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Prevention of thromboembolism after a fracture: is aspirin enough?

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Venous thromboembolism (VTE) is a serious complication that can arise during and after hospitalization, particularly following surgery under general anaesthesia. Particularly at risk are major orthopaedic surgical procedures such as elective knee or hip replacement and the treatment of hip fractures. In these patients, current guidelines recommend (low or low-moderate level of evidence) aspirin as a possible alternative to anticoagulant therapy for the prophylaxis of long-term venous thromboembolism after an initial period with anticoagulant drugs. Several randomized trials and meta-analyses demonstrate no significant differences in the risk of VTE when comparing aspirin with anticoagulants. However, it must be considered that most recommendations are based on elective orthopaedic surgery and that trials after fractures have excluded patients at high thrombotic risk. Consequently, the overall incidence of major clinical events (death and pulmonary embolism) was ~1% with wide confidence margins in even large non-inferiority studies. The incidence of asymptomatic VTE, especially distal, appears to be higher with aspirin. Patient preference and lower costs could play an important role in the choice in favour of aspirin.

Introduction

Venous thromboembolism (VTE), including deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a serious complication that can arise during and after hospital admission, particularly in patients undergoing surgery under general anaesthesia. It is estimated that more than 50% of hospitalized patients are at risk of VTE that is particularly high up to 2 months after general surgery performed for non-neoplastic causes. Major orthopaedic surgery is particularly high-risk, including knee or hip replacements, open reduction and internal fixation surgery for hip fractures, with an incidence of DVT between 10% and 40% in hospitalized patients and up to 40–60% for patients undergoing major orthopaedic surgery.

In the absence of pharmacological prophylaxis, the incidence of DVT detected by venography is ~54% after total hip replacement operations, of which 27% is represented by proximal DVT,[1] while symptomatic VTE is found in ~2–3% of cases. Again without prophylaxis, PE is responsible for ~5–10% of deaths in hospitalized patients. Estimates suggest the occurrence of fatal PE in hospitalized patients between 0.1% and 0.8% after elective general surgery, up to 3% after elective hip replacement, and 7% after hip fracture surgery.[1] With prophylaxis, overall VTE incidence is reduced to ~1–1.2%, with PE at 0.3% and DVT at 0.7%.[2] Major orthopaedic surgery of the distal extremities also carries a greater risk of VTE when compared to other surgical procedures, with an estimated incidence of ~4%, especially in the first 7–14 days after surgery. In terms of absolute incidence, the current contribution of post-traumatic DVT to the incidence of PE appears to be relatively modest: among the 5213 patients with PE enrolled in the Italian Contemporary management of Pulmonary Embolism (COPE) registry in 182 centres between 2018 and in 2021, only 7.3% had had a trauma and 1.8% a major trauma in the previous 4 weeks.[3] The very low incidence of these

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clinical events, especially fatal ones, leads to wide margins of confidence in comparing the effectiveness of prevention strategies, especially in non-inferiority studies.

Orthopaedic patients are particularly vulnerable due to the presence of all the pathophysiological processes of Virchow's triad: (1) use of the tourniquet and bed rest that lead to venous stasis; (2) trauma that causes activation of the coagulation cascade; (3) surgical manipulation of the limb causing endothelial damage; and (4) use of bone cement with consequent increase in coagulability. Major orthopaedic surgery also carries a significant risk of bleeding complications, with an estimated incidence of ~2–4%. Finally, individual risk factors, such as history of previous VTE or conditions such as thrombocytopaenia, can further amplify both the risks of VTE and bleeding. The exclusion of patients with these well-known high-risk characteristics from studies comparing preventive strategies requires further caution in evaluating the results.

Guideline recommendations

Antiplatelet and anticoagulant drugs can be used for the prevention and treatment of VTE in orthopaedic patients. Scientific societies have produced recommendations that are as evidence-based as possible.[4-6]

