■ SPECIALTY UPDATE: ARTHROPLASTY

Aspirin and the prevention of venous thromboembolism following total joint arthroplasty

COMMONLY ASKED QUESTIONS

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The number of arthroplasties being performed increases each year. Patients undergoing an arthroplasty are at risk of venous thromboembolism (VTE) and appropriate prophylaxis has been recommended. However, the optimal protocol and the best agent to minimise VTE under these circumstances are not known. Although many agents may be used, there is a difference in their efficacy and the risk of bleeding. Thus, the selection of a particular agent relies on the balance between the desire to minimise VTE and the attempt to reduce the risk of bleeding, with its undesirable, and occasionally fatal, consequences.

Acetylsalicylic acid (aspirin) is an agent for VTE prophylaxis following arthroplasty. Many studies have shown its efficacy in minimising VTE under these circumstances. It is inexpensive and well-tolerated, and its use does not require routine blood tests. It is also a 'milder' agent and unlikely to result in haematoma formation, which may increase both the risk of infection and the need for further surgery. Aspirin is also unlikely to result in persistent wound drainage, which has been shown to be associated with the use of agents such as low-molecular-weight heparin (LMWH) and other more aggressive agents.

The main objective of this review was to summarise the current evidence relating to the efficacy of aspirin as a VTE prophylaxis following arthroplasty, and to address some of the common questions about its use.

There is convincing evidence that, taking all factors into account, aspirin is an effective, inexpensive, and safe form of VTE following arthroplasty in patients without a major risk factor for VTE, such as previous VTE.

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The number of arthroplasties increases each year.[1] Patients undergoing an arthroplasty are at risk of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE).[2] In the absence of prophylaxis, VTE may occur in more than 35% of patients undergoing an arthroplasty. However, most are asymptomatic.[2-6] Because of the relatively high incidence of VTE, prophylaxis has been recommended after arthroplasty.[7] The best agents and optimum protocols to minimise VTE under these circumstances are not known. The most recently revised guidelines from the American College of Chest Physicians (ACCP) and associated guidance from the American Academy of Orthopaedic Surgeons (AAOS) offer valuable recommendations. Both accept mechanical and chemical prophylaxis.[2,8] Although there are many chemical agents for VTE prophylaxis, there is a difference in their efficacy and the risk of bleeding. The choice of agent therefore relies on a balance between the desire to minimise VTE and the attempt to reduce the risk of bleeding, with its undesirable and occasionally fatal consequences.[9-14]

Acetylsalicylic acid, which is generally known as aspirin, is an agent for the prevention of VTE following arthroplasty.[9,10,15-21] Many studies have reported its efficacy in minimising VTE following arthroplasty.[9,10,15-36] In recent years, there has been a dramatic shift, at least in North America, towards the use of aspirin as the main modality for VTE prophylaxis following arthroplasty.[9,12,16,20,27,37-43] A recent poll of > 1200 attendees of the annual meeting of the American Association of Hip and Knee Surgeons, in 2016, revealed that > 80% use aspirin as the main prophylaxis in their patients undergoing arthroplasty of the hip or knee.

There are various reasons for the popularity of aspirin as a prophylactic agent. Besides the proven efficacy, it is inexpensive and well-tolerated, and its use does not require routine blood monitoring.[4,7,12,18,21,23,44,45] It is also a 'milder' agent that is unlikely to result in haematoma formation, which may require further surgery, and which increases the risk of

infection.[27] Aspirin is also less likely to be associated with persistent wound drainage, with all its undesirable consequences, than agents such as low-molecular-weight heparin (LMWH) or other more aggressive agents.[4,14,23,46-51]

