Recommendations from the ICM-VTE: Foot & Ankle

The ICM-VTE Foot & Ankle Delegates*

1 - Should patients undergoing surgical debridement of diabetic foot ulcers receive routine VTE prophylaxis?

Response/Recommendation: There is currently no evidence in the literature to determine if a diabetic patient undergoing ulcer debridement requires venous thromboembolism (VTE) prophylaxis. There is, however, an increased risk for morbidity and mortality in diabetic foot ulcers (DFU) patients who develop VTE. Therefore, it is justified to propose that patients with DFU are given thromboprophylaxis, particularly if they have reduced mobility and other medical comorbidities. This may not be true for all cases of surgical debridement alone of DFU without additional interventions when prolonged limited weight-bearing is not required.

Strength of Recommendation: Limited.

Delegates vote: Agree 100.00% Disagree 0.0% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: There is increasing evidence that diabetes mellitus (DM) is associated with derangements in coagulation and fibrinolysis leading to a tendency to form thrombi[1,2]. The risk for developing VTE is also elevated in part due to associated co-morbid conditions and frequent hospitalization for acute medical conditions and surgery[3-5]. DM patients who develop VTE are more likely to suffer a complicated clinical course, including long-term major bleeding complications, recurrent VTE[5,6], major adverse limb events and a higher risk of all-cause mortality[6].

Aside from neuropathy, the tendency for thrombosis places DM patients at risk of developing DFU. Patients with DFU have increased mortality rates compared to non-ulcerated diabetic patients[7]. Compounded with VTE, DFU patients may also have delayed ulcer healing rates[4,8] and longer periods of immobility.

Despite many reports of elevated risk of VTE in DM patients, no specific recommendations can be found for managing diabetic patients at risk for VTE. For this review, a search in PubMed revealed 244 papers but none specifically discuss VTE prophylaxis for DFU patients undergoing surgery, nor for DM patients in general.

In a review of 2,488 patients with validated VTE in the Worcester Venous Thromboembolism Study, Piazza et al., reported a low rate of thromboprophylaxis among the 476 patients with VTE and DM[5]. Wang et al., highlighted the impact of a history of VTE on major adverse limb events (MALEs) and concluded that prevention of thrombotic events needed to be emphasized in patients requiring diabetic foot care[6]. Aside from increased all-cause mortality rates, they showed that a history of VTE was associated with a 1.6-fold increased risk of MALEs and a 1.4-fold higher risk of major amputation.

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2 - Is routine VTE prophylaxis needed for patients placed in walker boot immobilization?

Response/Recommendation: Patients in walker boot immobilization may be at increased risk of development of venous thromboembolism (VTE). Patients should be risk assessed, and VTE prophylaxis offered on an individual basis.

Strength of Recommendation: Limited.

Delegates vote: Agree 96.30% Disagree 0.0% Abstain 3.70% (Strong Consensus).

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Rationale: Immobilization of the lower limb in a walker boot can provide an alternative to a cast for post-operative and non-operative management of many foot and ankle-related conditions. Potential benefits include the removal for hygiene purposes, the ability to perform range of motion exercises, and the potential to adjust the fit with resolution of swelling. Furthermore, a boot does not require a clinic visit for definitive removal.

A 2017 Cochrane Review, which included eight randomized controlled trials (RCT), assessed the effectiveness of low-molecular-weight heparin (LMWH) for the prevention of VTE in patients with lower limb immobilization[9]. In patients who received no prophylaxis, the incidence of deep venous thrombosis (DVT) ranged from 4.3% to 40% but was reduced in patients who received prophylaxis. Most of the trials included in this review utilized only cast immobilization, while three studies also included patients immobilized in a brace. The authors concluded there was moderate-quality evidence that LMWH reduced the number of venous thromboembolic events. Another systematic review performed in 2019 found a lower risk of VTE when patients with temporary immobilization of the lower extremity received VTE prophylaxis[10].

For this recommendation, RCT investigating VTE prophylaxis regimens in patients in boot or brace immobilization were identified. In addition, RCT were also included if they reported the incidence of VTE in patients immobilized in a boot, orthosis, or brace in comparison to a control group in any other form of immobilization, or no immobilization.

Four RCT of VTE prophylaxis regimens including patients in orthoses or braces were identified. All of them were included in the previously mentioned systematic review[10]. In patients requiring immobilization after fracture or achilles tendon rupture, Lassen et al., reported the incidence of DVT identified by venography as 19% in a placebo group compared to 9% in those receiving reviparin (p=0.01)[11]. Lapidus et al., reported no significant difference in the incidence of DVT identified by phlebography between patients receiving dalteparin or placebo following immobilization after ankle fractures[12] or surgery for achilles tendon rupture (ATR)[13]. Finally, Samama et al., reported an incidence of VTE of 2.3% in patients receiving fondaparinaux compared to 7.9% in those receiving nadroparin[14]. None of the studies presented sub-group data or analysis of those patients in boot or orthosis immobilization, and in all trials most patients were immobilized in a cast.

Six additional RCT reporting the incidence of VTE during immobilization in a boot, brace or orthosis compared to another form of immobilization were identified. Kortekangas et al., investigated patients with ankle fractures treated with an orthosis versus a cast[15]. There were no symptomatic DVT in the 80 patients treated in an orthosis for three weeks. There were 3 (3.6%) DVT recorded in the 83 patients treated in a cast, although this difference was not statistically significant. Lehtonen et al., randomized patients with ankle fractures to post-operative

immobilization in a cast or early mobilization in a functional ankle brace[16]. Of the fifty patients treated in a cast, symptomatic DVT was identified in two patients (4%) compared to no DVT in the 50 patients in a brace.

