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EVIDENCE SUMMARY

Use of aspirin for the prevention of lower extremity deep venous thrombosis

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Whereas aspirin is recommended and widely used to prevent arterial thrombosis, its role in the prevention of deep venous thrombosis is not well defined. Aspirin is well accepted, easy to manage with few risks and low cost, and thus ideal for thromboprophylaxis if evidence shows it is effective. Recent guidelines and large studies were reviewed. Recent guidelines include aspirin as an acceptable thromboprophylactic agent after hip and knee orthopedic surgery despite continued publication of underpowered and contradictory studies. Two large randomized controlled trials pooled together suggest that low-dose (100 mg) aspirin is a reasonable alternative to prevent recurrence of venous thromboembolism (VTE) in patients who have been treated for a first episode of unprovoked VTE. We suggest that the current practice using aspirin to prevent thromboembolism include cautious discussion of the benefits and risks of this agent before use in a patient until precise clarification of dosage and treatment length is available. Despite inclusion of aspirin in the guidelines for orthopedic surgery, there is little evidence to support its use for primary prevention of VTE. Until definitive unbiased trials are published, we suggest that aspirin remain a realistic option to use for secondary prevention of VTE, especially compared with the option of using no prophylaxis. (J Vasc Surg: Venous and Lym Dis 2014;2:230-9.)

Since the first paper suggesting an effect of aspirin on platelets and thrombosis, the role of aspirin in prevention of venous thromboembolism (VTE) has been highly controversial.[1] A wide variety of aspirin-based thromboprophylactic regimens led to heterogeneous study designs,[2] leading to data that were difficult to pool and continued to be questioned.[3,4] During the 1980s, primary prevention of VTE, with means other than aspirin, became the standard of care, preventing performance of high-quality placebo-controlled randomized studies that could evaluate aspirin in various settings.[5]

In addition, debate continues about whether symptomatic lower extremity deep venous thrombosis (DVT) is an accurate marker of more serious events, such as pulmonary embolism (PE) and death, and which event should be defined as an end point for studies and guidelines.[5,6] We review the evidence regarding the use of aspirin for primary prevention of lower extremity DVT as well as review the latest guidelines based on this evidence. We also summarize the latest trials reporting the role of aspirin in preventing recurrent VTE.

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METHODS

English-language guidelines regarding prevention of DVT and VTE were retrieved with use of the Internet and the MEDLINE database. For each society guideline, the latest versions that provided a complete statistical analysis of their evidence were selected. The Surgical Care Improvement Project (SCIP) guidelines were selected a priori for American surgeons.[7]

The MEDLINE database was used to find individual studies released since 2000. Keywords used were *aspirin*, *antiplatelet*, *prevention*, *prophylaxis*, *thromboprophylaxis*, *venous thromboembolism*, *deep venous thrombosis* and *recurrence*, associated with *orthopedics*, *surgery*, *cancer*, *stroke*, *air-travel*, *women*. References were screened to retrieve the original articles; systematic reviews, case reports, and letters were excluded. Studies with VTE or PE outcome assessment without detailed data on DVT were excluded. Randomized controlled trials (RCTs) and prospective controlled studies involving fewer than 200 patients and retrospective cohorts evaluating fewer than 10,000 patients were also excluded.

RESULTS

Aspirin for primary prevention of lower extremity DVT

Orthopedic surgery. The role of aspirin as a sole thromboprophylactic agent in high-risk orthopedic patients has long been a subject of debate between societies (Table I).

In older guidelines, the American Academy of Orthopaedic Surgeons (AAOS) listed aspirin as a possible prophylactic agent,[8] whereas the American College of Chest Physicians (ACCP) guidelines[9] discounted the results of the Antiplatelet Trialists' collaboration (APTc) meta-analysis[2] and the Pulmonary Embolism Prevention (PEP) trial[10] and recommended against the use of aspirin as a sole thromboprophylactic agent. This divergence may have reflected some orthopedic surgeons' practice to reserve aspirin use for treatment of patients with low-risk fractures; however, the divergent opinions may have confused many practitioners, especially since the SCIP followed the ACCP guidelines.[7,11] However, the latest guidelines of both the AAOS and the ACCP support the use of aspirin as a thromboprophylactic agent (Table I).[5,12]

In 2011, the AAOS gave inconclusive recommendations regarding the choice of prophylaxis, despite strong statistical tools and large numbers of articles.[5] The heterogeneous quality of studies that assessed aspirin as well as the rarity of thromboembolic events resulted in poor sensitivity of the meta-analysis. Nevertheless, there was implicit support for aspirin or any agent as part of a multimodal approach to prevent thromboembolism, and the guidelines certainly do not recommend against aspirin (Table I).