There are other reasons why there has been a recent increasing use of aspirin as VTE prophylaxis in North America. One may relate to the advances in anaesthesia and surgical techniques that have changed the nature of arthroplasty.[10,17,20,21,25,32,52] The use of regional anaesthesia, multimodal pain management with less reliance on opioids, and the effective conservation of blood allows most patients to walk within hours of their surgery, unlike in the recent past, when patients would be unable to walk for several days after the operation. Many centres around the world now undertake arthroplasty as an outpatient procedure.[26,52-59] The increasing use of pre-operative training and exercise classes allows faster mobilisation after surgery.[60,61] The fact that an arthroplasty is a more routine and predictable procedure means that patients present earlier for surgery and are therefore more mobile pre-operatively. The reduction in waiting lists for surgery in some countries has also probably improved the pre-operative fitness of patients and thus facilitated their post-operative mobilisation.[62] Another reason for the move towards aspirin may relate to the economics of arthroplasty. For reasons of cost containment, healthcare providers may have to bear the costs of complications and re-admissions, which encourages strategies that minimise wound-related problems that may require treatment, including further surgery.[63,64] The association between haematoma formation, persistent wound drainage and periprosthetic infection has also sensitised the orthopaedic community towards the use of less aggressive VTE prophylaxes, such as aspirin, that minimise the risk of these complications.[27,47,50,65,66] There is also an increasing concern about infection with multiply resistant organisms, which are difficult to manage.[67,68] This problem means that the balance of risk and cost is now relatively more in favour of techniques that reduce infection.

Despite the popularity of aspirin in the United States, some European countries have refrained from adopting aspirin as VTE prophylaxis following arthroplasty. Some European guidelines, such as the Scottish Intercollegiate Guidelines Network (SIGN) and the National Institute for Health and Care Excellence (NICE), dispute its efficacy.[69,70] The committees that guide the formation of guidelines may receive evidence from experts in haematology, internal medicine and other subspecialties, who question the efficacy of aspirin as an antithrombotic agent. These committees work with controlled trial data and ignore registry data, which provide the evidence of the outcomes of orthopaedic procedures.

The main objective of this review is to summarise the current evidence relating to the efficacy of aspirin as VTE prophylaxis following arthroplasty, and to address some of the common questions that are asked by orthopaedic surgeons and other interested colleagues.

What is the mode of action of aspirin?

Aspirin is an extensively studied antithrombotic agent that irreversibly inhibits the activity of cyclooxygenase (COX) in platelets.[71-74] COX-1 and 2 isoenzymes catalyse the conversion of arachidonic acid to prostaglandin (PG) H2 and the production of thromboxane A2 (TXA2) and PGI2. TXA2 induces vasoconstriction, whereas PGI2 induces vasodilatation and inhibits the aggregation of platelets.[75] Aspirin exerts its activity by inhibiting COX-1, which in turn inhibits the production of TXA2. Aspirin can prevent the subendothelial deposition of platelets and the aggregation of new platelets.[76-78]

The Virchow triad, consisting of a combination of endothelial damage, venous stasis and hypercoagulability, can trigger the development of thrombosis.[79] All three components are relevant in lower limb arthroplasty. The development of a venous thrombus often starts in the region of a valve where the pattern of blood flow becomes abnormal, resulting in endothelial dysfunction.[72,79] Stagnant blood in a linear section of the blood vessel leads to hypoxia,[80] which in turn initiates thrombogenesis and the aggregation of platelets.[75]

Is aspirin effective in the prevention of VTE following arthroplasty and other orthopaedic procedures?

To our knowledge, a study by Salzman et al[81] is the first report in the English literature that demonstrated the efficacy of aspirin in reducing VTE after total hip arthroplasty (THA). There have been many subsequent studies further showing the efficacy and safety of aspirin for VTE prophylaxis following arthroplasty.[9,10,14-16,18-23,25,27-30,32,33,39,41,44,46,51,81-97]

One of the most important and commonly cited studies is the Pulmonary Embolism Prevention (PEP) Trial.[15] This multinational and prospective study, involving more than 24 000 patients, confirmed the efficacy of aspirin in the prevention of VTE for patients undergoing arthroplasty and for those with a fracture of the hip.[15] The use of aspirin reduced the incidence of PE and DVT post-operatively by at least a third. The study concluded that "there is now good evidence for considering aspirin routinely in a wide range of surgical and medical groups at high risk of VTE".[15] The publication of many further studies showing the same thing resulted in the ACCP endorsing aspirin with the highest grade of recommendation, and for the AAOS to accept aspirin as prophylaxis for patients undergoing arthroplasty.[13,18,19,22,23,25,29,31,34,65,98,99]

Does aspirin work on the venous circulation (black clot) or is its action limited to the arterial circulation (red clot)?

