

## GUIDELINES

# European guidelines on perioperative venous thromboembolism prophylaxis

## Aspirin

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There is a good rationale for the use of aspirin in venous thromboembolism prophylaxis in some orthopaedic procedures, as already proposed by the 9th American College of Chest Physicians' guidelines (Grade 1C). We recommend using aspirin, considering that it may be less effective than or as effective as low molecular weight heparin for prevention of deep vein thrombosis and pulmonary embolism after total hip arthroplasty, total knee arthroplasty and hip fracture surgery (Grade 1C). Aspirin may be less effective than or as effective as low molecular weight heparins for prevention of deep vein thrombosis and pulmonary embolism after other orthopaedic procedures (Grade 2C). Aspirin may be associated with a low

rate of bleeding after total hip arthroplasty, total knee arthroplasty and hip fracture surgery (Grade 1B). Aspirin may be associated with less bleeding after total hip arthroplasty, total knee arthroplasty and hip fracture surgery than other pharmacological 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).

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A synopsis of all recommendations can be found in the following accompanying article:

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### Introduction

Potent anticoagulants are generally considered as mandatory for venous thromboembolism (VTE) prevention after most surgical procedures. However, iatrogenic complications may occur and overcome the benefit of prevention. Furthermore, the acceleration of postoperative rehabilitation ('fast-track surgery') might decrease the risk of VTE. Some surgeons currently suggest to use aspirin instead of potent anticoagulants for VTE prevention after various surgical procedures, and especially after orthopaedic procedures, mainly hip and knee replacement. The goal of this chapter is to analyse the existing literature about the use of aspirin for the prevention of VTE events and to provide a rationale for its use in clinical practice.

### The efficacy of aspirin in venous thromboembolism prophylaxis

Aspirin was synthesised for the first time in 1897 by Hoffman. Then, it took more than 50 years for its potent

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antithrombotic properties to be recognised. Nowadays, aspirin is widely used to prevent arterial thrombotic events, mainly stroke or myocardial infarction.<sup>1</sup> It stands as one of the pillars of the preventive treatment of VTE in vascular patients. Aspirin is inexpensive, does not require monitoring and does not accumulate in patients with renal insufficiency.<sup>2</sup> Until the publication of the 9th American College of Chest Physicians Guidelines (ACCP 2012),<sup>3</sup> most international guidelines recommended against its use in VTE prophylaxis.<sup>4,5</sup>

However, several mechanisms of action may account for a role on the venous segment.<sup>6</sup> Amazingly, this idea is not new, as Sevittin, in a famous article published in 1970, stated that 'the release of substances from platelets can set in motion the coagulation process', already suggesting the role of platelets in VTE, and as a result the potential preventive role of aspirin.<sup>7</sup> Since then, many hypotheses have been developed, especially in two recent comprehensive reviews. Becattini and Agnelli<sup>8</sup> and Undas *et al.*<sup>9</sup> 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 VTE prophylaxis. Their arguments are summarised below.

The classical principal activity of aspirin is represented by the permanent inactivation of the cyclo-oxygenase activity of prostaglandin H synthase 1 (COX-1) resulting in the inhibition of the thromboxane A2 dependent amplification of the platelet response to diverse agonists and a resulting inhibition of platelet aggregation with impaired dense granule secretion. Higher doses of aspirin inactivate the cyclo-oxygenase 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 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.<sup>10–12</sup> 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, underlining the link with VTE. Activated platelets induce neutrophils to release their nuclear material in the form of NETs. Lapponi *et al.*<sup>11</sup> have shown recently that aspirin treatment prevented NETs formation. Therefore, indirectly, aspirin could prevent NETs-related thrombus. Bulut *et al.*<sup>13</sup> have shown that aspirin reduces endothelial and platelet-derived microparticles in patients with coronary artery disease after 8 weeks of daily treatment with

aspirin 100 mg. Wang *et al.*<sup>14</sup> studied the contributions of extracellular signal regulated protein in a rat model of pulmonary embolism. They showed 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,<sup>15</sup> as also observed with direct oral anticoagulants.<sup>16</sup> Aspirin might impair the acetylation of fibrinogen and induce enhanced clot lysis, although this has not been confirmed in all clinical settings, for example diabetes. Aspirin also inhibits factor XIII activation, which may lead to a decrease in the stability of fibrin clot.

