Aspirin and venous thromboembolism prophylaxis

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Abstract

There is a good rationale for the use of Aspirin in venous thromboembolism prophylaxis in some orthopaedic procedures, as already proposed by the 9th ACCP guidelines (Grade 1C). We recommend using aspirin, considering that it may be less effective than or as effective as LMWH for prevention of DVT and PE after THA, TKA and HFS (Grade 1C). Aspirin may be less effective than or as effective as LMWH for prevention of DVT and PE after other orthopaedic procedures (2C). Aspirin may be associated with a low rate of bleeding after THA, TKA and HFS (Grade 1B). Aspirin may be associated with less bleeding after THA, TKA and HFS than other pharmacologic agents (Grade 1B). No data are available for other orthopaedic procedures. We do not recommend Aspirin as thromboprophylaxis in general surgery (grade 1C). However, this type of prophylaxis could be interesting especially in low income countries (Grade 2C) and adequate large scale trials with proper study designs should be carried out (Grade 1C).

Key words
Aspirin – Venous thromboembolism – Orthopaedic surgery – Non-orthopaedic surgery
Bleeding
1 - Which rationale for the efficacy of aspirin in venous thromboembolism (VTE) prophylaxis?

Aspirin (acetylsalicylic acid) has been synthesized for the first time in 1897 by Hoffman. Then it took more than 50 years to evidence its potent antithrombotic properties. Nowadays, aspirin is widely used to prevent arterial thrombotic events, mainly stroke or myocardial infarction[1]. It stands as one of the pillars of the preventive treatment in vascular patients. Aspirin is inexpensive, does not require monitoring, and does not accumulate in patients with renal insufficiency[2]. Up to the publication of the 9th ACCP Guidelines (2012)[3], most international guidelines recommended against its use in VTE prophylaxis[4, 5]. However several mechanisms of action may account for a role on the venous segment[6]. Amazingly, this idea is not new, as Sevitt in a famous article published in 1970 already stated that « the release of substances from platelets can set in motion the coagulation process » already suggesting the role of platelets in venous thromboembolism, and as a result the potential preventive role of aspirin[7]. Since, many hypotheses have been developed, especially in two recent comprehensive reviews: Beccatini and Agnelli [8], and Undas et al[9], have recently reviewed extensively the different mechanisms of action of aspirin in order to try to explain why this old agent may be useful for venous thromboembolism prophylaxis. Their arguments are summarized below.

The classic principal activity of aspirin is represented by the permanent inactivation of the cyclooxygenase activity of prostaglandin H synthase 1 (COX-1) resulting in the inhibition the TXA2-dependent amplification of the platelet response to diverse agonists and to a resulting inhibition of platelet aggregation with impaired dense granule secretion. Higher doses of aspirin inactivate the cyclooxygenase activity of prostaglandin H synthase 2 (COX-2) leading to a decrease in prostacyclin and a potential prothrombotic effect.
Other important mechanisms of action have been suggested:

Aspirin may interfere with thrombin formation. It may act on the expression of tissue factor on monocytes/macrophages, leading to an impaired prothrombinase formation on platelets involving a reduced activation of factor V and an attenuation of thrombin generation. Aspirin may also reduce thrombin generation by acetylating prothrombin and/or platelet membrane components.

Chromatin (mainly DNA) structures named Neutrophil Extracellular Traps (NETs) are released from neutrophils[10-12]. They are supposed to increase the bacteria-killing activity and the inflammatory response of neutrophils. In addition to many other properties, NETs may act as a scaffold for thrombus formation, evidencing the link with venous thromboembolism. Activated platelets induce neutrophils to release their nuclear material in forms of NETs. Lapponi MJ et al. have nicely shown recently that aspirin treatment prevented NETs formation[11]. Therefore, indirectly, aspirin could prevent the NETs related thrombus part.

Bulut D et al. have shown that aspirin reduces endothelial and platelet-derived patients with coronary artery disease after 8 weeks of 100mg aspirin daily treatment[13].

