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Thromboembolism prophylaxis in orthopaedics: an update

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- Venous thromboembolism (VTE) is a serious complication during and after hospitalization, yet is a preventable cause of in-hospital death.
- Without VTE prophylaxis, the overall VTE incidence in medical and general surgery hospitalized patients is in the range of 10% to 40%, while it ranges up to 40% to 60% in major orthopaedic surgery. With routine VTE prophylaxis, fatal pulmonary embolism is uncommon in orthopaedic patients and the rates of symptomatic VTE within three months are in the range of 1.3% to 10%.
- VTE prophylaxis methods are divided into mechanical and pharmacological. The former include mobilization, graduated compression stockings, intermittent pneumatic compression device and venous foot pumps; the latter include aspirin, unfractionated heparin, low molecular weight heparin (LMWH), adjusted dose vitamin K antagonists, synthetic pentasaccharid factor Xa inhibitor (fondaparinux) and newer oral anticoagulants. LMWH seems to be more efficient overall compared with the other available agents. We remain sceptical about the use of aspirin as a sole method of prophylaxis in total hip and knee replacement and hip fracture surgery, while controversy still exists regarding the use of VTE prophylaxis in knee arthroscopy, lower leg injuries and upper extremity surgery.

Keywords: thromboprophylaxis; orthopaedics; venous thromboembolism

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Introduction

Venous thromboembolism (VTE) is a common complication during and after hospitalization for medical and surgical patients, including orthopaedic patients. More than half of all hospitalized patients are at risk for VTE, with a higher risk in surgical patients than in medical patients.[1] However, the overall VTE prophylaxis rates are in the range of 13% to 70%, implying a large variability between institutions and countries.[2-6] Without any prophylaxis, pulmonary embolism (PE) is responsible for 5% to 10% of deaths in hospitalized patients;[7-13] the incidence of fatal PE in hospitalized patients is 0.1% to 0.8% after elective general surgery, 2% to 3% after elective hip replacement and 4% to 7% after hip fracture surgery.[9] Similarly, the overall incidence of deep venous thrombosis (DVT) in medical and general surgery hospitalized patients is in the range of 10% to 40%; in comparison, the incidence of DVT ranges up to 40% to 60% in major orthopaedic surgery.[9] Death within one month of diagnosis occurs in approximately 6% of DVT patients and approximately 12% of PE patients.[14] The cumulative ten-year incidence of recurrent VTE reaches 39.9% (35.4% to 44.4%).[15]

Orthopaedic patients are at higher risk among all patients for DVT and VTE. In the early 2000s, despite the existence of VTE prophylaxis guidelines, the use of VTE prophylaxis was low;[1-3] currently, the adherence to in-hospital American College of Clinical Pharmacy (ACCP) guidelines, especially for orthopaedic patients, seems to be increasing.[13-17] There has been an increasing understanding that in the absence of the pathophysiologic processes included in Virchow's triad as described in 1884 (vascular endothelial damage, stasis of blood flow and hypercoagulability of blood), VTE is not usually developed.[17] In an orthopaedic patient undergoing an operation, all of the above pathophysiologic processes included in Virchow's triad are present: 1) use of tourniquet, immobilization and bed rest cause venous blood stasis; 2) surgical manipulations of the limb cause endothelial vascular injuries; 3) trauma increases thromboplastin agents; and

4) use of polymethylmethacrylate (PMMA) bone cement increase hypercoagulability. Therefore, in patients undergoing orthopaedic surgery and those with orthopaedic trauma, VTE prophylaxis and adherence to the respective guidelines is paramount.

This review article discusses the risk factors for VTE and the types of mechanical and current options for pharmacologic VTE prophylaxis, and provides the clinical evidence for current practice for VTE prophylaxis. Our aim was to perform a comprehensive review that readers would find interesting and useful to apply in clinical practice.

Risk factors for VTE

There have been many reported risk factors for VTE and recurrent VTE. According to SIGN (2010):[16] 1) risk factors for VTE include age, obesity, varicose veins, family history of VTE, thrombophilias, combined oral contraceptives, hormone replacement therapy, anti-oestrogens, pregnancy, puerperium, immobility, immobility during travel, hospitalization, anaesthesia and central venous catheters; and 2) risk factors for recurrent VTE include previous unprovoked VTE, male sex, obesity and thrombophilias.[16] Practically every patient admitted to a hospital has at least one of the above risk factors. According to Anderson et al:[17] 1) strong risk factors for VTE include a fracture of the hip or leg, hip or knee replacement, major general surgery, major trauma and spinal cord injury (SCI); 2) moderate risk factors include arthroscopic knee surgery, central venous catheters, chemotherapy, congestive heart or respiratory failure, hormone replacement therapy, malignancy, oral contraceptive therapy, paralytic stroke, pregnancy/postpartum, previous VTE and thrombophilia; and 3) weak risk factors include bed rest $>$ 3 days, immobilization and bedridden, increasing age, laparoscopic surgery, obesity, pregnancy/antepartum and varicose veins. Risk factors for VTE are cumulative.[18]

A risk stratification of the risk for VTE in surgical patients without prophylaxis classifies orthopaedic patients at the highest risk.[9] The ACCP (2008)[19] classified in-hospital patients without VTE prophylaxis in three categories (low, moderate and high risk). In the first category, patients who are fully mobile and those who are mobile and undergoing minor surgery are classified as having $<$ 10% risk. In the second category, most general surgery patients, open gynaecologic or urologic surgery patients, and medical patients who are bedridden or sick are classified as having a 10% to 40% risk. In the third category, the average orthopaedic patients who have undergone hip or knee arthroplasty or sustained a hip fracture, major trauma or SCI are included.[19] Randomized clinical trials have concluded that the rates of venographic documented DVT and proximal DVT 7 to 14 days after major orthopaedic surgery in patients who did not receive any VTE prophylaxis are approximately 40% to 60% and 10% to 30%, respectively.[9] After discharge from hospital, these orthopaedic patients are still at risk for VTE. Hypercoagulability can persist for six weeks after a hip fracture, while venous function remains significantly impaired for up to 42 days following hip fracture surgery.[20,21] VTE can occur up to three months after total knee and hip arthroplasty[22] and is the most common cause for readmission after total hip replacement (THR).[19] According to Planes et al,[23] 20% of THR patients with negative venogram at discharge and no VTE prophylaxis had a new DVT that developed over the subsequent three weeks based on repeat venogram. Also, approximately 30% of patients who experienced a DVT may experience recurrent DVT within 8 to 10 years after initial diagnosis and treatment.[24] With routine VTE prophylaxis in orthopaedic patients, fatal PE is uncommon, and the rates of symptomatic VTE within three months have been reduced to 1.3% to 10%.[19]

Mechanical VTE prophylaxis

The mechanical methods for VTE prophylaxis include mobilization, graduated compression stockings (GCS), intermittent pneumatic compression device (IPCD) and venous foot pumps (VFP).[25,26] Advantages of mechanical VTE prophylaxis include the lack of bleeding potential, no need for laboratory monitoring and no clinically important side effects.[9,27] Furthermore, the effectiveness of anticoagulants may be enhanced by some mechanical methods. In particular, IPCDs stimulate endogenous fibrinolytic activity by reduction of plasminogen activator inhibitor-1 levels.[27] Disadvantages of mechanical VTE prophylaxis methods include the difficulty of implementation or suboptimal compliance issues due to the limited movement of the patient and the discomfort they may bring,[25,26] needing to be worn continuously pre-, intra- and post-operatively for 72 hours, and lack of powerful evidence that any of the mechanical VTE prophylaxis methods may reduce the risk of death or PE.[9] Concerning GCS, these need to be sized and fitted properly, while it has been reported that they can cause impairment in tissue oxygenation.[28] Additionally, situations such as open fractures, peripheral arterial insufficiency, severe cardiac insufficiency, infection and ulceration of the lower limbs are contraindications for the use of mechanical VTE methods.[26]