The action of aspirin is not limited to the arterial circulation. As mentioned above, it inhibits platelet aggregation,[75] an important instigator of venous thrombosis.[76,78,100] Besides COX-1 inhibition, several mechanisms of action have been proposed for the antithrombotic effects of

aspirin in VTE prophylaxis. It suppresses the activation and aggregation of platelets via non-cyclooxygenase-1 pathways.[101] It also attenuates the generation of thrombin by the acetylation of antithrombin III[102] and prothrombin,[103] decreasing tissue factor expression on monocytes and macrophages[104] and impairing the formation of prothrombinase on platelets with reduced activation of factor V.[100] Aspirin acetylates fibrinogen and fibrin[105] and inhibits the activation of thrombin-mediated factor XIII,[106] resulting in the formation of looser networks of fibrin with increased lysability. There is some evidence that platelet activation in association with neutrophil recruitment is involved in the initiation and propagation of a DVT.[107] Neutrophil extracellular traps (NETs) are produced to allow neutrophils to trap and disarm microbes in the extracellular environment.[108] They stimulate the formation and deposition of fibrin which joins NETs in thrombi.[109] NETs stimulate both the extrinsic and intrinsic coagulation pathways.[110] Aspirin may reduce the phosphorylation of nuclear factor kappa B[111] to impair the formation of NETs.

It has been shown that aspirin reduces the risk of recurrent DVTs.[112,113] The randomised, multicentre, double-blind, placebo-controlled Aspirin for the Prevention of Recurrent Venous Thromboembolism Warfarin and Aspirin (WARFASA) trial showed that in patients with an initial unprovoked VTE (n = 403) who had completed six to 18 months of treatment with vitamin K antagonists and then were assigned to aspirin (100 mg/day) for two years, VTE recurred in 6.6% of those receiving aspirin compared with 11.2% of those receiving a placebo (p = 0.02).[112] Many other studies have further shown the efficacy of aspirin in minimising VTE following arthroplasty, all recording its action on the venous (black clot) circulation.[9,15,16,18-20,22,23,25,28,29,31,32,38-41,43,46,84,114]

Does aspirin prevent all VTEs or just DVTs?

The efficacy of aspirin in the prevention of VTE includes its ability to reduce the incidence of both proximal and distal DVTs, and non-fatal and fatal PEs.[6,14,15,18-21,23,28,32,33,35,39-41,44,84,87,88,90-92,94,95,99,115-118] The PEP trial showed the efficacy of aspirin in preventing PE.[15]

What dose of aspirin should be given to patients undergoing an arthroplasty?

The initial AAOS guidelines on VTE prevention advised the use of aspirin 325 mg twice daily with a 1C grade for the recommendation, acknowledging the lack of sufficient studies on the optimal dose.[114] The reason for using this dose is that 325 mgs is the equivalent of five grains, which was the original dose. A meta-analysis in the cardiology literature showed that high doses of aspirin (500 to 1500 mg/day) were no more effective than medium doses (160 to 325 mg/day) or low doses (75 to 150 mg/day).[119] Further studies have also shown that high doses of aspirin were associated with more gastrointestinal side effects.[11,42,43,79,120] Many studies have shown that a dose of 325 mg twice daily is effective for the prevention of symptomatic VTE.[8,10,18-22,25,27,34,44,85-87,89,94,105,117,121-125] There are equally many other studies showing the efficacy of low dose aspirin in minimising VTE, and a lower incidence of gastrointestinal bleeding than with the higher doses.[15,77,126-130] The PEP trial evaluated the efficacy of low dose aspirin (160 mg/day).[15] The relevant literature includes studies evaluating a wide range of doses of aspirin as VTE prophylaxis with doses of 75 mg,[13] 81 mg,[92] 100 mg,[17,51,98,131] 150 mg,[41,47,99] 160 mg,[15,132] 162 mg,[9,42,43] 250 mg,[133] 300 mg,[130] 325 mg,[95] 600 mg,[24] 650 mg,[9,27,42,43] 1200 mg,[82,84,115,129,130] 1300 mg,[31,33,35,93,134,135] and 3600 mg.[129,130] One unresolved issue in relation to the dose is the variation in the sensitivity to aspirin among patients.[136] There is no routine screening test that predicts this sensitivity. It has been shown that aspirin at doses of between 30 mg and 150 mg is sufficient to inhibit platelet COX-1 function.[72,73,77] A recent cross-over study at the Rothman Institute[43] showed that low dose aspirin (81 mg twice a day) was as effective as a higher dose (325 mg twice a day), with the lower dose being associated with fewer gastrointestinal side effects. The recommendation of that study was that low dose aspirin should be used for the prevention of VTE following arthroplasty.[43]

