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REVIEW

Is Aspirin Best Choice Today for Prophylaxis Against Venous Thromboembolism after Orthopedic Surgery?

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ABSTRACT

Recommendations for prophylaxis to prevent thrombosis in patients undergoing orthopedic surgery have been rapidly evolving, particularly with the FDA approval of new direct oral anticoagulants for this purpose. Over the past 2 decades, the guidelines produced by the American Association of Orthopedic Surgeons (AAOS) and the American College of Chest Physicians (ACCP) have shown major differences. The report includes ACCP and AAOS guidelines since 2004, current indications for prophylaxis in orthopedic patients, a comparison between ACCP and AAOS guidelines with respect to aspirin therapy for venous thromboembolism prophylaxis in orthopedic patients, the government approved anticoagulants for prophylaxis in the US, Europe, and Japan, and the dosage of anticoagulants for prophylaxis against thrombosis included in the current ACCP guidelines.
Level of Evidence: V; Descriptive review/Expert opinions.
Keywords: Venous thromboembolism prophylaxis; Orthopaedic surgery; Aspirin.

INTRODUCTION

According to 2014 national inpatient sample report from the Health Care Cost and Utilization project in the United States, over 44 million discharges were made by hospitals and academic medical centers [1]. At least 22% of these patients were surgical inpatients and risk stratification according to the American College of Chest Physicians (ACCP) estimated that 15% were at moderate risk, 24% were at high risk and 17%, were at very high risk for developing venous thromboembolism (VTE) [2].

In the United States, over 850,000 hip and knee arthroplasties are performed every year [3]. Of these patients from a 2011 report, 37% did not receive any prophylaxis and were found to have deep-vein thrombosis (DVT) by imaging studies [4]. In a 2010 study that focused on the prevalence and risk factors of VTE after hip arthroplasty, it was found that VTE occurred in 1.02% of patients within 90 days of surgery, and 0.05% of patients died of complications arising from VTE. Risk factors for VTE included comorbid conditions, particularly rheumatoid arthritis and osteoarthritis, a history of cardiovascular disease, and prior history of VTE [5,6].

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Despite significant advances in the prevention and treatment of VTE, pulmonary embolism (PE) still remains one of the most common preventable cause of hospital death [7-11]. PE is responsible for approximately 150,000 to 200,000 deaths per year in the United States [12,13]. Hence, it is necessary to make further improvements to find the safest and most effective means to prevent and manage VTE.

In 2009 and 2011, the American Association of Orthopedic Surgeons (AAOS) issued clinical practice guidelines with grades for each assessing the strength and evidence for patients undergoing hip or knee surgery. In 2009, AAOS first recommended aspirin monotherapy as a choice for VTE prophylaxis, at a dose of 325 mg twice daily, beginning on the day of surgery and continuing for 6 weeks, for patients without elevated preoperative VTE risk [14,15]. It was also recommended that aspirin therapy should be discontinued at least 7 days prior to surgery, because of its association with higher intraoperative blood loss [16]. In 2012, the American College of Chest Physicians (ACCP) accepted AAOS guidelines for aspirin monotherapy, included daily full-doses of aspirin (>300 mg) as an acceptable chemoprophylactic monotherapy option after total joint arthroplasty [17].

According to ACCP guidelines, patients undergoing total hip arthroplasty (THA), total knee arthroplasty (TKA), and hip fracture surgery (HFS) could receive low-molecular-weight heparin (LMWH) 12 hours preoperatively and 12 hours or more postoperatively. Taken together, one of the following drugs should be administered for a minimum of 10-14 days for antithrombotic prophylaxis: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted dose of vitamin K antagonist (such as warfarin) per the INR (international normalized ratio), aspirin, or an intermittent pneumatic compression device (IPCD) [17-19]. In this report, we reviewed the recommendations by AACP and AAOS since 2007 and compared them, focusing on the changing role of aspirin. The results show significant movement to the use of aspirin exclusively without anticoagulation therapy from both expert groups.

