

# What's new in VTE risk and prevention in orthopedic surgery

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## Abstract

A State of the Art lecture titled “What's New in VTE Risk and Prevention in Orthopedic Surgery” was presented at the ISTH congress in 2019. Patients undergoing orthopedic surgery have long been recognized to be at increased risk of venous thromboembolism (VTE) and were among the first patient groups to be studied in VTE prophylaxis trials. From the late 1950s to 2010s, prophylaxis trials in major orthopedic surgery tended to focus on venographic deep vein thrombosis and assessed thromboprophylaxis in all patients based on a population approach. In general, anticoagulants were favored over mechanical prophylaxis or aspirin, and longer-duration prophylaxis was favored over shorter durations. As discussed in this paper, more recently, orthopedic prophylaxis has started to become more nuanced and individualized. Modern trials are focusing on symptomatic VTE as outcomes; there has been a resurgence in interest in aspirin for prophylaxis, and there has been a slow move to studying ways to evaluate VTE risk in patients undergoing orthopedic surgery and recommending thromboprophylaxis to patients based on individual attributes, in whom risk stratification and weighing of benefit versus risk of thromboprophylaxis is becoming key. We also touch on VTE risk and guideline recommendations to prevent VTE in 2 other commonly encountered orthopedic populations: patients undergoing knee arthroscopy and those with distal leg fractures. Finally, we summarize relevant new data on this topic presented during the 2019 ISTH annual congress in Melbourne.

## KEYWORDS

aspirin, thromboprophylaxis, total hip arthroplasty, total knee arthroplasty, venous thromboembolism

## Essentials

- Patients having major orthopedic surgery are at increased risk of venous thromboembolism (VTE).
- Modern thromboprophylaxis based on risk profiles to weigh value of thromboprophylaxis.
- We review recommendations to prevent VTE in orthopedic populations.
- Finally, we summarize related new research presented at the 2019 ISTH Congress in Melbourne.

This manuscript was developed based on an invited State of the Art Session presented by Dr Kahn at the XXVII Congress of the International Society on Thrombosis and Haemostasis, July 6-10, 2019, Melbourne, Australia.

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## 1 | INTRODUCTION

In this article, we review new developments in the areas of risk of venous thromboembolism (VTE) and VTE prevention in major orthopedic surgery. We discuss the changing epidemiology of VTE in patients undergoing major orthopedic surgery, risk factors for VTE and new developments in risk prediction, recommendations pertaining to the use of aspirin for VTE prophylaxis after major orthopedic surgery, and recent and ongoing aspirin trials. We focus on hip and knee joint arthroplasty surgery due to a relative lack of modern evidence pertaining to hip fracture surgery. We also touch on risk of VTE and guideline recommendations for VTE prevention in 2 other commonly encountered orthopedic populations for which clinical questions regarding thromboprophylaxis frequently arise: patients undergoing knee arthroscopy and those with distal leg fractures. Finally, we summarize relevant new data on this topic that were presented at the 2019 ISTH annual congress in Melbourne.

## 2 | HISTORICAL PERSPECTIVE

Patients undergoing orthopedic surgery have long been recognized to be at increased risk of VTE and were among the first patient group to be studied in VTE prophylaxis trials.<sup>1</sup> With the advent of contrast venography in 1938, deep vein thrombosis (DVT) could be diagnosed more reliably, and the high frequency of venographically detected DVT made this patient group ideal for study in clinical trials. Indeed, an October 2019 search of PubMed yielded >400 individual randomized controlled trials of various forms of thromboprophylaxis in patients undergoing orthopedic surgery, primarily those undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA); earlier trials compared active treatment to placebo or no treatment, and later trials have compared different active prophylaxis modalities and different durations of treatment.

## 3 | HOW COMMON IS VTE AFTER TOTAL HIP OR TOTAL KNEE ARTHROPLASTY?

Without pharmacologic thromboprophylaxis, rates of DVT detected with routine contrast venography were in the order of 54% after total hip arthroplasty (THA), of which 27% were proximal DVT, and 64% after total knee arthroplasty (TKA), of which 15% were proximal DVT.<sup>2</sup> However, rates of symptomatic VTE, which refer to those that present with patient symptoms, rather than those detected with routine screening tests in asymptomatic patients, are far lower. Symptomatic VTE, which are considered outcomes of greater clinical importance to patients, occur in the range of ~2% to 3% after THA without pharmacologic prophylaxis and ~1% to 1.2% (THA: DVT 0.7%, pulmonary embolism [PE] 0.3%; TKA: DVT 0.9%, PE 0.3%) with pharmacologic prophylaxis.<sup>3-6</sup>

## 4 | BALANCING VTE AND BLEEDING: DO THE BENEFITS OF THROMBOPROPHYLAXIS ALWAYS OUTWEIGH THE RISKS?

Recently, Chan et al conducted a systematic review of randomized trials that compared different pharmacologic thromboprophylaxis regimens (apixaban, dabigatran, enoxaparin, fondaparinux, rivaroxaban) in THA or TKA patients, with a focus on the outcomes of symptomatic VTE, major bleeding, clinically relevant nonmajor bleeding and mortality.<sup>7</sup> Various definitions of major bleeding and clinically relevant nonmajor bleeding were used in the individual trials.<sup>8,9</sup> In total, 40 285 patients were included. Results showed that across trials, symptomatic VTE occurred on average in about 1% of patients, and the average rate of VTE was similar to or exceeded by the average rate of major bleeding, which occurred in 0.5% to 2% of patients and up to 4% to 5% of patients, if major bleeding and clinically relevant nonmajor bleeding, including surgical site bleeds, are combined.

