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Venous Thromboembolism (VTE) Prophylaxis for Hip and Knee Arthroplasty: Changing Trends

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Abstract Venous thromboembolism (VTE) has been identified as an immediate threat to patients undergoing major orthopedic procedures such as total hip arthroplasty (THA) and total knee arthroplasty (TKA). Given the known dangers of VTE, arthroplasty surgeons are sensitive to the need for VTE thromboprophylaxis. However, the modalities of thromboprophylaxis used to minimize the risks to patients have been variable. Clinical practice guidelines have been published by several professional organizations, while some hospitals have established their own protocols. The 2 most popular guidelines are those published by the Academy of Orthopaedic Surgeons (AAOS) and American College of Chest Physicians (ACCP), both from North America. Prior to 2012, these recommendations varied depending on underlying definitions, methodology, and goals of the 2 groups. For the first time, both groups have similar recommendations that focus on minimizing symptomatic VTE and bleeding complications. The key to determining the appropriate chemoprophylaxis for patients is to balance efficacy of a prophylactic agent, while being safe in regards to bleeding complications. However, a multimodal approach that focuses on early postoperative mobilization and the use of mechanical prophylaxis, in addition to chemoprophylaxis, is essential.

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Introduction

As the number of total joint arthroplasties performed worldwide continues to grow, a commensurate increase in the number of venous thromboembolism (VTE) events can be anticipated. Although the incidences of symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE) are low, the incidence of asymptomatic DVTs has been estimated to be 20 %–40 % of inpatients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA) [1]. Unfortunately, the risk of symptomatic VTE has remained stable over the past 2 decades. Therefore, the use of effective and safe chemoprophylaxis agents is crucial for minimizing the risk of VTE events in these patients. Despite several decades of experience and hundreds of clinical studies, there is still no consensus on the ideal method of thromboprophylaxis for patients undergoing THA and TKA. This inconsistency has raised the concern that many patients are at risk for insufficient prophylaxis or excessive bleeding risks. In a retrospective study involving 3497 patients who had THAs or TKAs between April 1, 2004 and December 31, 2006, Selby et al. found that only 40 % of patients received the 8th edition American College of Chest Physicians (ACCP) recommended thromboprophylaxis [2]. Out of the patients receiving non-ACCP recommended prophylaxis, 81 % received shorter than the minimum 10 days recommended, making them twice as likely to experience a DVT (3.76 % vs 2.01 %, P=0.003) and more than 8 times more likely to experience a PE (1.19 % vs 0.14 %, P=0.001).

In the past 2 years, there have been remarkable changes to the clinical guidelines for VTE prophylaxis, mostly pertaining to changes in the ACCP guidelines. This review will describe the new guidelines published by the American Academy of Orthopedic Surgeons (AAOS) and ACCP, their influences on how surgeons prescribe thromboprophylactic agents, and the currently available chemoprophylactic options.

ACCP and AAOS Guidelines

A number of concerns have been identified with the previous ACCP clinical guidelines. Until the eighth conference in 2008, prior methodologies emphasized multi-center, randomized clinical trials with venographically proven DVTs as the endpoint. The United States (US) Food and Drug Administration (FDA) recognizes venographically proven DVTs as a valid endpoint for the efficacy of VTE prophylactic drugs. This method is very expensive and often weighted toward studies utilizing aggressive pharmaceutical chemoprophylaxis. However, the vast majority of DVTs are asymptomatic. In addition, venography has been largely replaced by ultrasound (US) techniques in most major medical centers and hospitals. Moreover, the clinical significance of asymptomatic DVTs has been extensively debated. In a recent study, Parvizi et al. [3] found a very low correlation between the presence of DVTs and PEs, and, therefore, questioned the clinical significance of an asymptomatic DVT.