How long should aspirin be used for after an arthroplasty?

The initial AAOS guidelines on the prevention of VTE, published in 2007, recommended that aspirin prophylaxis should continue for six weeks after an arthroplasty.[114] The recent ACCP guidelines, on the other hand, recommended that aspirin prophylaxis should only be continued for ten to 14 days after arthroplasty, with the recommendation having strong evidence (Grade 1B), but also suggesting extended prophylaxis for 30 to 35 days with weak evidence (Grade 2C).[2] Other protocols advocate using aspirin until discharge from hospital,[31-33,115] or for seven days,[133] 14 days,[17,51,98] 21 days,[82,135] 28 days,[9,24,25,34,95,105,121] or six weeks.[16,18,20-22,99]

A recent study showed that most symptomatic VTEs (94%) occur within two weeks of an arthroplasty, with 89% occurring within the first week.[137] Based on this study and the recommendations of the ACACP, it is plausible that the administration of aspirin for two weeks following an arthroplasty may usually be sufficient. Since some studies have shown that the risk of VTE remains higher than the general population for much longer after an arthroplasty[113] and bearing in mind the low toxicity of aspirin, the use of extended prophylaxis, particularly in high-risk patients who are less mobile, may also be reasonable. In view of the complexity of the data on the length of prophylaxis and variation of a patient's response to aspirin, further studies examining the duration of prophylaxis using aspirin, or other agents, are needed.

Does aspirin have any adverse effects?

It appears that aspirin is safe and causes fewer complications than other chemical agents available for VTE prophylaxis.

Based on our institutional experience and evaluation of the literature, adverse events are rare with the use of aspirin.[9,16,20,27,42,43] It can, especially at higher doses, cause dyspepsia, gastroesophageal reflux, and an increased risk of upper gastrointestinal bleeding.[11,42,119] Aspirin can induce small and large bowel pathology (enteropathy); this was not well recognised previously.[9-13] It is not known what percentage of patients develop these adverse effects but gastrointestinal bleeding, if untreated, can be fatal.[42,43] Patients developing adverse events related to the administration of aspirin, should discontinue its use.[42]

Any prophylaxis given to patients for the prevention of VTE carries potential for unintended effects. Many studies have shown that LMWH increases the risk of minor and major bleeding and wound-related complications.[4,14,23,25,46,48-50] Bloch et al[47] recorded that dabigatran caused a significant increase in leakage from the wound ($p < 0.001$), an increase in the length of stay in hospital ($p = 0.04$) and higher rates of VTE ($p = 0.047$) when compared with the use of a multimodal prophylaxis protocol (LMWH inpatient and extended use of aspirin). Zou at al[51] compared oral rivaroxaban, LMWH and aspirin to prevent VTE in patients undergoing total knee arthroplasty (TKA). They found that rivaroxaban caused significantly greater hidden blood loss and more wound complications compared with LWMH and aspirin.[51] It is also believed that warfarin, because of its ability to inhibit proteins C and S, both of which have anticoagulant properties, can result in a temporary hypercoagulable state in the immediate post-operative period. In a study by Raphael et al,[20] patients receiving warfarin for VTE prophylaxis after arthroplasty had a six times higher incidence of PE compared with those receiving aspirin.

Does aspirin have any unintended beneficial effects?