This raises the question of whether our focus has been too much on thrombosis at the expense of bleeding complications and, by extension, that risk stratification of orthopedic surgery patients may be the key to achieving the ideal risk-benefit ratio and applying best options for safe and effective thromboprophylaxis. This is especially relevant as trends over time suggest that rates of VTE after major orthopedic surgery may be decreasing.

## 5 | EPIDEMIOLOGY AND TRENDS OVER TIME IN VTE OCCURRENCE AFTER MAJOR ORTHOPEDIC SURGERY

An important aspect of the epidemiology of VTE after major orthopedic surgery, reported more than 20 years ago, is that most cases occurred after hospital discharge. White and colleagues showed in 1998 that patients undergoing THA and TKA remained at risk of VTE for weeks after surgery.<sup>10</sup> Using the California discharge database, the median time to VTE was 17 days in 19 586 patients undergoing THA and 7 days in 24 059 patients undergoing TKA, and many of these events (76% after THA and 47% after TKA) occurred after hospital discharge. Of note, mean length of stay in that study for both THA and TKA was ~7 days but is much shorter now. These data provided the impetus for numerous clinical trials evaluating post-discharge, extended-duration thromboprophylaxis, compared with prophylaxis restricted to the duration of hospital stay. Results of these trials have informed guideline panels to recommend extended duration prophylaxis (up to 28-35 days) after major orthopedic surgery.<sup>5,11,12</sup>

Recent studies have suggested that overall rates of VTE after major orthopedic surgery are falling. A study from a national database from England and Wales of 10-year trends (2005-2014) in medical complications in 540 623 patients undergoing THA found that despite a population with increasing levels of comorbidity, the 90-day mortality rate decreased from 0.60% to 0.15%,

the 30-day DVT rate decreased from 1.15% to 0.28%, and the 30-day PE rate decreased from 0.77% to 0.40%.<sup>13</sup> A recent systematic review of 255 studies that included almost 6.3 million patients found a consistent decline in mortality within 3 months after elective THA or TKA (from 1.15% pre-1980 to 0.24% post-2000) that was independent of method of prophylaxis.<sup>14</sup> Why have rates of VTE and mortality decreased? This is likely due to some combination of improvements in surgical techniques and perioperative care, including unicompartamental surgery, shorter operative procedure times, greater use of regional anesthesia, more effective analgesia, faster postoperative mobilization, increased use of day-case procedures, shorter duration of hospitalization, and more consistent use and/or longer duration of prophylaxis.<sup>15</sup>

## 6 | WHAT ABOUT MOVING BACK TO SHORTER DURATIONS OF PROPHYLAXIS?

In view of trends over time toward decreasing rates of VTE in patients with major orthopedic surgery, what about moving back to shorter durations of prophylaxis, for at least some patients, such as “fast-track” patients? Fast-track surgery uses enhanced recovery protocols based on evidence-based care principles including use of spinal anesthesia, opioid-sparing analgesia, and early mobilization with discharge to the patient’s own home. New intriguing data from a prospective study supports shorter-duration prophylaxis. In a cohort management study, elective unilateral THA or TKA patients received in-hospital-only anticoagulant prophylaxis if their length of stay was anticipated to be  $\leq 5$  days. Outcome data within 90-day follow-up was obtained via the Danish National Patient Registry and medical records. Among 18 407 procedures, 95.5% had lengths of stay  $\leq 5$  days (median, 2 days) and had in-hospital anticoagulant prophylaxis only; no mechanical prophylaxis was used. Mean age was 67 years. The incidence of symptomatic VTE within 90 days was low, at 0.40% (0.16% PE, 0.22% DVT, 0.02% combined DVT and PE). Two PEs (0.01%) were fatal. Risk factors for VTE were aged  $>85$  years and body mass index (BMI)  $>35$  kg/m<sup>2</sup>.<sup>16</sup> While this was not a randomized controlled trial, results suggested that thromboprophylaxis after discharge may not be necessary in fast-track THA and TKA with length of stay of  $\leq 5$  days. Further studies, ideally randomized controlled trials, are needed to assess the safety of this approach, especially in higher-VTE-risk fast-track patients.

What does this mean for our orthopedic surgery patients? On the one hand, these patients are at increased risk for VTE, and risk persists for weeks after surgery, which is why extended-duration prophylaxis is guideline recommended. On the other hand, the average risk of VTE after major orthopedic surgery may be decreasing over time and is similar to or may be lower than the risk of bleeding with pharmacologic thromboprophylaxis. Further, shortened duration prophylaxis for lower-VTE-risk patients having fast-track orthopedic procedures may prove, with further study, to be effective.

The key to optimizing prophylaxis in this patient group is better risk stratification, as discussed below.

## 7 | CONCEPT OF POPULATION VERSUS INDIVIDUAL APPROACH TO PROPHYLAXIS

To date, the literature, including guidelines, has primarily focused on using a population (sometimes called whole group) approach to orthopedic surgery thromboprophylaxis. The population approach is based on the concept that for major orthopedic surgery, surgery-attributed risk far outweighs the contribution of patient-specific risk factors; thus, surgery itself guides prophylaxis decisions. The advantages of this approach is that it simplifies practice and increases the likelihood of implementation. However, an individual approach is increasingly appealing; its concept is that the individual’s risk of developing VTE (and bleeding) should be assessed and used to guide individual prophylaxis decisions. Ideally, this approach should use validated risk assessment models (RAMs) specific to patients undergoing orthopedic surgery, similar to risk stratification and RAMs recommended by various national and international guidelines for use in hospitalized medical and non-orthopedic surgical patients.<sup>17-20</sup> An individual approach to prophylaxis would take into account patient risk factors for VTE and bleeding in addition to the surgery itself to help guide prophylaxis decisions.