In essence, the ACCP guidelines were more focused on efficacy, often under emphasizing the risk of bleeding, which is associated with serious complications including hematoma, infection, and reoperation. Moreover, the ACCP described a major bleeding episode as overt bleeding associated with at least 1 of the following: death or life threatening clinical event; bleeding confirmed as retroperitoneal, intracranial or intraocular; transfusion of more than 2 packed units of blood cells or whole blood; or decrease of hemoglobin more than 2 g/dL compared with relevant postoperative level [4]. These criteria generally do not apply to THA and TKA patients. Galat et al. [5] reported that patients with wound complications requiring reoperation within 30 days of TKA were 10 times more likely to have subsequent major surgery and associated morbidities than those without. However, failure to meet the ACCPs strict criteria of major bleeding event resulted in under reporting of bleeding complications in many studies. Investigations by both Keeney et al. [6] and Novicoff et al. [7] revealed a dramatic increase in bleeding after adopting the ACCP protocols. Finally, not only did the orthopedic surgeons experience an increase in bleeding, but they were also prohibited from using less aggressive and less expensive options such as aspirin with mechanical compression devices, even in young patients with a very low VTE risk [8–10].

Another major concern with the ACCP guidelines was that numerous potential financial conflicts of interest were found with many authors. As a result, the Institute of Medicine issued recommendations regarding guideline development that discouraged any financial conflict of interest among its authors of clinical guidelines [11].

Due to the many concerns raised regarding the ACCP guidelines, the AAOS formed its DVT/PE workgroup in 2007 and issued its own recommendations by reviewing the available literature on VTE with symptomatic DVT, PE, and mortality as endpoints [12•]. The goal was to achieve more balance between minimizing risk and maximizing efficacy, while minimizing conflicts of interest during the guideline development. Patients were classified based on their medical history to identify their risk of VTE and bleeding. The AAOS guidelines were in conflict with the ACCP guidelines until the ninth edition of the ACCP recommendations, which was published in 2012 [13•].

In 2012 edition, the ACCP addressed almost all the concerns found in their previous clinical guidelines. Their methodology was changed dramatically to focus on more symptomatic and significant outcomes like bleeding and wound drainage. While the AAOS was unable to recommend neither a specific modality of prophylaxis nor the optimal duration of treatment, the ACCP recommended several choices. The conflicts of interest issue was addressed with more than half their authors declaring no potential financial conflict of interests. They also recommend a mobile intermittent pneumatic compression device (IPCD) that has a compliance monitoring chip as supported in a study by Colwell et al. [14]. Importantly, neither guideline could identify any literature that supported the use of IVC filters to prevent PE. Moreover, both guidelines recommended against routine US screening.

Chemoprophylaxis

VTE prophylaxis for THA and TKA patients are available in chemical and/or mechanical forms. In recent years, there has been significant progress toward developing more effective and practical thromboprophylaxis agents to include either injectable low molecular weight heparin (LMWH) [15] or the latest oral anticoagulant agents (factor Xa inhibitors and direct thrombin inhibitors) [16, 17]. Chemical prophylaxis agents included in the clinical guidelines were aspirin, warfarin, LMWH, fondaparinux, dabigatran, rivaroxaban, and apixaban. All are approved in United States as we use apixaban at Mayo. This review will concentrate on studies that were influential to the formation of AAOS and ACCP recommendations. The following paragraphs will also describe briefly the current chemical prophylaxis suggested by ACCP guidelines and the recent available research papers.

Aspirin

Aspirin has been a popular chemoprophylaxis agent for the last 3 decades. It is still widely used in North America, although it is considered less available in Europe [18].The ACCP guidelines [4] recommended aspirin as a chemoprophylaxis agent, rather than no prophylaxis at all (Grade 1B). This is due to the Pulmonary Embolism Prevention (PEP) trial [19], which concluded that low-dose aspirin, when taken for 35 days, would result in 7 times less symptomatic DVT cases, but in 3 bleeding cases and 2 nonfatal myocardial infarction per 1000 patients. On the other hand, AAOS guidelines recommend the use of pharmacologic agents and/or mechanical compressive device for prevention of VTE, but is inconclusive on which strategy is optimal [12•].

In a study by Vulcano et al. the rate of VTE between aspirin was compared with warfarin in adjunct to multimodal prophylaxis (ie, early mobilization post operatively, pneumatic compression devices, and regional anesthesia) [20]. The results showed a lower rate of VTE, PE, proximal DVT, and distal DVT for the aspirin group. However, the findings may be biased since aspirin was given to low-risk patients and warfarin was given to high-risk patients.