The committee writing the eighth edition of the ACCP guideline was criticized for lack of objectivity and potential conflict of interest.[13] In 2012, the ninth edition was completely revised.[12] Selecting symptomatic instead of objective VTE as outcome, this version reintegrated the PEP trial and cited aspirin as an option for orthopedic patients after hip fracture and elective hip or knee replacement (grade 1B; Table I). Low-molecular-weight heparin (LMWH) is recommended over other agents, including aspirin, but with lower strength of recommendation (grade 2C). No specific dosage or duration of aspirin treatment was given.

American clinicians who are willing to prescribe aspirin as a sole thromboprophylactic agent after hip or knee surgery are now also supported by the latest SCIP recommendations (until the end of 2014),[7] whereas in the United Kingdom, the latest National Institute for Health and Clinical Excellence (2010)[14] and Scottish Intercollegiate Guidelines Network (2010)[15] recommend against it (Table I).

A few contradictory studies have been reported close to the publication of these recommendations (Table II). Interestingly, two large retrospective studies analyzing data from more than 100,000 patients after hip and knee surgery found no significant difference between aspirin and LMWH in prevention of VTE.[16,17] Another single-center retrospective study comparing aspirin and warfarin in more than 20,000 patients was significantly in favor of aspirin.[18] However, one RCT[19] and one prospective controlled study[20] found aspirin inferior to enoxaparin or warfarin, respectively. Although not of the highest quality evidence, these recent studies maintain and fuel the debate beyond the recommendations in orthopedic surgery.

General surgery and major trauma. The APTc was the first meta-analysis that pooled several smaller RCTs to compare low- with high-dose aspirin in more than 4500 surgical patients (Table III).[2] The conclusions favored aspirin but were criticized.[3,9]

In 2012, the ACCP devoted an entire chapter in the ninth edition of their guidelines to this issue (Table I).[21] Surprisingly, supporting data regarding the use of aspirin in nonorthopedic surgical patients were solely based on the 29% risk reduction reported in the PEP trial (Tables I and II). These guidelines recommend low-dose aspirin in nonorthopedic surgery patients with high risk of VTE, with low risk of bleeding, and for whom LMWH or unfractionated heparin is contraindicated or unavailable (2C). For all other surgical indications and patients with major trauma, neither low- nor high-dose aspirin is indicated as a thromboprophylactic agent in any guidelines. In particular, there are no guidelines or targeted studies evaluating the role of aspirin in prevention of VTE after noncardiac vascular surgery. Interestingly, many patients undergoing vascular procedures are typically prescribed aspirin preoperatively and often receive intraoperative heparin, further complicating assessment of the role of aspirin alone in this patient population.

Cancer. Aspirin as a thromboprophylactic agent is not cited in the guidelines for patients with cancer, either in general or for perioperative use. In the ACCP,[21,22] the American Society for Clinical Oncology,[23] and the International Society on Thrombosis and Haemostasis[24] guidelines, other agents should be prescribed (Table I). No specific studies have been reported in this setting, with the single exception for low-dose aspirin as an alternative thromboprophylactic agent in cancer patients treated with thalidomide or lenalidomide combined with steroids or chemotherapy, typically for myeloma (Table I).[25-27]

High-risk medical and stroke patients. The APTc meta-analysis included, in addition to surgical patients, several studies with high-risk medical patients and reported in favor of aspirin.[2] These results were pooled in the PEP trial analysis[10] and reported by the ACCP committee. Citing low-quality evidence, there was no recommendation regarding the use of aspirin for these patients.

