REVIEW ARTICLE

Aspirin in the prevention and treatment of venous thromboembolism

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Summary. This review summarizes available evidence on effects of aspirin on incidence and outcomes of venous thromboembolism (VTE). From a pathophysiological point of view, inhibition of platelet aggregation is associated with an impaired thrombus formation both in an experimental model of venous thrombosis and *in vivo*. Epidemiological evidence in support of a beneficial effect of acetylsalicylic acid on VTE incidence is provided by the Antiplatelet Trialists' Collaboration meta-analysis of studies on the use of antiplatelet agents in cardiovascular risk reduction, showing a significant 25% risk reduction of pulmonary embolism. Moreover, a meta-analysis on older trials of antiplatelet agents in postsurgical VTE prevention and the large Pulmonary Embolism Prevention trial demonstrate a protective effect of the same magnitude: 25–30%. However, as low-molecular-weight heparins (LMWH) and vitamin K antagonists (VKA) have shown a superior efficacy and safety profile, and no direct comparisons have been made between aspirin, LMWH and VKA in prolonged use, the most recent guidelines advise against aspirin monotherapy for thromboprophylaxis in the surgical patient. Currently, there is no evidence to support a role for aspirin in air travel-related VTE. Regarding prevention of recurrent VTE, studies are ongoing to determine the potential role of aspirin after a first unprovoked VTE.

Keywords: aspirin, prevention, review, venous thromboembolism.

Introduction

Use of acetylsalicylic acid (ASA) or aspirin forms the cornerstone of prevention in the setting of arterial thrombosis. The use of antiplatelet therapy in a variety of patients at increased risk for arterial thromboembolism was associated

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with a significant 22% risk reduction of a combined endpoint of myocardial infarction (MI), stroke or vascular death in a large meta-analysis by the Antiplatelet Trialists' Collaboration (APTc) [1]. Aspirin causes an irreversible inhibition of cyclo-oxygenase, an essential enzyme for the production of thromboxane A_2 (TxA_2) in the platelet. TxA_2 is a powerful stimulant of platelet aggregation, and use of aspirin subsequently results in effective inactivation of the platelet. As platelets play a role in the initiation and propagation of venous thromboembolism (VTE) as well, antiplatelet agents may play a role in the treatment and prevention of VTE. Even before the use of aspirin became widespread in arterial thromboprophylaxis, several small studies showed a protective effect in VTE prevention [2,3]. In the above-mentioned meta-analysis on antiplatelet therapy in cardiovascular prevention, 32 trials provided information on the incidence of symptomatic pulmonary embolism (PE). Antiplatelet therapy significantly reduced the risk of fatal or non-fatal PE by 25% (150 PE cases/32777 patients in antiplatelet group, 200 cases/32758 patients in adjusted control group) [1].

Although all current guidelines on prevention of VTE in surgery nowadays advocate the use of vitamin K antagonists (VKA) or low-molecular-weight heparin (LMWH) as the method of choice for thromboprophylaxis [4], findings from the Hip and Knee Registry demonstrate that in the period from 1996 to 2001, 4–7% of patients who underwent primary total hip or total knee arthroplasty used only aspirin thromboprophylaxis [5]. With the advent of novel therapeutic modalities in VTE prevention, little attention has been paid to the role of aspirin. On the contrary, use of aspirin is advocated as a method for prevention of air travel-related deep vein thrombosis (DVT) [6]. Moreover, two trials are ongoing that address the use of aspirin in long-term prevention of recurrent VTE. As this more than a century-old drug is discussed with renewed interest, we review the available evidence on the use of aspirin in the prevention of VTE in different clinical settings.

Contribution of platelets to the pathogenesis of VTE

According to the triad of Virchow, three major factors contribute to the development of VTE [7]: stasis of blood flow, blood hypercoagulability and a damaged vessel wall. Several

Table 1 Selection of studies on venous thromboembolism (VTE) prevention by aspirin in surgical patients