Unfractionated Heparin (UFH)

Heparin is one of the oldest thromboprophylaxis agents for VTE following major surgery. However, due to the inconvenient method of administration (subcutaneous injection 2–3 times a day) and an increased frequency of complications such as heparin-induced thrombocytopenia (HIT), the use of this agent has decreased in popularity. In fact, UFH is very rarely included as a studied agent in recent publications [21].

Leyvraz et al. [22] studied 349 patients undergoing THA in 28 European orthopedic departments. All patients had venograms completed 10 days after the surgery. The results showed DVT events in 16 % of UFH patients and 12.6 % of LMWH patients, (P=0.45) and the incidence of proximal DVT was much lower in LMWH group (2.9 % and 13.1 %, respectively; P<0.001). Bleeding events were low and comparable between both groups.

Low Molecular Weight Heparin (LMWH)

Low molecular weight heparin is generated from unfractionated heparin either through physical, chemical, or enzymatic depolarization [4]. Some of the available LMWHs are enoxaparin, dalteparin, and tinzaparin. Among these 3, only 3 (enoxaparin and dalteparin) are indicated in major orthopedic surgery [23].

A meta-analysis study involving16 randomized controlled trials (RCTs) compared enoxaparin with the newer anticoagulants (rivaroxaban, dabigatran, apixaban) [24•].The study concluded that newer anticoagulants are higher in efficacy, but also have higher risk of bleeding. The risk of symptomatic VTE was lower with rivaroxaban (relative risk [RR] 0.48, 95 % confidence interval [CI] 0.31–0.75), and similar with dabigatran (RR=0.71, CI 0.23–2.12) and apixaban (RR= 0.82, CI 0.41–1.64). In terms of safety outcome, rivaroxaban was associated with a significant increase in the risk of clinically relevant bleeding (RR=1.25, CI 1.05–1.48; P=0.01). Dabigatran did not show a significant increase compared with enoxaparin (RR=1.12, CI 0.94–1.35; P=0.21), regardless of the dosage used (150 or 220 mg). However, this study found that apixaban was associated with a significant reduction in risk of bleeding (RR=0.82, CI 0.69–0.98; P=0.03). On the same paper, after balancing efficacy and safety (symptomatic DVT or PE with clinically relevant bleeding events), no significant difference was found between LMWH and newer anticoagulant agents. However, it is important to note that all papers reviewed in this meta-analysis were sponsored by pharmaceutical companies.

Another review tried to compare indirectly between dalteparin and enoxaparin as prophylaxis in patients following THA [25]. From 9 RCTs that were studied (all compared with placebo), results demonstrated comparable safety and efficacy between these 2 LMWHs. Both have 50 % risk reduction of VTE compared with placebo (RR=0.50, P<0.001) and no increase in major bleeding (RR=1.19, P=0.76), heparin induced thrombocytopenia (RR=1.13, P=0.83) or death (RR 0.72, P=0.59). Although this study showed similar efficacy and safety between enoxaparin and dalteparin, more RCTs comparing these 2 agents are needed to actually see the difference.

One of the older reviews [26] compared the cost-effectiveness between enoxaparin and warfarin for DVT prophylaxis following THA. The study showed that the occurrence of DVT was lower in the enoxaparin group (13.6 %) compared with warfarin group (20.6 %). In ACCP guidelines [4], the single most suggested thromboprophylactic agent was LMWH, unless patients had a high risk for bleeding or were uncooperative with injections.

Warfarin

Warfarin is a vitamin K antagonist, and has been widely used in United States as an anticoagulant agent since 1954 for various indications [27]. It derived its name because it was discovered at the University of Wisconsin (WARF = Wisconsin Alumni Research Foundation). It was the first oral anticoagulant. However, the usage is restricted by the bleeding risk, potential drug interaction, and requirement for constant monitoring (INR).

Warfarin has been compared with low molecular weight heparin (LMWH) as prophylaxis for TKA in several multicenter clinical trials [28–32]. To summarize, all studies

showed that LMWH was a more effective agent to prevent DVT formation ($P<0.05$), but no difference to warfarin in preventing symptomatic events including PE, in part since most of studies measured primary outcome as asymptomatic DVT. Moreover, LMWH resulted in more bleeding episodes compared with warfarin, although the difference is not significant ($P>0.05$).