### The efficacy/safety ratio of aspirin in orthopaedic surgery

All relevant articles are summarised in Table 1.

### Is aspirin effective for prevention of deep venous thrombosis and pulmonary embolism in orthopaedic surgery?

The 9th American College of Chest Physicians' (ACCP) guidelines of 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).<sup>3</sup> 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 Pulmonary Embolism Prevention (PEP) trial, comparing 160 mg of aspirin daily for 35 days against placebo.<sup>17</sup> This trial included 17 444 patients after HFS and hip arthroplasty. There was a 28% relative risk decrease in symptomatic DVT. There was no decrease in fatal pulmonary embolism. There was no difference in bleeding.

Since 2012, one systematic review was published in 2015, including three meta-analyses and three prospective randomised controlled trials (RCT) with 46 254 patients operated on mainly for THA, TKA and HFS.<sup>18</sup> All studies included were published prior to 2012, and the PEP trial was also included. Although some results were conflicting, aspirin was considered to be more effective than placebo in primary VTE prevention. No recent data are available for THA, TKA and HFS.

No data about aspirin effectiveness are available for orthopaedic procedures other than THA, TKA or HFS. As the risk for DVT and pulmonary embolism after other orthopaedic procedures may be considered as lower 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 to have a high thrombotic risk.

Very recently, Wilson *et al.*<sup>19</sup> performed another systematic review of 13 studies, some of them having been

**Table 1** Studies relevant to the efficacy/safety ratio of aspirin in orthopaedic surgery

Ref.	Year of publication	Type of study	Number of cases	Orthopaedic procedure	Prophylactic treatment used	Results	Conclusion
Graor et al. <sup>17</sup>	1992	RCT (unpublished)	243	Total hip arthroplasty (THA), total knee arthroplasty (TKA) THA, hip fracture surgery (HFS)	Aspirin vs. low molecular weight heparin (LMWH) Aspirin vs. placebo	Significant increase of VTE with aspirin. Less bleeding with aspirin 28% decrease of relative risk for symptomatic venous thromboembolism (VTE). No difference in bleeding	LMWH more effective than aspirin Aspirin more effective than placebo. Aspirin as safe as placebo
Westrich et al. <sup>22</sup> Intermountain Joint Replacement Center Writing Committee	2006 2012	RCT RCT	275 696	TKA THA, TKA	Aspirin vs. enoxaparin Aspirin vs. warfarin or LMWH	No significant difference in VTE rates Significant increase of VTE rate after aspirin treatment. No difference in bleeding or deaths	Enoxaparin not superior to aspirin Anticoagulants superior to aspirin for VTE prophylaxis
Anderson et al. <sup>24</sup>	2013	RCT	778	THA	Aspirin vs. LMWH	No difference in VTE rates. Less bleeding after aspirin treatment	Aspirin neither superior nor inferior for VTE prophylaxis. Less bleeding with aspirin
Drescher et al. <sup>21</sup>	2014	Systematic review	1408	THA, TKA, HFS	Aspirin vs. anticoagulants	No significant difference in VTE rates, lower bleeding risk with aspirin	Aspirin as effective as anticoagulants with lower bleeding risk
Jiang et al. <sup>27</sup>	2014	RCT	120	TKA	Aspirin vs. LMWH and rivaroxaban	No symptomatic VTE. No death. Less bleeding with aspirin	Aspirin as effective as LMWH and rivaroxaban. Less bleeding with aspirin
Kaye et al. <sup>20</sup>	2015	RCT	170	Knee arthroscopy	Aspirin vs. placebo	No VTE event	Thromboprophylactic treatment not recommended
Sahabally et al. <sup>18</sup>	2015	Systematic review	46 254	THA, TKA, HFS	Aspirin vs. anticoagulants		Aspirin more effective than placebo. Aspirin as effective as LMWH and may reduce bleeding
Lieberman et al. <sup>24</sup>	2016	Systematic review	34 764	THA	Aspirin vs. alternatives	No difference in pulmonary embolism (PE) rates	Prophylactic treatment may be ineffective to prevent PE
Wilson et al. <sup>19</sup>	2016	Systematic review	Various				Aspirin suitable alternative to other thromboprophylactic agents