Study (reference)	Comparison	Population; method of assessment VTE	Effect
Antiplatelet Trialists' Collaboration meta-analysis (1994) [21]	Antiplatelet agents vs. control	DVT assessed by fibrinogen scan or venography: 5181 patients (4669 surgical patients, 512 high-risk medical patients) PE: 9446 patients (8891 surgical patients, 555 high-risk medical patients)	DVT: antiplatelet group 640/2576 (24.8%); control group 875/2605 (33.6%) PE: antiplatelet group 47/4716 (1.0%); control group 129/4730 (2.7%)
Gent *et al.* (1996) [24]	Aspirin 100 mg b.i.d. vs. Orgaran® 750 IU b.i.d.	Hip surgery; venography at day 14 after operation	Abnormal venography: aspirin group 39/87 (44.3%); Orgaran® group 25/90 (27.8%)
Gehling *et al.* (1998) [25]	Aspirin 500 mg b.i.d. vs. Clivarin® 1750 IU daily	Lower extremity injury requiring immobilizing casts; sonography followed by venography	Abnormal venography: aspirin group 7/144 (4.8%); Clivarin® group 9/143 (6.3%)
Lotke *et al.* (1996) [26]	Aspirin 325 mg b.i.d. vs. warfarin	Total hip or total knee arthroplasty; venography and V/Q scan	Large calf, popliteal or femoral clots at venography: aspirin group 55/166 (33.1%); warfarin group 36/146 (24.7%) High probability V/Q scan: aspirin group 16/166 (9.6%); warfarin group 12/146 (8.2%)
Pulmonary Embolism Prevention trial (2000) [28]	Aspirin 160 mg vs. placebo; in addition to standard therapy	13356 patients undergoing surgery for hip fracture and 4088 patients with elective arthroplasty; clinically suspected VTE confirmed by additional investigations	Any VTE: aspirin group 105/6679 (1.6%); placebo group 165/6677 (2.5%)

DVT, deep vein thrombosis; PE, pulmonary embolism; V/Q scan, ventilation-perfusion scan.

lines of evidence suggest that activation of platelets does play an important role in the development and propagation of venous thrombi [8]. In an analysis of 50 venous thrombi obtained from femoral valve pockets, Sevitt showed areas that were characterized by fibrin and erythrocytes, mostly located in proximity of the endothelium, as well as areas dominated by a platelet–fibrin network, located more distally in the growing thrombus [9]. In early thrombus formation, scanning electron microscopy studies show aggregated platelets to be attached to venous endothelium [10]. Moreover, inhibition of P-selectin, a signaling molecule exposed on the surface of an activated platelet, which initiates inflammatory signaling pathways in underlying endothelium and recruits monocytes, results in impaired thrombus formation both in an experimental model of venous thrombosis and *in vivo* [11].

Plasma levels of 11-dehydro-thromboxane B_2 (11-TxB_2), a stable metabolite of TxA_2, reflect the extent to which platelets are activated. In an animal model of PE, pretreatment with aspirin reversed the increase in plasma concentrations of TxB_2 [12]. Urinary 11-TxB_2 levels are also elevated in patients with confirmed VTE compared with controls [13]. Activated platelets release several vasoactive agents such as prostaglandins, serotonin, adenosine diphosphate and adenosine triphosphate, which stimulate aggregation even more. Additionally, both serotonin and TxA_2 are potent pulmonary vasoconstrictors. Release of these vasoactive agents may be of pathophysiological significance for the hemodynamic consequences of an acute PE [14,15]. Intriguingly, in animals pretreated with aspirin or methysergide (a serotonin antagonist), an attenuated hypotensive response was observed after experimentally induced PE, with a subsequent reduction in mortality [16]. Inhibition of platelet activation and aggregation by aspirin may therefore reduce incidence, propagation of thrombus growth and direct adverse hemodynamic effects of DVT and PE.

Prevention of VTE in high-risk patients

VTE is a common disease, with an estimated incidence rate of 1 per 1000 inhabitants in the general population [17]. Recent orthopedic surgery is a major risk factor for development of acute VTE. Without any prophylaxis, the risk of asymptomatic DVT after a hip operation is reported to be 50% or greater [18]. Given the high incidence of VTE, there is a clear need for effective thromboprophylaxis. Therefore, it is not surprising that in 1969, in view of reports on the recently discovered inhibitory role of aspirin on platelet aggregation [19], the Medical Research Council (MRC) decided to conduct a double-blind, randomized trial on the effects of aspirin on postoperative venous thrombosis [20]. However, in 303 patients admitted for elective general surgery, use of aspirin 1 day prior to and 5 days postsurgery did not result in a reduction of the incidence of DVT, defined by abnormal ^{125}I-fibrinogen scan.