METHODS

All the data were obtained from the AAOS and ACCP guidelines and compared since 2007 up until the currently posted recommendations. The AAOS and ACCP differed in their recommendations for postoperative VTE prophylaxis for patients undergoing orthopedic surgeries before 2012, and aspirin monotherapy was not recommended by ACCP as an acceptable therapeutic option. In 2012, endorsement of aspirin monotherapy by ACCP was made for use after orthopedic surgery. We reviewed the current literature on the timeline for the ACCP guidelines of VTE prophylaxis for orthopedic patients. Studies highlighting VTE prophylaxis for surgeries other than orthopedic procedures were excluded.

RESULTS

Table 1 shows the timeline for ACCP guidelines for VTE prophylaxis for orthopedic patients. With regard to hip surgery and hip arthroplasty, since 2004 the preferred agent has been low-molecular-weight heparin. The doses, duration, and frequency of administration are shown in Table 2. In 2012, aspirin was placed on the acceptable

Table 1. ACCP Guidelines for VTE Prophylaxis Orthopedic Patients.

	2004	2008	2012	2016
Hip Surgery	LMWH (preferred), Fondaparinux, Warfarin, target INR=2.5, LDUH	LMWH (preferred), Fondaparinux, Warfarin, target INR=2.5, LDUH	LMWH (preferred), Fondaparinux, Warfarin, target INR=2.5, LDUH, Aspirin	LMWH (preferred), Fondaparinux, Warfarin, target INR=2.5, LDUH, Aspirin
Hip Arthroplasty	LMWH (preferred), Fondaparinux, Warfarin, target INR=2.5	LMWH (preferred), LDUH Fondaparinux, Warfarin, target INR=2.5	LMWH (preferred), LDUH Fondaparinux, Apixaban, Rivaroxaban, Dabigatran, Aspirin, Warfarin, target INR=2.5	LMWH (preferred), LDUH Fondaparinux, Apixaban, Rivaroxaban, Dabigatran, Aspirin, Warfarin, target INR=2.5
Knee Arthroplasty	LMWH (preferred), Fondaparinux, Warfarin, target INR=2.5	LMWH (preferred), LDUH Fondaparinux, Warfarin, target INR=2.5	LMWH (preferred), LDUH Fondaparinux, Apixaban, Rivaroxaban, Dabigatran, Aspirin, Warfarin, target INR=2.5	LMWH (preferred), LDUH Fondaparinux, Apixaban, Rivaroxaban, Dabigatran, Aspirin, Warfarin, target INR=2.5
Knee Arthroscopy	No routine thromboembolic prophylaxis, except for early mobilization, LMWH for high risk patients	No routine thromboembolic prophylaxis, except for early mobilization, LMWH for high risk patients	No routine thromboembolic prophylaxis, except for early mobilization, LMWH for high risk patients	No routine thromboembolic prophylaxis, except for early mobilization, LMWH for high risk patients

LMWH, low-molecular-weight heparin; LDUH, low-dose unfractionated heparin; INR, international normalized ratio.

Table 2. Current Indications and Dosage for FDA Approved LMWH in VTE Prophylaxis for Orthopedic Patients.

Indication	Enoxaparin	Dalteparin	Tinzaparin
Hip Arthroplasty	30 mg *sc* every 12 hours or 40 mg *sc* once daily up to 14 days	2,500 IU *sc* 4-8 hours after surgery, then 5000 IU *sc* once daily	Not Approved
Knee Arthroplasty	30 mg *sc* every 12 hours up to 14 days	Not Approved	Not Approved

agent list for the first time by ACCP, and it was retained for the 2016 guidelines. It should be noted that the new direct oral anticoagulants were not included for hip surgery patients either in 2012 or in 2016. This is in contrast to patient's undergoing hip arthroplasty. Although low-molecular-weight heparin is still the preferred agent for these patients, the use of apixaban, rivaroxaban, and dabigatran as options was added in 2012 and retained in the 2016 guidelines. Importantly, aspirin was included in these 2 most recent ACCP guidelines for hip arthroplasty patients. In both hip surgery and hip arthroplasty patient groups, warfarin with a target INR of 2.5 and a range of 2.0–3.0 was also listed as an acceptable option. For patients with knee arthroplasty, the recommendations are identical to those undergoing hip arthroplasty. For the less invasive procedure of knee arthroscopy, no routine thromboprophylaxis was recommended, except for early mobilization. Importantly, low-molecular-weight heparin was recommended for patients undergoing knee arthroscopy who are at higher thrombotic risk. The shortcoming for most patients in this category is that they are not frequently assessed thoroughly, if at all, for thrombotic risk, which can be both genetic and acquired. The use of low-molecular-weight heparin for patients undergoing knee arthroscopy may be indicated if the patient has a hypercoagulable state.