In ATR, Groetelaers et al., investigated 60 patients randomized to either a cast or an Achillotrain flexible brace following minimally invasive repair[17]. Symptomatic DVT occurred in two (8%) of patients in the cast group compared to none in the Achillotrain group. Patients in the Achillotrain group were allowed to weight-bear and began mobilization earlier than the cast group. The United Kindom Study of tendo Achilles Rehabilitation (UKSTAR) RCT compared a brace against cast immobilization in ATR managed conservatively in 540 patients[18]. Symptomatic DVT was recorded in 2% of patients in a functional brace compared to 1% in a plaster (p = 0.51). Aufwerber et al., reported the incidence of asymptomatic DVT on ultrasound imaging in 150 patients following ATR surgery[19]. DVT was recorded in 29% of patients in a dynamic orthosis, compared to 31% of patients immobilized for two weeks in cast and then transferred into an Aircast boot. Patients in the dynamic orthosis group were permitted to begin weight bearing and mobilization earlier following surgery. The clinical importance of asymptomatic DVT remains uncertain[20-22].

In a RCT by Lamb et al., 584 patients with ankle sprains were randomized to receive a below-knee cast, Aircast brace, Bledsoe boot or tubular compression bandage. DVT was identified in one patient in every treatment group except for the compression bandage[23].

None of these six studies identified a statistically significant difference in the incidence of VTE between forms of immobilization. With the exception of the study by Aufwerber et al.[19], the incidence of VTE was a secondary outcome. As the search strategy was focused on VTE, it is acknowledged that other trials investigating the use of a brace or orthosis and reporting VTE only as a secondary outcome may not have been captured in the search. However, it is expected that such studies are likely to be similarly underpowered to detect a difference in the incidence of symptomatic DVT.

In summary, limited evidence was identified to establish if routine VTE prophylaxis reduces the risk of VTE in walker boot immobilization. All four RCT of VTE prophylaxis combined data for patients in a boot or orthosis with patients in cast immobilization. In six RCT comparing patients immobilized in a boot or orthosis versus those in cast immobilization there were no statistically significant differences in the incidence of VTE. These studies displayed heterogeneity in the type of injury, operative versus non-operative intervention and the type of orthosis. Additional variation, even within individual studies, in weight bearing status and mobilization of the ankle and foot are also likely to affect the incidence of VTE. However, the literature demonstrates that VTE may occur in patients placed in boot or brace immobilization, when the patients are instructed to weight-bear at < 50% early after surgery[19].

In view of the limitations, future research specifically investigating VTE in patients immobilized in a walker boot is needed. We recommend that patients should be assessed and

VTE prophylaxis offered on an individual basis according to patient factors, weight-bearing status and mobilization status.

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3 - Does the weight-bearing status of the patient after foot and ankle surgery influence the selection of VTE prophylaxis?

Response/Recommendation: Non-weight-bearing restrictions of the lower extremity are an independent risk factor for venous thromboembolic (VTE) events. This risk is mitigated by load-bearing of the operative limb greater than 50%. No additional conclusions can be made regarding the selection of VTE prophylaxis as it relates to non-weight-bearing based on the available literature.

Strength of Recommendation: Limited.

Delegates vote: Agree 100.00% Disagree 0.0% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: A period of non-weight-bearing restrictions after foot and ankle (F&A) surgery is often required to protect the surgical limb and optimize outcomes. Weight-bearing restrictions after F&A surgery commonly coincide with immobilization of the operative limb (e.g., in a plaster cast or orthosis). These postoperative restrictions, though seemingly innocuous, are not without risks. To this end, immobilization of the lower extremity has been identified as a strong contributor to VTE complications[24,25]. The pathomechanism of immobilization and VTE events is related to the diminished venous return conferred by immobility and static positioning of the limb[26,27]. The impact, if any, that non-weight-bearing restrictions have on the development of VTE complications is not as clearly understood, and the relevance that non-weight-bearing restrictions should have on post-surgical VTE prophylaxis selection is debated.

There is a relative dearth of literature reporting on the association of VTE complications and non-weight-bearing restrictions. The literature by and large has focused on immobilization specifically and non-weight-bearing as an independent factor in VTE complications. However, weight-bearing has been shown to increase venous emptying of the lower extremity and may be of clinical relevance in the development of VTE events[28].

A level I prospective study evaluated 150 patients that underwent open achilles tendon repair[29]. Patients were randomized to a protocol consisting of either early full weight-bearing in an orthosis or a conventional postoperative protocol consisting of two weeks of non-weight-bearing in a cast followed by 4 weeks weight-bearing in an orthosis. No patients were prescribed VTE prophylaxis, and all patients were screened for VTE with bilateral doppler ultrasounds two and six weeks after surgery. The authors identified that loading of the limb less than or equal to 50% of the body weight in the first week following surgery was an independent risk factor for developing VTE and conferred 4.3 times higher odds of developing a VTE in the first two weeks after surgery. Notably, there was no association of VTE, and the number of steps taken per day, which indicates that loading of the operative limb is independently relevant to developing VTE complications.

A separate study by Barg et al., investigated risk factors for VTE in a series of 665 patients undergoing total ankle replacement over a 9-year period[30]. Patients were instructed to weight-bear while immobilized in a cast or orthosis starting three to four days after surgery unless they had concomitant osteotomies. All patients were prescribed prophylaxis with low-molecular-weight heparin (LMWH) 5000 IU. Three-point nine percent of patients developed a symptomatic deep venous thrombosis (DVT).

Multiple regression analysis identified the absence of full post-operative weight-bearing as an independent risk factor for symptomatic VTE, with an odds ratio of 4.53.