The role of aspirin in stroke patients has been studied separately in the ACCP guidelines.[28] In 2008, a Cochrane systematic review assessed the role of antiplatelet therapy in the setting of acute stroke.[29] Only two RCTs were included, and pooled together, the analysis was inconclusive. Although it remains unclear whether aspirin alone is as efficacious as heparin in the prevention of VTE, the International Stroke Trial did not find any significant difference between these two drugs in prevention of PE.[30] The ACCP recommends initiating aspirin within 48 hours of acute ischemic stroke (1A), with a benefit in prevention of VTE, but recommends additional use of another agent in patients with stroke and restricted mobility (2B) (Table I). The American College of Physicians did not suggest aspirin as an alternative thromboprophylactic agent for any medical patients, including for stroke (Table I).[31]

Long-distance air travel. Only one RCT compared aspirin with LMWH or no prophylaxis in long-distance air travelers (300 travelers randomized, 249 analyzed).[32]

Table I. Summary of selected guidelines regarding the use of aspirin in prevention of deep venous thrombosis (*DVT*)

Society (authors)	*Year*	*Target population*	*Recommendation regarding the use of aspirin in prevention of DVT*	*Grade of recommendation*	*Evidence source regarding aspirin*
Surgical patients					
AAOS[5]	2011	Orthopedic surgery patients	Elective hip and knee arthroplasty: unable to recommend for or against specific prophylactics in these patients.	Inconclusive	Westrich et al[19] PEP trial[10] Lotke et al[44] Lieberman et al[a]
ACCP, 9th edition (Falck-Ytter et al[12])	2012	Orthopedic surgery patients	Total hip or knee arthroplasty, hip fracture: aspirin is one of the recommended thromboprophylaxis options. LMWH is recommended over aspirin with a lower strength of recommendation.	1B 2C	PEP trial[10]
ACCP, 9th edition (Gould et al[21])	2012	Nonorthopedic surgical patients Major trauma patients	Aspirin should not be an alternative for pharmacologic prophylaxis in most nonorthopedic surgical patients. Aspirin is not integrated in the recommendation for DVT prophylaxis among major trauma patients (other agents are recommended). For general and abdominal-pelvic surgery patients at high risk for DVT in whom both LMWH and UFH are contraindicated or unavailable and who are not at high risk for major bleeding complications, low-dose aspirin is an alternative (other agents are equally recommended).	2C	Low dose: extrapolated from a subgroup of the PEP trial (hip fracture surgery)[10] High dose: 8 studies from the APTc meta-analysis,[2] new analysis of pooled data
SCIP[7]	2013	All surgical patients	Elective total knee or hip replacement surgery, hip fracture: aspirin is one of the recommended thromboprophylaxis options. Intracranial neurosurgery, general surgery, gynecologic surgery, urologic surgery: aspirin is not a recommended prophylaxis option.		ACCP 9th edition guidelines[12]
Cancer patients					
ASCO (Lyman et al[23])	2013	Patients with cancer	Aspirin is not integrated in the recommendation for DVT prophylaxis among other cancer patients (other agents are recommended). Low-dose aspirin is an alternative to LMWH in lower-risk patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens plus chemotherapy or dexamethasone.	1B	Two RCT substudies from the same group (Palumbo et al,[26] Larocca et al[27])

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Table I. Continued.

Society (authors)	*Year*	*Target population*	*Recommendation regarding the use of aspirin in prevention of DVT*	*Grade of recommendation*	*Evidence source regarding aspirin*
ISTH (Farge et al[24])	2013	Patients with cancer	Aspirin is not integrated in the recommendation for DVT prophylaxis among other cancer patients (other agents are recommended). Low-dose aspirin is an alternative thromboprophylactic drug in patients treated with thalidomide/lenalidomide combined with steroids or chemotherapy (mainly myeloma patients).	2C	One RCT substudy (Palumbo et al[26]) and one meta-analysis including five studies (of 50) with aspirin (four myeloma and one prostate cancer) (El Accaoui et al[25])
Nonsurgical patients					
ACP (Qaseem et al[31])	2011	All hospitalized nonsurgical patients (including stroke)	Aspirin is not integrated in the recommendation for DVT prophylaxis (other agents are recommended).	Recommendation for the use of other thromboprophylactic agents: 1B	The International Stroke Trial[30]
ACCP, 9th edition (Lansberg et al[28])	2012	Ischemic stroke patients	Early aspirin therapy (initial dose 160-325 mg within 48 h) recommended for all ischemic stroke and TIA patients, with acknowledged benefit in reduction of DVT. Not to be used as sole thromboprophylactic agent in patients with restricted mobility (other agents are recommended).	1A 2B	Cochrane systematic review of 2 trials (Sandercock et al[29])
ACCP, 9th edition (Kahn et al[22])	2012	Nonsurgical patients	No recommendation can be made regarding aspirin in DVT prophylaxis because of low-quality evidence in acutely ill medical patients. Other agents are recommended.	Recommendation for the use of other thromboprophylactic agents: 1B, 2B, 2C	PEP trial meta-analysis of the APTc data[10]
		Long-distance travelers	Recommendation against the use of aspirin.	2C	LONFLIT3 study (Cesarone et al[32])
General guidelines					
NICE[14]	2010	All surgical and nonsurgical patients	Do not regard aspirin or other antiplatelet agents as adequate prophylaxis for DVT.		PEP trial and meta-analysis of the APTc, for each subgroup of patients[10]
SIGN[15]	2010	All surgical and nonsurgical patients	Use of aspirin as the sole agent for DVT prophylaxis is not recommended as other available agents are more effective.	Grade C	APTc meta-analysis (53 studies)[2] and PEP trial[10]