Mobilization through early walking is probably the most simple and applicable method of VTE prophylaxis.[26] Early walking has been associated with a lower incidence of post-THR symptomatic VTE,[29] while in combination with motor physical therapy it can be associated with early return to the community, shorter hospitalization time, fewer complications and lower six-month mortality.[30]

However, it must be noted that although the early and frequent ambulation of hospitalized patients at risk for VTE is an important principle of patient care, the majority of hospital-associated, symptomatic VTE events occur after patients have started to ambulate. Therefore, mobilization alone does not provide adequate VTE prophylaxis for hospitalized patients and should often be regarded with caution.[19]

The latest available guidelines from the ACCP (2012)[31] suggest the use of mechanical methods in addition to pharmacological prophylaxis during hospitalization in patients with high risk for VTE after major orthopaedic surgery. In particular, the use of ICPDs with portable batteries is recommended in order to achieve maximum compliance after THR, total knee replacement (TKR) or hip fracture surgery.[31]

Pharmacologic VTE prophylaxis

The options for pharmacologic VTE prophylaxis include aspirin, unfractionated heparin (UFH), low molecular weight heparin (LMWH), adjusted dose vitamin K antagonists (VKA), synthetic pentasaccharid factor Xa inhibitor (fondaparinux) and newer oral anticoagulants.

Aspirin

Aspirin (acetylsalicylic acid) is an inexpensive, orally administered and widely available medication with a controversial use as a prophylactic agent for VTE. In 2008, ACCP guidelines clearly recommended against the use of aspirin alone as VTE prophylaxis for any patient group, and therefore for any orthopaedic patient.[19] However, the 2012 ACCP guidelines do recommend the use of aspirin as VTE prophylaxis for patients undergoing THR, TKR or hip fracture surgery because it appeared that the use of aspirin for VTE prophylaxis in these patients is more effective compared with placebo.[31] Nevertheless, in the same guidelines, the use of LMWH in preference to the other recommended agents including aspirin is concluded.[31]

The American Association of Orthopaedic Surgery (AAOS) guidelines (2007)[32] recommended aspirin as a potential pharmacological agent for VTE prophylaxis in patients at low risk for VTE. However, the AAOS recommendation was amended to 'we suggest the use of pharmacologic agents and/or mechanical compressive devices for the prevention of VTE in patients undergoing elective THR or TKR, and who are not at elevated risk beyond that of the surgery itself for VTE or bleeding'; the AAOS, following an update in 2011, recognized that the evidence base for the optimal pharmacotherapy for VTE was insufficient.[33,34]

The SIGN guidelines (2010, updated in 2015)[16] are clearer about aspirin. According to SIGN, 'as other agents are more effective for prevention of VTE, aspirin is not recommended as the sole pharmacological agent for VTE prophylaxis in orthopaedic patients'.[16]

Overall, it seems that the use of aspirin as a VTE prophylaxis agent in orthopaedic patients remains controversial. According to a meta-analysis in 2016, although aspirin is a suitable therapy for the prevention of VTE in THR and TKR, as recommended by the ACCP and AAOS, the evidence available is of limited quality and still remains unclear about the dosage and duration of administration of aspirin for VTE prophylaxis.[35]

Vitamin K antagonists

VKA is a group of oral anticoagulants whose anticoagulation effect is produced by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide, thereby modulating the γ-carboxylation of glutamate residues (Gla) on the N-terminal regions of vit K-dependent proteins.[36] Two common VKA drugs are acenocoumarol (mean half-life, 9 hours; range, 8 to 11 hours)[25,37] and warfarin (mean half-life, up to 2.5 days).[25,36] The use of VKAs requires monitoring and the most common way to monitor a VKA therapy is the prothrombin (PT) test. This test provides information about PT activity through the measurement of the International Normalized Ratio (INR).[26,36]

VKAs are recommended by the latest ACCP guidelines for VTE prophylaxis in patients undergoing THR, TKR or hip fracture surgery.[31] There is a series of guidelines from articles published in *CHEST* providing suggestions for the monitoring of a patient treated with a VKA.[36,38,39] A therapeutic INR range of 2.0 to 3.0 with a target INR of 2.5 is recommended rather than a lower or higher range. It is suggested that INR monitoring should start after the initial two or three doses of the VKA. For patients who are receiving a stable dose of oral anticoagulants, INR monitoring should be at an interval of no longer than every four weeks; for patients under VKA therapy with consistently stable INR, an INR testing frequency of up to 12 weeks rather than every four weeks has been recommended.[36,38,39] When warfarin is administered, an initial effect on INR usually occurs within the first two to three days. Consequently, when a rapid anticoagulant effect is required, heparin or LMWH should be administered concurrently. This administration should be overlapped for at least two days with warfarin until INR reaches the therapeutic range to allow for further reduction of factors X and II.[36]

Unfractionated heparin

UFH is a heterogeneous mixture of glycosaminoglycans that binds to antithrombin (AT) via a unique pentasaccharide sequence and catalyses the inactivation of thrombin, factor Xa and other clotting enzymes.[40] The heparin/AT complex inactivates thrombin (factor IIa) and factors Xa, IXa, XIa and XIIa.[41] Heparin must be administrated parenterally since it is

not absorbed orally. The two preferred administration routes are continuous intravenous (IV) infusion and subcutaneous. The subcutaneous administration is associated with reduced bioavailability and therefore a higher dose compared with IV administration is required in order to overcome this difference. If an immediate anticoagulation effect is needed, an IV bolus injection of heparin could accompany the initial subcutaneous administration.[42-44] The use of UFH may lead to haemorrhagic complications; this risk increases with the amount of dose and concomitant administration of fibrinolytic agents or glycoprotein IIb/IIIa inhibitors. Additionally, recent surgery, trauma, invasive procedures or concomitant haemostatic defects increase the risk of bleeding. Because anticoagulant response varies among patients, monitoring UFH with tests and adjusting the dose is standard practice.

UFH is recommended by the latest ACCP guidelines for VTE prophylaxis in patients undergoing THR, TKR or hip fracture surgery.[31] When administered in therapeutic doses, the anticoagulant effect of UFH is usually monitored using the activated partial thromboplastin time (aPTT or APTT).[40] However, the anticoagulant effects of the UFH can rapidly be reversed with the use of IV protamine sulphate; 1 mg of protamine sulphate will neutralize approximately 100 IU of UFH.[40] UFH may also lead to non-haemorrhagic side effects, such as heparin-induced thrombocytopenia (HIT) and osteoporosis. Besides its anticoagulation effects, UFH also inhibits osteoblast formation and activates osteoclasts promoting bone loss.[45,46] HIT is the most important non-haemorrhagic side effect of UFH. HIT is associated with the formation of anti-heparin antibodies/platelet factor, thrombocytopenia and prothrombotic effect that may contribute to haemorrhage, thrombosis and embolism, and may lead to death. If VTE develops during or soon after UFH administration, physicians should suspect the possibility of HIT. In contrast, if thrombocytopenia occurs, alternative anticoagulation should be used until HIT is excluded. In any suspicion of HIT, UFH should be suspended immediately.[53,54]

Low molecular weight heparin

LMWH is derived from UFH by chemical or enzymatic depolymerization. Their molecular weight is approximately one-third that of UFH (mean, 4000 to 5000 D; range, 2000 to 9000 D). Compared to UFH, LMWH has a more favourable benefit-to-risk ratio in animal models, with superior pharmacokinetic properties. The inhibitory activity of LMWH against factor Xa is greater than thrombin and exhibits less binding to cells and proteins than UFH. Consequently, LMWH preparations have more predictable pharmacokinetic and pharmacodynamic properties, a longer half-life and a lower risk of non-haemorrhagic side effects than UFH. LMWH is administered subcutaneously via injection, in one or two daily doses without the need of monitoring. The use of LMWH is more convenient than UFH, and thus has replaced UFH for almost any clinical indications.[40,42]

