QALY) for patients 55 to 85 years of age. The results of their analysis revealed aspirin was more cost effective than warfarin in the majority of patients undergoing TKAs. In patients with a high probability of VTE and a

low probability of bleeding, however, warfarin was more cost effective. The authors also noted that, as patient age increased, the difference in cost between the two drugs decreased. Previously evaluated studies exhibited aspirin as an effective VTE prophylactic agent, and this study demonstrated it is also a more cost-effective option, another important factor to consider when prescribing thromboprophylaxis.

APPLICABILITY TO CLINICAL PRACTICE

Multiple medications are both safe and effective in the prevention of VTE events in patients undergoing TKA. In the past, warfarin was the most commonly utilized prophylactic agent, and it continues to be the agent of choice in patients who have previously undergone heart valve repair. However, due to its multiple potential drug interactions, frequent required laboratory monitoring of the INR, and difficulty maintaining a therapeutic INR, warfarin is being used far less frequently. Clinicians have begun favoring aspirin and factor Xa inhibitors, and both of these agents been endorsed by the AAOS and AACP as sole options for management of VTE prophylaxis in patients undergoing TKA.

Several studies, as discussed above, have demonstrated the superiority of aspirin and factor Xa inhibitors over LMWH and warfarin in terms of efficacy of DVT prevention. Factor Xa inhibitors are costlier and demonstrate an increased bleeding risk compared to aspirin. Neither drug requires laboratory monitoring, and once daily and twice daily dosing options are available for both drugs.

After extensive review of the literature, this author's opinion is that, in low risk patients undergoing TKA, aspirin is a safe and effective chemoprophylactic agent for DVT prevention. Aspirin has a limited risk profile, is cost effective and available over the counter, and does not require laboratory monitoring. The dosing regimen is simple and consists of one 81 mg tablet

twice daily for six weeks postoperatively. Further, in the case of overdose, a reversal agent is available. Clinicians must be prudent in analyzing each patient's DVT risk preoperatively so as to choose the most superior prophylactic agent based on the patient's history and anticipated period of immobilization.

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