## 8 | INDIVIDUAL RISK FACTORS FOR VTE AFTER MAJOR ORTHOPEDIC SURGERY

What is known about risk factors for VTE in patients undergoing major orthopedic surgery? As shown in Table 1, key risk factors include previous VTE, high BMI, and older age, among others.<sup>5,21</sup> Recent data from the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis (MEGA) study further highlight the importance of a previous history of VTE on the risk of VTE after orthopedic surgery and emphasizes the importance of inquiring about previous VTE when taking a preadmission history. Among 3741 patients with prior VTE who were not on long-term anticoagulation, 580 (16%) had surgery. Recurrent VTE after surgery was common, and those who had major orthopedic surgery were among the highest-risk group (hazard ratio [HR], 4.0 [95% confidence interval [CI], 1.3-12.4] for recurrence at 1 month), with a cumulative incidence of recurrent VTE of 2% at 1 month, 3% at 3 months, 5% at 6 months, and 10.5% at 1 year.<sup>22</sup> Although there was no information on use of thromboprophylaxis, one would predict universal use of prophylaxis in major orthopedic surgery patients. These data suggest that our current prophylaxis approach to patients undergoing major orthopedic surgery with prior VTE may be inadequate; namely, such patients may require an increased dose and/or duration of thromboprophylaxis. However, this requires study in well-designed randomized trials

**TABLE 1** Risk factors for VTE in patients undergoing major orthopedic surgery

Risk factor	Multivariable odds ratio
Previous VTE	3.4-26.9
Cardiovascular disease	1.4-5.1
Charlson comorbidity index $\geq 3$	1.5-2.6
BMI $> 25 \text{ kg/m}^2$	1.8
Family history of VTE	1.4
Older age (per 5 y increase vs age $<40$ y)	1.1
Age $\geq 85$ y	2.1
Varicose veins	3.6
Ambulation before postoperative day 2	0.7

Note: Individual independent risk factors based on multivariable analysis. Ranges for odds ratio as provided in Falck-Ytter et al.<sup>5</sup>

Source: Falck-Ytter et al.<sup>5</sup>

<sup>a</sup>BMI, body mass index; VTE, venous thromboembolism.

that assess both the efficacy and safety of more aggressive prophylaxis approaches.

## 9 | COMBINING RISK FACTORS INTO RISK ASSESSMENT MODELS IN THA OR TKA

Some investigators have tried to develop dedicated orthopedic RAMs, specific to surgical intervention. In a recent systematic review, 5 VTE risk prediction scores in patients undergoing THA or TKA were identified; the number of component variables in the scores ranged from 5 to 26 (Table 2).<sup>23</sup> While this work on RAMs is promising, the review identified several limitations. Some scores were developed using inadequate methodology, were inadequately reported, or were insufficiently validated. No RAM has been independently validated or used in a prospective impact study; thus, impact on patient outcomes and decision making is unknown. Additional research is needed before RAMs can be used to guide VTE prophylaxis decisions in patients undergoing major orthopedic surgery.

As important as predicting risk of VTE is predicting risk of bleeding. However, there are no bleeding RAMs that have been sufficiently validated in orthopedic surgery populations. The American College of Chest Physicians (ACCP) 2012 guidelines suggest assessing these general risk factors for bleeding: previous major bleeding (and previous bleeding risk similar to current risk); severe renal failure; concomitant use of antiplatelet agent(s); and surgical factors, such as history of or difficult-to-control surgical bleeding during current operative procedure, extensive surgical dissection, and revision surgery.<sup>5</sup> However, the specific risk-of-bleeding thresholds for using mechanical compression devices or no prophylaxis instead of anticoagulant thromboprophylaxis have not been established.

Thus, while individualized risk prediction to help guide thromboprophylaxis decisions in orthopedic surgery is increasingly

**TABLE 2** Risk prediction scores in THA or TKA patients

Study	Predictors used in a risk score
Dauty, 2012 <sup>49</sup>	Age, sex, average walking distance, use of gait aid or community support, social support at discharge
Parvizi, 2014 <sup>50</sup>	Knee surgery, Charlson index, atrial fibrillation, postoperative DVT, COPD, anemia, depression, BMI
Parvizi, 2016 <sup>50</sup>	Bilateral arthroplasty, revision arthroplasty, age, anemia, congestive heart failure, lymphoma, fluid/electrolyte disorder, metastatic cancer, peripheral artery disease, solid tumor, weight loss, chronic lung or heart disease, blood transfusion, previous VTE, myeloproliferative neoplasm, thrombophilia, myocardial infarctions, varicose veins, fracture, sepsis, joint infection, atrial fibrillation, stroke, apnea
Bohl, 2016 <sup>51</sup>	Age, sex, BMI, preoperative hematocrit, procedure type
Bateman, 2017 <sup>52</sup>	Caprini score

BMI, body mass index; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; THA, total hip arthroplasty; TKA, total knee arthroplasty; VTE, venous thromboembolism.

Source: Kunutsor et al.<sup>23</sup>

appealing, we are not yet at the point of implementing this approach into clinical practice. However, with the current menu of options for prophylaxis, including anticoagulants, aspirin, and mechanical prophylaxis,<sup>5,12</sup> in the future, better risk assessment could be used to help identify which option(s) an individual patient should receive and could inform the duration of prophylaxis.