- In 2012, the American College of Chest Physicians (ACCP) Guidelines[4] recommended aspirin for the prophylaxis of VTE after total hip or knee replacement, with a level of evidence (LoE) 1B (moderate), compared to no prophylaxis. The same LoE was assigned to injectable anticoagulants and direct oral anticoagulants (DOACs). For fractures of the distal ends of the lower limbs requiring limb immobilization, no prophylaxis was recommended (2B); same indication for patients without history of VTE undergoing knee arthroscopy.
- In 2018, the National Institute for Health and Care Excellence (NICE) Guidelines[5] recommend low-molecular-weight heparin (LMWH) for 10 days, followed by aspirin (75–150 mg) for a further 28 days, after hip replacement. Alternatively, for this type of intervention, LMWH or DOAC for 28 days is recommended. After knee replacement, a 14-day prophylaxis with aspirin or LMWH or DOAC is recommended. For fractures of the pelvis, hip and proximal end of the femur, or of the distal ends of the lower limbs, prophylaxis with LMWH (or fondaparinux) for 1 month is recommended. No prophylaxis is generally recommended for arthroscopic knee surgery.
- The 2019 American Society of Hematology (ASH) Guidelines[6] recommend, in patients undergoing total hip and knee replacement, mechanical or pharmacological antithrombotic prophylaxis with aspirin or oral anticoagulant (low LoE): in this case, the use of DOACs is suggested compared to LMWH (moderate LoE). Any DOAC can be used (low LoE). If a DOAC is not used, the second choice is LMWH. For hip fracture operations, prophylaxis is still recommended, favouring LMWH or unfractionated heparin (UFH) (low LoE).

Prevention with aspirin: what evidence?

Aspirin, by inhibiting cyclooxygenase enzymes (COX-1 and COX-2), effectively reduces platelet aggregation and activation already at doses of 50–100 mg. This mechanism of action has proved effective in managing thrombotic risk, for which aspirin is widely used as a first-line drug for thromboprophylaxis at the arterial side of the circulation.

In patients undergoing major orthopaedic surgery, particularly hip fractures, aspirin has been shown to reduce the incidence of symptomatic VTE by 30% compared to placebo in the Pulmonary Embolism Prevention (PEP) trial[7] and more recently, in the Prevention of Clot in Orthopedic Trauma (PREVENT CLOT) trial,[8] to be non-inferior (at a dose of 81 mg b.i.d.) compared to enoxaparin in terms of mortality and risk of PE (*Table 1* and *Figure 1*). It should be considered that the combined absolute incidence of death in the PREVENT CLOT trial was 0.75%, and that of death related or possibly related to PE was 0.34%, while that of clinically relevant PE was ~1%, with no differences between treatments. The incidence of distal, but not overall, DVT was lower with LMWH [0.86% vs. 1.45%, absolute difference 0.58 (0.20–0.96)].

The Extended Venous Thromboembolism Prophylaxis Comparing Rivaroxaban to Aspirin Following Total Hip and Knee Arthroplasty II (EPCAT II) trial was the largest study in long-term prophylaxis after non-traumatic, elective, unilateral major orthopaedic surgery, enrolling 3424 patients undergoing total hip or knee arthroplasty treated with rivaroxaban for 5 days (14 days for knee replacement and 35 days for hip replacement). Subsequently, patients were randomized to treatment with aspirin (81 mg o.d.) or to continue with rivaroxaban.[9] All enrolled patients were at low risk for VTE (beyond orthopaedic surgery) and could ambulate within 24 h after surgery. In this population, the overall incidence of symptomatic VTE (primary endpoint) was 0.67% with no difference between aspirin and rivaroxaban.

A large meta-analysis of 13 trials on 6060 patients compared the use of aspirin vs. different anticoagulants (LMWH, rivaroxaban and warfarin) after knee or hip replacement. The analysis found no significant differences in the rate of VTE [relative risk (RR) 1.12; 95% confidence interval (CI) 0.78–1.62] or major bleeding (RR 1.11; 95% CI 0.47–2.59).[11]

The Cluster-Randomised, crossover, non-Inferiority trial of aSpirin compared to low molecular weight heparin for venous Thromboembolism prophylaxis in hip or knee ArthropLasty, a registry-nested study (CRISTAL), published after the aforementioned meta-analysis, compared aspirin in 9711 patients (100 mg o.d.) and enoxaparin (40 mg o.d.) for 35 days after hip replacement and 14 days after knee replacement[10] with the primary endpoint being symptomatic VTE at 90 days. Enoxaparin was superior to aspirin [1.82% vs. 3.45% ($P = 0.007$)], a difference attributable to a lower rate of distal DVT (1.2% vs. 2.4%) similar to what was observed in the PREVENT CLOT trial (8) (*Figure 1*). There were no significant differences in terms of major bleeding (<0.5%) and mortality.