Table 2 shows the current indications and dosage for FDA approved low-molecular-weight heparin in VTE prophylaxis for orthopedic patients. There are 2 dosing options for enoxaparin, which are 30 mg subcutaneous every 12 hours or 40 mg subcutaneous once daily. These doses are recommended for up to 14 days for both hip arthroplasty and knee arthroplasty. The low-molecular-weight heparin preparation dalteparin has never been approved for knee replacement surgery, but it is approved for hip replacement surgery with a nuance not present with enoxaparin dosing. The first dose of dalteparin, given 4-8 hours after surgery, is half the dose given on the next day. Following the initial dose of 2500 units, 5000 units are delivered subcutaneously once daily. The low-molecular-weight heparin compound tinzaparin was taken off the US market in 2012 after a voluntary recall. It was never approved as an acceptable low-molecular-weight heparin compound for hip replacement surgery or knee replacement surgery.

Table 3 provides a comparison between ACCP and AAOS guidelines for VTE prophylaxis in orthopedic patients. The table shows the differences in the recommendations up to 2012, with the most noteworthy point that aspirin was listed as an acceptable monotherapy by the AAOS guidelines in 2009, and by the ACCP guidelines published in 2012. It should be noted that aspirin monotherapy was not recommended as follow-up therapy after initiation with an anticoagulant. Aspirin was recommended for VTE prophylaxis in orthopedic patients in the 2007 AAOS guidelines, which suggested its use for 6 weeks for patients who do not have a preoperative elevated risk for thrombosis. The ACCP guidelines did not list aspirin (greater than 300 mg) as acceptable therapy after total joint arthroplasty until 2012.

Table 4 shows the government approved anticoagulants for VTE prophylaxis after hip and knee surgery in the USA, in Europe, and in Japan. The first approved anticoagulant in the USA was low-molecular-weight heparin in 1993. The newer anticoagulants, rivaroxaban,

Table 3. ACCP versus AAOS Aspirin-Related Guidelines or VTE Prophylaxis in Orthopedic Patients.

Timeline	ACCP	AAOS
2007	-	Patients undergoing THA/TKA should receive aspirin, LMWH, fondaparinux, or warfarin
2008	Patients undergoing hip/knee replacement should receive LMWH, fondaparinux, or warfarin; recommendation against use of LDUH or aspirin as sole method for THA/TKA	-
2009	-	AAOS includes aspirin monotherapy as VTE prophylaxis—25 mg twice daily, beginning on day of surgery and continuing for 6 weeks for patients without preoperative elevated VTE risk
2011	-	Aspirin and use of mechanical prophylaxis for prevention of VTE in patients with elective THA/TKA
2012	For the first time, aspirin (>300 mg) as acceptable therapy included after total joint arthroplasty	-

dabigatran, and apixaban, were approved much later. In 2012, rivaroxaban was the first of these to be approved for prophylaxis against thrombosis in orthopedic surgery patients, with apixaban and dabigatran approved in 2014. Aspirin, now recommended for use in both ACCP and AAOS guidelines, does not require FDA approval for use. The anticoagulants approved for VTE prophylaxis in the United States closely parallel those approved in Europe, except for the slightly earlier approval in Europe for low-molecular-weight heparin and rivaroxaban. Interestingly, in Japan, of the new oral anticoagulants recommended for use, only edoxaban has been approved. Low-molecular-weight heparin was approved for use after hip and knee surgery many years after it was approved for use in both Europe and in the United States.

Table 5 shows the dosing of anticoagulants for VTE prophylaxis after hip and knee surgery for the ACCP guidelines. With regard to the most recent guidelines in 2016, there are several noteworthy points. First, for duration of dosing, low dose unfractionated heparin and low-molecular-weight heparin are recommended for 7-10 days (although low-molecular-weight heparin may be used for 35 days in total hip arthroplasty). Fondaparinux is similarly recommended for use for 10 days. Warfarin, on the other hand, is recommended for 10-21 days and up to 35 days in total hip arthroplasty. The newer direct oral anticoagulants are all recommended for use between

Table 4. Government Approved Therapies Other Than Warfarin for VTE Prophylaxis after Hip and Knee Surgery.