The administration of aspirin as VTE prophylaxis may also carry some unintended beneficial events. It has recently been shown that the incidence of mortality after arthroplasty is lower in patients using aspirin than in those using warfarin,[9,14,20] LMWH, ximelagatran, fondaparinux, or rivaroxaban.[14,138] Hunt et al[139] showed that mechanical and chemical thromboprophylaxis with heparin with or without aspirin were associated with a decreased 90-day mortality in 409 096 patients undergoing primary THA. They also reported[140] that the 45-day mortality with aspirin after TKA was slightly lower than the mortality with heparin, although this did not reach statistical significance. The latter is not surprising as myocardial infarction and not PE is the main cause of mortality following arthroplasty.[141] PE is responsible for between 11.7% and 17.1% of 90-day mortality,[138,141,142] while a myocardial infarction is responsible for 25.9%.[141] The true cause of death in many patients who do not have an autopsy remains unknown. It is likely that some cases recorded as PE occur as a result of cement or marrow embolisation and are not a true VTE.[143] The incidence of cardiac events leading to death following arthroplasty may be underestimated. In a study by Blom et al,[142] ischaemic heart disease was found to be responsible for 41.2% of deaths after THA.

The anti-platelet effects of aspirin are well-established for the secondary prevention of cardiovascular disease.[119] Aspirin also reduces cardiac-related peri-operative mortality.[144] Although this unintended benefit of aspirin in patients undergoing an arthroplasty has received little attention, one notable study by Parry et al[13] reported that death from all cardiovascular causes decreased from 0.75% (13 of 1727 patients) to zero after switching from no prophylaxis to that involving 75 mg aspirin after THA. The beneficial effect of aspirin relates to its ability to prevent arterial thrombosis that is the cause of myocardial infarction and stroke.[145-147] It has recently been shown that major non-cardiac operations are also associated with a temporarily increased risk of arterial thrombosis, encompassing myocardial infarction and stroke.[145,146,148-150] A study based on the Danish national registry, which included patients undergoing a primary THA or TKA (n = 95 227), who were matched to controls, showed that the incidence of myocardial infarction was significantly increased in the first two weeks after THA (adjusted hazard ratio (HR), 25.5; 95% CI, 17.1 to 37.9) and TKA (adjusted HR, 30.9; 95% CI, 11.1 to 85.5) compared with controls.[149]

THA or TKA may be complicated by a stroke.[148,150] Mortazavi et al[150] reported that the incidence of stroke following arthroplasty was 0.2% (36 of 18 745). Of the 36 strokes, two were haemorrhagic and 34 were ischaemic. They found that 25% of patients developing a stroke died within the first post-operative year.[150] Although it is rare following arthroplasty, the consequences of a stroke can be devastating, particularly in elderly patients.[148,150] A recent systematic review found that aspirin was superior to other anticoagulants in the prevention of arterial thrombosis after THA and TKA.[151] Future studies with larger samples may better delineate the role of aspirin in preventing stroke after arthroplasty.

Aspirin may have another beneficial effect, in that it may reduce the incidence of heterotopic ossification following THA.[152,153] The anti-inflammatory effect of aspirin may also contribute to better control of pain and the decreased use of opioids.[26]

Is aspirin cost-effective?

Aspirin is inexpensive and reduces the direct and indirect costs associated with VTE prophylaxis.[20,23,27,37,132,154-156] Gutowski at al[154] reported that the use of aspirin compared with warfarin following arthroplasty reduced the costs related to VTE by shortening the length of hospital stay and lowering the incidence of PE and of all complications related to VTE prophylaxis ($p < 0.001$ for all). They did not take into account the cost of monitoring treatment with warfarin, which is time-consuming, invasive, and expensive.[4,20,66]

Many other studies have shown that the use of aspirin after arthroplasty results in a shorter hospital stay than

when using other agents.[20,23,27,154] There are various reasons for this finding. The use of aspirin does not require blood tests (like warfarin) that can delay discharge from hospital until target therapeutic levels are obtained. Aspirin has anti-inflammatory properties that may aid rehabilitation and the return of function. Keyas et al[155] compared the effect of aspirin and LMWH on the early return of movement of the knee after TKA and found that movement returned faster in the aspirin group ($p < 0.001$). The early return in function reduces the incidence of complications and the costs associated with rehabilitation. An early discharge from hospital for patients on aspirin may relate to the lower incidence of wound-related complications [9,20,22] and of further surgery.[16]