Factor Xa Inhibitor (Fondaparinux, Rivaroxaban, Apixaban)

There are 2 types of factor Xa inhibitors, the indirect and direct. Fondaparinux and idraparinux are examples of indirect factor Xa inhibitors. They are synthetic, highly selective factor Xa inhibitors that work in a pentasaccharide form. However, the development of idraparinux was terminated due to prolonged elimination half-life and increased risk of bleeding longer than 6 months. On the other hand, direct factor Xa inhibitors work by binding to the active site of factor Xa, thus, blocking the interaction with its substrate [33–35]. Examples of oral direct factor Xa inhibitors are rivaroxaban, apixaban, edoxaban, and betrixaban [35]. Rivaroxaban and apixaban are recommended by the ACCP in the same manner as the fondaparinux [4]. However, the increase in efficacy is accompanied by increased bleeding risks, which is why LMWH remains the most recommended chemoprophylaxis [13•].

A multicenter RCT from Japan studied the effect of fondaparinux compared with placebo and the dose–response effect (0.75 mg, 1.5 mg, 2.5 mg, and 3.0 mg) in patients with TKA or THA (2 separate sub-studies) [34]. In the TKA substudy, the incidence of VTE was 34.2 %, 21.3 %, 16.2 %, and 9.5 % in groups receiving fondaparinux 0.75 mg, 1.5 mg, 2.5 mg and 3.0 mg, respectively, compared with the placebo group (65.3 %). In THA substudy, the incidence of VTE was 24.2 %, 4.6 %, 7.4 %, and 14.4 %, compared with the placebo group (33.8 %). In both substudies, each group receiving fondaparinux showed significant reduction in asymptomatic VTE events compared with placebo ($P<0.001$), while no major or minor bleeding difference was found between the fondaparinux and placebo groups.

Turpie et al. [36] completed a meta-analysis on VTE prevention between fondaparinux and enoxaparin in patients undergoing elective major orthopaedic surgery (THA, TKA, and ORIF of hip fractures). The result showed greater reduction of VTE events in the fondaparinux groups (6.8 %) compared with enoxaparin (13.7 %), and the result was consistent in all studies reviewed. Despite more major bleeding events that occurred in the fondaparinux group ($P=0.008$), clinically relevant bleeding that led to death or occurred in critical organs did not differ between the 2 groups. According to ACCP recommendation [4] fondaparinux is suggested as chemoprophylaxis agent in patients undergoing THA or TKA, but its use needs thorough judgment based on the patients' bleeding risks, and is positioned with a lower recommendation than LMWHs. Therefore, due to bleeding concerns, the use of fondaparinux in North America is not as popular as other VTE prophylaxis for arthroplasty [37].

Rivaroxaban

Rivaroxaban is a FDA approved oral direct factor Xa inhibitor that also requires no monitoring. There have been 4 Phase III randomized trials [38–41] to assess the efficacy of rivaroxaban as a VTE prophylaxis agent in total joint arthroplasty patients. Lassen et al. [38] showed that 10 mg of rivaroxaban taken once daily was more effective than 40 mg of enoxaparin administered once daily in reducing overall VTE for TKA patients (RR=9.2 %, $P<0.001$). There was no difference in major bleeding between rivaroxaban and enoxaparin groups (0.6 % vs 0.5 %; $P>0.05$). In a different study comparing 10 mg of rivaroxaban once a day with 30 mg enoxaparin every 12 hours in TKA patients, Turpie et al. [39] found the rivaroxaban group yielded a lower overall VTE incidence and mortality rate compared with enoxaparin group (absolute risk reduction 3.19 %, 95 % CI 0.71–5.67; $P=0.0118$). No difference in major bleeding events between both group (0.7 % vs 0.3 %; $P=0.109$). In the latest retrospective review, Jensen et al. [42] associated rivaroxaban with more re-operations than LMWH after TKA (3.94 % vs 1.8 %; $P=0.046$).