A prospective multi-center study by Mizel et al., included 2,733 over the course of a year. Patient demographics, administered medication, orthopaedic procedure and postoperative ordinations including anticoagulation and weight-bearing status was reported by the treating orthopaedic surgeon. Postoperative follow-up averaged 91 days and symptomatic DVT were confirmed by venogram or ultrasonography. Of the six patients that developed DVT, all had been non-weight-bearing corresponding to a relative risk of 1.0 (95% confidence interval [CI] 1.0009 to 1.008, p = 0.014). Two of these 6 patients had received anticoagulation. Furthermore, 4 of the 6 patients with DVT developed non-fatal pulmonary emboli (PE), though whether these received anticoagulation was not specified[31].

A retrospective analysis of a series of patients over a one-year period at a single hospital was conducted by Thomas and Van Kampen on a series of patients to evaluate risk factors for symptomatic VTE[32]. The authors reported that 7 of the 381 (1.84%) patients included in their analysis developed DVT, 4 of which developed a PE. Chart review revealed that all patients that had a PE were instructed to be non-weight-bearing for injuries consisting of ankle fractures (2), distal tibia and fibula fracture (1), and achilles rupture (1). None of the patients underwent surgery and no prophylaxis was prescribed. The study was not powered to determine the statistical significance of weight-bearing restrictions on VTE events, but these findings are notable, nonetheless.

A prospective descriptive study was performed on a group of 216 patients who underwent various F&A surgeries[33]. Short leg cast immobilization and non-weight-bearing for at least 4 weeks was required in 130 patients, while 88 patients underwent hallux surgery that did not require immobilization or weight-bearing restrictions. No patients received VTE prophylaxis. Screening by ultrasound at 2 and 6 weeks after surgery revealed an overall incidence of DVT of 5.09% with no clots being identified in the hallux valgus subgroup who were permitted to weight-bear immediately, and 8.46% incidence in the group immobilized in a cast with non-weight-bearing restrictions. These results are descriptive, as the study was not sufficiently powered to determine individuals risk factors; however, these findings do coincide with previous reports that have identified an association between non-weight-bearing restrictions and VTE event.

These findings in summation do suggest that non-weight-bearing restrictions are an independent risk factor for VTE events and merit the attention of the surgeon. The literature supporting this conclusion, however, is limited, with the work of Aufwerber et al., representing the only Level I evidence identifying this association. The pathomechanism of non-weight-bearing restrictions on VTE is likely related to the resultant restricted venous return, which does conversely increase with weightbearing. Clinicians should consider non-weight-bearing restrictions when determining patients' risks for VTE events following F&A surgery. This risk may be mitigated by permitting at least partial loading of the limb even when immobilized[29]. No recommendation regarding the use of additional VTE prophylaxis medications or interventions for patients requiring non-weight-bearing after surgery can be made. Determining the need for chemoprophylaxis based on non-weight-bearing restrictions following surgery has not been independently investigated. It is notable, however, that a recent Cochrane review did investigate LMWH VTE prophylaxis specifically in patients with lower limb immobilization but did not specifically analyze non-weight-bearing restrictions[25]. From the authors' analysis of 3,680 participants from 8 randomized controlled trials, it was concluded that LMWH prophylaxis did significantly lower incidence of DVT in patients requiring lower extremity immobilization. These results were based on moderate-quality evidence. Investigation regarding the use of VTE prophylaxis in patients undergoing F&A surgery requiring postoperative weight bearing restrictions is needed.

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4 - Concerning VTE risk, which surgeries can be considered major, and which surgeries can be considered non-major in foot and ankle surgery?

Response/Recommendation: There is insufficient data to characterize foot and ankle surgical procedures as either major or non-major risk with regard to postoperative venous thromboembolic (VTE) event risk. Certain diagnoses, such as

achilles rupture, do seem to demonstrate a higher rate of VTE, but this may be independent of surgical or non-surgical management and instead relate to impaired venous return. Patient-specific risk factors are critical towards understanding the risk of VTE after foot and ankle (F&A) surgery, and may include age > 50 years, splint or cast immobilization, Charlson Comorbidity Index (CCI) > 2, varicose veins, history of VTE, hypercoagulability disorder, and inflammatory arthritis.

Strength of Recommendation: Limited.

Delegates vote: Agree 100.00% Disagree 0.0% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: Historically, discussion regarding the incidence of VTE disease in orthopaedic surgery—and the concordant use of chemoprophylaxis to prevent deep venous thrombosis (DVT) and pulmonary embolism (PE) has revolved around VTE risk inherent to a given procedure. Procedures such as total hip arthroplasty (THA) or total knee arthroplasty (TKA), as well as hip fracture surgical fixation, have uniformly high rates of VTE in the absence of preventative measures[34]. Professional societies such as the American College of Chest Physicians (ACCP) have thus explicitly recommend administering chemoprophylaxis "for patients undergoing major orthopaedic surgery (THA, TKA, hip fracture surgery [HFS])"[35]. In defining a subset of orthopaedic procedures as major, however, the ACCP guidelines did not conversely define other procedures as minor. They only noted that chemoprophylaxis was unnecessary in "in patients with isolated lower-leg injuries requiring leg immobilization". Indeed, while the word "major" appears 201 times in the 2012 ACCP guidelines, the word "minor" appears only twice, and specifically pertaining to minor bleeding events.

The challenges providers face when addressing VTE among F&A patients are manifold. First, while the rate of VTE is much lower amongst F&A patients than after THA or TKA patients, it is certainly neither zero nor uniform across all patients and procedures[36]. This makes any risk-benefit analysis of using chemoprophylaxis far more nuanced, as one weighs the risk of DVT and PE against adverse outcomes such as bleeding events, wound ooze, and even heparin-induced thrombocytopenia[37]. Second, without overwhelming implications of any procedure itself determining use of chemoprophylaxis, patient-specific risk factors play an increasingly important role, undermining a "one size fits all" approach to VTE prevention[38,39]. Lastly, it may not be a procedure per se that provokes a DVT or PE, but rather the pathologic condition itself (e.g., achilles tendon rupture with gastrocsoleus retraction), often independently of operative versus nonoperative management, as well as the requisite period of non-weight bearing and/or immobilization[40,41].