Ultimately, considering the low incidence of major events in randomized trials that excluded patients at greater thromboembolic risk, the non-inferiority of low-dose aspirin compared to anticoagulants must for now be limited to patients at low risk, without previous thromboembolic events. Aspirin is recommended in the presence of low thrombotic risk and is typically used in long-term prophylaxis after a period of 5–10 days with anticoagulants.

Table 1 Main studies on aspirin vs. anticoagulant therapy in the prevention of venous thromboembolism after orthopaedic surgery

Study	Comparison	*n*	Mean age	Exclusion criteria	Follow-up duration	Events (DVT, mortality)	Haemorrhagic events
PEP trial[7]	Aspirin (160 mg) vs. placebo	13 356	79	• Other absolute clinical indication for aspirin (e.g. AMI) • Contraindication to aspirin (e.g. active peptic ulcer)	35 days	HR (95% CI) • DVT 0.71 (0.52-0.97) • PE 0.74 (0.45-1.21) • VTE 0.71 (0.54-0.94) • Vascular death 0.93 (0.78-1.11) • Non-vascular death 1.01 (0.84-1.10)	Excess of 6 post-operative bleeding (with transfusion) per 1000 patients in the aspirin group ($P = 0.04$)
EPCAT II trial[9]	Aspirin (81 mg) vs. rivaroxaban (10 mg o.d.)	3424	63	• Fracture of the hip or distal extremities of the lower limbs in the previous 3 months • Metastatic cancer	90 days	Difference in percentage points (95% CI) • VTE 0.06 (−0.55-0.66) $P < 0.001$ (non-inferiority)	Major bleeding 0.18 (−0.65-0.29) $P =$ ns Clinically relevant bleeding 0.30 (−1.07-0.47) $P =$ ns
CRISTAL trial[10]	Aspirin (100 mg) vs. enoxaparin (40 mg o.d.)	9711	67	• Patients already on oral anticoagulant treatment before surgery • Hip and/or knee prosthetic surgery not secondary to osteoarthritis	90 days	Difference in percentage points (95% CI) • VTE 1.97 (0.54-3.41) $P = 0.007$ (superiority for enoxaparin) • Mortality 0.05 (0.05-0.15) $P =$ ns	Major Bleeding 0.05 (−0.35-0.25) $P =$ ns
METRC trial[8]	Aspirin (81 mg b.i.d.) vs. enoxaparin (30 mg b.i.d.)	12 211	45	• Hospitalization > 48 h after the trauma • >3 doses of thromboprophylaxis before enrolment • Fractures of the hand and distal ends of the foot • History of VTE • Other indication to anticoagulant or aspirin	90 days	Difference % (95% CI) • Mortality 0.05 (−0.27-0.38) non-inferiority $P < 0.001$ • PE 0 (−0.43-0.43) • DVT 0.80 (0.28-1.31)	Bleeding −0.54 (−1.78-0.69) $P =$ ns

AMI, acute myocardial infarction; DVT, deep-vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; HR, hazard ratio; RR, relative risk.