## 10 | ROLE OF ASPIRIN FOR VTE PROPHYLAXIS IN MAJOR ORTHOPEDIC SURGERY

The pragmatic advantages of aspirin for VTE prophylaxis are numerable; it is inexpensive, oral, widely available, easy to use, and potentially has a lower risk of bleeding than anticoagulant prophylaxis.

Some older studies (primarily the Pulmonary Embolism Prevention [PEP] trial<sup>24</sup>) suggested that aspirin used for 35 days was effective for VTE prophylaxis in hip fracture and patients undergoing THA, when compared to placebo. In the 2012 ACCP guidelines<sup>5</sup> and 2018 European guidelines,<sup>25</sup> aspirin was among the recommended (Grade 1B) pharmacologic prophylaxis options for patients undergoing THA, TKA, and hip fracture surgery, compared to no pharmacologic prophylaxis. However, how does aspirin compare to anticoagulant prophylaxis, a more relevant comparison?

In the recently published 2019 American Society of Hematology (ASH) guidelines on prevention of VTE in surgical hospitalized patients, evidence from 7 prophylaxis trials (n = 1884 patients) that directly compared aspirin to various anticoagulants (unfractionated

heparin, low-molecular-weight heparin [LMWH], vitamin K antagonist, direct oral anticoagulant [DOAC]) was reviewed.<sup>12</sup> Overall, the studies were small and of low quality. There were no statistically significant differences between aspirin and various anticoagulant comparators for symptomatic proximal DVT (relative risk [RR], 1.49; 95% CI, 0.51-4.34), symptomatic PE (RR, 1.49; 95% CI, 0.37-6.09), major bleeding (RR, 2.63; 95% CI, 0.64-10.79), or death (RR, 2.32; 95% CI, 0.15-36.90). While the direction of the point estimates tended to favor anticoagulants, the estimates are imprecise and the overall certainty of the evidence is very low. Based on the evidence, for patients undergoing THA or TKA, the ASH guideline panel suggests using either aspirin or anticoagulants (conditional recommendation based on very low certainty in the evidence of effects), and identified that there is a need for large well-designed clinical trials using clinically important end points comparing aspirin with other pharmacologic methods following THA and TKA. The National Institute for Health and Clinical Excellence guidelines also include aspirin alone as an option for thromboprophylaxis after TKA (for 14 days), but for THA 10 days of LMWH is recommended before use of aspirin alone for an additional 28 days.<sup>19</sup>

Hence, aspirin used alone may have a role to play in orthopedic prophylaxis, and guidelines are suggesting its use, albeit tentatively and with provisos, based on the low certainty of the evidence. Higher-quality evidence is needed.

## 11 | THE EPCAT II TRIAL (ASPIRIN OR RIVAROXABAN FOR VTE PROPHYLAXIS AFTER HIP OR KNEE ARTHROPLASTY)

A recent large Canadian trial examined an interesting hybrid approach to using aspirin for VTE prophylaxis after major orthopedic surgery. The Extended Venous Thromboembolism Prophylaxis Comparing Rivaroxaban to Aspirin Following Total Hip and Knee Arthroplasty (EPCAT II) trial was a multicenter, double-blind non-inferiority randomized trial that enrolled patients undergoing elective unilateral THA or TKA.<sup>26</sup> Postoperatively, all participants received oral rivaroxaban 10 mg daily for 5 days, and were then randomized to either continue oral rivaroxaban 10 mg daily (control group) or to take oral aspirin 81 mg daily (intervention group) for an additional 30 days in patients undergoing THA and an additional 9 days in patients undergoing TKA. Participants were followed for 90 days. The trial was a noninferiority design based on a 1.0% control group event rate and a 1% minimal clinically important difference.

In total, 3424 patients were enrolled in the trial. Results showed that aspirin was noninferior to rivaroxaban, with symptomatic VTE (including symptomatic PE, proximal DVT, or both) occurring in 0.64% and 0.70% of participants, respectively ( $P = .84$ ;  $P < .001$  for noninferiority). Results were similar in analyses stratified by surgery type (THA or TKA) and by chronic aspirin use (yes or no). Major bleeding occurred in 0.47% of the aspirin group and 0.29% of the rivaroxaban group ( $P = .42$ ).

In terms of the generalizability of EPCAT II trial results, we emphasize that only patients with elective, unilateral THA or TKA were enrolled, and patients with hip or lower-limb fracture in past 3 months, metastatic cancer, or recent major bleeding were excluded. Among enrolled patients, very few (<3%) had a history of prior VTE, recent surgery, or cancer, which are high-risk characteristics for postoperative VTE.

## 12 | APPLYING EPCAT II RESULTS TO OUR PRACTICE

Based on the EPCAT II trial, would we use aspirin alone to prevent VTE after THA or TKA? No, because aspirin alone for extended thromboprophylaxis was not assessed in the trial. Would we use aspirin for extended thromboprophylaxis after an initial 5 days of a DOAC (in this case, rivaroxaban), that is, a hybrid DOAC/aspirin protocol, in *all* patients undergoing THA or TKA? No, and this relates to the issue of risk stratification. As discussed above, the EPCAT II trial included relatively lower-VTE-risk and -bleeding-risk patients undergoing THA and TKA. Various high-VTE-risk groups were not well represented, for example, patients with prior VTE, strong family history of VTE, known thrombophilia, morbid obesity, or advanced cancer.