Therapy	USA	Europe	Japan
Apixaban (Eliquis®)	2014	2014	-
Dabigatran (Pradaxa®)	2014	2014	-
Rivaroxaban (Xarelto®)	2012	2011	-
Edoxaban (Savaysa®)	-	-	2011
Aspirin	Approved for use through ACCP and AAOS guidelines; does not require FDA approval	Does not require EMA approval	-
LMWH (Lovenox/ Enoxaparin)	1993	1990	2008

14 and 35 days postoperatively. Aspirin as monotherapy has a recommended duration of therapy of 35 days. It is also noteworthy that among the direct oral anticoagulants, rivaroxaban and apixaban are used at a dose which is half that used to treat patients with atrial fibrillation or deep vein thrombosis/ pulmonary embolism. Dabigatran, on the other hand, is recommended for use in patients undergoing hip or knee surgery at the same dose used to treat patients with atrial fibrillation or deep vein thrombosis/pulmonary embolism. The 2012 ACCP guidelines included rivaroxaban only among the newer anticoagulants, and as noted earlier, it was the 2012 guidelines that recommended aspirin (>300 mg twice daily), started preoperatively and continued postoperatively for 35 days.

DISCUSSION

This report compares the guidelines prepared by a society representing coagulation/anticoagulation expert groups with the guidelines from the AAOS. The conclusion is that after decades of recommendations for the exclusive use of an anticoagulant, there has been movement in the recent set of guidelines toward the use of aspirin, as an antiplatelet agent, even though it largely inhibits thrombosis in the arterial circulation.

Warfarin has long been used as an anticoagulant to reduce thrombotic risk after orthopedic surgery. It carries with it the advantages of familiarity by most physicians, the ability to have the patient managed by a warfarin clinic, and the ready availability of a reversal agent. The disadvantages are numerous, but less so in orthopedic surgery where the treatment duration is limited to approximately 2 weeks. The physiologic disadvantage is that the anticoagulation effect does not reach its full impact until at least 3 days and more often up to 9 days after initiation of warfarin therapy. It requires INR monitoring on at least one or 2 occasions

Table 5. ACCP Guidelines for VTE Prophylaxis Orthopedic Patients.

	2004	2008	2012	2016
LDUH	250 IU per kg *sc* twice daily for 7-10 days	250 IU per kg *sc* twice daily for 7-10 days	250 IU per kg *sc* twice daily for 7-10 days	250 IU per kg *sc* twice daily for 7-10 days
LMWH (Enoxaparin)	30 mg *sc* twice daily or 40 mg *sc* once daily; start 12-24 hours after surgery and continue for 7-10 days; may continue for 35 days in THA	30 mg *sc* twice daily or 40 mg *sc* once daily; start 12-24 hours after surgery and continue for 7-10 days; may continue for 35 days in THA	30 mg *sc* twice daily or 40 mg *sc* once daily; start 12-24 hours after surgery and continue for 7-10 days; may continue for 35 days in THA	30 mg *sc* twice daily or 40 mg *sc* once daily; start 12-24 hours after surgery and continue for 7-10 days; may continue for 35 days in THA
Fondaparinux	2.5 mg *sc*; start 6-8 hours after surgery and continue for 10 days; may continue for 35 days in THA	2.5 mg *sc*; start 6-8 hours after surgery and continue for 10 days; may continue for 35 days in THA	2.5 mg *sc*; start 6-8 hours after surgery and continue for 10 days; may continue for 35 days in THA	2.5 mg *sc*; start 6-8 hours after surgery and continue for 10 days; may continue for 35 days in THA
Warfarin	2-10 mg *po* immediately after surgery with target INR=2.5; Continue for 10-21 days, up to 35 days in THA	2-10 mg *po* immediately after surgery with target INR=2.5; Continue for 10-21 days, up to 35 days in THA	2-10 mg *po* immediately after surgery with target INR=2.5; Continue for 10-21 days, up to 35 days in THA	2-10 mg *po* immediately after surgery with target INR=2.5; Continue for 10-21 days, up to 35 days in THA
Rivaroxaban	-	-	10 mg orally daily for 14-35 days postoperatively	10 mg orally daily for 14-35 days postoperatively
Apixaban	-	-	-	2.5 mg orally twice daily for 14-35 days postoperatively
Dabigatran	-	-	-	150 mg orally twice daily for 14-35 days postoperatively
Aspirin	-	-	>300 mg twice daily started preoperatively and continued postoperative for 35 days	>300 mg twice daily started preoperatively and continued postoperative for 35 days