In 1994, the APTc summarized data on the effect of antiplatelet therapy as VTE prophylaxis in surgical patients from numerous studies, which followed upon the MRC trial

[21]. In total, 53 trials were eligible, providing data on 5181 patients in which the presence of postoperative DVT was systematically evaluated, and 9446 patients were evaluated for PE. Both antiplatelet therapy vs. control and antiplatelet therapy in combination with heparin vs. heparin monotherapy were compared. The following antiplatelet regimens were evaluated: ASA monotherapy; ASA in combination with dipyramidol; monotherapy with hydroxychloroquine; and ticlodipine as monotherapy. The numbers of participants per study were relatively small. In total, use of any antiplatelet regimen alone or in combination with heparin resulted in a statistically significant 39% odds reduction of DVT incidence and a 64% reduction in the odds of developing a symptomatic PE. In absolute numbers, in the 2576 patients treated with antiplatelet therapy, 640 cases of venographically or ^{125}I-fibrinogen scan confirmed DVT were noted (24.8%). In the control arm, 875 cases among 2605 patients (33.6%) were found. In trials evaluating the occurrence of symptomatic PE, use of antiplatelet therapy resulted in 47 cases in 4716 patients (1.0%), whereas in the control arm of the studies 129 cases of PE in 4730 patients were noted (2.7%, OR 0.36, $P < 0.00001$). Not every trial provided data on risk of bleeding, but in the 45 trials reporting non-fatal major bleeding, defined by need for transfusion, antiplatelet therapy resulted in a marginally significant ($P < 0.04$) increase in risk: 0.7% in the antiplatelet therapy group vs. 0.4% in the control group. The authors concluded that the results indicate that antiplatelet therapy should be considered as an effective form of thromboprophylaxis. This meta-analysis received much criticism [22]. Indeed, trials analyzed in the meta-analyses did not fulfil the modern design standards of a clinical trial. For example, the trials included unblinded studies and studies with improper randomizations. In a subgroup analysis of open studies vs. blinded studies, attained risk reduction for blinded studies was 25.8% compared with 50% for the open studies. Moreover, studies were heterogeneous with respect to patient population and used antiplatelet therapy. In addition, the conclusions have been contradicted by another meta-analysis of VTE prevention after hip surgery [23]. Imperiale and Speroff combined the results of different treatment groups from 56 trials, including eight trials in which aspirin was the treatment arm. All treatments with the exception of aspirin significantly reduced the risk of DVT and only LMWH reduced the risk of PE.

A number of more recent studies evaluated the use of aspirin compared with an active control group as summarized in Table 1. Gent et al. conducted a double-blind randomized controlled trial with aspirin 100 mg b.i.d. compared with a LMWH (Danaparoid®; 750 IU b.i.d.) among 251 patients who underwent hip fracture surgery [24]. Subclinical VTE, detected with venography at day 14 after operation, was present in 27.8% in the Danaparoid® group vs. 44.3% in the aspirin group (RR 0.63, 95% CI: 0.41–0.96, $P = 0.028$). Six of 88 patients in the Danaparoid® group and 12 of 84 patients in the aspirin group developed proximal DVT or PE, resulting in a non-significant relative risk reduction of 52% in favor of Danaparoid®. An other study evaluated the use of aspirin vs.

the LMWH Reviparir® [25]. Two hundred and eighty-seven patients presenting with lower extremity injury that required immobilizing casts or bandages were randomized to aspirin 500 mg b.i.d. or Reviparir® s.c. 1750 IU daily. Symptomatic DVT occurred in nine of 143 (6.3%) patients treated with LMWH vs. seven of 144 (4.8%) patients treated with aspirin. Lotke et al. evaluated VTE by postoperative perfusion scintigraphy and leg venography among 388 patients who underwent hip or knee surgery and were randomized to warfarin or aspirin (325 mg b.i.d.) [26]. There was no statistically significant difference between both treatment groups with regard to changes in thrombotic load measured by scintigraphy, venography or bleeding. In a smaller study with similar design, proximal DVT or PE occurred in 9.2% in the warfarin group and 10.6% in the aspirin group in 194 patients who underwent surgery for hip fracture [27].