Over the last 20 years, many studies reported in favour of LMWH over other anticoagulant factors.[47-52] According to Palmer et al,[47] 'in orthopaedic surgery, LMWH is significantly superior to both UFH and warfarin for prevention of DVT, and results in significantly less minor bleeding complications when compared to UFH, but significantly more minor bleeding when compared to warfarin'. Howard et al[48] reported that 'LMWH is more efficacious than either adjusted dose of UFH or warfarin, when used to prevent DVT and proximal DVT following TKR'. Other studies supported that LMWH is better for DVT prophylaxis in TKR compared with warfarin or aspirin.[49,50] Handoll et al[51] reported that LMWH and UFH are similarly effective in preventing DVT after hip fracture surgery, while Mismetti et al[52] concluded that VKAs are less effective than LMWH, without any significant difference in bleeding risk in patients undergoing orthopaedic surgery.

An uncommon but potentially devastating complication of anticoagulation with LMWH is HIT syndrome, as reported with UFH. The inverse variance-weighted average that determined the absolute risk for HIT with LMWH was 0.2%, compared with 2.6% with UFH.[55] The latest ACCP guidelines recommended LMWH as an optimal method for VTE prophylaxis in patients undergoing THR, TKR or hip fracture surgery.[31] According to these guidelines, the use of LMWH is recommended in preference to the other agents they have recommended as alternatives for VTE prophylaxis.[31] Due to these characteristics, LMWH should be considered the gold standard for VTE prophylaxis in orthopaedic patients.

Fondaparinux

Fondaparinux is a synthetic pentasaccharide with a molecular weight of 1728 D, a specific anti-Xa activity that is higher than that of LMWH (approximately 700 units/mg compared with 100 units/mg, respectively) and a half-life that is longer than that of LMWH (17 hours compared with 4 hours, respectively). After subcutaneous injection, there is a rapid and complete absorption of fondaparinux. A steady state is reached after the third or fourth once-daily dose. Fondaparinux is excreted unchanged in the urine with a terminal half-life of 17 hours in young individuals and 21 hours in elderly volunteers. Pharmacologically, fondaparinux binds to AT and produces a conformational change at the reactive site of AT that enhances its reactivity with factor Xa. The dose of fondaparinux is 2.5 mg daily for VTE prophylaxis and for the treatment of acute coronary syndromes. For the treatment of DVT or PE, fondaparinux is given at a dose of 7.5 mg for patients with a body weight of 50 to 100 kg; the dose is

decreased to 5 mg for patients weighing < 50 kg and increased to 10 mg in those weighing > 100 kg.[40]

A benefit of fondaparinux over other injectable agents such as UFH and LMWH is that it does not inactivate thrombin (factor IIa), has no effect on the platelets and does not cross-react with the serum of patients with HIT.[26]

A 2007 study with a total inclusion of > 144 000 patients reported a lower incidence of VTE with fondaparinux (1.5%) compared with enoxaparin (2.3%), dalteparin (2.1%) and UFH (4.2%).[56] Also, the latest ACCP guidelines recommend fondaparinux as a method of VTE prophylaxis for patients undergoing THR, TKR or hip fracture surgery.[31] However, the same guidelines report that the close balance between desirable and undesirable effects makes the use of fondaparinux for extended VTE prophylaxis less appealing, particularly compared with LMWH.[31]

Newer oral anticoagulants

Compared with VKAs, the newer oral anticoagulant drugs have the advantage of the ability to administer at fixed doses without the need of laboratory monitoring. Subsequently, they have the potential to overcome several drawbacks of VKAs.[57]

Rivaroxaban

Rivaroxaban is an orally administered direct inhibitor of activated factor X (Xa). In 2008, rivaroxaban received marketing authorization for VTE prophylaxis in adult patients undergoing elective THR or TKR.[58] It was found to be more effective than enoxaparin in preventing VTE after THR or TKR in phase III clinical trials.[59-62] Rivaroxaban is administered in a fixed daily oral dose of 10 mg for VTE prophylaxis after elective THR and TKR.[58] The latest ACCP guidelines recommend rivaroxaban as a method of VTE prophylaxis in patients undergoing THR and TKR.[31] However, the same guidelines report that rivaroxaban has not been evaluated in hip fracture surgery.[31] Therefore, rivaroxaban is currently not recommended for hip fracture surgery.

Dabigatran

Dabigatran is a selective, reversible, direct thrombin inhibitor. It is administered as dabigatran etexilate, which is an orally absorbable prodrug, since dabigatran itself is a strongly polar molecule that is not absorbed from the gut. Phase III clinical studies evaluated the use of dabigatran etexilate for VTE prophylaxis after elective THR and TKR, for the treatment of VTE, and for the prevention of stroke or systemic embolism in nonvalvular atrial fibrillation. The drug has been approved in many countries for VTE prophylaxis in patients undergoing THR or TKR.[57] Its efficacy was analysed in studies that compared dabigatran etexilate (220 or 150 mg per day) with enoxaparin in patients undergoing THR or TKR.[63,64] Both studies reported that dabigatran etexilate was as effective as enoxaparin for VTE prophylaxis. For VTE prophylaxis, the dosing schedules of dabigatran are 150 mg and 220 mg daily, starting with a half dose given soon after surgery.[57]

In 2012, Uchino et al[65] reported an association of dabigatran with an increased risk of myocardial infarction or acute coronary syndrome in a broad spectrum of patients when tested against different controls. Nevertheless, the latest ACCP guidelines recommend dabigatran as a method of VTE prophylaxis in patients undergoing THR or TKR.[31] However, the same guidelines report that dabigatran has not been evaluated in hip fracture surgery.[31] Therefore, dabigatran is currently not recommended for hip fracture surgery.

Apixaban

Apixaban is a direct factor Xa inhibitor that has been approved for VTE prophylaxis following THR and TKR, for the treatment of acute DVT or PE, and for risk reduction for recurrent DVT and PE after initial diagnosis and treatment.[66,67] There are studies that compared the efficacy of apixaban versus enoxaparin that led to the approval of apixaban for VTE prophylaxis.[68-70] The current recommended dosage for VTE prophylaxis after THR and TKR is 2.5 mg twice daily starting 12 to 24 hours after surgery and continuing for 35 days for THR and 12 days for TKR.[66,67]

The latest ACCP guidelines recommend apixaban as a method of VTE prophylaxis in patients undergoing THR or TKR.[31] However, the same guidelines report that apixaban has not been evaluated in hip fracture surgery.[31] Therefore, apixaban is currently not recommended for hip fracture surgery.

Guidelines

Several papers and respective guidelines have been published for VTE prophylaxis in major orthopaedic surgery. Currently, some of the most commonly used guidelines worldwide are those published from the ACCP (2012),[31] AAOS (2011),[34] SIGN (2010, updated in 2015)[16] and the National Institute for Health and Care Excellence (NICE) (2018).[71] In addition, there are guidelines published from several national associations, such as those published from the Hellenic Association of Orthopaedic Surgery and Traumatology (2009).[25] Among the internationally used guidelines, it is our opinion that those of the ACCP are the more thorough and provide the most adequate guidance for VTE prophylaxis in orthopaedic patients, especially concerning the pharmacological VTE prophylaxis. The latest ACCP guidelines (9th edition, 2012) provide guidelines for several orthopaedic entities and types of surgery.