The confusion shared by F&A clinicians and patients alike is reflected by the diverse clinical practice guidelines put forth by multiple professional societies pertaining to surgery of the lower extremity, including F&A procedures. As noted, for example, the ACCP does not recommend use of chemoprophylaxis after F&A surgery[35]. In contrast, the National Institute for Health and Care Excellence (NICE) in the United Kingdom does recommend that surgeons use of chemoprophylaxis after lower extremity procedures other than THA, TKA, or HFS when patients have one or more risk factors, but conflates risk factors such as a prior history of VTE in an individual or first degree relative with more ubiquitous risk factors such as age > 60 years, lower limb procedures lasting > 60 minutes, and body mass index (BMI) > 30 kg/m[2][42] Moreover, the American Orthopaedic Foot & Ankle Society (AOFAS) has stated that there is insufficient data for it to recommend for or against the use of routine VTE prophylaxis after F&A surgery, and that further research is necessary[43].

Thus, the decision to use chemoprophylaxis after F&A surgery must integrate not only the nature of the procedure, but also patient-specific risk factors, many of which have yet to be defined. Validated risk assessment tools do exist, but have been honed around non-orthopaedic procedures such as general or vascular surgery[44,45]. Among the most commonly used risk assessment scales is that purported by Caprini, which assigns a point value to each of forty elements that allows clinicians to stratify patients by risk status, with ≥ 5 total points considered "highest risk"[46]. It does distinguish between minor and major surgery but does so based on whether the time of surgery crosses a threshold of 45 minutes; any surgery of > 45 minutes duration is considered major. In practice, patients aged 41 - 60 years (1 point) undergoing a minor surgical procedure (1 point) who have a BMI > 25 kg/m^2 (1 point) would be considered "high-risk" (3 - 4 points), making it difficult to know how to apply this instrument to the F&A population. A recent study by Dashe et al., retrospectively compared the incidence of DVT and PE among 300 orthopaedic patients with pelvic or acetabular fractures, empirically deemed to be at "high-risk", to the incidence among 548 patients with foot and ankle fractures deemed to be at "low-risk"[47]. It found that those patients with pelvic and acetabular fractures did indeed demonstrate a higher rate of VTE (8% vs. 1.6%, p < 0.0001), but the traditional Caprini score threshold of 5 did not appropriately differentiate those at "highest risk" between the two groups, and the authors instead recommended a threshold of 10 points. Unfortunately, even this latter score threshold loses utility when applied to F&A patients without fractures, because it largely emanates from the 5 points assigned to "hip, pelvis or leg fracture (< 1 month)"[46].

Complicating matters is the fact that certain specific diagnoses within F&A surgery do seem to correlate with a heightened risk of VTE. Achilles tendon ruptures have been reported to have a rate of DVT ranging from 0.4% to 34%[48,49]. This reported wide variability emanates largely from whether patients in a given study are routinely screened with ultrasound, or whether only symptomatic patients are imaged. Studies, however, have highlighted rates of symptomatic DVT as high as 23.5% and, most notably, have not necessarily found a difference between operatively versus nonoperatively treated patients[41,50,51]. Thus, rather than achilles tendon repair

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being considered a "major surgery", it may be that achilles ruptures as a whole are better identified as a "major diagnosis". Even more confusing, it is not entirely clear that chemoprophylaxis effectively lowers the rate of VTE after achilles rupture based on prospective, randomized study[49].

Extrapolating the idea that more proximal procedures in the lower extremity have higher rates of VTE than those performed more distally, it intuits that within F&A specifically one might find a progressive increase in the rate of postoperative VTE when moving from the forefoot to the hindfoot/ankle to the lower leg. A study by Hejiboer et al., compared the rate of VTE and adverse bleeding events among two separate, matched cohorts of 5,286 patients undergoing below knee procedures with and without chemoprophylaxis using propensity score matching[37]. The authors did identify an increase in the rate of VTE as one moved more proximally within the F&A, including the forefoot (0.8%), hindfoot/ankle (1.4%), and lower leg (3.4%) among patients who did not receive chemoprophylaxis. The study also found an analogous increase among patients receiving chemoprophylaxis who underwent procedures to the forefoot (0.2%), hindfoot/ankle (0.4%), and lower leg (1.0%), and was able to demonstrate a 3-fold reduction in the rate of VTE when using chemoprophylaxis but a 2-fold increase in bleeding events. This finding highlights the inherent trade-offs of preventative measures.

Ultimately, in F&A surgery, as compared to THA and TKA, patient risk factors play a disproportionate role in precipitating a higher rate of VTE. Risk factors in the literature have included age > 50 years, splint or cast immobilization, achilles tendon ruptures, increased comorbid burden as reflected in a CCI > 2, varicose veins, history of VTE, either in a given individual or first degree relative, a known hypercoagulability disorder, and inflammatory arthritis[38,39,52-55]. This must be kept firmly in mind when interpreting studies. For example, a recent meta-analysis that incorporated six prospective randomized controlled trials (RCT) comprising 1,600 patients undergoing isolated F&A surgery found a rate of VTE of 8.3% among patients with chemoprophylaxis as compared to 11.7% without (relative risk [RR] 0.72, 95% confidence interval [CI] 0.55 - 0.94, p = 0.02)[56]. It concluded that, while chemoprophylaxis is efficacious, "event rates are low and symptomatic events are rare". On the other hand, the authors highlight that the average age of patients in all six RCT was < 50 years. Separately, all six studies excluded patients with a prior history of VTE. Both are likely contributing risk factors for VTE after F&A surgery, limiting the ability to extrapolate their findings to broader populations.