Wang L et al. have studied the contributions of the extracellular signal-regulated protein in a rat model of pulmonary embolism[14]. They have been able to show that aspirin reduced lung damage, while attenuating inflammation and congestion, and improved the prognosis.

Low dose aspirin may also modify the size of fibrin fibres while leading to the formation of thicker fibres and larger network pores, increasing clot permeability[15], as also observed with direct oral anticoagulants (DOACs) [16]. Aspirin could impair the acetylation of fibrinogen and induce an enhanced clot lysis. However, this hasn’t been confirmed in several
Aspirin also inhibits factor XIII activation, which may lead to a decrease in the stability of the fibrin clot.

As a result, all these theoretical knowledge and experimental data help to better understand the potential role of aspirin in preventing venous thromboembolism.

2 - Which data on the efficacy/safety ratio of aspirin in orthopaedic surgery

A - Is aspirin effective for prevention of DVT and PE in orthopaedic surgery?

The 9th ACCP guidelines (2012) recommend the use of aspirin in patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA) for a minimum of 10 to 14 days (Grade 1B)[3]. Aspirin is also recommended in patients undergoing hip fracture surgery (HFS) for a minimum of 10 to 14 days (Grade 1B). These recommendations are mainly based on the PEP trial, comparing 160 mg of aspirin daily for 35 days against placebo[17]. This trial included 17,444 patients after hip fracture surgery and hip arthroplasty. There was a 28% relative risk decrease in symptomatic DVT. There was no decrease in fatal PE. There was no difference in bleeding.

Since 2012, one systematic review has been published in 2015, including 3 meta-analyses and 3 prospective RCT with 46,254 patients operated on mainly for THA, TKA and HFS[18]. All studies included have been published prior to 2012, and the PEP trial was also included. Although some results were conflicting, aspirin was considered more effective than placebo in primary VTE prevention. No recent data is available for THA, TKA and HFS.

No data about aspirin effectiveness is available for orthopaedic procedures other than THA, TKA or HFS. As the risk for DVT and PE after other orthopaedic procedures may be considered as lower for many procedures than after THA, TKA and HFS, aspirin might be
considered as effective in these cases. Procedures in cancer patients (femur, pelvis, spine surgery) have still to be considered with a high thrombotic risk.

Very recently, Wilson et al. performed another systematic review of 13 studies, some of them having been published from 2012 to 2015[19]. They reported that there was insufficient evidence from trials with moderate to severe risk of bias being present to suggest aspirin was more or less effective than LMWH, warfarin or dabigatran for the prevention of VTE in TKA or THA. Compared with aspirin, rates of asymptomatic deep vein thrombosis (DVT) in TKA may be reduced with rivaroxaban but insufficient evidence existed to demonstrate an effect on incidence of symptomatic DVT. Compared with aspirin there was evidence of more wound complications following THA and TKA with dabigatran and in TKA with rivaroxaban. Some studies highlighted concerns over bleeding complications and efficacy of aspirin. As a conclusion, they suggested suggest that aspirin may be considered a suitable alternative to other thromboprophylactic agents following THA and TKA.

One study randomized 170 knee arthroscopy patients into two groups: aspirin or placebo[20]. No case of VTE was identified in the whole population. The use of aspirin in this low-risk population undergoing arthroscopic knee surgery was not recommended.

**B - Is aspirin as effective as other pharmacologic/non pharmacologic agents for prevention of DVT and PE in orthopaedic surgery?**

In the ACCP 2012 guidelines, LMWH is recommended over aspirin in patients undergoing total hip arthroplasty or total knee arthroplasty (Grade 2C)[3]. LMWH is recommended over aspirin in patients undergoing hip fracture surgery (Grade 2C). These recommendations are based on two trials of low quality including 469 patients[18, 21]. The pooled results showed
an increased risk of symptomatic DVT (RR 1.87) in the aspirin group. PE could not be evaluated. There was no reported death or major bleeding.