AAOS, American Academy of Orthopaedic Surgeons; *ACCP,* American College of Chest Physicians; *ACP,* American College of Physicians; *APTc,* Antiplatelet Trialists' collaboration; *ASCO,* American Society for Clinical Oncology; *ISTH,* International Society on Thrombosis and Haemostasis; *LMWH,* low-molecular-weight heparin; *NICE,* National Institute for Health and Clinical Excellence; *PEP trial,* Pulmonary Embolism Prevention trial; *RCT,* randomized controlled trial; *SCIP,* Surgical Care Improvement Project; *SIGN,* Scottish Intercollegiate Guidelines Network; *TIA,* transient ischemic attack; *UFH,* unfractionated heparin.

[a]The reference given in the guideline bibliography was Lieberman JR, Geerts WH. Prevention of venous thromboembolism after total hip and knee arthroplasty. J Bone Joint Surg Am 1994;76:1239-50, but it does not correspond to the RCT described in the guidelines. This RCT was not found in MEDLINE.

Only LMWH was associated with no DVT (0 of 82; 0%), whereas aspirin (3 of 84, 3.6%) and control patients (4 of 83; 4.8%) had similar outcomes. Owing to the lack of any other evidence and the low incidence of DVT in this population, the ACCP recommends against the use of aspirin for prevention of VTE in long-distance air travelers (2C) (Table I).[22]

Aspirin for prevention of recurrent VTE

The results of two large RCTs treating 1224 patients were released in 2012 (Tables IV and V). The trials compared low-dose aspirin with placebo after an initial anticoagulant treatment (6 weeks minimum, most at least

Table II. Selection of studies evaluating the use of aspirin in prevention of deep venous thrombosis (*DVT*) in orthopedic surgery