In summary, there is insufficient data to characterize F&A surgical procedures as either major or non-major as this pertains to the risk of postoperative VTE. Certain diagnoses such as achilles rupture do seem to demonstrate a higher rate of VTE, but patient risk factors are especially critical as compared to patients undergoing THA and TKA or HFS. Large scale, prospective, RCT are necessary to define subpopulations of

patients at heightened risk, as well as elucidate the relative utility of various chemoprophylactic strategies.

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5 - Is routine VTE prophylaxis required for patients undergoing forefoot and midfoot surgery who would be allowed to fully weight-bear?

Response/Recommendation: The risk of venous thromboembolism (VTE) following forefoot and midfoot is rare, with pulmonary embolism (PE) and even more so, fatal PE being exceedingly rare. The rates appear to be lower in forefoot surgery as opposed to midfoot surgery, while both appear low. We do not recommend routine anticoagulants for VTE prevention following elective a forefoot and midfoot in low-risk patients, especially after immediate weight-bearing. We do encourage further high-quality research into routine VTE chemoprophylaxis.

Strength of Recommendation: Limited.

Delegates vote: Agree 100.00% Disagree 0.0% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: There is limited data to support routine prophylaxis for VTE events in foot and ankle (F&A) surgery patients. This is especially true regarding forefoot and midfoot surgery where patients are often allowed to weight-bear fully. In the field of F&A surgery, there is relatively little data available to guide clinical decision-making regarding VTE prophylaxis, especially in comparison to other fields of orthopaedics. One single surgeon study found only 22 clinically symptomatic VTE in 2,774 patients (0.79%) over the span of 10 years[57]. Other authors have found a relatively high rate of otherwise asymptomatic VTE in F&A surgery patients (25.4%)[58] at 2- and 6-week screening ultrasounds. All of the detected deep venous thromboses (DVT) were distal to the popliteal vein and all patients were undergoing hindfoot or midfoot surgery and were made non-weight-bearing[58]. There is very little data on the risk of VTE in patients who are undergoing forefoot and midfoot surgery.

In our systematic review, we identified 34 potential studies out of 318 reviewed that may discuss the incidence of VTE and prophylaxis in forefoot and midfoot patients who were allowed to weight-bear immediately after surgery. However, only 29 reported on the incidence of VTE after forefoot and midfoot procedures[57-85].

In a total of 38,105 reported forefoot procedures, 37 patients (0.097%) had a VTE while 7 patients (0.018%) had a PE. Of these patients, 2 (0.005%) had a fatal PE. Regarding midfoot surgery, 750 patients were included, of which 26 had a DVT (3.4%) and 2 had a PE (0.266%). No fatal PE were reported for patients undergoing midfoot surgery.

Relatively few authors have examined the effect of chemoprophylaxis on the incidence of VTE in forefoot and mid-

foot surgery. Heijboer et al., retrospectively compared patients who received aspirin (ASA) as DVT prophylaxis to those that received no prophylaxis[69]. Of the patients undergoing forefoot and midfoot surgery, they found 8 VTE in 1,004 patients (0.79%) who did not receive any DVT prophylaxis, and 2 VTEs in 1,004 patients (0.19%) receiving ASA. Griffiths et al., performed a retrospective review of an unspecified mix of different F&A procedures, some receiving ASA as prophylaxis and other receiving no prophylaxis[64]. They found similar rates of VTE in both cohorts, with 4 DVT in 1,068 patients receiving ASA (0.37%) and 3 DVT in the 1,559 patients with no prophylaxis (0.19%). Rates of PE were also similar, with 1 PE in the ASA group (0.09%) and 3 in the group with no prophylaxis (0.19%). No studies compared types of routine anticoagulation. There are no randomized controlled trials or even prospective studies comparing routine prophylaxis and its effect on VTE incidence.

Regarding risk factors for VTE, a few studies did examine the impact of various risk factors on rate of VTE. One study that only included patients undergoing forefoot surgery found age over 60 to be a risk factor[77]. Two studies exclusively evaluating midfoot surgery found longer tourniquet duration and female gender, increasing age, obesity, inpatient status, and non-elective surgery to be risk factors[58,70-84]. Additionally, Ahmed et al., evaluated a mix of forefoot and midfoot patients, and found obesity to be an independent risk factor for VTE[57]. Finally, Saragas et al., evaluated mix of forefoot, midfoot, and hindfoot patients, and found flat foot reconstruction surgery to be an independent risk factor for VTE[81].

The incidence of reported VTE is extremely low in forefoot surgery, and low in midfoot surgery. There is little data to support the use of routine prophylaxis for midfoot and especially forefoot surgery. The limited amounted of data impedes clinical decision-making regarding VTE chemoprophylaxis. Based on the data available we do not recommend routine anticoagulants for VTE prevention following elective forefoot and midfoot in low-risk patients. Given the lack of high-quality studies, we strongly encourage further research into the effect of VTE prophylaxis on the incidence of VTE in forefoot and midfoot surgery.

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6 - Is routine VTE prophylaxis needed for patients undergoing achilles tendon repair?

Response/Recommendation: In the absence of concrete evidence, we recommend that venous thromboembolism (VTE) prophylaxis (mechanical and/or chemical) be administered to patients at high risk of VTE (as determined by the risk stratification scores), unless contraindicated. Routine administration of chemoprophylaxis for patients undergoing achilles repair is not supported with the current literature.

Strength of Recommendation: Weak.