The cost-effectiveness of aspirin *versus* other agents has also been studied. Jameson et al[157] reported that the annual cost of VTE prophylaxis with potent anticoagulants in patients undergoing arthroplasty in the United Kingdom and Wales was about £13 million, compared with about £110 000 if aspirin was used. Schousboe et al[132] compared aspirin and LMWH and showed that, using quality-adjusted life-years (QALYs), the use of aspirin was cost-effective for patients with no history of VTE after THA and for those who are aged > 80 years after TKA. They were uncertain about the most cost-effective method of VTE prophylaxis for those undergoing TKA who are aged < 80 years. A recent cost-effectiveness analysis, comparing the use of aspirin and warfarin after arthroplasty,[156] clearly showed that aspirin was cost-effective and saved more QALYs than warfarin in all age groups.[156] The realistic costs of administering potent anticoagulants are even higher when one takes into account the increased rate of wound-related problems, haematoma formation, and subsequent deep infection.[20,27,50,65]

Can aspirin be administered with other nonsteroidal anti-inflammatory drugs (NSAIDs) or COX-II inhibitors?

NSAIDs and aspirin are often prescribed together to address pain and for VTE prophylaxis after arthroplasty. NSAIDs can be conventional non-selective agents, or COX-II selective or COX-IV selective. The antiplatelet effect of aspirin is almost entirely COX-I dependent. Conventional non-selective NSAIDs and aspirin inhibit the same COX enzymes, and therefore may interact. Meek et al[158] investigated the interaction between aspirin and different selective (meloxicam and etoricoxib) and non-selective (ibuprofen and naproxen) NSAIDs on thrombocyic function. Meloxicam and etoricoxib caused no significant change in aspirin's thrombocyic inhibition, which, in contrast, was prevented by ibuprofen and naproxen. Aspirin cannot bind to COX-I if the binding site is already occupied by a NSAID. The effect of this is that the administration of non-selective NSAIDs a few hours before aspirin may impede the antithrombocyte effect. When NSAIDs bind to COX-I, it is reversible.[159] Hence, the timing of the administration of the non-selective NSAID and aspirin should be taken into consideration regarding the time interval for their potential for interaction. Ibuprofen and naproxen reduce the antithrombocytic effect of aspirin when single dosages of NSAID are administered two hours before aspirin, but not if the same NSAID is used two hours after aspirin.[160,161] On the other hand, many studies have shown that aspirin can be administered with selective COX-II inhibitors (celecoxib)[26,59] and COX-III inhibitors (paracetamol)[26] without interfering with its antithrombocytic effect.

Is there a difference between the efficacy, adverse events, and cost of the enteric- and non-enteric- coated formulations?

Aspirin is associated with gastrointestinal symptoms, which can result in damage to the gastric mucosa by the suppression of the mucosal synthesis of prostaglandin and its topical irritant effects on the epithelium.[11,72,162,163] Aspirin thus reduces mucosal defences, including epithelial cell turnover and repair, blood flow, and the secretion of mucus and bicarbonate.[73,79,164] Enteric-coated aspirin is covered with a combination of cellulose, silicon and other inactive ingredients. This allows it to dissolve in the duodenum rather than the stomach.[165] Several authors have reported that enteric-coated aspirin causes significantly less mucosal damage than uncoated aspirin,[162,165,166] with others refuting this claim.[17,18] With the conflicting reports in the literature, it is not currently known whether enteric-coated aspirin is superior to non-enteric-coated aspirin with regard to VTE prophylaxis or the incidence of adverse effects. A recent study showed that the rate of gastrointestinal upset and nausea in patients receiving 325 mg of aspirin was higher (9 of 282, 3.2%) than those who received 81 mg (3 of 361, 0.8%; $p = 0.04$). However, gastrointestinal bleeding was 0.7% in the 325 mg group and 1.1% in the 81 mg group ($p = 0.70$).[167] According to the British National Formulary, the cost of 28 aspirin (75 mg) tablets is 84 pence and the cost for the same number of enteric-coated tablets is 87 pence.