Table 1. ACCP, SIGN, and AAOS guidelines for VTE prophylaxis for patients undergoing elective THR or TKR

Study	Guidelines	Clinical evidence (grade)	Duration of prophylaxis
ACCP (2008[19], 2012[31])	LMWH	1B	At least 10 to 14 days, and up to 35 days
	Low dose UFH	1B	
	VKA	1B	
	Fondaparinux	1B	
	Apixaban	1B	
	Dabigatran	1B	
	Rivaroxaban	1B	
	Aspirin	1B	
	IPCD	1C	
	Preference of LMWH to fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH	2B	
	Preference of LMWH to VKA and aspirin	2C	
SIGN (2010, updated 2015[16])	LMWH In combination with mechanical prophylaxis	A	Extended prophylaxis (grade A)
	Fondaparinux		
	Rivaroxaban		Optimal duration of extended prophylaxis is unclear
	Dabigatran		
	Aspirin is not recommended as a single pharmacologic agent for VTE prophylaxis	C	–
AAOS (2011[34])	Use of pharmacologic agents and/or mechanical methods	Moderate	–
	Unclear about which prophylactic strategy (or strategies) is/are optimal or suboptimal. No recommendation for or against specific prophylactics in these patients	Inconclusive	Patients and physicians discuss the duration of prophylaxis (consensus)

Total hip and knee replacement

For patients undergoing THR or TKR (Table 1), current ACCP guidelines recommend the use of LMWH, low-dose UFH, VKA, fondaparinux, apixaban, dabigatran, rivaroxaban, aspirin (all Grade 1B) or IPCD (Grade 1C) for at least 10 to 14 days and up to 35 days.[19,31] The use of LMWH is suggested in preference to the other recommended agents (Grade 2B and 2C when it comes to adjusted-dose VKA or aspirin).[31] When LMWH is used for VTE prophylaxis in patients undergoing THR or TKR, the administration is recommended to start either 12 hours or more pre-operatively or 12 hours or more post-operatively, rather than within 4 hours or less pre-operatively or 4 hours or less post-operatively.[31] During hospitalization, the use of dual prophylaxis with an IPCD device for at least 18 hours daily along with an antithrombotic agent is recommended. Doppler ultrasonography (DUS) screening before hospital discharge is not recommended for asymptomatic patients.[31]

AAOS guidelines suggest the use of pharmacologic agents and/or mechanical compressive devices for the prevention of venous thromboembolism in patients undergoing elective THR or TKR and who are not at elevated risk beyond that of the surgery itself for VTE or bleeding (moderate grade of recommendation).[34]

SIGN guidelines recommend the use of pharmacological prophylaxis (with LMWH, fondaparinux, rivaroxaban or dabigatran) combined with mechanical prophylaxis unless contraindicated (Grade A).[16]

NICE guidelines (Table 2) suggest LMWH for 10 days and then aspirin for another 28 days or LMWH for 28 days in combination with anti-embolism stockings until discharge for patients undergoing elective THR.[71] For patients undergoing elective TKR, they suggest aspirin (75 mg or 150 mg) for 14 days, or LMWH for 14 days in combination with anti-embolism stockings until discharge.[71] Rivaroxaban, apixaban or dabigatran are also recommended by NICE guidelines as options for the prevention of venous thromboembolism in adults undergoing elective THR or TKR.[71]

Hip fracture surgery

Hip fractures are common causes of orthopaedic treatment and are increasing with an ageing population.[72] These patients are at high risk for DVT and PE. While patients who do not receive any anticoagulation therapy on admission are easy to manage with existing protocols, those who are on anticoagulation treatment for other medical reasons are more complex cases.[73]

For patients undergoing hip fracture surgery (Table 3), ACCP guidelines recommend the use of LMWH, low-dose UFH, VKA, fondaparinux, aspirin (all Grade 1B) or an IPCD (Grade 1C) for at least 10 to 14 days and up to 35 days.[19,31] The use of LMWH is recommended in preference to the other agents (Grade 2B and 2C when it comes to adjusted-dose VKA or aspirin).[31] When LMWH is used for VTE prophylaxis in patients undergoing hip fracture surgery, it is recommended to begin administration either 12 hours or more pre-operatively or 12 hours or more post-operatively, rather than within 4 hours or less pre-operatively or 4 hours or less post-operatively.[31] During hospitalization, the use of dual prophylaxis with an IPCD device for at least 18 hours daily along with an antithrombotic agent is recommended. DUS screening before hospital discharge is not recommended for asymptomatic patients.[31]

Table 2. NICE guidelines for VTE prophylaxis for patients undergoing elective THR or TKR

NICE study (2018[71])	Guidelines	Duration of prophylaxis
For patients undergoing elective THR	LMWH for 10 days and then aspirin	10 days LMWH Further 28 days aspirin
	LMWH in combination with anti-embolism stockings (until discharge)	28 days
	Rivaroxaban Apixaban Dabigatran	>14 days
For patients undergoing elective TKR	Aspirin (75 or 150 mg)	14 days
	LMWH in combination with anti-embolism stockings (until discharge)	14 days
	Rivaroxaban Apixaban Dabigatran	>14 days

Table 3. ACCP, SIGN, British Orthopaedic Association, and NICE guidelines for VTE prophylaxis for patients undergoing hip fracture surgery

Study	Guidelines		Clinical evidence (grade)	Duration of prophylaxis
ACCP (2008[19], 2012[31])	LMWH		1B	At least 10 to 14 days, and up to 35 days
	Low dose UFH		1B	
	VKA		1B	
	Fondaparinux		1B	
	Aspirin		1B	
	IPCD		1C	
	Preference of LMWH to fondaparinux, low dose UFH		2B	
	Preference of LMWH to VKA and aspirin		2C	
SIGN (2009[74]) British Orthopaedic Association (2007[75])	In combination with mechanical prophylaxis	LMWH	A	4 weeks
		UFH	A	
		Fondaparinux	A	
	Aspirin is not recommended as a single pharmacological agent for VTE prophylaxis		D	–
NICE (2018[71])	LMWH Fondaparinux		–	1 month

SIGN guidelines for VTE prophylaxis in patients with hip fractures are available from the previous edition (2009).[74] These guidelines recommend that heparin (UFH or LMWH) or fondaparinux may be used for pharmacological VTE prophylaxis in hip fracture surgery (Grade A)[74] and do not recommend aspirin monotherapy as an appropriate pharmacological VTE prophylaxis after hip fracture surgery (Grade D).[74] Regarding fondaparinux, SIGN guidelines suggest that patients without a contraindication should receive fondaparinux for 28 days starting 6 hours after surgery (Grade A).[16,74]

Concerning the timing of LMWH, a recent review by Ktistakis et al[73] suggests that LMWH should be started on admission of the patient with a hip fracture, stopped 12 hours before surgery and restarted 6 to 12 hours post-operatively. The duration of the pharmacological VTE prophylaxis continues for 28 to 35 days post-operatively according to product characteristics.[73] Similar are the British Orthopaedic Association and NICE guidelines, which suggest administration of heparin (UFH or LWMH) 6 to 12 hours after surgery for four weeks, early mobilization of the frail patient and simultaneous use of mechanical VTE prophylaxis.[71,75]