Given these conflicting results, the Pulmonary Embolism Prevention (PEP) trial was eagerly awaited. In this multicenter trial, 13356 patients undergoing surgery for hip fracture and 4088 patients who underwent elective knee or hip arthroplasty were randomized to treatment with aspirin 160 mg once daily or placebo [28]. The study treatment started preoperatively and was continued until day 35 postoperatively. Use of any other thromboprophylaxis, including heparin, LMWH or mechanical compression devices did not preclude entry to the trial. Patients were followed with respect to mortality and in-hospital morbidity up to day 35. Clinically suspected DVT had to be confirmed by venography or duplex ultrasonography. PE was diagnosed by a positive pulmonary angiography, a high-probability ventilation-perfusion scan, an intermediate probability scan with venographic evidence of DVT, or PE at autopsy. Among the 13356 patients admitted for hip surgery, any VTE occurred in 105 of 6679 patients allocated to aspirin therapy (1.6%) and in 165 of 6677 patients receiving placebo (2.5%). This 36% relative risk reduction was highly statistically significant (95% CI: 17–50%, $P = 0.0003$). Surprisingly, there was no reduction in other vascular events and overall mortality. The total number of non-fatal MI or fatal ischemic heart disease was even higher in the group randomized to aspirin therapy (105 patients assigned to aspirin vs. 79 assigned placebo). Use of aspirin was associated with an absolute increase of six postoperative bleeding episodes requiring transfusion per 1000 patients. In the elective arthroplasty group, the total number of VTE was lower and was not statistically significant lower in the aspirin group. The authors conclude that their study provides good evidence that aspirin can be used routinely in a wide range of surgical patients at high risk of VTE, and for continuing throughout the period of increased risk.

However, at close scrutiny, this conclusion may be too preliminary as the PEP trial was not designed to answer the question whether aspirin can replace therapy with LMWH or VKA. Indeed, one could argue that the prophylactic benefit of aspirin was mainly apparent in patients who did not receive additional prophylaxis after the hospital stay, as the main difference in VTE incidence occurred in weeks 2–5.

Furthermore, the incidence of VTE was not different in the aspirin group from that in the placebo group in the 3424 patients with hip fractures who additionally received LWMH as thromboprophylaxis.

There is still much uncertainty on the role of aspirin in prevention of VTE in high-risk individuals undergoing surgery. Results from older, smaller and sometimes qualitatively suboptimal studies are conflicting, even if data are correctly pooled in meta-analysis. The PEP trial did show proof for the concept that aspirin does reduce VTE incidence, but the more clinically relevant questions on which prophylactic agent to use and how long to continue were not addressed. In contrast, the evidence for efficacy and safety of LMWH is much more convincing. In general, use of LMWH, unfractionated heparin (UF) or dose-adjusted VKA has proven to reduce the risk for symptomatic VTE by about 50% and is therefore nowadays considered common practice in direct postoperative care [4]. After short-term (7–10 days) anticoagulant prophylaxis, incidence of non-fatal symptomatic VTE is reduced to 3.2% during 3 months postsurgery [29]. For these reasons, it is not surprising that recent guidelines issued by the American College of Chest Physicians (ACCP) recommend against the use of aspirin monotherapy as VTE prophylaxis for any patient group [4].

Prevention of air travel-related DVT

Several case–control studies examined the relative risk of air travel and VTE and collectively suggest a weak positive association between air travel and risk of developing VTE [30–32]. The role of specific factors related to air travel in the pathophysiology of VTE is as yet unknown. Episodes of symptomatic VTE and fatal PE after air travel in particular receive media attention and fuel apprehension of VTE in airline passengers. A few studies examined the role for pharmacological interventions and use of compression stockings. In the only study which evaluated the use of aspirin, aspirin was compared with a LMWH or a control group [33]. In total, 249 subjects were available for analyses. Eighty-four subjects received 400 mg aspirin per day over 3 days, starting 12 h before air travel; 82 subjects received one injection of weight-adjusted enoxaparine (1000 IU kg^{-1} body weight) prior to air travel; and 83 subjects served as controls. The presence of postflight DVT was assessed by bilateral compression ultrasound. In the control group, four subjects (4.8%) had a DVT and two subjects had an asymptomatic superficial thrombosis. In the aspirin group, three subjects with DVT (3.6%) and three subjects with superficial thrombosis were found. Prophylactic treatment with a LMWH resulted in the absence of DVT and one subject with a superficial thrombosis. This non-blinded trial failed to demonstrate a protective effect of aspirin in the prevention of VTE in air travel. As the study was clearly underpowered, a positive effect could not be excluded. Although lay media still advocate the use of aspirin to prevent travel-associated VTE [6], there is no evidence hitherto to support this.