RCT, randomised controlled trial.

published from 2012 to 2015. They reported that there was insufficient evidence from trials with moderate to severe risk of bias being present to suggest that aspirin was more or less effective than low molecular weight heparin (LMWH), warfarin or dabigatran for the prevention of VTE in TKA or THA. Compared with aspirin, rates of asymptomatic DVT in TKA may be reduced with rivaroxaban, but insufficient evidence existed to demonstrate an effect on the 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.<sup>20</sup> As a conclusion, they suggested that aspirin may be considered a suitable alternative to other thromboprophylactic agents following THA and TKA.

One study randomised 170 knee arthroscopy patients into one of two groups: aspirin or placebo.<sup>21</sup> 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.

### **Is aspirin as effective as other pharmacological/nonpharmacological agents for prevention of deep venous thrombosis and pulmonary embolism in orthopaedic surgery?**

In the ACCP 2012 guidelines, LMWH was recommended over aspirin in patients undergoing THA or TKA (Grade 2C).<sup>3</sup> LMWH is recommended over aspirin in patients undergoing HFS (Grade 2C). These recommendations are based on two trials of low quality (one published article and one abstract only) including 469 patients.<sup>22</sup> The pooled results showed an increased risk of symptomatic DVT (RR 1.87; 95% CI 1.3 to 2.7) in the aspirin group. Pulmonary embolism could not be evaluated. There was no reported death or major bleeding.

Since 2012, three systematic reviews have been published. Drescher *et al.*<sup>23</sup> included eight prospective RCTs and 1408 patients. All studies included were published prior to 2012. There was no difference in the occurrence of DVT between aspirin and anticoagulants. There was a nonsignificant trend favouring anticoagulation following hip fracture repair. The risk of bleeding was lower with aspirin than anticoagulants following hip fracture repair, with a nonsignificant trend favouring aspirin after arthroplasty. Rates of pulmonary embolism were too low to provide reliable estimates. Compared with anticoagulation, aspirin may be associated with a 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 a lower bleeding risk.

Sahebally *et al.*<sup>18</sup> included one meta-analysis, five prospective RCTs and one prospective study with 9599

patients (two recent studies). Although results were conflicting, aspirin was considered to be as effective as LMWH in primary VTE prevention and may reduce bleeding.

Lieberman *et al.*<sup>24</sup> collected 21 studies including 34 764 patients. Prophylactic treatments used were LMWH (13 590 patients), oral factor Xa inhibitors (6609 patients), oral direct thrombin inhibitors (5965 patients), indirect factors Xa/IIa inhibitors (3444 patients), aspirin (2427 patients), warfarin (489 patients), mobile compression device (199 patients) and placebo (2041 patients). Across all included studies, the estimated rate of pulmonary embolism was 0.21%, and was consistent throughout the 17 years spanning these RCTs. The authors suggested that no prophylactic treatment was able to decrease the risk of pulmonary embolism significantly.

### **Recent studies**

The Intermountain Joint Replacement Center Writing Committee<sup>25</sup> included 696 cases of elective THA or TKA and compared aspirin with warfarin or LMWH. DVT was diagnosed 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 were no differences in major or minor bleeding, or deaths.

Anderson *et al.*<sup>26</sup> included 778 cases of elective THA and compared aspirin with LMWH. The method of diagnosis of DVT was not clearly described. Aspirin was neither inferior nor superior. There were less clinically relevant bleeding events in the aspirin group. Jiang *et al.*<sup>27</sup> included 120 cases of elective TKA and compared aspirin combined with mechanical measures postoperatively (60 cases) with LMWH and rivaroxaban sequentially in combination with mechanical measures postoperatively (60 cases). DVT was detected in 10 (17%) and 11 (18%) cases, respectively ( $P=0.500$ ). There were no symptomatic VTEs or deaths during the follow-up period.