over 2 weeks. Because it does not reach its full anticoagulant potential for days after surgery, rarely was there bleeding at the site. The use of warfarin greatly decreased

the incidence of venous thromboembolism after orthopedic surgery, but the question remained whether it was the best of the choices to reduce the number of thrombotic events.

When low-molecular-weight heparin was introduced, different preparations were used after orthopedic surgery. The data suggested that there was a further reduction when using any of the preparations of low-molecular-weight heparin, compared to warfarin, in the incidence of postoperative venous thrombi. The advantages of the low-molecular-weight heparin over warfarin are a more consistent patient response, limited impact by other drugs, and no affect of vitamin K in the diet. Also, no INR measurement is required. There were several disadvantages to low-molecular-weight heparin, however. The first issue focused on when the first postoperative dose should be given, with the understanding that it would reach its full anticoagulation potential within a few hours, unlike warfarin. Not unexpectedly, there was increased bleeding at the surgical site when the first dose was given within 4 hours of wound closure. The drug free interval was extended to 8 or 12 hours after surgery because of increased bleeding at the surgical site. In addition, the use of low-molecular-weight heparin was found to be associated with a risk for heparin-induced thrombocytopenia as a complication. It was ultimately concluded that the low-molecular-weight heparin—enoxaparin—had a comparable safety and bleeding profile as aspirin for patients who have undergone total knee arthroplasty [20].

There was a further reduction in the incidence of postoperative venous thrombosis in studies comparing the pentasaccharide drug fondaparinux versus low-molecular-weight heparin [17,18,20]. Despite this improved efficacy, the uncertainty of dealing with a bleeding patient using fondaparinux was greater because an impairment in renal function prolongs the half life of the drug and because protamine is not able to reverse the anticoagulation induced by fondaparinux. These, and other factors, led to the use of low-molecular-weight heparin over fondaparinux. In a recent study, the authors reported that there was no evidence that drugs like fondaparinux, enoxaparin, or warfarin were superior to aspirin in the prevention of VTE, DVT, or PE [20].

Finally, one of the new direct oral anticoagulants, rivaroxaban, at 10 mg daily was introduced for prophylaxis against venous thromboembolism in patients undergoing hip or knee replacement. The advantages for the patient were significant, in that the drug is taken orally and, therefore, the duration of therapy after surgery could easily be made longer without a loss in patient satisfaction. Prophylaxis with rivaroxaban for a period of about one month was easily introduced, which is beneficial as there is still an increased risk of venous thromboembolism in the third and fourth week after orthopedic surgery. There is also no monitoring of the anticoagulant effect of rivaroxaban. The disadvantage was most often an unfamiliarity with the drug. Indeed, even though rivaroxaban clearly outperformed warfarin therapy, at the time that rivaroxaban was FDA approved, many orthopedic surgeons who use anticoagulants still selected warfarin over rivaroxaban. After rivaroxaban was approved for prophylaxis against venous thrombosis, two other direct oral anticoagulants, apixaban and dabigatran, were also approved by the FDA for this purpose. Despite the approval of the factor Xa and factor IIa inhibitors and their superior bleeding profiles, many

orthopedic surgeons have resisted changing their prescribing patterns, and have continued to use warfarin [21,22]. The results of recent randomized clinical trials of these new oral anticoagulants showed apixaban to be the most convenient and more effective alternative to Lovenox after knee arthroplasty without increased bleeding risk [23,24]. The lack of any reversal agent was a major concern for clinicians [25]. However, andexanet alfa which reverses rivaroxaban, apixaban and other anti-factor Xa inhibitors was approved for use by the FDA in May, 2018. Idarucizumab, an inhibitor of dabigatran, was approved by the FDA in 2015.