Knee arthroscopy

The reported incidence of DVT without prophylaxis after knee arthroscopy varies from 0.2% to 18%[76,77] and consensus on VTE prophylaxis after knee arthroscopy has not been reached (Table 4).[78] Current ACCP guidelines suggest no VTE prophylaxis rather than prophylaxis for patients undergoing knee arthroscopy without a history of prior VTE (Grade 2B).[31] However, Krych et al[79] suggested that patients with a history of VTE, malignancy, or two or more classic risk factors are at increased risk for VTE after knee arthroscopy; therefore, VTE prophylaxis should be considered in these select patients. Another study that compared the results of LMWH administration and the use of GCS after knee arthroscopy reported that in these patients, prophylactic LMWH for one week reduced a composite end point of asymptomatic proximal DVT, symptomatic VTE and all-cause mortality more than GCS.[80] However, a third study reported that VTE prophylaxis with LMWH for eight days after knee arthroscopy or during the full period of immobilization due to casting or bracing was not effective for the prevention of symptomatic VTE.[81] NICE guidelines suggest considering LMWH for 14 days for patients undergoing arthroscopic knee surgery if total anaesthesia time is more than 90 minutes or if the patient's VTE risk outweighs the risk of bleeding.[71]

Isolated lower-leg injuries distal to the knee

Routine use of VTE prophylaxis in ambulatory patients in a short leg cast is controversial.[83] The incidence of DVT

Table 4. Guidelines for VTE prophylaxis for patients undergoing various orthopaedic operations

Orthopaedic operation	Study	Guidelines	Clinical evidence (grade)/ Level of evidence
Knee arthroscopy	ACCP (2012[31])	No VTE prophylaxis rather than prophylaxis for patients undergoing knee arthroscopy without a history of prior VTE	2B
	Krych et al (2015[79])	Consider pharmacologic VTE prophylaxis for patients with a history of VTE, malignancy, or 2 or more classic risk factors	Level III (case-control study)
	NICE (2018[71])	LMWH for 14 days if: - total anaesthesia over 90 minutes or - VTE risk outweighs bleeding risk	
Isolated lower-leg injuries distal to the knee	ACCP (2012[31])	No VTE prophylaxis rather than pharmacological VTE prophylaxis in patients with isolated lower-leg injuries requiring leg immobilization	2C
Isolated foot and ankle surgery	Calder et al (2016[93])	Routine chemoprophylaxis is not indicated	A/Level II
	NICE (2018[71])	Consider pharmacological VTE prophylaxis if: - immobilization is required - total anaesthesia over 90 minutes or - VTE risk outweighs bleeding risk	
Cast immobilization	Testroote et al (2014[90]) Zee et al (2017[91])	LMWH for patients undergoing casting	Moderate-quality evidence
	NICE (2018[71])	LMWH or fondaparinux for patients whose VTE risk outweighs bleeding risk Consider stopping prophylaxis after 42 days	
Achilles tendon rupture	Patel et al (2012[92])	Routine use of VTE prophylaxis might be unwarranted	Level III
	Calder et al (2016[93])	Routine use of mechanical anti-VTE methods	B/Level II
Upper limb surgery	NICE (2018[71])	VTE prophylaxis is generally not needed if patients receive local or regional anaesthesia Consider VTE prophylaxis if: - total time under general anaesthesia over 90 minutes - difficulty to mobilize due to operation	–
Shoulder arthroplasty	Day et al (2015[94])	Mechanical prophylaxis combined with aspirin Pharmacological prophylaxis with agents other than aspirin may be warranted in patients with a demonstrated risk of VTE	Epidemiologic study (database analysis with survey of experts)

following short leg cast immobilization is in the range of 4% to > 16%.[84-86] Some researchers support that the incidence of symptomatic VTE is equivocal to THR, while others report no sufficient evidence to warrant routine use of VTE prophylaxis in these patients.[87,88] According to Metz et al,[82] there is no sufficient evidence to warrant routine use of VTE prophylaxis in ambulatory patients with below-knee or lower-leg immobilization after an isolated lower-leg injury, because there is a too-low incidence of symptomatic VTE that is not able to show a relevant clinical benefit from VTE prophylaxis. Current ACCP guidelines suggest no VTE prophylaxis rather than pharmacologic VTE prophylaxis in patients with isolated lower-leg injuries requiring leg immobilization (Grade 2C).[31]

Cast immobilization of the lower limb has been implicated by some authors in the occurrence of VTE events.[89] A 2014 meta-analysis showed a 4.3% to 40% incidence of DVT after casting and recommended the use of LMWH for all patients undergoing casting.[90] A recent update of that study reported moderate-quality evidence and showed that the use of LMWH in outpatients reduced DVT when immobilization of the lower limb was required, when compared with no prophylaxis or placebo.[91] NICE guidelines suggest prophylaxis with LMWH or fondaparinux for patients with lower limb immobilisation whose risk of VTE outweighs the risk of bleeding.[71] The duration of the prophylaxis should be considered to stop at 42 days.[71]

The use of VTE prophylaxis after Achilles tendon rupture remains controversial. A level III 2012 study reported that the overall incidence of symptomatic DVT and PE was low after Achilles tendon rupture; therefore, routine use of anticoagulation prophylaxis might be unwarranted.[92] However, a 2016 meta-analysis (Level II) recommended routine use of mechanical VTE prophylaxis methods after Achilles tendon rupture whether treated surgically or non-operatively as there is a high risk of VTE (Grade B recommendation).[93] The same study does not recommend routine pharmacologic prophylaxis for patients undergoing isolated foot and ankle surgery (Grade A recommendation).[93]

Elective spine surgery

Guidelines for elective spine surgery (Table 5) have been included in the previous edition of the ACCP guidelines (2008).[19] For patients undergoing spine surgery who do not have additional VTE risk factors, there is a weak recommendation (Grade 2C) for not routine use of VTE prophylaxis other than early and frequent ambulation. However, for patients undergoing spine surgery who have additional VTE risk factors such as advanced age, malignancy, presence of neurologic deficits, history of VTE or an anterior surgical approach, ACCP guidelines recommend that

Table 5. ACCP (2008[19]) guidelines for VTE prophylaxis for patients undergoing spine surgery and those with a spine injury

Spine surgery/injury	Guidelines	Clinical evidence (grade)
Elective spine surgery with no additional thromboembolic risk factors	Early and frequent ambulation No routine use of other types of VTE prophylaxis	2C
Elective spine surgery with additional thromboembolic risk factors or an anterior surgical approach	Low dose UFH	1B
	LMWH	1B
	Optimal use of peri-operative IPC	1B
	GCS	2B
Elective spine surgery with multiple risk factors for VTE	Combination of a pharmacological method with the optimal use of a mechanical method	2C
Acute SCI	Routine VTE prophylaxis	1A
	LMWH after primary haemostasis	1B
	IPC and low dose UFH	1B
	IPC and LMWH	1C
	No use of low dose UFH alone	1A
Acute SCI with contraindication of pharmacologic VTE prophylaxis agents because of high bleeding risk	Optimal use of IPC and/or GCS	1A
	When the high bleeding risk decreases, pharmacological VTE prophylaxis substituted for or added to the mechanical VTE prophylaxis	1C
Incomplete SCI associated with evidence of a spinal haematoma on CT or MRI	Mechanical prophylaxis instead of pharmacological agents, at least for the first few days after the injury	1C
SCI	Against the use of an IVC filter for VTE prophylaxis	1C
Patients undergoing rehabilitation following acute SCI	Continuation of LMWH	1C
	Conversion to an oral VKA (INR target, 2.5; range, 2.0 to 3.0)	

one of the following VTE prophylaxis options be used: post-operative low-dose UFH (Grade 1B); post-operative LMWH (Grade 1B); or optimal use of peri-operative IPC (Grade 1B) or GCS (Grade 2B) as an alternative. For patients undergoing spine surgery who have multiple risk factors for VTE, the combination of a pharmacologic method with the optimal use of a mechanical method is recommended (Grade 2C).[19]