No data about comparative aspirin effectiveness are available for orthopaedic procedures other than THA, TKA or HFS. As the risks of DVT and pulmonary embolism after other orthopaedic procedures are considered to be lower than after THA, TKA and HFS, comparative effectiveness of aspirin might be considered similar. No data about comparative effectiveness of aspirin and direct anticoagulant agents are available yet.

### **Is aspirin well tolerated for prevention of deep venous thrombosis and pulmonary embolism in orthopaedic surgery? Is aspirin as well tolerated as other pharmacological/nonpharmacological agents for prevention of deep venous thrombosis and pulmonary embolism in orthopaedic surgery?**

The PEP trial<sup>17</sup> showed no difference in bleeding between aspirin and placebo. Since 2012, two systematic

studies have been published. Drescher *et al.*<sup>23</sup> included eight prospective RCTs and 1408 patients. All studies included were 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 a substantially lower bleeding risk following hip fracture repair. Similarly, aspirin may be associated with a lower bleeding risk after lower extremity arthroplasty. Sahebally *et al.*<sup>18</sup> included one meta-analysis, five prospective RCTs and one prospective study with 9599 patients (two recent studies). Although some results were conflicting, aspirin may reduce bleeding.

### Recent studies

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No data about the complication risk of aspirin prophylaxis are available for orthopaedic procedures other than THA, TKA or HFS. No data about comparative effectiveness of aspirin and direct anticoagulant agents are available.

### What are the indications for aspirin in prevention of deep venous thrombosis and pulmonary embolism in orthopaedic surgery?

Since 2012 and the ACCP guidelines,<sup>3</sup> aspirin is recommended for prevention of DVT and pulmonary embolism after THA, TKA and HFS without patient selection (Grade 1B). However, there may be a concern about an increased risk of DVT reported in some studies. Although there are no data currently available about this point, it may be advantageous to exclude patients with an elevated risk of DVT from aspirin prophylaxis.

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

Although no prospective comparative RCT is currently available, prospective cohort studies suggest that the use of a rapid recovery programme after THA and TKA may

be associated with a low risk of DVT, irrespective of the type of DVT prophylaxis used.

Husted *et al.*<sup>28</sup> analysed 1977 consecutive, unselected patients who were operated on for primary THA, TKA or bilateral simultaneous TKA in a standardised fast-track set-up from 2004 to 2008. Patients received DVT prophylaxis with LMWH starting 6 to 8 h after surgery until discharge. All readmissions 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), pulmonary embolism or sudden death. Three deaths (0.15%) were associated with clotting episodes and, overall, 11 clinical DVTs (0.56%) and six pulmonary embolisms (0.30%) were found. During the final 2 years of the study (854 patients), when patients were mobilised within 4 h postoperatively and the duration of DVT prophylaxis was shorter (1 to 4 days), the mortality was 0% and the incidences of DVT were 0.60% after TKA, 0.51% after THA and 0% after bilateral simultaneous TKA. Pulmonary embolism occurred in 0.30% of patients after TKA, 0% after THA and 0% after bilateral simultaneous TKA. These data suggest that the risks of clinical DVT and of fatal and nonfatal pulmonary embolism after THA and TKA following a fast-track set-up with early mobilisation, short hospitalisation and short duration of DVT prophylaxis are low.

Jørgensen *et al.*<sup>29</sup> followed prospectively 4924 consecutive unselected unilateral primary THAs and TKAs. DVT prophylaxis included LMWH or factor Xa inhibitors only during hospitalisation when length of stay was 5 days or less. Symptomatic thromboembolic events were observed in 0.84% of the patients and VTEs were observed in 0.41% during a 90-day follow-up: five pulmonary embolisms (0.11%) and 14 DVTs (0.30%). There were four (0.09%) surgery-related deaths, of which one (0.02%) was due to pulmonary embolism, and six (0.13%) deaths of unknown cause after discharge. Data suggest that the incidence of thromboembolic events is low in fast-track THA and TKA patients with length of stay 5 days or less.