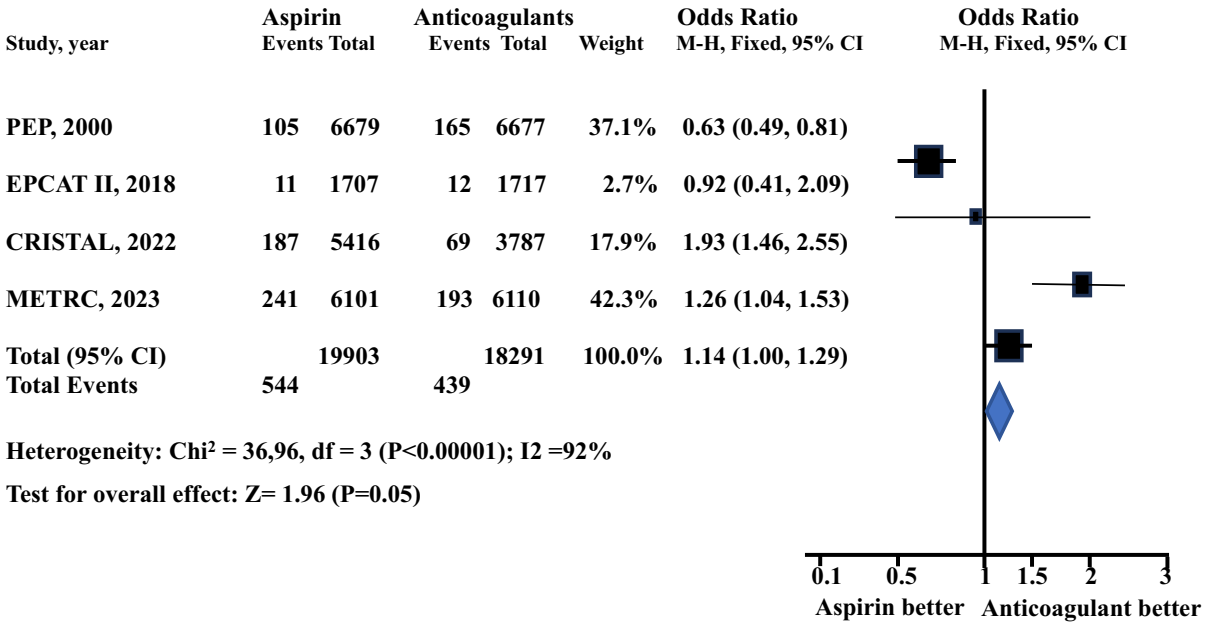

Figure 1 Effectiveness of aspirin vs. anticoagulant therapy in the prevention of venous thromboembolism after orthopaedic surgery (results of the four main randomized studies). Endpoint: venous thromboembolic events (pulmonary embolism + deep-vein thrombosis). In the PEP study, the comparator was placebo; however, 18% of patients were on unfractionated heparin, and 25% of patients were on low-molecular-weight heparin.

Aspirin is not recommended as a single drug in the immediate post-operative period, except in selected low-risk cases operated on for lower limb problems, as an alternative to LMWH. As an extension prophylactic treatment, after a period of anticoagulation, the recommended dose of aspirin is 81 mg/day, whereas when used as a single prophylaxis, the dose can be 81 or 160 mg/day.[12]

Anticoagulant therapies: what evidence?

Low-molecular-weight heparin

Several randomized trials have established the effectiveness of LMWH as a first-line prophylaxis of VTE after major orthopaedic surgery of the lower extremities. Low-molecular-weight heparin has a high capacity to specifically inactivate the coagulation cascade by inhibiting factor Xa and thrombin. Furthermore, these agents have a half-life of ~4 h, as compared to only about 1 h for UFH. Similarly to UFH, LMWH can be antagonized, albeit partially, by protamine sulfate. Finally, it must be remembered that LMWH should be avoided in patients with severe renal insufficiency and requires dose adjustment in obese patients. Numerous trials have compared LMWH with placebo, DOACs, UFH, and warfarin. In controlled trials conducted between the 1980s and 1990s, LMWH consistently demonstrated to reduce the risk of symptomatic VTE of ~50% compared to placebo in patients undergoing prosthesis and/or reduction in hip fractures or knee replacement.[13-15] Furthermore, most trials have demonstrated the ability of LMWH to reduce the risk of VTE by ~33% compared to warfarin.[16] Finally, in patients undergoing major orthopaedic surgery, several randomized studies and meta-analyses have demonstrated greater efficacy of LMWH compared to UFH (5000 U b.i.d.) with similar risk of bleeding, and similar efficacy to high-dose UFH (7500 U b.i.d.), with lower risk of bleeding.

Fondaparinux

Fondaparinux is a synthetic sulfated pentasaccharide acting as an indirect inhibitor of factor Xa, and is considered a second-line drug in VTE prophylaxis in major orthopaedic surgery of the lower limbs. It is definitely an option for patients with heparin-induced thrombocytopaenia. The drug is administered at a dose of 2.5 mg subcutaneously once a day. It is contraindicated in patients weighing <50 kg or with renal insufficiency. In a 2016 meta-analysis, 25 studies were considered for a total of 21 000 patients: the drug demonstrated a significant reduction in symptomatic VTE compared to placebo (0.2% vs. 1.2%; RR 0.15; 95% CI 0.06–0.36), however with a higher risk of major bleeding (1.2% vs. 0.5%; RR 2.56; 95% CI 1.48–4.44).[17] Compared to LMWH, the rate of symptomatic VTE is comparable (0.6% in both; RR 1.03; 95% CI 0.65–1.63), with a higher of major bleeding with fondaparinux (2.5% vs. 1.8%; RR 1.38; 95% CI 1.09–1.75).