Spinal cord injury

Guidelines for SCI have been included in the previous edition of ACCP guidelines (2008).[19] For all patients with acute SCI it is recommended that routine VTE prophylaxis should be administered (Grade 1A); in these patients, VTE prophylaxis with LMWH is recommended to commence once primary haemostasis is evident (Grade 1B). Alternatively, combined use of IPC and either low-dose UFH (Grade 1B) or LWMH (Grade 1C) should be administered. Additionally, for patients with acute SCI, ACCP guidelines (8th edition, 2008) recommended the optimal use of IPC and/or GCS if anticoagulants are contraindicated because of high bleeding risk early after the injury (Grade 1A). When the high bleeding risk decreases, it is recommended that pharmacologic VTE prophylaxis be substituted for or added to the mechanical VTE prophylaxis (Grade 1C). For patients with an incomplete SCI associated with evidence of a spinal haematoma on CT or MRI, the use of mechanical instead of pharmacologic VTE prophylaxis is recommended, at least for the first few days after the injury (Grade 1C). Following acute SCI, ACCP guidelines (2008) recommended against the use of low-dose UFH alone (Grade 1A).[19] Also, the use of an IVC filter for VTE prophylaxis is not recommended for patients with SCI (Grade 1C).[19] For patients undergoing rehabilitation following acute SCI, continuation of LMWH for VTE prophylaxis or conversion to an oral VKA (INR target, 2.5; range, 2.0 to 3.0) is recommended (Grade 1C).[19]

Upper extremity surgery

Guidelines for VTE prophylaxis after shoulder replacement surgery have not been established; currently, the standard of care after shoulder replacement surgery is no VTE prophylaxis.[94] A review of VTE events after shoulder surgery (total shoulder replacement arthroplasty, hemiarthroplasty and arthroscopy) reported a range of VTE incidence of 0.02% to 13%, confirming the existence of variable rates across different hospital settings.[95]

Day et al reported that VTE after shoulder replacement is, in general, lower than VTE after lower extremity replacement, despite the fact that VTE prophylaxis is not the standard of care after upper extremity arthroplasty as for the lower extremity.[94] Also, they reported that complications associated with VTE prophylaxis, such as wound haematoma, were not significantly different between lower extremity and shoulder replacement arthroplasty.[94] These authors concluded that the risk of bleeding combined with the lower rates of VTE without prophylaxis does not warrant routine pharmacologic VTE prophylaxis for shoulder replacement surgery.[94] However, some of the authors of this study use mechanical VTE prophylaxis combined with aspirin after upper extremity arthroplasty in patients who are not at increased risk for VTE, while they propose VTE prophylaxis with agents other than aspirin in patients with a risk of VTE.[94]

NICE guidelines suggest considering VTE prophylaxis in patients undergoing upper limb surgery and who are

under general anaesthesia for more than 90 minutes, or in patients who might have difficulties to mobilise due to their operation.[71] However, a patient who undergoes an upper limb surgery under local or regional anaesthesia is generally not in need of VTE prophylaxis.[71]

Adherence to ACCP guidelines

ACCP guidelines for VTE prophylaxis are a very useful tool available to clinicians for prevention of VTE in patients undergoing major orthopaedic surgery. In the last 30 years, nine editions of the guidelines have been published from the ACCP, with the most recent in 2012. However, there is a gap between guideline recommendations and clinical practice. A recent review of the literature and meta-analysis concluded that adherence to the guidelines during hospitalization seems to be increasing, while adherence rates to global VTE prophylaxis decrease due to an insufficient implementation of guidelines after discharge.[96]

Antiplatelet drugs and VTE prophylaxis in orthopaedics

Antiplatelet drugs are widely prescribed for the prevention of cardiovascular events.[97] The number of patients who undergo percutaneous coronary intervention (PCI) each year in western countries is about 2 million; 90% of these interventions involve insertion of intracoronary stents and approximately 5% of these patients will need to undergo non-cardiac surgery within the first year after stenting. To avoid stent thrombosis, these patients are in need of long-term treatment with antiplatelet drugs such as clopidogrel and aspirin.[98,99] Subsequently, there is a clinical problem for orthopaedic and trauma surgeons of how to manage patients on these antiplatelet drugs who require surgery.[97]

According to Dineen et al,[97] aspirin should not be stopped pre-operatively when prescribed for secondary prevention after stroke, angina, myocardial infarction or any type of coronary revascularization. Exceptions include intracranial surgery, operations on the spinal medullary canal and on the posterior chamber of the eye. It is safe to continue aspirin peri-operatively in nearly all routine orthopaedic practice.[97] When aspirin is prescribed for primary prevention of cerebral or cardiovascular events, it may safely be stopped 7 to 10 days before surgery.[97]

According to the same authors, there should not be a discontinuation of clopidogrel during the re-endothelialization phase of a coronary stent or if prescribed for unstable angina or following myocardial infarction.[97] Also, it should not be discontinued in high-risk patients such as those with a history of thrombosis of a stent, a low ejection fraction, diabetes mellitus and prothrombotic conditions.[97] In patients who receive clopidogrel for indications other than the above, the drug may safely be stopped 7 to 10 days before elective orthopaedic surgery and it should be restarted 24 to 48 hours after the planned operation. All the benefits of clopidogrel without significantly increasing the risk can be nearly provided by a bridging therapy with aspirin.[97]

AAOS guidelines suggest that patients should discontinue antiplatelet drugs before undergoing elective THR or TKR with a moderate grade of recommendation.[34] However, a recent review and meta-analysis about clopidogrel and hip fracture surgery recommended that patients who receive clopidogrel and have a hip fracture can be managed by normal protocols with early surgery. This review also supported that operating early on patients receiving clopidogrel is safe and does not appear to confer any clinically significant bleeding risk, and that clopidogrel, if possible, should not be withheld throughout the peri-operative period due to increased risk of cardiovascular events associated with stopping clopidogrel. The authors suggest that care should be taken intra-operatively to minimize blood loss due to the increased potential for bleeding.[100]

Conclusions

Patients undergoing major orthopaedic surgery such as THR, TKA or hip fracture surgery are at highest risk for VTE during and after hospitalization; therefore, these patients should be administered VTE prophylaxis, mechanical and/or pharmacological. For optimal use of the available VTE prophylaxis methods there are several guidelines published. Based on our review, the ACCP guidelines for VTE prophylaxis are adequate enough and should be endorsed for daily clinical practice. VTE prophylaxis with LMWH seems to be more efficient overall compared with the other available methods of VTE prophylaxis and is recommended in preference to other methods for VTE prophylaxis. Scepticism remains about the use of aspirin as a sole method for VTE prophylaxis in THR, TKR and hip fracture surgery, as there is still some controversy about its use. Lastly, controversy still exists regarding VTE prophylaxis after knee arthroscopy, lower-leg injuries and upper extremity surgery. In this regard, more studies are necessary to draw important conclusions.

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REFERENCES

1. Cohen AT, Tapson VF, Bergmann JF, et al. ENDORSE Investigators. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet* 2008;2;371:387-394.

2. Otero R, Uresandi F, Cayuela A, et al. Use of venous thromboembolism prophylaxis for surgical patients: a multicentre analysis of practice in Spain. *Eur J Surg* 2001;167:163-167.

3. Yu HT, Dylan ML, Lin J, Dubois RW. Hospitals' compliance with prophylaxis guidelines for venous thromboembolism. *Am J Health Syst Pharm* 2007;64:69-76.

4. Eikelboom JW, Mazzarol A, Quinlan DJ, et al; American College of Chest Physicians. Thromboprophylaxis practice patterns in two Western Australian teaching hospitals. *Haematologica* 2004;89:586-593.

5. Amin A, Stemkowski S, Lin J, Yang G. Thromboprophylaxis rates in US medical centers: success or failure? *J Thromb Haemost* 2007;5:1610-1616.

6. Tapson VF, Decousus H, Pini M, et al; IMPROVE Investigators. Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. *Chest* 2007;132:936-945.