Study (year)	*Type of study*	*Type of patients (No.)*	*Regimen compared*	*DVT rate*	*Bleeding data*	*Comments*
PEP trial (2000)[10]	RCT	Hip fracture (13,356) Elective hip or knee arthroplasty (4088)	Aspirin 160 mg vs placebo (5 weeks of treatment) Additional methods allowed: Hip fracture: UFH (18%), LMWH (26%), and stockings (30%)	Hip fracture: Aspirin = 1.0% Placebo = 1.5% ($P = .03$) HR reduction (95% CI): 29% (3-48) Elective surgery: Aspirin = 0.7% Placebo = 0.9% (P not specified) HR (95% CI): 0.78 (0.40-1.53)	Hip fracture: Fatal bleeds: Aspirin = 0.2% Placebo = 0.2% Any postoperative bleeding needing transfusion: Aspirin = 2.9% Placebo = 2.4% Absolute excess per 1000 (SD): 6 (3)	Criticisms about predefined/published outcomes, presentation of bleeding data, concomitant use of other thromboprophylactic drugs
Westrich et al[19] (2006)	RCT (single center)	Total knee arthroplasty (275)	Aspirin 325 mg twice a day vs enoxaparin 30 mg (followed by 40 mg at discharge) All patients received IPC and epidural anesthesia.	Aspirin = 17.8% Enoxaparin = 14.1% ($P = .27$)	Postoperative drainage: Aspirin: 901 mL Enoxaparin: 793 mL ($P = .03$)	Systematic postoperative Doppler ultrasound Results given per-protocol only (264 patients)
Intermountain Joint Replacement Center Writing Committee[20] (2012)	Prospective cohort, controlled study (single center)	Total joint arthroplasty (696) (primary or revision)	Aspirin 325 mg twice a day for standard-risk patients vs warfarin for elevated-risk patients vs warfarin or enoxaparin (comparator group) Associated with systematic foot or calf intermittent compression device	Aspirin: 4.6% ($P = .03$) Warfarin: 0.8% ($P = 1.00$) Comparator: 0.7%	No significant difference between groups for major bleeding or death	Not randomized Treatment was given on the basis of risk assessment, but the control "comparator" group was not matched (risk stratified) in analyzing data
Jameson et al[16] (2011)	Retrospective cohort	Total hip arthroplasty (108,584) (primary)	Aspirin vs LMWH Mechanical device allowed (82% in aspirin group, 72% in LMWH group)	Aspirin = 0.99% LMWH = 0.94% Adjusted OR (95% CI): 0.91 (0.79-1.06) ($P = .23$)	Cerebrovascular accident/GI hemorrhage: Aspirin = 0.77% LMWH = 0.72% Adjusted OR (95% CI): 0.92 (0.77-1.09) ($P = .34$) Return to theater: Aspirin = 0.31 LMWH = 0.36 Adjusted OR (95% CI): 1.15 (0.88-1.50) ($P = .29$)	Aspirin group: n = 22,942 LMWH group: n = 85,642 DVT and bleeding rates still not significant after adjustment based on propensity score matching
Jameson et al[17] (2012)	Retrospective cohort (single center)	Knee arthroplasty (156,798) (primary)	Aspirin vs LMWH	Aspirin = 0.66% LMWH = 0.63% Adjusted OR (95% CI): 0.93	Cerebrovascular accident/GI hemorrhage Aspirin = 0.37%	Aspirin group: n = 36,159 LMWH group: n = 120,639

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Table II. Continued.

Study (year)	*Type of study*	*Type of patients (No.)*	*Regimen compared*	*DVT rate*	*Bleeding data*	*Comments*
				(0.81-1.08) ($P = .37$)	LMWH = 0.39% Adjusted OR (95% CI): 1.01 (0.83-1.22) ($P = .94$) Return to theater: Aspirin = 0.26% LMWH = 0.19% Adjusted OR (95% CI): 0.73 (0.58-0.94) ($P = .01$)	
Raphael et al[18] (2013)	Retrospective cohort (single center)	Total joint arthroplasty (28,923) (primary or revision)	Aspirin 325 mg twice a day vs warfarin	Unmatched data: Warfarin = 0.99% Aspirin = 0.29% ($P < .001$) HR (95% CI): 3.50 (1.75-8.19)	Hematoma/ bleeding: Warfarin = 0.13% Aspirin = 0% ($P = .07$)	Aspirin group: n = 2800 Warfarin group: n = 26,123 Results in favor of aspirin with unmatched 3:1 and 5:1 matched analysis.

CI, Confidence interval; *GI,* gastrointestinal; *HR,* hazard ratio; *IPC,* intermittent pneumatic compression; *LMWH,* low-molecular-weight heparin; *OR,* odds ratio; *PEP trial,* Pulmonary Embolism Prevention trial; *RCT,* randomized controlled trial; *UFH,* unfractionated heparin.

3 months) in patients who presented with a first unprovoked VTE, either DVT or PE. The Warfarin and Aspirin (WARFASA) trial showed a 42% reduction in recurrence of VTE with aspirin compared with placebo.[33] The Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) trial showed a nonsignificant reduction of the primary end point but a significant decrease in the rate of major vascular events, a secondary composite outcome of VTE and arterial events.[34] The designs of both studies were prospectively matched, and meta-analysis showed a 32%

Table III. Summary of the Antiplatelet Trialists' collaboration meta-analysis assessing the use of antiplatelet therapy in prevention of deep venous thrombosis (*DVT*) in surgical patients