After the EPCAT II trial was published, orthopedic surgeons and thrombosis physicians met at one of our centers and agreed on using the risk assessment approach shown in Figure 1, which takes into account patient-specific risk factors for VTE, inclusion and exclusion criteria of the EPCAT II trial, and baseline characteristics of EPCAT II participants. If adopted in other centers, it is important for each center to establish who will conduct this risk assessment (eg, orthopedic resident, surgeon, or nurse; internal medicine or thrombosis consultant), and when and where it will be conducted (eg, preoperatively in the clinic, preoperatively in the hospital, postoperatively).

Thus, pending the results of ongoing aspirin trials (described below), our approach is to use the hybrid prophylaxis protocol studied in EPCAT II for lower risk patients (patients similar to those enrolled in EPCAT II), and preferentially use anticoagulant prophylaxis (and not aspirin alone) in all other patients undergoing THA or TKA who are eligible to receive pharmacologic thromboprophylaxis. We use mechanical prophylaxis for those who are at risk of bleeding or are bleeding.

## 13 | ONGOING ASPIRIN TRIALS

Building on the available evidence base on the use of aspirin for major orthopedic surgery thromboprophylaxis, the next logical step is to study the use of aspirin alone as solo prophylaxis. Two large trials are under way:

1. The Comparative Effectiveness of Pulmonary Embolism Prevention After Hip and Knee Replacement (PEPPER) trial (<https://clinicaltrials.gov/ct2/show/NCT02810704>), funded by the US-based

**FIGURE 1** Suggested risk stratification for hybrid DOAC/aspirin prophylaxis after total hip arthroplasty or total knee arthroplasty\*. \*Hybrid DOAC/aspirin prophylaxis = DOAC at prophylaxis dose (rivaroxaban 10 mg orally daily was used in EPCAT II trial) for 5 days, followed by aspirin 81 mg orally daily for 30 days (patients undergoing THA) or 9 days (patients undergoing TKA). If patient is on long-term anticoagulation, usual long-term anticoagulant should be reinitiated postoperatively per thrombosis service recommendations. DOAC, direct oral anticoagulant; GI, gastrointestinal; THA, total hip arthroplasty; TKA, total knee arthroplasty; VTE, venous thromboembolism

Patient <u>not</u> a candidate for hybrid prophylaxis and should receive usual prophylaxis with DOAC alone if:	
Previous VTE	<input type="checkbox"/>
Active cancer/chemotherapy or hormonal therapy	<input type="checkbox"/>
On oral contraceptives or hormonal replacement therapy	<input type="checkbox"/>
Known thrombophilia	<input type="checkbox"/>
Sickle cell disease	<input type="checkbox"/>
Two or more first degree family members with VTE	<input type="checkbox"/>
Undergoing bilateral THA or TKA	<input type="checkbox"/>
Hip/lower limb fracture or orthopedic surgery in past 3 months	<input type="checkbox"/>
Major surgery in past 3 mo	<input type="checkbox"/>
Obesity (weight >100 kg)	<input type="checkbox"/>
Previous GI bleed	<input type="checkbox"/>
Gastric bypass surgery	<input type="checkbox"/>

Patient-Centered Outcomes Research Institute, is a randomized, open-label clinical trial conducted at ~28 US sites that will randomize 25 000 patients undergoing THA or TKA to either aspirin 162 mg orally on the day of surgery, then 81 mg orally twice daily; rivaroxaban 10 mg orally daily; or warfarin initially dosed based on body weight to achieve an International Normalized Ratio of 2.0. The study interventions will be started right after surgery and will continue for 30 days. Pneumatic compression will be used in hospital. The primary efficacy outcomes are clinically important VTE (PE and DVT leading to hospital readmission) and all-cause mortality at 6 months, ascertained by audit of hospital readmissions within 6 months of surgery via routine postoperative central telephone surveillance of patient-reported outcome events augmented by on-site research coordinator follow-up and validation of suspected end-point events. The primary safety outcome is bleeding (major, clinically important, wound related). Joint function and patient well-being will also be assessed. The study is expected to be completed in 2021.

- The EPCAT III trial (<https://clinicaltrials.gov/ct2/show/NCT04075240>), funded by Canadian Institutes of Health Research, will build on the EPCAT II trial results. Using a double-blind, double dummy design, the trial will directly compare aspirin 81 mg orally daily alone, versus rivaroxaban 10 mg orally daily for 5 days followed by aspirin 81 mg orally daily alone for 30 days after THA and 9 days after TKA in 5400 patients undergoing THA or TKA at 15 Canadian centers. The study interventions will be started postoperatively depending on local practice, either on the day of surgery or postoperative day 1, but not less than 6 hours after surgery. Data on compression stockings and devices will be collected, but their use is not mandated in the protocol. The primary efficacy outcome is symptomatic VTE occurring after

randomization over the 90-day study period, and the primary safety outcome is bleeding (major or clinically relevant nonmajor). The study is expected to be completed in 2024.

## 14 | ADDITIONAL ORTHOPEDIC SURGERY TOPICS: KNEE ARTHROSCOPY AND DISTAL LEG FRACTURES

Below, we discuss the level of VTE risk in 2 commonly encountered orthopedic populations, those undergoing knee arthroscopy and those with distal leg fractures; review guideline recommendations; and present our own approach to thromboprophylaxis in these patients.