Delegates vote: Agree 100.00% Disagree 0.0% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: A systematic review was conducted to answer this clinical question. The search revealed five randomized control trials and a few retrospective studies including one on a very large cohort in a national registry. Overall, there was considerable heterogeneity between the studies. There was variability in the type of VTE prophylaxis, duration of prophylaxis, and the mode of diagnosis of VTE. The postoperative protocols also varied in immobilization type, duration, and weight-bearing status. Results from the studies could therefore not be pooled together. A previous meta-analysis on foot and ankle surgery including achilles tendon ruptures reported a symptomatic VTE incidence of 7% (95% confidence interval [CI] 5.5-8.5%) and radiologically diagnosed VTE incidence of 35.5% (95% CI 26.4-44.3%)[86]. The meta-analysis recommended that VTE chemoprophylaxis should be administered to patients undergoing achilles tendon surgery.

The RCT that we evaluated included a small cohort size ranging from 26 to 150. Three clinical trials were conducted by the same investigators on the role of mechanical prophylaxis. These studies included ultrasound screening of patients at 2 and 6 weeks after achilles tendon repair. They compared early functional mobilisation[87], calf intermittent pneumatic compression (IPC)[88] or foot IPC[89] to not having these in the rehabilitation after an achilles tendon repair. The calf IPC reduced the incidence of ultrasound screened VTE at two weeks (odds ratio [OR] = 2.60; 95% CI 1.15 - 5.91; p =0.022) but not at six weeks (OR 0.94, 95% CI 0.49 - 1.83). There was no difference with the early functional mobilisation or foot IPC.

The other RTC with moderate study quality compared chemical VTE prophylaxis using low-molecular-weight heparin (LMWH) to placebo. One study with 88 patients reported a reduction in VTE with LMWH compared to placebo for patients undergoing achilles tendon rupture who were immobilized in a plaster cast (OR, 0.24; 95% CI, 0.06 - 0.98)[90]. The study was on a larger cohort of 440 patients who were immobilized in a cast because of lower leg injuries. The achilles tendon injury patients were a sub-cohort. The study did not provide details of how the achilles tendon injuries were treated. Another RCT study included a cohort of 105 patients undergoing surgical repair of achilles tendon and immobilized in a plaster cast. There was no difference in the incidence of VTE among patients receiving LMWH (34%) vs. placebo (36%)[91].

A retrospective study reviewed the incidence of VTE among 28,546 patients with achilles tendon rupture who were treated surgically or non-operatively[92]. None of these patients, because of national guidelines, received VTE prophylaxis. The incidence of VTE within 180 days, that required hospitalization, in this large cohort was 1.36%.

One study on 341 patients with achilles tendon rupture, undergoing surgical repair and cast immobilization, had a deep venous thrombosis (DVT) incidence of 46% detected by ultrasound screening[93]. None of the patients in the latter study received VTE prophylaxis. Variation in the incidence of symptomatic VTE has also been observed. One study including a cohort of 1,172 patients who received surgical treatment of achilles tendon rupture and were not given VTE prophylaxis had a symptomatic VTE incidence of 0.76%[93]. Another study reported symptomatic VTE in 23.5% of 115 patients who received non-operative treatment of achilles tendon rupture[94]. Yet the incidence of symptomatic VTE was 4.5% in a cohort of 288 patients with achilles tendon rupture who were treated non-operatively in a weight-bearing boot and who did not receive any VTE prophylaxis[95]. The role of aspirin (ASA) as a VTE prophylaxis remains unclear. One retrospective audit study did not detect any reduction in the rate of VTE in patients with achilles tendon rupture who received ASA[96].

We also reviewed a few other studies that were either low-quality and/or included very small cohort size. Based on our understanding of the current literature, the incidence of symptomatic VTE in patients with achilles tendon rupture who are treated surgically or non-operatively continues to be relatively low. The available literature does not provide justification for routine administration of VTE prophylaxis for patients with achilles tendon rupture. In the absence of such evidence, we recommend that VTE prophylaxis should be reserved for patients at high-risk of VTE, as determined by risk stratification scores.

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7 - Is there a role for routine VTE prophylaxis undergoing ankle and/or hindfoot fusion?

Response/Recommendation: The risk of venous thromboembolism (VTE) following ankle or hindfoot fusion surgery is rare, with pulmonary embolism (PE) and even more so, fatal PE being exceedingly rare. We cannot recommend routine anticoagulants for VTE prevention following elective ankle/hindfoot fusion in low-risk patients. We do encourage further high-quality research into routine VTE chemoprophylaxis following foot and ankle (F&A) surgery.

Strength of Recommendation: Limited.

Delegates vote: Agree 96.30% Disagree 0.0% Abstain 3.70% (Strong Consensus).

Rationale: The argument for prophylaxis for VTE events in F&A surgery is at best equivocal. Compared to the depth of literature in total joint replacement or trauma, the current state of knowledge in F&A studies is based on a few large cohort studies[97-102]. As such, the true incidence of VTE is only partially described. In a prevalence study of ultrasonographic surveillance of VTE in low-risk patients after elective F&A surgery, 25.4% of patients had clinically silent VTE[103]. In contrast, in a single institution, single surgeon study over a span of 10 years, 22 of 2,774 (0.79%) patients had a clinically symptomatic VTE[97]. However, not much data has been reported following incidence and prevention of VTE associated with ankle and hindfoot (isolated subtalar, isolated talonavicular, tibiotalocalcaneal, triple, double) fusion.

In our systematic review, we identified 45 potential studies out of 350 screened that that present the incidence of VTE and prophylaxis in ankle and hindfoot fusion patients. However, only 29 reported on the incidence of VTE after ankle and hindfoot fusion procedures[98-127]. In 84,337 reported procedures, 333 patients (0.39%) had a VTE while 32 patients (0.004%) had a PE. Of these patients, 2 (0.0003%) had a fatal PE.