It is the opinion of the panel that the low risk of symptomatic DVT after THA and TKA followed by an enhanced recovery programme and the lower risk of bleeding might compensate for the possible higher rate of DVT after aspirin prophylaxis than with other pharmacological agents. The panel suggests that aspirin prophylaxis could be routinely associated with a rapid recovery programme after THA and TKA.

Use of IPC devices is recommended by the ACCP<sup>3</sup> in patients undergoing major orthopaedic surgery in association with an antithrombotic agent (Grade 2C). This recommendation was based on the analysis of five trials including more than 2400 patients, which reported a 70% reduction in the DVT rate when IPC devices were used.

Westrich *et al.*<sup>22</sup> performed a prospective randomised study of 275 patients undergoing unilateral TKA under spinal epidural anaesthesia (SEA), comparing IPC associated with either enoxaparin or aspirin. 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 DVT rates in the enoxaparin group and the aspirin group were 14.1 and 17.8% ( $P = \text{not significant}$ ), respectively. When used in combination with pneumatic compression devices and SEA, enoxaparin was not superior to aspirin in preventing DVT after TKA.

### What should be the dose and duration of treatment for aspirin in prevention of deep venous thrombosis and pulmonary embolism in orthopaedic surgery?

Many different regimens have been described in the literature.<sup>19</sup> There is a considerable range for dose (from 75 to 1000 mg daily) and duration of treatment (from 2 days to 6 weeks). Selection criteria are not routinely provided. There is a trend to decrease dose<sup>30</sup> and duration of treatment.<sup>29</sup> However, the current literature does not allow a definitive recommendation concerning dose and duration of treatment and patient selection.

### Efficacy/safety ratio of aspirin in nonorthopaedic surgery

Data on the efficacy and safety of aspirin in nonorthopaedic, nontraumatic surgery date back to the 1980s. The studies were presented in a meta-analysis by the Antiplatelet Trialists' Collaboration published in 1994.<sup>31</sup> The investigators used doses mainly between 1000 and 1500 mg daily, partly also in combination with dipyridamole. Treatment duration was 1 or 2 weeks. Diagnosis of DVT was made either by systematic radiolabeled fibrinogen uptake scan or by venography.

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

One randomised, double-blind study comparing aspirin with unfractionated heparin was conducted by Vinazzer

*et al.*<sup>32</sup> in patients undergoing elective general surgery. A dose of 500 mg of aspirin was compared with that of unfractionated heparin 5000 IU twice daily, and 1210 patients were included in that study. Diagnosis of the primary outcome of DVT was based on obligatory Doppler imaging. No statistically significant difference was found in the rates of DVT (3.9 vs. 2.4%) or pulmonary embolism (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 pulmonary embolism in patients with general surgery, but 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 in recent years.

### Is aspirin appropriate for venous thromboembolism prophylaxis in the perioperative period?

Several authors are still reluctant to recommend the use of aspirin for VTE prophylaxis.<sup>33</sup> Aspirin is less potent than LMWH and the new direct anticoagulants, 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.<sup>34</sup> Aspirin may be proposed in moderate-risk orthopaedic patients or in highly selected high-risk patients scheduled for THA or TKA combined with an enhanced recovery procedure, or in hip fracture patients with a high bleeding risk. IPC should always be used when aspirin is prescribed as the only pharmacological agent. However, the current literature does not provide rationale for precise recommendation about management (dose, duration, follow-up parameters), interactions with other diseases and medicines, or patient and surgery selection. Data are lacking for nonorthopaedic surgery patients and for intensive care patients.