Is the use of aspirin for the prevention of VTE accepted by any regulatory body or guidelines?

The fourth and eighth editions of the ACCP evidence-based clinical practice guidelines, published in 2004 and 2008, respectively, recommended against the use of aspirin for VTE prophylaxis in patients undergoing arthroplasty.[3,5] The guidelines were based mainly on studies that assessed the efficacy of agents for the prevention of mostly asymptomatic distal DVT rather than PE. Little evidence about the efficacy of chemical prophylaxis in reducing all-cause mortality was available. There are few studies that deal with the use of aspirin for the prevention of early post-operative DVT.[34,168] Studies evaluating the incidence of DVT, including asymptomatic DVT, in the early post-operative period use DVT as a surrogate endpoint for PE. These studies are mostly conducted by pharmaceutical companies in their

effort to gain regulatory approval for the agents.[169] The previous guidelines have raised concerns among orthopaedic surgeons, particularly because they did not consider all-cause mortality and there was a need to establish a balance between VTE prophylaxis and post-operative bleeding.

The ACCP guidelines were extensively quoted in the United Kingdom in a House of Commons Health Select Committee report on VTE.[3,5] The Committee also took evidence from organisations such as charities and individuals who were not required to declare their interests.[170] After guidance was produced by NICE, which recommended chemical prophylaxis using LMWHs rather than aspirin, an all-party Parliamentary Thrombosis Group was established to raise awareness of the issue by writing to hospital trusts on parliamentary notepaper. The parliamentary group was supported by a consultancy group that was partly funded by pharmaceutical companies.[171] Recently, the workings of this type of group have been considerably tightened by the Parliamentary Standards Commissioner to prevent the misuse of Parliamentary logos and insignias.[172]

In 2007, the AAOS issued a guideline focused on the prevention of symptomatic rather than asymptomatic VTE.[8,114] This recommended aspirin 325 mg twice daily for six weeks for patients at standard risk of PE and major bleeding, those with a standard risk of PE and elevated risk of major bleeding, and those with an elevated risk of PE and major bleeding groups separately.

In the United Kingdom, NICE produced guidelines in 2010 that were similar to the eighth edition of the ACCP guidelines. These recommended against the use of aspirin for VTE prophylaxis.[69] Other important orthopaedic organisations in the United Kingdom, such as the British Hip Society, accept the use of aspirin for VTE prophylaxis.[173] Despite the NICE guidelines, some surgeons in the United Kingdom continue to use aspirin, with many centres reporting their encouraging experience.[13,28,29,41,47,174] In a similar way to the change in the ACCP guidelines, it may be that NICE will change its evidence base and endpoints for the evaluation of the efficacy of aspirin used in this way.

The ninth edition of the ACCP guidelines, published in 2012, used different endpoints for the prevention of all VTEs, the risk for serious bleeding and mortality related to VTE and antithrombotic therapy. These strongly recommend (Grade 1B) the use of aspirin as an agent for VTE prophylaxis.[2] The inclusion of experts with relevant financial conflicts in the previous panels of the ACCP committee had been criticised.[175] Following this, the committee of the ninth edition made a major change and only approved members with minimal to no financial conflict of interest. Of the 150 initial candidates, 13 were rejected because of a conflict of interest and 18 were included with an agreement for active management of their conflict of interest that removed their right to give an opinion on the final recommendations.