Of these studies, only two reported prescribing routine VTE prophylaxis after surgery (low-molecular-weight heparin for 6 weeks[122] and rivaroxaban for 4-6 weeks[123]). The incidence of VTE in the two studies was 2.2% (2/90). Of these studies, only one investigated the use of chemoprophylaxis in a prospective, cohort study in which patients took a daily dose of rivaroxaban until they were allowed weight-bearing as tolerated[123]. Five studies reported no use of routine VTE prophylaxis following ankle and hindfoot surgery[98,103,109,124,127]. The incidence of clinically diagnosed VTE reported in these studies was 0.18% (13/7,159). Interestingly, patients on thromboprophylaxis had higher incidence of VTE. No studies compared types of routine anticoagulation. There were no randomized controlled trials regarding routine prophylaxis and its effect on VTE incidence.

RECOMMENDATIONS FROM THE ICM-VTE: FOOT & ANKLE

Of the twenty-nine studies reporting on the incidence of VTE in ankle and hindfoot fusion patients, three performed a statistical analysis which investigated who is at increased risk for developing a VTE[102,103,117]. Two studies identified obesity as an independent risk factor for developing a VTE[102,117]. Other risk factors include: female gender, increasing age (not defined), inpatient status, nonelective surgery, and increased tourniquet time[103-117].

The incidence of reported VTE and PE in patients undergoing ankle and hindfoot fusions is low. While the evidence seems to suggest that routine prophylaxis for ankle and hindfoot fusion surgery is unnecessary, we caution against using poor data to make decisions regarding one's own surgical practice. Given the paucity of high-quality data regarding the utility of chemoprophylaxis following ankle and hindfoot fusions, we encourage further research into studying the effects of VTE prophylaxis on the incidence of VTE.

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8 - Is routine VTE prophylaxis required for patients undergoing total ankle arthroplasty?

Response/Recommendation: There is contradictory data on the role of chemoprophylaxis for the prevention of venous thromboembolism (VTE) events after total ankle arthroplasty (TAA). VTE rates after TAA appear to be substantially lower than those after total hip or knee arthroplasty in the absence of chemoprophylaxis, but they are certainly not negligible. Subpopulations of patients such as those with a prior history of VTE or known thrombophilia may be at sufficiently heightened risk to justify chemoprophylaxis. The implications of prolonged below-knee immobilization or nonweightbearing as well as the risk-benefit ratio of chemoprophylaxis in the perioperative setting needs to be further elucidated.

Strength of Recommendation: Limited.

Delegates vote: Agree 100.00% Disagree 0.0% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: While routine use of chemoprophylaxis is widely recommended following hip and knee arthroplasty,

studies examining the rate of VTE events such as deep vein thrombosis (DVT) and pulmonary embolism (PE) after TAA are scarce and remain confounded by methodological limitations[128,129]. It is also critical not to make overgeneralized recommendations that equate arthroplasty procedures across all joints. Hip and knee arthroplasties are more proximal procedures that technically entail complete dislocation of the involved joints, potentially kinking major vessels during surgery. Moreover, immediate postoperative mobilization and weight bearing are generally permitted following these procedures. In contrast, TAA is a more distal procedure whereby the ankle joint is not fully dislocated, and the surrounding vasculature is not acutely distracted or angulated, and patients generally undergo a period of immobilization and non-weightbearing. It is therefore plausible that the TAA procedure may not increase the incidence of DVT or PE per se, but rather, the superimposed host-specific risk factors in patients undergoing TAA may account for this reported incidence[130,131].

A retrospective study by Jameson et al., examining the rates of VTE after foot and ankle (F&A) surgery within the National Health Service (NHS) found that among 1,633 patients who underwent TAA, there was only a single non-fatal PE (0.06%) and no DVT[131]. The authors concluded that "venous thromboembolism following foot and ankle surgery is extremely rare" and that "prophylaxis is not required in most of these patients." However, the study relied on a hospital admissions database and identified patients who were readmitted to an NHS hospital for DVT or PE following a F&A procedure. Since a substantial number of VTE events never require inpatient readmission, the reported data may underestimate the actual rate of VTE after F&A surgery.

A large-scale meta-analysis by Calder et al., pooled 43,381 patients across 28 studies to assess the rate of VTE after both operative and nonoperative management of F&A conditions[132]. This was a heterogenous mix of retrospective cohort, prospective cohort, and randomized controlled studies, some of which focused solely on nonoperative management. The authors found that overall rates of clinically symptomatic VTE were 0.6% (95% confidence interval [CI] 0.4–0.8%) and 1% (95% CI 0.2–1.7%) with and without the use of chemoprophylaxis, respectively. Rates were higher among patients who underwent radiologic assessment with ultrasound or venography irrespective of symptoms, wherein the incidence of VTE with and without chemoprophylaxis was 12.5% (95% CI 6.8–18.2%) and 10.5% (95% CI 5.0–15.9%), respectively. They also found that patients undergoing management of achilles ruptures had a higher rate of VTE compared to the general population (7% clinical and 35.3% radiological), prompting the authors to recommend chemoprophylaxis for this specific surgical population, although they did not comment on patients undergoing TAA.

A review article by Barg et al., examined the incidence of VTE after TAA among 31 studies published between 1999 and 2013 and found a wide variation in VTE rates ranging from 0 to 9.8%, and concluded that "the incidence of thromboembolic complications was comparable with that of symptomatic deep vein thrombosis in patients with total knee or hip replacement"[133]. One major confounder in analyzing these data collectively, however, was that a formal meta-analysis was not performed, and the use of chemoprophylaxis was common but nonetheless variable amongst both individual patients as well as between studies. Manual tabulation of the included studies revealed that 3,613 patients underwent 3,826 TAA, yielding an overall DVT rate of 1.3% and PE rate of 0.03%[134]. Given substantial variability in the use of chemoprophylaxis as well as the non-inclusion of patient risk factors for VTE, a definite conclusion could not be drawn from this study.