Since 2012, two systematic reviews have been published. Drescher et al included 8 prospective RCT and 1,408 patients[21]. All studies included have been published prior to 2012. There was no difference in the occurrence of DVT between aspirin and anticoagulants. There was a non-significant trend favouring anticoagulation following hip fracture repair. The risk of bleeding was lower with aspirin than anticoagulants following hip fracture repair, with a non-significant trend favouring aspirin after arthroplasty. Rates of pulmonary embolism were too low to provide reliable estimates. Compared with anticoagulation, aspirin may be associated with higher risk of DVT following hip fracture repair, although bleeding rates were substantially lower. Aspirin was similarly effective after lower extremity arthroplasty and may be associated with lower bleeding risk.

Sahebally et al included 1 meta-analysis, 5 prospective RCT and 1 prospective study with 9,599 patients (2 recent studies)[18]. Although results were conflicting, aspirin was considered as effective as LMWH in primary VTE prevention and may reduce bleeding.

Recent studies

Woller et al included 696 cases of elective THA or TKA and compared aspirin to warfarin or LMWH[22]. Diagnosis of DVT was suspected by a questionnaire and confirmed by imaging if necessary. There was an increased rate of DVT in the aspirin group (8% vs 1%, P=0.001). There was no difference in major or minor bleeding and deaths.

Anderson et al included 778 cases of elective THA and compared aspirin to LMWH[23]. Diagnosis of DVT was not clearly described. Aspirin was neither inferior nor superior. There were less clinically relevant bleeding events in the aspirin group.
No data about comparative aspirin effectiveness is available for other orthopaedic procedures than THA, TKA or HFS. As the risk for DVT and PE after other orthopaedic procedures is considered as lower than after THA, TKA and HFS, comparative aspirin might be considered similar.

No data about comparative effectiveness of aspirin and direct anticoagulant agents is available yet.

C - Is aspirin safe for prevention of DVT and PE in orthopaedic surgery? Is aspirin as safe as other pharmacologic/non pharmacologic agents for prevention of DVT and PE in orthopaedic surgery?

The PEP trial showed no difference in bleeding between aspirin and placebo[17]. Since 2012, two systematic studies have been published.

Drescher et al included 8 prospective RCT and 1,408 patients[21]. All studies included have been published prior to 2012. The risk of bleeding was lower with aspirin than anticoagulants following hip fracture repair, with a nonsignificant trend favouring aspirin after arthroplasty. Compared with anticoagulation, aspirin may be associated with substantially lower bleeding risk following hip fracture repair. Similarly, aspirin may be associated with lower bleeding risk after lower extremity arthroplasty.

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No data about complication risk of aspirin prophylaxis is available for other orthopaedic procedures than THA, TKA or HFS.

No data about comparative effectiveness of aspirin and direct anticoagulant agents is available.

D - What may be the indication for aspirin in prevention of DVT and PE in orthopaedic surgery?

Since 2012 and the ACCP guidelines, aspirin is recommended for prevention of DVT and PE after THA, TKA and HFS without patient selection (Grade 1B). However, there may be a concern about an increased risk of DVT by unselected patients reported in some studies. Although there are no data currently available about this point, it may be advantageous to exclude patients with elevated risk of DVT from aspirin prophylaxis.

In patients with increased risk of bleeding, no prophylaxis or the use of intermittent pneumatic compression device (IPCD) is recommended by ACCP rather than pharmacologic prophylaxis (Grade 2C). No more recent data is currently available.