In a study comparing 10 mg of rivaroxaban taken 6 hours postoperatively against 40 mg enoxaparin administered on the preoperative evening as prophylaxis for THA, Eriksson et al. found rivaroxaban to be significantly more effective than enoxaparin in preventing total VTE (1.1 % vs 3.7 %, RR of 2.6 %, $P<0.001$) but not in symptomatic events (96.8 % vs 97.0 %; $P<0.05$). No difference in occurrence of major bleeding ($P=0.18$) [40]. In another study comparing usage of rivaroxaban with extended duration of 35 days against administration of enoxaparin for 10–14 days, Kakkar et al. found rivaroxaban to be significantly more effective than enoxaparin in limiting total VTE and symptomatic episodes (RR=7.3 %, CI 5.2–9.4; $P<0.0001$). No significant difference on any bleeding during treatment was noted ($P=0.25$) [41].The current controversy for rivaroxaban is the timing of first dosage. In the above-mentioned 4 studies, rivaroxaban was administered 6 to 8 hours postoperatively, but it may be safer to start the first dosage the next day especially if the drug does have any effect on the development of symptomatic events.

Studies to date may not have found significant differences in adverse event between direct factor Xa inhibitors and LMWH, but direct factor Xa inhibitors do have a bleeding risk that is still higher than LMWH. Lassen et al. [43] conducted an analysis from 4 phase III clinical trials (ie, RECORD1–4 [Regulation of Coagulation in Orthopaedic Surgery to prevent deep venous thrombosis and pulmonary embolism]). These trials involved 12,383 patients undergoing

THA or TKA, which then randomized to receive either oral rivaroxaban 10 mg once daily or subcutaneous enoxaparin 40 mg once daily (RECORD 1–3) or enoxaparin 30 mg twice daily (RECORD 4). The adverse event was observed only during the active treatment period. These studies showed that patients who underwent TKA had more complications compared with THA patients despite the types of prophylaxis given. Moreover, although the number of bleeding events were higher in rivaroxaban treatment groups, the difference was not significant. This could be one of the reasons rivaroxaban has been approved in more than 115 countries worldwide for the prevention of VTE after TKA or THA.

Apixaban

Apixaban is a direct oral factor Xa inhibitor that has not been approved by FDA in United States. Lassen et al. [44–46] conducted a series of studies comparing apixaban against different doses of enoxaparin as prophylaxis for total joint arthroplasty patients. For TKA patients, when 2.5 mg of apixaban taken twice daily was assessed against 30 mg of enoxaparin administered twice daily, both groups showed extremely low overall VTE rates, but apixaban resulted in significantly less bleeding risk [44]. In another study where 2.5 mg of apixaban taken twice daily was compared against 40 mg of enoxaparin administered once daily, Lassen et al. found the overall VTE and mortality rate to be significantly lower in the apixaban group [45]. There was no significant difference found between the 2 groups in terms of non-major bleeding risks. For THA VTE prophylaxis, when 2.5 mg of apixaban taken twice a day was compared with 40 mg enoxaparin taken once daily by Lassen et al., results showed that apixaban was more effective in lowering overall VTE events and mortality rate [46]. The same study showed that with every 147 patients, apixaban prevented 1 VTE event without any additional bleeding risk. These 3 studies suggested that 2.5 mg of apixaban taken twice daily is the more effective prophylactic agent when compared with 40 mg of enoxaparin administered once daily, but showed the same efficacy when comparing 30 mg of enoxaparin administered twice daily. A meta-analysis performed by Russell et al. to investigate the efficacy of 2.5 mg of apixaban or 10 mg rivaroxaban against enoxaparin as prophylaxis after total hip and knee arthroplasty summarized that oral factor Xa inhibitors were superior to enoxaparin in preventing DVT, but there was no difference in the rate of PE, mortality, or postoperative wound infections [47].

Direct Thrombin Inhibitor (Dabigatran)

Direct thrombin inhibitors (DTIs) work by binding specifically to the active center of thrombin and inactivate free and fibrin-bound thrombin. This process is reversible leaving small amount of free and active thrombin to control hemostasis [35].