The Health and Medicine Division (HMD) of the National Academies of Sciences, Engineering, and Medicine (the Academies) in the United States applies a meticulous research process, aimed at providing straightforward objective answers to difficult questions of national importance. The HMD was previously the Institute of Medicine (IOM), which produced eight standards for developing rigorous, trustworthy clinical practice guidelines (CPG).[176] The CPGs of the AAOS meet all the IOM standards. The AAOS addresses bias beginning with the selection of CPG group members. Applicants with financial conflicts of interest related to the CPG topic cannot participate if the conflict occurred within one year of the start date of the CPG's development or if an immediate family member has, or has had, a financial conflict. Additionally, all CPG development group members sign a form agreeing to remain free of financial conflicts for one year following the publication of the CPG.[177]

NICE also has a requirement that members of guideline committees declare their interests. Colleges and professional organisations may be asked to nominate individuals to give evidence to public bodies but they may not have a formal process for taking declarations of interest from the individual. The guidelines for witnesses to Parliamentary committees do not include a requirement to declare interests. Committees have the power to require evidence to be given under oath, but this is rarely used. Witnesses to committees enjoy absolute privilege in respect of the evidence that they give, enshrined in Article 9 of the Bill of Rights 1689. They are thus immune from both civil and criminal proceedings arising from the evidence that they give.[178]

Should aspirin be given to all patients undergoing an arthroplasty as VTE prophylaxis?

The risk for VTE following an arthroplasty is not the same for all patients. Many risk factors for VTE have been identified. A few recent studies, including one from the United Kingdom, recommended that VTE prophylaxis following arthroplasty should be individualised, based on the risk factors.[41,99,179] A few studies in the United States have also evaluated the impact of various risk factors on the incidence of VTE following arthroplasty and developed an algorithmic approach.[180-183] A recent study using the National Inpatient Sample data identified 1 721 806 patients undergoing arthroplasty, among whom 15 775 (0.9%) developed VTE post-operatively. All known risk factors for VTE were assessed. Relative weights of all independent predictors of VTE after arthroplasty were determined. Hypercoagulability, metastatic cancer, stroke, sepsis, and chronic obstructive pulmonary disease had some of the highest scores. Patients with any of these conditions had a risk of post-operative VTE of > 3%. The authors used this model, and developed an iOS (iPhone operating system, Apple, Inc., Cupertino, California) application (VTEstimator, MedApp LLC, Wilmington, Delaware) that could be used to assign patients into low or high risk for VTE after arthroplasty.[183] Thus, although aspirin is an effective agent for VTE prophylaxis, the use of more potent agents such as LMWH, newly intro-

duced oral agents or warfarin should be considered in patients at a much higher risk in whom the added risk of bleeding with the use of potent agents may be justified. It is possible that individual risk assessment can be improved by the use of tests such as rotational thromboelastometry, which may be used either pre-operatively or potentially during surgery to assess individual patients.[184] Further studies would be needed, but this technique might identify some high risk patients in whom LMWH should be used, other medium risk patients who should be treated with aspirin and some low risk patients who do not need prophylaxis. Although there is currently no evidence that genetic testing for Factor V Leiden and genetic variants of prothrombin is beneficial,[185] the future development of genetic testing remains a possibility.

Taking all factors into account, there is convincing evidence that aspirin is one of the most effective, inexpensive and safest methods for VTE prophylaxis following arthroplasty, including those with a fracture of the hip. The use of aspirin is associated with a much lower incidence of complications and carries additional benefits, such as a reduction in the incidence of myocardial infarction. Although the optimal dose and length of prophylaxis remains unknown, the evidence is that low dose aspirin (between 70 mg and 100 mg twice a day) for a few weeks may be sufficient for most patients. VTE prophylaxis following arthroplasty should be individualised, perhaps using decision-making tools such as algorithmic-based iOS apps. Further research is required into the role of thromboelastometry and the measurement of the response to treatment using low-dose aspirin. The use of more potent agents, such as the newly introduced oral agents and LMWH, which are associated with a higher incidence of bleeding and wound-related complications, may be justified in patients at higher risk of VTE.

Take home message:

- The main objective of this review was to summarise the current evidence relating to the efficacy of aspirin as a VTE prophylaxis following total joint arthroplasty, and to address some of the common questions about its use that are asked by orthopaedic surgeons and other interested colleagues.
- There is convincing evidence that, taking all factors into account, aspirin is an effective, inexpensive, and safe form of VTE prophylaxis following total joint arthroplasty in patients without a major risk factor for VTE, such as previous VTE.

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