7. Cohen AT, Agnelli G, Anderson FA, et al; VTE Impact Assessment Group in Europe (VITAE). Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost* 2007;98:756-764.

8. Clagett GP, Anderson FA Jr, Levine MN, Salzman EW, Wheeler HB. Prevention of venous thromboembolism. *Chest* 1992;102(suppl):391S-407S.

9. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(suppl):338S-400S.

10. Lindblad B, Sternby NH, Bergqvist D. Incidence of venous thromboembolism verified by necropsy over 30 years. *BMJ* 1991;302:709-711.

11. Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? *J R Soc Med* 1989;82:203-205.

12. Alikhan R, Peters F, Wilmott R, Cohen AT. Fatal pulmonary embolism in hospitalised patients: a necropsy review. *J Clin Pathol* 2004;57:1254-1257.

13. Farfan M, Bautista M, Bonilla G, et al. Worldwide adherence to ACCP guidelines for thromboprophylaxis after major orthopedic surgery: A systematic review of the literature and meta-analysis. *Thromb Res* 2016;141:163-170.

14. White RH. The epidemiology of venous thromboembolism. *Circulation* 2003;107(suppl 1):I4-I8.

15. Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematologica* 2007;92:199-205.

16. Scottish Intercollegiate Guidelines Network (SIGN). *Prevention and management of venous thromboembolism. SIGN publication no. 122*. Edinburgh: SIGN; 2010.

17. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003;107(suppl 1):I9-I16.

18. Dorfman M, Chan SB, Maslowski C. Hospital-acquired venous thromboembolism and prophylaxis in an integrated hospital delivery system. *J Clin Pharm Ther* 2006;31:455-459.

19. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). *Chest* 2008;133:381S-453S.

20. Wilson D, Cooke EA, McNally MA, et al. Changes in coagulability as measured by thrombelastography following surgery for proximal femoral fracture. *Injury* 2001;32:765-770.

21. Wilson D, Cooke EA, McNally MA, et al. Altered venous function and deep venous thrombosis following proximal femoral fracture. *Injury* 2002;33:33-39.

22. White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med* 1998;158:1525-1531.

23. Planes A, Vochelle N, Darmon JY, et al. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. *Lancet* 1996;348:224-228.

24. Roger VL, Go AS, Lloyd-Jones DM, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation* 2012;125(1):e2-e220. Erratum in: *Circulation* 2012;125(22):e1002.

25. Sourmelis SV. *Guidelines for Prevention of Deep Vein Thrombosis in Orthopaedics*. Athens: HAOST; 2009.

26. Leme LE, Sguizzatto GT. Prophylaxis of venous thromboembolism in orthopaedic surgery. *Rev Bras Ortop* 2015;47:685-693.

27. Davis P. Venous thromboembolism prevention--an update. *J Orthop Nurs* 2004;8:50-56.

28. Agu O, Hamilton G, Baker D. Graduated compression stockings in the prevention of venous thromboembolism. *Br J Surg* 1999;86:992-1004.

29. White RH, Gettner S, Newman JM, Trauner KB, Romano PS. Predictors of rehospitalization for symptomatic venous thromboembolism after total hip arthroplasty. *N Engl J Med* 2000;343:1758-1764.

30. Hoenig H, Rubenstein LV, Sloane R, Horner R, Kahn K. What is the role of timing in the surgical and rehabilitative care of community-dwelling older persons with acute hip fracture? *Arch Intern Med* 1997;157:513-520.

31. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141:e278S-e325S.

32. Unit ACPG ed. *AAOS clinical guideline on preventing venous thrombo- embolic disease in patients undergoing elective hip and knee arthroplasty*. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2011.

33. Mont MA, Jacobs JJ. AAOS clinical practice guideline: preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. *J Am Acad Orthop Surg* 2011;19:777-778.

34. American Academy of Orthopaedic Surgeons. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. Evidence-based guidelines and evidence report. http://www.aaos.org/research/guidelines/VTE/VTE_full_guideline.pdf (date last accessed 11 April 2017.

35. An VV, Phan K, Levy YD, Bruce WJ. Aspirin as thromboprophylaxis in hip and knee arthroplasty: a systematic review and meta-analysis. *J Arthroplasty* 2016;31: 2608-2616.

36. Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133:160S-98S.

37. Godbillon J, Richard J, Gerardin A, et al. Pharmacokinetics of the enantiomers of acenocoumarol in man. *Br J Clin Pharmacol* 1981;12:621-629.

38. Hirsh J, Dalen J, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 2001;119(suppl):8S-21S.

39. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141:e152S-e84S.

40. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141:e24S-e43S.

41. Rosenberg R, Bauer K. *The heparin-antithrombin system: a natural anticoagulant mechanism*. 3rd ed. Philadelphia, PA: Lippincott; 1994.

42. Hirsh J, Bauer K, Donati M, Gould M, Samama MM, Weitz JI. Parenteral anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133:141S-59S.

43. Hull RD, Raskob GE, Hirsh J, et al. Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal-vein thrombosis. *N Engl J Med* 1986;315:1109-1114.

44. Pini M, Pattachini C, Quintavalla R, et al. Subcutaneous vs intravenous heparin in the treatment of deep venous thrombosis--a randomized clinical trial. *Thromb Haemost* 1990;64:222-226.

45. Bhandari M, Hirsh J, Weitz JI, et al. The effects of standard and low molecular weight heparin on bone nodule formation in vitro. *Thromb Haemost* 1998;80:413-417.

46. Shaughnessy SG, Young E, Deschamps P, Hirsh J. The effects of low molecular weight and standard heparin on calcium loss from fetal rat calvaria. *Blood* 1995;86:1368-1373.

47. Palmer AJ, Koppenhagen K, Kirchhof B, Weber U, Bergemann R. Efficacy and safety of low molecular weight heparin, unfractionated heparin and warfarin for thrombo-embolism prophylaxis in orthopaedic surgery: a meta-analysis of randomised clinical trials. *Haemostasis* 1997;27:75-84.

48. Howard AW, Aaron SD. Low molecular weight heparin decreases proximal and distal deep venous thrombosis following total knee arthroplasty. A meta-analysis of randomized trials. *Thromb Haemost* 1998;79:902-906.

49. Westrich GH, Haas SB, Mosca P, Peterson M. Meta-analysis of thromboembolic prophylaxis after total knee arthroplasty. *J Bone Joint Surg [Br]* 2000;82-B: 795-800.

50. Brookenthal KR, Freedman KB, Lotke PA, Fitzgerald RH, Lonner JH. A meta-analysis of thromboembolic prophylaxis in total knee arthroplasty. *J Arthroplasty* 2001;16:293-300.

51. Handoll HH, Farrar MJ, McBirnie J, et al. Heparin, low molecular weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures. *Cochrane Database Syst Rev* 2002;(4):CD000305.

52. Mismetti P, Laporte S, Zufferey P, et al. Prevention of venous thromboembolism in orthopedic surgery with vitamin K antagonists: a meta-analysis. *J Thromb Haemost* 2004;2:1058-1070.

53. Levine RL, McCollum D, Hursting MJ. How frequently is venous thromboembolism in heparin-treated patients associated with heparin-induced thrombocytopenia? *Chest* 2006;130:681-687.

54. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995;332:1330-1335.

55. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood* 2005;106:2710-2715.

56. Shorr AF, Kwong LM, Sarnes M, et al. Venous thromboembolism after orthopedic surgery: implications of the choice for prophylaxis. *Thromb Res* 2007;121:17-24.

57. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141:e44S-e88S.

58. Kubitza D, Berkowitz SD, Misselwitz F. Evidence-Based Development and Rationale for Once-Daily Rivaroxaban Dosing Regimens Across Multiple Indications. *Clin Appl Thromb Hemost* 2016;22:412-422.