Prevention of recurrent VTE

There is little discussion on the initial treatment and long-term treatment of a first episode of unprovoked VTE. After at least 5 days' therapy with UF or LMWH started together with VKA therapy, the latter is continued for 6–12 months [34]. As VTE recurs frequently and about 30% of the patients with an unprovoked VTE develop recurrence within the first 10 years [35], continuation of VKA therapy after the first treatment period is rather appealing. Although continued use of VKA certainly reduces the number of recurrences during the treatment period, after discontinuation the rate of recurrence is not reduced [36]. In the decision to prolong VKA therapy after the initial treatment period, the estimated annual risk of major bleeding of approximately 2.4% should be taken into account [37]. The annual risk of major bleeding is only 0.1% in patients on long-term low-dose aspirin therapy [38]. As aspirin may show a modest effect in VTE prevention in high-risk surgical patients, it has recently been suggested as an alternative to prolonged VKA therapy. Certainly, given the more beneficial efficacy: safety ratio, use of aspirin for could be an effortless, low-cost and, at population level, effective strategy for secondary prevention of VTE.

This concept is currently tested in two large-scale randomized controlled trials [39,40]. The designs of both studies are harmonized to enable a meta-analysis. Patients with unprovoked VTE (both DVT and PE) are randomized to aspirin 100 mg daily or placebo, starting after 6 or 12 months' VKA therapy. Predefined endpoints are confirmed symptomatic DVT or PE, cardiovascular events (MI, stroke) and all-cause mortality. As a major safety parameter, the incidence of major bleeding will be assessed. In total, 3000 patients have to be followed up for 3 years to detect a 30% risk reduction of recurrent VTE in the aspirin group vs. placebo. Results from both studies will provide an answer to the question of whether aspirin is efficacious and safe in prevention of recurrent VTE after a first unprovoked VTE.

Conclusions

Aspirin deserves a prominent place in the repertory of any physician working in the field of cardiovascular medicine. As a powerful inhibitor of platelet aggregation, use of aspirin results in a robust risk reduction of MI, stroke and vascular death in a broad spectrum of patients at risk for cardiovascular events. As platelets also play a role in the pathogenesis of venous thrombosis, it is not surprising to expect a protective effect of aspirin on incidence of VTE as well. Several conclusions can be drawn from our appraisal of the literature on aspirin in prevention of VTE

The first evidence in support of a beneficial effect of aspirin on VTE incidence is provided by the APTc meta-analysis of studies on the use of antiplatelet agents in cardiovascular risk reduction, showing a significant 25% risk reduction. Moreover, a meta-analysis on older trials of antiplatelet agents in postsurgical VTE prevention and the large PEP trial demon-

strate a protective effect of the same magnitude, 25–30%. However, there is extensive evidence that prolonged use of LMWH or VKA during the hospital stay and first weeks postoperatively reduces VTE risk by 50%, with an acceptable safety profile. As no direct comparisons have been made between aspirin, LMWH and VKA in prolonged use, the most recent ACCP guidelines advise against aspirin monotherapy for thromboprophylaxis in the surgical patient. Currently, there is no evidence to support a role for aspirin in air travel-related VTE. Regarding prevention of recurrences, studies are ongoing to determine the potential role of aspirin after a first unprovoked VTE. A lower risk of major bleeding in patients on long-term low-dose aspirin therapy compared with VKA therapy, and an anticipated efficacy in reducing the risk of recurrences (approximately 30% compared with placebo), strengthen the rationale for evaluating the use of aspirin in prevention of recurrent VTE.

In conclusion, there is evidence that use of aspirin is associated with a reduction in postoperative VTE risk, although it has been surpassed in efficacy by other anti-coagulants. However, given the more beneficial efficacy: safety ratio, use of aspirin could be an effortless, low-cost and, at population level, effective strategy for secondary prevention of VTE. We should not forget the antithrombotic merits of this old, cheap and versatile drug.

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