Dabigatran is the first oral DTI approved for the chemoprophylaxis following major orthopaedic procedures. It was first approved by Health Canada and European Medicines Agency in 2008, and is now available in more than 75 countries. It has the benefit of oral administration, being highly specific, has a reversible effect, does not require monitoring, and has a slow onset. Thus, the hemostatic process may take place after procedures and before the effect of anticoagulant commences [48]. In the US, dabigatran etexilate is an FDA approved oral direct thrombin inhibitor for prevention of atrial fibrillation and stroke, but not for VTE prophylaxis after THA and TKA.

A trial by Eriksson et al. [49] compared dabigatran against enoxaparin (oral dabigatran 220 mg, oral dabigatran 150 mg, subcutaneous enoxaparin 40 mg; all once daily). Efficacy outcomes measured were symptomatic DVT, venographic DVT, and/or symptomatic PE. The safety outcome measured was bleeding events during the course of study. The result showed efficacy outcome (total VTE and death) of 37.7 %, 36.4 %, and 40.5 % for enoxaparin, 220 mg dabigatran, and 150 mg dabigatran, respectively. The major bleeding occurrence also did not differ significantly among 3 groups (1.3 % vs 1.5 % vs 1.3 %, respectively; $P > 0.05$).

Ginsberg et al. [50] also found both doses of dabigatran to be comparable with 30 mg of enoxaparin taken twice daily in terms of bleeding episodes for total knee arthroplasty patients. Based on the above trials, ACCP concluded that dabigatran was comparable to enoxaparin / LMWH in terms of efficacy and bleeding risks.

Mechanical Prophylaxis

Mechanical prophylaxis is any compressive device applied to an affected limb. It can be a compressive stockings, Intermittent Pneumatic Compression Devices (IPCD), or similar working devices. A single center study conducted in Stockholm reported no significant difference in VTE incidence in 5310 THA and TKA patients after discontinuing the use of postoperative compression stockings. The incidence was 2.7 % and 2.3 % ($P=0.4$) before and after the cessation, respectively [51].

ACCP guidelines suggest the use of IPCD be at least 18 hours a day as an adjunct to chemoprophylaxis, or in patient with high risk of bleeding [13•]. The AAOS guidelines recommend use of mechanical compressive devices in patients with known bleeding disorders, such as hemophilia or active liver disease or as with chemoprophylaxis in patient with previous VTE [12•].

Intermittent Pneumatic Compression Devices (IPCD)

Some studies have found that mechanical prophylaxis such as IPCDs are quite effective in reducing the risk of DVT and PE

in arthroplasty patients by more than 50 % without any risk for bleeding. However, in the past, patients' treatment ceased upon discharge from hospital and adherence to routine application became a challenge. Therefore, the introduction of portable, battery-powered devices allow patients to utilize these devices in the hospital or at home. Moreover, a monitoring chip implanted in the device helps monitor a patient's compliance. Colwell et al. [14] showed in a multicenter randomized controlled trial comparing IPCD against enoxaparin that IPCD was just as effective as enoxaparin in preventing proximal and distal DVT and PE events, but resulted in a much lower bleeding risk (1.3 % IPCD vs 4.3 % LMWH). There was no difference in mortality rate. As a side note, this paper disclosed that 1 or more of its authors or immediate family received benefits from the commercial party.

Combined Modalities

Combined prophylactic modalities have been shown to improve the efficacy [52, 53]. However, it is still unclear whether this advantage also applies to total joint arthroplasty, whether the combined modalities are indeed better than either chemoprophylaxis or mechanical compression device alone, or whether they can prevent pulmonary emboli. In a systematic review and meta-analysis of 1399 patients, Kakkos et al. [54] found that in TKA, the rate of DVT was reduced from 18.7 % with anticoagulant alone to 3.7 % with combined modalities (RR=0.27; P=0.03). For THA, the rate of DVT was reduced from 9.7 % with anticoagulant alone to 0.9 % with additional intermittent mechanical leg compression (RR=0.17; P <0.001). However, when anticoagulant was added to compression compared with compression alone, the rate of DVT was insignificantly reduced from 8.7 % to 7.2 % for THAs, but no data was available for the TKA group. Further research with a larger population on the role of combined modalities of thromboprophylaxis in total joint replacement and in other high risk orthopedic surgeries is needed.