Although no prospective comparative randomized study is currently available, prospective cohort studies suggest that the use of a rapid recovery program after THA and TKA may associated with a low risk of DVT, irrespective of the type of DVT prophylaxis used.
Husted et al analysed 1,977 consecutive, unselected patients were operated with primary THA, TKA, or bilateral simultaneous TKA (BSTKA) in a standardized fast-track set-up from 2004–2008[24]. Patients received DVT prophylaxis with low-molecular-weight heparin starting 6–8 h after surgery until discharge. All re-admissions and deaths within 30 and 90 days were analysed using the national health register, concentrating especially on clinical DVT (confirmed by ultrasound and elevated D-dimer), PE, or sudden death. 3 deaths (0.15%) were associated with clotting episodes and overall, 11 clinical DVTs (0.56%) and 6 PEs (0.30%) were found. During the last 2 years (854 patients), when patients were mobilized within 4 h postoperatively and the duration of DVT prophylaxis was shorter (1–4 days), the mortality was 0% (95% CI: 0–0.5), incident cases of DVT in TKA was 0.60% (CI: 0.2–2.2), in THA it was 0.51% (CI: 0.1–1.8), and in BSTKA it was 0% (CI: 0–2.9). Incident cases of PE in TKA was 0.30% (CI: 0.1–1.7), in THA it was 0% (CI: 0–1.0), and in BSTKA it was 0% (CI: 0–2.9). These data suggest that the risk of clinical DVT, and of fatal and non-fatal PE after THA and TKA following a fast-track set-up with early mobilization, short hospitalization, and short duration of DVT prophylaxis is low.

Jørgensen et al followed prospectively 4924 consecutive unselected unilateral primary THA and TKAs[25]. DVT prophylaxis included low-molecular-weight heparin or factor Xa-inhibitors only during hospitalization when length of stay was ≤5 days. Symptomatic thromboembolic events were observed in 0.84% of the cases (95% CI 0.62% to 1.15%) and VTEs were observed in 0.41% (0.26% to 0.64%) during 90-day follow-up: 5 PE (0.11% (0.05% to 0.25%)) and 14 DVT (0.30% (0.18% to 0.50%)). There were 4 (0.09% (0.04% to 0.23%)) surgery-related deaths, of which 1 (0.02% (0.00% to 0.12%)) was due to PE, and 6 (0.13% (0.06% to 0.28%)) deaths of unknown causes after discharge. Data suggest that the incidence of thromboembolic events is low in fast-track THA and TKA patients with LOS of ≤5 days.
It is the opinion of the panel that the low risk of symptomatic DVT after THA and TKA followed by an enhanced recovery program and the lower risk of bleeding might compensate for the possible higher rate of DVT after aspirin prophylaxis than with other pharmacologic agents. The panel suggests that aspirin prophylaxis could be routinely associated with a rapid recovery program after THA and TKA.

Use of IPCD is recommended by ACCP in patients undergoing major orthopaedic surgery in association with an antithrombotic agent (Grade 2C). This recommendation was based on the analysis of 5 trials including more than 2400 patients, which reported a 70% reduction in the DVT rate when IPCD was used.

Westrich et al performed a prospective randomized study about 275 five patients undergoing unilateral TKA under spinal epidural anaesthesia, comparing a IPCD associated with either enoxaparin or aspirin[26]. All patients had an in-hospital ultrasound screening test on postoperative days 3 to 5 and a second follow-up ultrasound 4 to 6 weeks after surgery. The overall deep venous thrombosis rates in groups A and B were 14.1% and 17.8% (P = not significant), respectively. When used in combination with pneumatic compression devices and SEA, enoxaparin was not superior to aspirin in preventing deep venous thrombosis after total knee arthroplasty.

3 - Which data on the efficacy/safety ratio of aspirin in non-orthopaedic surgery

Data on the efficacy and safety of aspirin in non-orthopaedic, non-traumatic surgery date back to the 1980ies. The studies were presented in a meta-analysis by the Antiplatelet Trialists’ Collaboration published in 1994[27]. The investigators used doses mainly between 1000 and 1500 mg/day, partly also in combination with dipyramidole.
Treatment duration was one or two weeks. Diagnosis of deep vein thrombosis was made either by systematic radiolabeled fibrinogen uptake scan or by venography.