## 15 | RISK OF VTE AFTER KNEE ARTHROSCOPY

Based on data from a number of large, population-based studies, the occurrence of VTE after knee arthroscopy is infrequent (<0.5%) for most patients. A recent UK National Health Service study of severe adverse outcomes of arthroscopic surgery in 700 000 patients described a 0.08% rate of any PE and a 0.001% rate of fatal PE within 90 days.<sup>27</sup> A Kaiser Permanente study of more than 20 000 patients undergoing knee arthroscopy described a 0.25% rate of DVT and a 0.17% rate of PE.<sup>28</sup> An American College of Surgeons National Surgical Quality Improvement Program study (N = 12 271) found DVT rates of 0.46% and PE rates of 0.05% within 30 days after knee arthroscopy,<sup>29</sup> and a Mayo Clinic Olmsted County study (N = 4833) reported DVT rates of 0.36% and PE rates of 0.04%; all events



occurred within the first 6 weeks of surgery.<sup>30</sup> A systematic review of 9 randomized arthroscopic surgery trials reported that symptomatic DVT and PE rates were 4.13 (95% CI, 1.78-9.60) and 1.45 (95% CI, 0.59-3.54) per 1000 procedures, respectively.<sup>31</sup> A recent overview of the literature found that in patients undergoing knee arthroscopy, symptomatic VTE occurred in 0.6% (95% CI, 0.4-0.7) following heterogeneous types of arthroscopic knee procedures.<sup>32</sup>

Risk factors that have been described for VTE after knee arthroscopy include history of VTE, cancer, prior surgery within 30 days, operating room time >1.5 hours, black race, and oral contraceptive use.<sup>28-30</sup>

## 16 | RISK OF VTE AFTER DISTAL LEG FRACTURE

VTE is infrequent after distal leg fracture. Data from a Canadian prospective cohort study (N = 1200) showed that the risk of symptomatic VTE in nonoperative distal leg fracture was 0.6%.<sup>33</sup> A Danish registry study (N = 57 619) reported that within 6 months of operative distal leg fracture, 1.0% experienced a VTE event.<sup>34</sup> A recent overview of the literature found that in lower leg-cast patients with various injuries, symptomatic VTE occurred in 2.0% (95% CI, 1.3-2.7).<sup>32</sup>

In the Danish study, risk factors for VTE included previous VTE (HR, 6.3), oral contraceptives (HR, 4.2), obesity (HR, 2.7), coagulopathy (HR, 2.5), peripheral arterial disease (HR, 2.3), and cancer (HR, 1.7). The importance of previous VTE as a risk factor was further emphasized by a recent report from the MEGA study, which showed that patients with previous VTE who subsequently required lower leg casting had a 4.5-fold risk of developing recurrent VTE, which translated to an absolute risk of 3.2% within 3 months.<sup>35</sup> A meta-analysis of 15 studies reporting outcome data on 80 678 patients found that only advancing age and injury type were predictive of VTE and cautioned against using individual risk factors to guide the use of thromboprophylaxis.<sup>36</sup> Risk assessment models have been developed to predict risk of VTE after lower leg casting or trauma,<sup>37</sup> including the Leiden-Thrombosis Risk Prediction for Patients With Cast Immobilization (L-TRiP[cast])score<sup>38</sup> and the Trauma, Immobilization and Patients' characteristics (TIP) score.<sup>39</sup> However, prospective validation, ideally with implementation studies, are required.

## 17 | EFFECTIVENESS OF THROMBOPROPHYLAXIS AFTER KNEE ARTHROSCOPY OR LOWER LEG CASTING

The Thrombosis Prophylaxis After Knee Arthroscopy (POT-KAST) and Thrombosis Prophylaxis During Plaster Cast Lower Leg Immobilization (POT-CAST) randomized controlled trials assessed the effectiveness and safety of LMWH versus placebo given for

8 days after knee arthroscopy (n = 1451) or for the full period of immobilization after lower leg casting (n = 1435).<sup>40</sup> Results showed that VTE prophylaxis with LMWH was ineffective after knee arthroscopy or lower leg casting. In the POT-KAST trial, 0.7% randomized to LMWH versus 0.4% randomized to placebo developed VTE (RR, 1.6; 95% CI, 0.4-6.8), with very low rates of major bleeding (0.1% in both groups). In the POT-CAST trial, 1.4% randomized to LMWH versus 1.8% randomized to placebo developed VTE (RR, 0.8; 95% CI, 0.3-1.7), with no episodes of major bleeding in either group. Overall rates of VTE were low in all groups, consistent with the observational data presented above; however, it should be noted that patients with a history of VTE were excluded from participation in the 2 trials.

A subsequent secondary analysis of the POT-CAST trial identified that while BMI >30 kg/m<sup>2</sup>, family history of VTE, Achilles tendon rupture, and surgical treatment of traumatic leg injury increased VTE risk, thromboprophylaxis remained ineffective in these high-risk subgroups.<sup>38</sup>

Recently, a 2019 meta-analysis reviewed 13 randomized trials (6857 participants) that compared thromboprophylactic agents to each other or to no pharmacologic prophylaxis to prevent VTE in patients with temporary lower-limb immobilization after injury.<sup>41</sup> Across trials, LMWH reduced the risk of symptomatic DVT (odds ratio [OR], 0.40; 95% credible interval [CrI], 0.12-0.99) and PE (OR, 0.17; 95% CrI, 0.01-0.88) compared to no treatment, and fondaparinux reduced the risk of symptomatic DVT (OR, 0.10; 95% CrI, 0.01-0.94) but not PE (OR, 0.47; 95% CrI, 0.01-9.54). However, as event rates for symptomatic DVT and PE in untreated patients were low, absolute risk reductions were very small. Major bleeding was very uncommon. The authors concluded that better risk assessment and studies of individualized treatment based on level of risk should be research priorities.