APTc (1994)[2]	*Antiplatelet group*[a]	*Control group*[b]	*Adjusted % of patients with DVT*[c]	*% Odds reduction (SD)*	*Bleeding data* (all surgery patients)	*Drawbacks*
Traumatic orthopedic surgery	454	444	Antiplatelet: 35.9% Control: 41.9% ($P = .02$)	31% (13)	Nonfatal major bleed: Antiplatelet: 0.7% Control: 0.4% ($P = .04$) Absolute excess per 1000 (SD): 3 (2)	Individual studies and therefore meta-analysis suffer from major methodological bias[3,12]
Elective orthopedic surgery	427	436	Antiplatelet: 37.5% Control: 53.2% ($P < .0001$)	49% (11)		
General surgery	1434	1459	Antiplatelet: 19.4% Control: 27.1% ($P < .00001$)	37% (8)	Reoperation, hematoma, or infection due to bleed: Antiplatelet: 7.8% Control: 5.6% ($P = .003$) Absolute excess per 1000 (SD): 22 (9)	
All surgery	2315	2339	Antiplatelet: 26.0% Control: 34.8% ($P < .00001$)	39% (6)		

APTc, Antiplatelet Trialists' collaboration; *SD,* standard deviation.
[a]Aspirin (range, 600-3900 mg) *and/or* other antiplatelet *and/or* antithrombotic drug.
[b]Placebo *or* antithrombotic drug alone if the antiplatelet was associated to an antithrombotic drug in the antiplatelet arm.
[c]For calculating adjusted percentages, adjusted totals were calculated after converting any unevenly randomized trials to even ones, by counting control groups more than once.

Table IV. Warfarin and Aspirin (*WARFASA*) and Aspirin to Prevent Recurrent Venous Thromboembolism (*ASPIRE*) trials: Use of aspirin for prevention of the recurrence of venous thromboembolism (*VTE*)—methodological comparison

RCT (date published)	*WARFASA (May 2012)*[33]	*ASPIRE (November 2012)*[34]
Country(ies)	Italy	Australia, New Zealand, Singapore, India, Argentina
Collecting period	May 2004 to August 2010	May 2003 to August 2011
Inclusion criteria	First unprovoked VTE[a] Treated for 6 to 18 months with VKA	First unprovoked VTE[a] Treated for 6 weeks to 24 months with VKA
Dose, length of treatment	Aspirin 100 mg vs placebo, once daily, for 2 years	
Sample size designed	400	3000, reduced to 1500 in 2005
Primary prespecified outcome	Symptomatic, objectively confirmed recurrence of VTE, defined as the composite of DVT or nonfatal or fatal PE[b]	
Secondary prespecified outcomes	Nonfatal MI, unstable angina, stroke, TIA, acute ischemia of the lower limbs, and death from any cause	Major vascular event (composite of VTE, MI, stroke, or cardiovascular death) and measure of the net clinical benefit[c]
Safety outcomes	Bleeding[d]	
Potential conflict of interest	Both studies were partially supported by Bayer HealthCare. Aspirin and placebo tablets were supplied by Bayer HealthCare. The authors declared that Bayer played no role in the design of the study, in data collection or analysis, or in manuscript preparation. Three authors from WARFASA and 4 from ASPIRE declared receiving consulting or lecturing fees from Bayer.	

DVT, Deep venous thrombosis; *MI,* myocardial infarction; *PE,* pulmonary embolism; *RCT,* randomized controlled trial; *TIA,* transient ischemic attack; *VKA,* vitamin K antagonists.

[a]VTE included symptomatic and objectively confirmed proximal (popliteal vein or more proximal leg veins) DVT, PE, or both DVT and PE.

[b]The primary end point was changed during the study to be consistent with contemporary trials on extended treatment for VTE.

[c]Net clinical benefit means reduction in the rate of the composite of VTE, MI, stroke, major bleeding, or death from any cause.

[d]Either major or clinically relevant nonmajor bleeding. Major bleeding: overt bleeding that was fatal, or occurred in a critical location, or was associated with a decrease in the hemoglobin level of at least 2.0 g/dL, or required a transfusion of 2 units or more of whole blood or red blood cells; includes need for surgical revision in the ASPIRE trial. Clinically relevant nonmajor bleeding: overt bleeding that did not meet any of the criteria for major bleeding and required medical intervention in the WARFASA trial or needed discontinuation of the drug for more than 14 days in the ASPIRE trial.

decrease in recurrent VTE as well as a 34% reduction in the risk of major vascular events. Aspirin was not associated with increased rates of bleeding or death in any of the trials.