In the aspirin group 178/1434 (19.4%) patients and in the control group (open or placebo) 369/1459 (27.1%) developed objectively confirmed deep vein thrombosis, % odds reduction 37% (8% standard deviation). When pulmonary embolism was evaluated in those studies which used systematic screening for DVT, 16/3408 (0.5%) on Aspirin and 58/3419 (1.7) controls developed pulmonary embolism, which means a 71% (with 14% standard deviation) odds reduction, the difference was statistically significant. The Antiplatelet Trialists’ Collaboration group evaluated rate of bleeding together in trials that included general and orthopaedic surgery. There was an increase of transfusions (0.7% in those on antiplatelet therapy and 0.4% in those without, p=0.04) in patients on antiplatelet agents, and also other complications, such as haematoma or wound infections due to haematomas were significantly more frequent in the Aspirin group (7.8% versus 5.6%, p=0.003).

One randomized double blind study comparing aspirin with unfractionated heparin was conducted by Vinazzer et al in patients with elective general surgery[28]. 500mg of aspirin were compared to 5000 IU twice daily of unfractioned heparin, 1210 patients were included into that study. Diagnosis of the primary outcome DVT was based on obligatory Doppler imaging. No statistically significant difference was found in the rates of DVT (3.9 versus 2.4%) or PE (0.3 each) and the risk of bleeding was also similar (0.7% each).

From the available data we conclude that aspirin might decrease the risk of DVT and PE in patients with general surgery, however, total numbers of patients are low (less than 4000 on aspirin in open or placebo controlled trials in total) and the study procedures lack high standard quality of the recent years.
Conclusion - Is there any room for aspirin in VTE prophylaxis (perioperative and intensive care)?

Several authors are still reluctant with the use of aspirin for VTE prophylaxis[29]. Aspirin is indeed less potent than LMWH and the new DOACs, but the induced bleeding risk is also lower. In addition, pending the steadily decreasing VTE risk in surgical patients, the benefit risk ratio and the duration of treatments are changing. More attention has to be given to the bleeding risk[30]. Aspirin may be proposed in moderate risk orthopaedic patients or in highly selected high-risk patients scheduled for a THR or a TKR combined with an enhanced recovery procedure (ERAS), or in hip fracture patients with a high bleeding risk. Intermittent pneumatic compression should always been combined when aspirin is prescribed as the only pharmacological agent. Data are lacking for non-orthopaedic surgery patients and for intensive care patients.
RECOMMENDATIONS

1. Aspirin is effective for prevention of DVT and PE after THA, TKA and HFS (Grade 1B). Aspirin may be effective for prevention of DVT and PE after other orthopaedic procedures (Grade 2C). Aspirin is not recommended for prevention of DVT and PE after knee arthroscopy for low risk patients (Grade 1C).

2. We recommend using aspirin, considering that it may be less effective than or as effective as LMWH for prevention of DVT and PE after THA, TKA and HFS (Grade 1C). Aspirin may be less effective than or as effective as LMWH for prevention of DVT and PE after other orthopaedic procedures (2C).

3. Aspirin is associated with a low rate of bleeding after THA, TKA and HFS (Grade 1B). Aspirin is associated with less bleeding after THA, TKA and HFS than other pharmacologic agents (Grade 1B). No data are available for other orthopaedic procedures.

4. Aspirin may be indicated for prevention of DVT and PE after THA, TKA and HFS for patients without high risk of DVT (2C).

5. Aspirin may be indicated for prevention of DVT and PE after orthopaedic procedures for patients with increased bleeding risk (Grade 2C).

6. Aspirin for prevention of DVT and PE after THA and TKA should be associated with a rapid recovery (fast track) program (2C).

7. Aspirin for prevention of DVT and PE after THA, TKA and HFS should be associated with IPCD device (Grade 1C).

8. We do not recommend Aspirin as thromboprophylaxis in general surgery (grade 1C). However, this type of prophylaxis could be interesting especially in low income countries (Grade 2C) and adequate large scale trials with proper study designs should be carried out (Grade 1C).
References