### Recommendations

- We recommend the use of aspirin as an option for venous thromboembolism (VTE) prevention after total hip arthroplasty, total knee arthroplasty and hip fracture surgery (Grade 1B).
- We suggest the use of aspirin for VTE prevention after total hip arthroplasty, total knee arthroplasty and hip fracture surgery (high-risk procedures) in patients without high VTE risk (Grade 2C).
- We suggest the use of aspirin for VTE prevention after low-risk orthopaedic procedures in patients with a high VTE risk or other high-risk orthopaedic procedures in patients without a high VTE risk (Grade 2C).
- We suggest the use of aspirin for VTE prevention after total hip arthroplasty, total knee arthroplasty and hip fracture surgery in patients with an increased bleeding risk (Grade 2C).

- We suggest the use of aspirin for VTE prevention after total hip arthroplasty or total knee arthroplasty in a rapid recovery (fast-track) programme (Grade 2C).
- We recommend combining aspirin with intermittent pneumatic compression (IPC) devices for VTE prevention after total hip arthroplasty, total knee arthroplasty and hip fracture surgery (Grade 1C).
- We recommend no pharmacological VTE prevention after low-risk orthopaedic procedures in patients without high VTE risk (e.g. knee arthroscopy) (Grade 1C).
- No recommendation can be made concerning dose and duration of aspirin treatment and patient selection.
- We do not recommend aspirin for 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).