Duration

The ACCP guidelines recommend a minimum of 10 to 14 days of prophylaxis in patients undergoing THA or TKA. However, it suggests extending the thromboprophylaxis to 35 days in the outpatient period (Grade 2B) [13•].

Conflicts of Interest

With so many choices of thromboprophylaxis currently available on the market, orthopaedic surgeons have to be cautious when deciding the most suitable prophylaxis for their patients. The AAOS and ACCP guidelines, current literature, and individual needs of each patient must be taken into consideration. Moreover, when reviewing study results for each modality, one has to be aware of any potential financial conflicts of interest. A recent evidence-based review by Lee et al. revealed that out of 71 eligible studies identified, 52 were industry funded, 14 were not and the remaining 5 did not disclose the source of funding [55•]. Most of these industry-sponsored studies were performed in Western countries. The review further showed a significant correlation between the funding source and qualitative conclusions. Only 3.8 % of the 52 industry-sponsored studies had unfavorable conclusions, whereas 21.4 % of the 14 non-industry-sponsored studies indicated that the modality examined were neither effective nor safe. Since more studies are sponsored by industry than not, one will find more favorable conclusions to the use of the sponsored prophylactic agents or recommendations for extended use. The limitation to the review by Lee et al. is that the number of non-industry-sponsored studies was small, and therefore the authors' analysis was sensitive to the conclusions of those studies. In another study to evaluate thromboembolic complications after fast-track THA and TKA, Husted et al. found that if patients were mobilized within 4 hours after surgery and given prophylaxis for 1–4 days duration, no DVT, PE, or mortality was found in the study [56]. The authors also questioned whether extended prophylaxis was actually needed when patients were mobilized early since the majority of studies on extended prophylaxis were partly sponsored by pharmaceutical companies.

Asian Perspective

There are large variations in reported cases of postoperative DVT after THA and TKA in Asian populations, even within the same country. The general consensus is that the rates are lower in Asia as compared with Western countries [4, 57–60]. However, due to lack of reported data which leads to substantial under-estimation of VTE incidence, this consensus is debatable [61, 62]. However, several multicenter study such as the SMART (Surgical Multinational Asian Registry in Thrombosis), AIDA (Assessment of the Incidence of Deep Vein Thrombosis in Asia), and Asia Pacific Thrombosis Advisory Board stated that the incidence rates of DVT in Asian populations are similar compared with the Western [63–65]. The paucity and variation in available data regarding the incidence of DVT in arthroplasty patients makes it difficult to prepare guidelines and protocols for thromboprophylaxis [63, 64]. The variations in data can be due different methods of detection, different designs of studies, lack of patients' incidence data, and different lifestyles and dietary content. Despite declaration of minimal incidence of

DVTs, developed Asian countries such as Korea, Japan, and China have established their own guidelines. This shows some consensus that clinical protocols and guidelines are necessary for each country regardless of the actual incidences reported. In addition, these guidelines can differ due to poor understanding of risk factors like ethnicity and genetic susceptibility.

Conclusions

The number of arthroplasties performed worldwide continues to increase annually. VTE remains a clinical concern due to the risk of symptomatic VTE and fatal PE. For the first time in history, the AAOS and ACCP are mostly in alignment in their latest recommendations. Both guidelines now focus on symptomatic events and bleeding risks. There should be a balance between efficacy and safety because inappropriate anticoagulation results in excessive bleeding. There are still limitations in the published guidelines that represent the limitations in the current literature. Further research is needed to identify patients at risk of VTE and bleeding. The final decision on ideal thromboprophylaxis remains with the treating physician who is most familiar with each patient's unique medical history. The current clinical guidelines provide an orthopaedic surgeon with more latitude, and choices of VTE prophylaxis without emphasis on aggressive chemical, and often unneeded, prophylaxis. Modern arthroplasty advocates early postoperative mobilization and use of mechanical prophylaxis in combination with chemoprophylaxis. The key to determining the appropriate chemical prophylaxis for patients is to balance safety and efficacy while minimizing bleeding.

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Compliance with Ethics Guidelines

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