In a study by Chu et al., the authors investigated the risk of VTE with aspirin vs. other anticoagulants after hip and knee arthroplasty [26]. The authors compared post-operative VTE between patients who received aspirin only versus anticoagulants, and patients who received both aspirin and anticoagulants. VTE prophylaxis at appropriate once or twice daily frequency with the following anticoagulants were considered: warfarin at any dose, LDUH at doses between 5000-7500 units, prophylactic doses of LMWH (enoxaparin at 30-40 mg, dalteparin at 2500-5000 units, or tinzaparin at 3500-4500 units), fondaparinux at 2.5 mg, dabigatran at 75-150 mg, rivaroxaban at 10 mg, or apixaban at 2.5 mg. Aspirin for VTE prophylaxis was considered at any dose in non-combination formulations. The Caprini VTE risk score for thrombosis after hip and knee arthroplasty showed that aspirin was comparable to anticoagulants; patients who received both aspirin and anticoagulants had a higher risk score owing to longer lengths of hospital stay, and a higher number of comorbidities [26].

A report published in February, 2018, in the New England Journal of Medicine describes a trial involving 3,424 patients undergoing total hip or knee arthroplasty. They all received once daily oral rivaroxaban at 10 mg, until postoperative day 5. At that point, they were randomly assigned to either continue rivaroxaban at the same dose or switch to aspirin at 81 mg daily for an additional 9 days after total knee arthroplasty or for 30 days after total hip arthroplasty. These patients were followed for 90 days for symptomatic venous thromboembolism and bleeding complications. The 2 groups were identical in terms of anticoagulation efficacy and bleeding complications. However, it is important to note that all of the patients were first treated with an anticoagulant, and none of the patients were treated with aspirin as monotherapy without an anticoagulant for the first 5 postoperative days. Thus, this observation of equivalence between low-dose aspirin and rivaroxaban only applies to patients beyond postoperative day 5. There are advantages to using aspirin over rivaroxaban with regard to cost, and potentially ease of use, from day 5 forward. The results of this trial, therefore, do not address the efficacy of aspirin as monotherapy initiated immediately after surgery in the absence of an anticoagulant [27].

With no perfect drug introduced over decades for prophylaxis against venous thrombosis in orthopedic surgery, the medical community revisited the use of aspirin. Aspirin has been found comparable to anticoagulant agents in preventing VTE and non-fatal PE [28]. Aspirin was previously shown to protect against symptomatic DVT and PE by 29% and 43%, respectively, versus placebo in a PE prevention trial in 2000 [29]. Aspirin might be advantageous over other anticoagulants because of its lower bleeding risk profile, rapid reversal capability, cost-effectiveness, and no requirement

for laboratory monitoring or insurance approval [30-34]. A study by the American Association of Hip and Knee Surgeons (AAHKS) showed that enoxaparin/LMWH was the most efficacious agent, but 68% of surgeons reported that aspirin was easiest to use with the lowest risk profile for bleeding and any wound drainage procedures [19].

There were some major changes over the past few decades that made the antiplatelet effect of aspirin, which has a much lower bleeding risk than the any anticoagulant, seem to be a reasonable option. First, the patients are now mobile much sooner after surgery. The surgical procedures are not nearly as complex, invasive, or take as long as they have in the past. The studies that were performed over the past 5-10 years indicated not only to the AAOS, but also to the experts in coagulation and anticoagulation that aspirin may now be an acceptable choice in many patients.

A study by The Intermountain Joint Replacement Center Writing Committee that included over 300 hospitals in the United States showed that aspirin presents a viable option to prevent VTE for selected patients undergoing total joint replacement therapy. The distinction between patients is the main challenge. It is important to determine between low-risk patients in whom aspirin may be sufficient, from patients with a higher risk of thrombosis who may benefit more from anticoagulants [35].

Taken together, the results of this study show the progression toward aspirin and away from anticoagulants by both orthopedic surgeons and specialists in coagulation. There is every reason to believe that there will be continued movement toward aspirin as surgical techniques and perioperative care after orthopedic surgery continues to improve.

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