Direct oral anticoagulants

Several DOACs, such as dabigatran (thrombin inhibitor), rivaroxaban, apixaban, and edoxaban (factor Xa inhibitors), have been approved as an alternative to LMWH in the prophylaxis of VTE after major orthopaedic surgery. Direct oral anticoagulants are recognized as a first-line option for VTE prophylaxis after hip or knee replacement. However, data in the literature are scarce for hip fracture surgeries. In terms of bleeding risk, the data are conflicting. A meta-analysis of 22 randomized trials ($n = 32\,159$) compared oral factor Xa inhibitors (rivaroxaban, apixaban, or edoxaban) with LMWH in preventing VTE after hip or knee replacement. The analysis showed a lower incidence of symptomatic DVT with oral anticoagulant (4 fewer events/1000), however at the expense of a greater risk of bleeding (2 more events/1000).[18] A subsequent meta-analysis instead

highlighted a lower incidence of DVT with oral factor Xa inhibitors. In the absence of direct comparisons between DOACs, a network meta-analysis of six randomized studies on rivaroxaban (two studies; $n = 8255$), apixaban (one study; $n = 5395$), dabigatran (two studies; $n = 7400$), and edoxaban (one study; $n = 8240$) indirectly compared these drugs with each other without showing significant differences between DOACs in the prevention of VTE.[19] The bleeding risk was lower with apixaban than with rivaroxaban (RR 0.47; 95% CI 0.36–0.61), dabigatran (RR 0.69; 95% CI 0.51–0.94), and edoxaban (RR 0.54; 95% CI 0.41–0.69). A lower risk of bleeding was also observed with dabigatran compared to rivaroxaban (RR 0.68; 95% CI 0.53–0.87) and edoxaban (RR 0.77; 95% CI 0.60–0.99).

Emerging drugs: inhibitors of factor XIa

All currently available antithrombotic therapies carry an inherent risk of bleeding. Inhibitors of factor XIa, a component of the intrinsic pathway of the coagulation cascade that plays an amplifying role in the pathway leading to the formation of thrombin, may represent a step forward in further reducing the risk of bleeding.[20]

Individuals with an inherited factor XI defect (haemophilia C) typically demonstrate a lower risk of VTE or ischaemic stroke than the general population. On the contrary, thrombotic events are significantly greater in those with higher levels of factor XI. Finally, in factor XI deficiency, haemorrhagic events are also reduced. Selective blockade of factor XIa could therefore reduce the risk of thrombosis while maintaining adequate haemostasis. Numerous factor XIa inhibitors are being studied for VTE prophylaxis in major orthopaedic surgery, as well as for other clinical indications. A recent meta-analysis of randomized clinical trials compared factor XIa inhibitors with LMWH after major orthopaedic surgery demonstrating ~50% reduction in the incidence of VTE (symptomatic or asymptomatic) and a significant reduction in clinically relevant major or non-major bleeding.[21] This result is particularly significant if we consider that in phase II studies (dose–response), the effectiveness of even sub-therapeutic doses of the drug under study is evaluated. In the sensitivity analysis considering full doses of these drugs, the relative reduction in the risk of VTE rose to 75%. The relative reduction in bleeding risk was also 55%, mainly determined by the reduction of clinically relevant non-major bleeding. This observation will need to be confirmed in larger phase III studies.

Conclusions

Randomized trials and meta-analyses have shown that there is no significant difference in the risk of clinically relevant or fatal VTE comparing aspirin and anticoagulant therapies after post-traumatic or elective major orthopaedic surgery, particularly in patients at low thrombotic risk. Significant differences in favour of anticoagulant therapy consist only in the incidence of distal DVT. Some guidelines indicate the use of aspirin as a possible alternative to oral anticoagulant therapy and LMWH considered as first-line drugs. In clinical practice, aspirin is not used as a first-line drug in the immediate post-operative period, but generally remains reserved for long-term prophylaxis after at least a more or less prolonged period of anticoagulant therapy.

The studies that have compared aspirin and anticoagulant therapies are very heterogeneous, both in terms of the populations studied and the types and dosages of anticoagulants. Economic considerations and patient preference will play a decisive role, especially in some socio-economic contexts.

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