## 18 | WHAT DO THE GUIDELINES RECOMMEND?

### 18.1 | For patients with isolated distal leg fracture and immobilization

The 2012 ACCP guidelines suggest no prophylaxis rather than pharmacologic prophylaxis (Grade 2B).<sup>5</sup> The 2018 European Society of Anaesthesiology (ESA) guidelines recommend no pharmacologic VTE prevention in patients without high VTE risk (Grade 1C), and suggest using aspirin for VTE prevention after low-risk orthopedic procedures in patients with high VTE risk (Grade 2C).<sup>42</sup> The 2019 ASH guidelines do not address this patient group.

### 18.2 | For patients undergoing knee arthroscopy

The 2012 ACCP guidelines suggest no prophylaxis rather than pharmacologic prophylaxis in patients without a history of VTE (Grade

2B).<sup>5</sup> The 2018 ESA guidelines recommend no pharmacologic VTE prevention after low-risk orthopedic procedures (eg, knee arthroscopy) in patients without high VTE risk (Grade 1C), and suggest aspirin for VTE prevention in patients with high VTE risk (Grade 2C).<sup>42</sup> The 2019 ASH guidelines do not address this patient group.

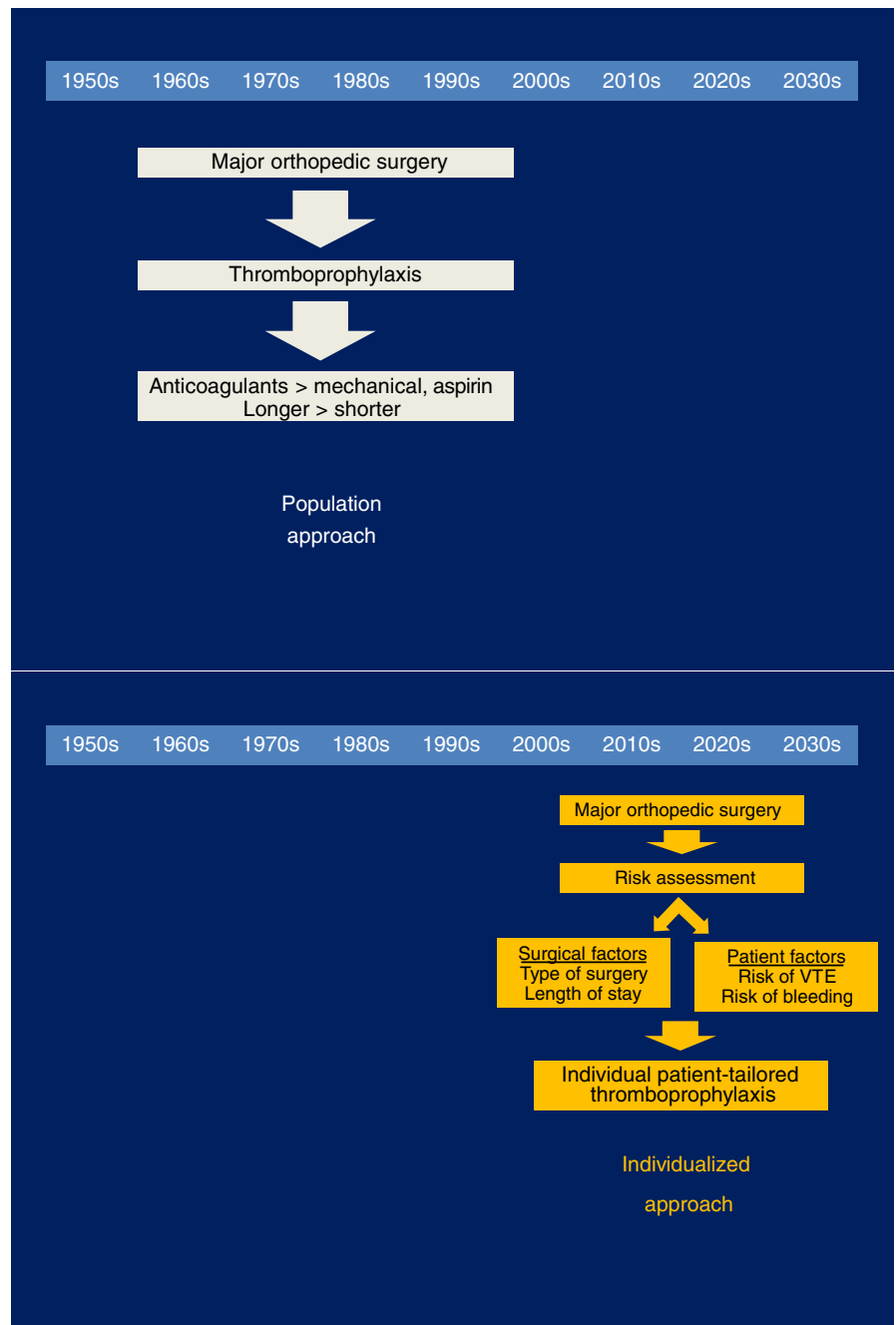
obesity, cancer, and use of oral contraceptives. Using some form of prophylaxis (whether pharmacologic or mechanical), typically during the period of immobilization, makes clinical sense in these higher-risk patients, even if not yet evidence based. The most appropriate prevention strategy for these higher-risk patients—including type of drug, dose, method (drug vs compression), and duration of treatment—is as yet unknown.