59. Eriksson BI, Borris LC, Friedman RJ, et al; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008;358:2765-2775.

60. Kakkar AK, Brenner B, Dahl OE, et al; RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008;372:31-39.

61. Lassen MR, Ageno W, Borris LC, et al; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008;358:2776-2786.

62. Turpie AG, Lassen MR, Davidson BL, et al; RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet* 2009;373:1673-1680.

63. Eriksson BI, Dahl OE, Büller HR, et al; BISTRO II Study Group. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. *J Thromb Haemost* 2005;3:103-111.

64. Eriksson BI, Dahl OE, Rosencher N, et al; RE-MODEL Study Group. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007;5:2178-2185.

65. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. *Arch Intern Med* 2012;172:397-402.

66. Madan S, Shah S, Dale P, Partovi S, Parikh SA. Use of novel oral anticoagulant agents in venous thromboembolism. *Cardiovasc Diagn Ther* 2016;6:570-581.

67. Squibb BM. Eliquis (apixaban): US prescribing information. http://packageinserts.bms.com/pi/pi_eliquis.pdf (date last accessed 10 April 2017).

68. Lassen MR, Raskob GE, Gallus A, et al. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med* 2009;361:594-604.

69. Lassen MR, Raskob GE, Gallus A, et al; ADVANCE-2 investigators. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet* 2010;375:807-815.

70. Lassen MR, Gallus A, Raskob GE, et al; ADVANCE-3 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med* 2010;363:2487-2498.

71. National Institute for Health and Clinical Excellence. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. https://www.nice.org.uk/guidance/ng89. Last accessed April 5, 2018

72. Yassa R, Khalfaoui MY, Hujazi I, Sevenoaks H, Dunkow P. Management of anticoagulation in hip fractures: A pragmatic approach. *EFORT Open Rev* 2017;2:394-402.

73. Ktistakis I, Giannoudis V, Giannoudis PV. Anticoagulation therapy and proximal femoral fracture treatment: an update. *EFORT Open Rev* 2017;1:310-315.

74. Scottish Intercollegiate Guidelines Network (SIGN). Management of hip fractures in older people. Edinburgh: SIGN, 2009. http://www.sign.ac.uk/pdf/sign111.pdf Last accessed April 5, 2018.

75. British Orthopaedic Association. The care of patients with fragility fracture. http://www.fractures.com/pdf/BOA-BGS-Blue-Book.pdf. Last accessed April 5, 2018.

76. Ramos J, Perrotta C, Badariotti G, Berenstein G. Interventions for preventing venous thromboembolism in adults undergoing knee arthroscopy. *Cochrane Database Syst Rev* 2008;(4):CD005259.

77. Mauck KF, Froehling DA, Daniels PR, et al. Incidence of venous thromboembolism after elective knee arthroscopic surgery: a historical cohort study. *J Thromb Haemost* 2013;11:1279-1286.

78. Berger RE, Pai M, Rajasekhar A. Thromboprophylaxis after Knee Arthroscopy. *N Engl J Med* 2017;376:580-583.

79. Krych AJ, Sousa PL, Morgan JA, et al. Incidence and risk factor analysis of symptomatic venous thromboembolism after knee arthroscopy. *Arthroscopy* 2015;31:2112-2118.

80. Camporese G, Bernardi E, Prandoni P, et al; KANT (Knee Arthroscopy Nadroparin Thromboprophylaxis) Study Group. Low-molecular-weight heparin versus compression stockings for thromboprophylaxis after knee arthroscopy: a randomized trial. *Ann Intern Med* 2008;149:73-82.

81. van Adrichem RA, Nemeth B, Algra A, et al; POT-KAST and POT-CAST Group. Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting. *N Engl J Med* 2017;376:515-525.

82. Metz R, Verleisdonk EJ, van der Heijden GJ. Insufficient Evidence for Routine Use of Thromboprophylaxis in Ambulatory Patients with an Isolated Lower Leg Injury Requiring Immobilization: results of a Meta-Analysis. *Eur J Trauma Emerg Surg* 2009;35:169-175.

83. Heyes GJ, Tucker A, Michael AL, Wallace RG. The incidence of deep vein thrombosis and pulmonary embolism following cast immobilisation and early functional bracing of Tendo Achilles rupture without thromboprophylaxis. *Eur J Trauma Emerg Surg* 2015;41:273-276.

84. Reilmann H, Weinberg AM, Förster EE, Happe B. [Prevention of thrombosis in ambulatory patients]. *Orthopade* 1993;22:117-120.

85. Kujath P, Spannagel U, Habscheid W. Incidence and prophylaxis of deep venous thrombosis in outpatients with injury of the lower limb. *Haemostasis* 1993;23(suppl 1):20-26.

86. Kock HJ, Schmit-Neuerburg KP, Hanke J, Rudofsky G, Hirche H. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. *Lancet* 1995;346:459-461.

87. Healy B, Beasley R, Weatherall M. Venous thromboembolism following prolonged cast immobilisation for injury to the tendo Achillis. *J Bone Joint Surg [Br]* 2010;92:646-650.

88. Jameson SS, Augustine A, James P, et al. Venous thromboembolic events following foot and ankle surgery in the English National Health Service. *J Bone Joint Surg [Br]* 2011;93:490-497.

89. Guss D, DiGiovanni CW. Venous thromboembolic disease in foot and ankle surgery. *JBJS Rev* 2015;3(12): 01874474-201512000-00004.

90. Testroote M, Stigter WA, Janssen L, Janzing HM. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. *Cochrane Database Syst Rev* 2014;(4):CD006681.

91. Zee AA, van Lieshout K, van der Heide M, Janssen L, Janzing HM. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-limb immobilization. *Cochrane Database Syst Rev* 2017;8:CD006681.

92. Patel A, Ogawa B, Charlton T, Thordarson D. Incidence of deep vein thrombosis and pulmonary embolism after Achilles tendon rupture. *Clin Orthop Relat Res* 2012;470:270-274.

93. Calder JD, Freeman R, Domeij-Arverud E, van Dijk CN, Ackermann PW. Meta-analysis and suggested guidelines for prevention of venous thromboembolism (VTE) in foot and ankle surgery. *Knee Surg Sports Traumatol Arthrosc* 2016;24:1409-1420.

94. Day JS, Ramsey ML, Lau E, Williams GR. Risk of venous thromboembolism after shoulder arthroplasty in the Medicare population. *J Shoulder Elbow Surg* 2015;24:98-105.

95. Ojike NI, Bhadra AK, Giannoudis PV, Roberts CS. Venous thromboembolism in shoulder surgery: a systematic review. *Acta Orthop Belg* 2011;77:281-289.

96. Farfan M, Bautista M, Bonilla G, et al. Worldwide adherence to ACCP guidelines for thromboprophylaxis after major orthopedic surgery: A systematic review of the literature and meta-analysis. *Thromb Res* 2016;141:163-170.

97. Dineen PF, Curtin RJ, Harty JA. A review of the use of common antiplatelet agents in orthopaedic practice. *J Bone Joint Surg [Br]* 2010;92:1186-1191.

98. Steinhubl SR, Berger PB, Mann JT III, et al; CREDO investigators. Clopidogrel for the reduction of events during observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomised controlled trial. *JAMA* 2002;288:2411-2420.

99. Vicenzi MN, Meislitzer T, Heitzinger B, et al. Coronary artery stenting and non-cardiac surgery--a prospective outcome study. *Br J Anaesth* 2006;96:686-693.

100. Soo CG, Della Torre PK, Yolland TJ, Shatwell MA. Clopidogrel and hip fractures, is it safe? A systematic review and meta-analysis. *BMC Musculoskelet Disord* 2016;17:136.