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## References

- 1 Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: antithrombotic therapy and prevention of thrombosis, 9th edn: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141** (Suppl 2):e637S–e668S.
- 2 Eikelboom JW, Hirsh J, Spencer FA, et al. Antiplatelet drugs: antithrombotic therapy and prevention of thrombosis, 9th edn: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; **141** (Suppl 2):e89S–e119S.
- 3 Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th edn: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; **141** (Suppl 2):e278S–e325S.
- 4 Samama C-M, Albaladejo P, Benhamou D, et al. Venous thromboembolism prevention in surgery and obstetrics: clinical practice guidelines. *Eur J Anaesthesiol* 2006; **23**:95–116.
- 5 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** (Suppl 6):381S–453S.
- 6 Karthikeyan G, Eikelboom JW, Turpie AGG, Hirsh J. Does acetyl salicylic acid (ASA) have a role in the prevention of venous thromboembolism? *Br J Haematol* 2009; **146**:142–149.
- 7 Sevitt S. Thrombosis and embolism after injury. *J Clin Pathol* 1970; **4**: 86–101.
- 8 Becattini C, Agnelli G. Aspirin for prevention and treatment of venous thromboembolism. *Blood Rev* 2014; **28**:103–108.
- 9 Undas A, Brummel-Ziedins K, Mann KG. Why does aspirin decrease the risk of venous thromboembolism? On old and novel antithrombotic effects of acetyl salicylic acid. *J Thromb Haemost* 2014; **12**:1776–1787.
- 10 Brinkmann V, Zychlinsky A. Beneficial suicide: why neutrophils die to make NETs. *Nat Rev* 2007; **5**:577–582.
- 11 Lapponi MJ, Carestia A, Landoni VI, et al. Regulation of neutrophil extracellular trap formation by anti-inflammatory drugs. *J Pharmacol Exp Ther* 2013; **345**:430–437.
- 12 von Brühl M-L, Stark K, Steinhart A, et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. *J Exp Med* 2012; **209**:819–835.
- 13 Bulut D, Becker V, Mügge A. Acetylsalicylate reduces endothelial and platelet-derived microparticles in patients with coronary artery disease. *Can J Physiol Pharmacol* 2011; **89**:239–244.
- 14 Wang L, Wu J, Zhang W, et al. Effects of aspirin on the ERK and PI3K/Akt signaling pathways in rats with acute pulmonary embolism. *Mol Med Rep* 2013; **8**:1465–1471.
- 15 Antovic A, Perneby C, Ekman GJ, et al. Marked increase of fibrin gel permeability with very low dose ASA treatment. *Thromb Res* 2005; **116**:509–517.
- 16 Martin AC, Gouin-Thibault I, Sigaret V, et al. Multimodal assessment of nonspecific hemostatic agents for apixaban reversal. *J Thromb Haemost* 2015; **13**:426–436.
- 17 Pulmonary Embolism Prevention, PEP, Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000; **355**:1295–1302.
- 18 Sahebally SM, Healy D, Walsh SR. Aspirin in the primary prophylaxis of venous thromboembolism in surgical patients. *Surgeon* 2015; **13**: 348–358.
- 19 Wilson DGG, Poole WEC, Chauhan SK, Rogers BA. Systematic review of aspirin for thromboprophylaxis in modern elective total hip and knee arthroplasty. *Bone Joint J* 2016; **98-B**:1056–1061.
- 20 Ogonda L, Hill J, Doran E, et al. Aspirin for thromboprophylaxis after primary lower limb arthroplasty: early thromboembolic events and 90 day mortality in 11,459 patients. *Bone Joint J* 2016; **98-B**:341–348.
- 21 Kaye ID, Patel DN, Strauss EJ, et al. Prevention of venous thromboembolism after arthroscopic knee surgery in a low-risk population with the use of aspirin. A randomized trial. *Bull Hosp Jt Dis* (2013) 2015; **73**:243–248.
- 22 Westrich GH, Bottner F, Windsor RE, et al. VenaFlow plus Lovenox vs VenaFlow plus aspirin for thromboembolic disease prophylaxis in total knee arthroplasty. *J Arthroplasty* 2006; **21** (6 Suppl 2):139–143.
- 23 Drescher FS, Sirovich BE, Lee A, et al. Aspirin versus anticoagulation for prevention of venous thromboembolism major lower extremity orthopedic surgery: a systematic review and meta-analysis. *J Hosp Med* 2014; **9**: 579–585.
- 24 Lieberman JR, Cheng V, Cote MP. Pulmonary embolism rates following total hip arthroplasty with prophylactic anticoagulation: some pulmonary emboli cannot be avoided. *J Arthroplasty* 2017; **32**:980–986.
- 25 Intermountain Joint Replacement Center Writing Committee. A prospective comparison of warfarin to aspirin for thromboprophylaxis in total hip and total knee arthroplasty. *J Arthroplasty* 2012; **27**:1–9.
- 26 Anderson DR, Dunbar MJ, Bohm ER, et al. Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. *Ann Int Med* 2013; **158**:800–806.
- 27 Jiang Y, Du H, Liu J, Zhou Y. Aspirin combined with mechanical measures to prevent venous thromboembolism after total knee arthroplasty: a randomized controlled trial. *Chin Med J (Engl)* 2014; **127**:2201–2215.
- 28 Husted H, Otte KS, Kristensen BB, et al. Low risk of thromboembolic complications after fast-track hip and knee arthroplasty. *Acta Orthop* 2010; **81**:599–605.
- 29 Jørgensen CC, Jacobsen MK, Soeballe K, et al. Thromboprophylaxis only during hospitalisation in fast-track hip and knee arthroplasty, a prospective cohort study. *BMJ Open* 2013; **3**:e003965.
- 30 Parvizi J, Huang R, Restrepo C, et al. Low-dose aspirin is effective chemoprophylaxis against clinically important venous thromboembolism following total joint arthroplasty. *J Bone Joint Surg* 2017; **99**:91–98.
- 31 Antiplatelet Trialists Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994; **308**:235–246.
- 32 Vinazzer H, Loew D, Simma W, Brücke P. Prophylaxis of postoperative thromboembolism by low dose heparin and by acetylsalicylic acid given simultaneously. A double blind study. *Thromb Res* 1980; **17**:177–184.
- 33 Cohen AT, Imfeld S, Markham J, Granziera S. The use of aspirin for primary and secondary prevention in venous thromboembolism and other cardiovascular disorders. *Thromb Res* 2015; **135**:217–225.
- 34 Sharrock NE, González Della Valle A, Go G, et al. Potent anticoagulants are associated with a higher all-cause mortality rate after hip and knee arthroplasty. *Clin Orthop Rel Res* 2008; **466**:714–721.