## 19 | OUR APPROACH

While we generally do not offer thromboprophylaxis to patients with isolated distal leg fracture and/or cast immobilization or those undergoing knee arthroscopy, we use our clinical judgment in individual patients with high-VTE-risk features, including previous VTE,

## 20 | ISTH MELBOURNE REPORT

A number of abstracts relating to VTE risk and risk prediction after orthopedic surgery were presented at ISTH Melbourne.



**FIGURE 2** Shifting landscape in major orthopedic surgery prophylaxis. VTE, venous thromboembolism



The risk of VTE after different types of orthopedic surgery and the additional effect of genetic risk factors for VTE were estimated in an interesting analysis of the MEGA study by Zambelli et al.<sup>43</sup> Overall, orthopedic surgery was associated with an increased risk of VTE, which was highest in the first 30 days postoperatively (OR, 17.5) but remained high even as long as 1 year after surgery (OR, 3.7). The risk was further enhanced in patients with the factor V Leiden mutation, non-O blood type, and elevated factor VIII levels. Spine, knee, and below-knee surgeries were associated with the highest risk for VTE, while patients who had hip or upper-limb surgery had a lower but still increased risk. In a retrospective study of patients undergoing TKA who received rivaroxaban prophylaxis, Mian and colleagues<sup>44</sup> described that longer tourniquet time and greater BMI were associated with development of VTE within 14 days of surgery in univariate analysis, but time to initiate prophylaxis was not. Finally, Douillet and colleagues<sup>45</sup> reported on the development and validation of a single, simplified score from 2 previously developed RAMs, the TIP score and the L-TRiP(cast) score, to predict risk of VTE after lower-limb immobilization due to trauma. The combined 14-item L-TRiP(cast) score accurately stratified patients into high- and low-risk categories, which could prove useful in the future to guide prescribing of thromboprophylaxis.

Three abstracts reported results of biomarker substudies that attempted to elucidate mechanisms of VTE development in participants of the POT-CAST (patients with lower leg trauma requiring casting) and POT-KAST (patients undergoing knee arthroscopy) VTE prophylaxis trials. Touw et al<sup>46</sup> described that while lower-leg trauma led to increased phospholipid-dependent procoagulant (PPL) activity, measurement of PPL activity was not useful to identify patients who developed VTE after lower-leg trauma or knee arthroscopy. Touw et al also described that levels of factor VIII, factor IX, factor XI, von Willebrand factor, fibrinogen and D-dimer did not increase postoperatively in patients who had knee arthroscopy; thus, the increased risk of thrombosis after knee arthroscopy does not appear to relate to levels of these procoagulant factors.<sup>47</sup> Finally, while participants with lower-leg trauma had evidence of increased thrombin generation compared to a group of random controls, results of the thrombin generation assay were not useful to identify patients who developed VTE after lower-leg trauma or knee arthroscopy.<sup>48</sup>

## 21 | CONCLUSION AND FUTURE DIRECTIONS

The epidemiology of VTE after major orthopedic surgery is changing, and VTE risk in many patients is lower than in previous decades. While rates of VTE may be decreasing overall, some patients (particularly those with prior VTE) remain at increased risk.

There is a shifting landscape in major orthopedic surgery prophylaxis (Figure 2). From the late 1950s to the 2010s, trials tended to focus on venographic DVT, assessing prophylaxis in all patients based on a population approach. In general, anticoagulants were

favored over mechanical prophylaxis or aspirin, and longer-duration prophylaxis was favored over shorter durations. More recently, orthopedic prophylaxis is starting to become more nuanced and individualized. Modern trials are focusing on symptomatic VTE as outcomes, and there has been a slow move to studying and recommending thromboprophylaxis based on individual attributes of patients, in whom risk stratification and weighing of benefit versus risk is becoming key. This reflects a shift from a population approach to an individual approach to prophylaxis.

Optimal choices for VTE prophylaxis (drug, duration) in patients undergoing THA and TKA are evolving. Interest in aspirin as a means of prophylaxis has resurged, and ongoing large clinical trials will help define optimal aspirin prophylaxis for patients undergoing THA and TKA. In the meantime, based on EPCAT II trial data, we believe that standard-VTE-risk patients undergoing THA and TKA can be considered for a hybrid approach (initial DOAC prophylaxis followed by extended-duration aspirin prophylaxis), while higher-VTE-risk patients should still receive extended-duration anticoagulant prophylaxis. VTE prophylaxis is not guideline recommended in patients undergoing standard-risk knee arthroscopy or patients with a lower-leg fracture, but our practice is always to inquire about prior VTE and other high-risk features that may warrant prophylaxis on an individual basis.

In terms of research priorities, validated RAMs are needed to individualize decision making in patients undergoing orthopedic surgery, followed by implementation studies of individualized treatment based on level of risk. This will enable us to identify low-risk orthopedic patients who do not require thromboprophylaxis, as well as high-risk patients who may require higher doses and increased duration of prophylaxis. Research on thromboprophylaxis in hip fracture surgery is also needed. Finally, while beyond the scope of this article, studies of new thromboprophylaxis agents with more favorable risk-benefit profiles are awaited with great interest.

### RELATIONSHIP DISCLOSURES

Dr Kahn reports receiving advisory board fees from BMS Pfizer, Sanofi, and Aspen. Dr Shivakumar reports personal fees from Pfizer Inc and personal fees from Bayer Inc, outside the submitted work.

### AUTHOR CONTRIBUTIONS

Dr Kahn and Dr Shivakumar cowrote the paper.

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