A separate study by Barg et al., evaluated the rate of symptomatic VTE among 665 patients who underwent 701 TAA, all of whom received low-molecular-weight heparin (LMWH) for six weeks postoperatively[135]. The authors found a DVT rate of 3.9% and concluded that "the incidence of symptomatic DVT after total ankle replacement and use of low-molecular-weight heparin is comparable with that in patients undergoing total knee or hip replacement." The study did not explicitly recommend the routine use of chemoprophylaxis after TAA but given that chemoprophylaxis is routinely administered after hip and knee arthroplasty, some may argue that this would imply that a similar recommendation should be followed for TAA[128,129].

Horne et al., performed a retrospective chart review of symptomatic VTE rates among 637 patients undergoing 664 TAA[136]. The participating surgeons used LMWH for two weeks only if "risk factors" were identified, including a prior history of VTE or coagulopathy, as well as continued antiplatelet or anticoagulation therapy among patients who were taking these medications preoperatively. Overall, they reported that two patients (0.31%) developed a DVT alone and two patients (0.31%) developed a DVT and PE. Among the 434 patients who were not on chemoprophylaxis preoperatively or postoperatively, only two (0.46%) developed a DVT. The authors concluded that "patients without identifiable risk factors do not appear to require chemoprophylaxis." In this study, however, 203 patients (31.9%) either had a history of VTE or known thrombophilia and were therefore given chemoprophylaxis for two weeks, or were on preoperative aspirin, warfarin, LMWH, rivaroxaban (Xarelto), clopidogrel (Plavix), or dabigatran etexilate (Pradaxa) that was restarted immediately postoperatively. Presumably, it was the latter group of patients who had a heightened comorbidity burden and would be of interest to F&A surgeons. However, the authors noted that there were no bleeding events requiring reoperation, nor wound complications associated with chemoprophylaxis, although the rates of operative complications were not clearly reported.

Other studies examining complications after TAA have reported DVT rates between 0% and 5.4%, but were retrospective

in nature, as well as inconsistent in the indications for chemoprophylaxis, duration of use, and length of immobilization and non-weightbearing postoperatively[137-144].

The study by Horne et al., did raise the specter of catastrophic complication from VTE[136]. One patient with a prior history of DVT developed bilateral DVT and a saddle PE four weeks postoperatively despite being prescribed LMWH for the first two weeks, which was as per standard protocol. A second patient who was not prescribed chemoprophylaxis developed bilateral PE with dyspnea and increased oxygen requirement on the second postoperative day. Another patient without history of VTE developed a femoral DVT diagnosed at 3 months, while a fourth developed DVT while on aspirin. Thus, 3 of the 4 VTE events occurred in the absence of chemoprophylaxis, either because patients were never prescribed prophylaxis or because the length of prescription had expired. Given that the authors explicitly reported no complications associated with the use of chemoprophylaxis but did note the occurrence of several VTE events, one might conversely conclude that the use of such agents should be liberalized. It is thus evident that VTE risk-benefit analysis following F&A surgery is arguably more nuanced than that reported by this or any other study in current literature.

While VTE remains a genuine but poorly defined risk following TAA and other F&A procedures, it should be noted that numerous other studies have also highlighted the risk of complications related to the use of chemoprophylaxis. A study by Heijboer et al., compared the rate of VTE and adverse bleeding events among two matched cohorts of 5,286 patients undergoing F&A surgery with and without chemoprophylaxis using propensity score matching[145]. They found a three-fold reduction in VTE events, although there was a two-fold increase in bleeding events. Less frequently discussed is the risk of an immunogenic form of heparin-induced thrombocytopenia (HIT), which may occur in 0.2% of patients[146]. HIT carries an amputation rate of 22% and a mortality rate of 11%, with a published case report describing a mortality after a single dose of LMWH after F&A surgery[147]. Separately, the study by Barg et al., noted that while there were no bleeding complications, three patients (0.5%) developed thrombocytopenia by day seven with platelet counts that fell below 100,000/mm^3 and resolved after stopping LMWH[135]. Notwithstanding, the risks of chemoprophylactic agents following F&A and other types of orthopaedic surgery are rarely discussed in current literature.

It is worth noting that below-knee cast immobilization and non-weight bearing status have also been implicated as a risk factor for VTE[148-152]. Not all of these studies demonstrated a protective effect with chemoprophylaxis, and some instead showed a higher risk of VTE with the use of chemoprophylaxis, largely because of the selection bias with use of such agents in higher-risk patients. The study by Barg et al., did show a higher rate of VTE associated with a non-weight bearing status (odds ratio 3.57, 95% CI 2.18 to 5.85, p < 0.001)[135].

In F&A surgery compared to hip and knee arthroplasty, inherent patient risk factors play a disproportionate role in precipitating a VTE. Risk factors identified in the literature have included age > 50 years, splint or cast immobilization, achilles tendon ruptures, increased comorbidity burden as reflected by a Charlson comorbidity index > 2, varicose veins, history of VTE either in a given individual or first degree relative, known hypercoagulability disorder, and inflammatory arthritis[130,131,148,153-155]. These factors should be kept in mind when considering chemoprophylaxis after TAA, especially since patient risk factors arguably supersede procedural risk factors when it comes to F&A surgery.

In summary, there is enormous variability in the reported rate of VTE events after TAA. While the rate is certainly lower compared to the rate following total hip or knee arthroplasty without the use of chemoprophylaxis, it is certainly not negligible, and subpopulations of patients with superimposed comorbidities clearly remain at heightened risk. This includes patients with a prior history of VTE or hypercoagulability. Unfortunately, current data are generally retrospective and limited in their ability to discern patient-specific risk factors, and few studies have evaluated the downsides of using chemoprophylaxis. Large-scale, prospective randomized controlled trials are necessary to identify patients at risk of VTE after TAA in order to facilitate risk-benefit discussions between patients and providers.

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Appendix

*e*A Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/G852).

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