DISCUSSION

Aspirin is accepted, easy to administer, and cost-effective,[35,36] and thus it is a logical choice for primary prevention of DVT. The latest guidelines support its use for high-risk orthopedic surgery patients.[5,12] However, studies provide only low-quality evidence, especially compared with more widely used anticoagulants. As study events are relatively low incidence, RCTs need to enroll tens of thousands of patients to show a significant difference between aspirin and controls; for example, Karthikeyan et al[37] recommend a study with a sample size of 14,572 patients to detect a reduction in the event rate from 2.0% to 1.4% with 80% power. In addition, on the basis of experience with arterial and vein graft studies, aspirin resistance due to genetic polymorphisms shows that thromboprophylactic agents may need to be adapted for personalized medicine, rather than broad guidelines for populations of patients.[38,39]

After a first episode of VTE treated with anticoagulation, a high incidence of recurrence persists during the first 3 months after treatment cessation.[40] The two recent RCTs, WARFASA and ASPIRE, provided evidence that aspirin may be better than nontreatment in this context. Nevertheless, questions remain about these statistically well-powered and well-administered studies. Both trials and their authors were supported by the pharmaceutical industry. End points changed during the studies for better homogeneity and comparison; although converging study design is laudable, modifications may also introduce involuntary bias, which is difficult to evaluate. In addition, there is a recent trend toward viewing arterial thrombosis and VTE as two close entities, in their mechanisms as well as in their treatments.[41] The ASPIRE study illustrated this trend with a secondary composite outcome grouping arterial and venous events, showing a positive result in favor of aspirin.

Another trend important to observe is the potential role of statins in VTE prevention, especially in potential modification of aspirin effects.[41] In addition, new anticoagulants have to be considered, despite potential risks associated with the inability to reverse them; recent RCTs have evaluated rivaroxaban[42] and dabigatran[43] with promising results, even though their superiority compared with aspirin has still to be defined. Another question for future trials may examine the role of aspirin in the treatment of

Table V. Warfarin and Aspirin (*WARFASA*) and Aspirin to Prevent Recurrent Venous Thromboembolism (*ASPIRE*) trials: Use of aspirin for prevention of the recurrence of venous thromboembolism (*VTE*)—results and conclusions

RCT	*WARFASA*[33]			*ASPIRE*[34]			*Pooled data (WARFASA and ASPIRE)*[34]
Number of patients randomized in	402			822			1224
Aspirin group	205			411			616
Placebo group	197			411			608
Number of index events	DVT	PE	Both	DVT	PE	Both	
Aspirin group	122 (60%)	83 (40%)	NS	236 (57%)	112 (27%)	59 (14%)	
Placebo group	130 (66%)	67 (34%)	NS	232 (56%)	119 (29%)	56 (14%)	
Percentage of permanent discontinuation[a]							
Global	16.1%			30.3%			
Aspirin group	17.6%			28.5%			
Placebo group	14.7%			32.1%			
Primary outcome (recurrence of VTE)							
Aspirin group	28/205 (6.6% per year)			57/411 (6.5% per year)			85/616
Placebo group	43/197 (11.2% per year)			73/411 (4.8% per year)			116/608
HR (95% CI)	0.58 (0.36-0.93); $P = .02$			0.74 (0.52-1.05); $P = .09$			0.68 (0.51-0.90); $P = .007$
Adjusted HR (95% CI)[b]	0.53 (0.32-0.85); $P = .009$			0.72 (0.51-1.01); $P =$ NS			NS
Secondary outcomes	Death	Arterial event		Net clinical benefit	Major vascular events		Major vascular events
Aspirin group	6/205	8/205		71/411	62/411		98/616
Placebo group	5/197	5/197		99/411	88/411		136/608
HR (95% CI)	1.04 (0.32-3.42)	1.43 (0.47-4.37)		0.67 (0.49-0.91); $P = .01$	0.66 (0.48-0.92); $P = .01$		0.66 (0.51-0.86); $P = .002$
Bleeding							
Aspirin group	4/205			14/411			18/616
Placebo group	4/205			8/411			12/608
HR (95% CI)	0.98 (0.24-3.96); $P = .97$			1.73 (0.72-4.11); $P = .22$			1.47 (0.70-3.08); $P = .31$
Additional observation (recurrence of DVT)							
Aspirin group	16/205			39/411			55/616
Placebo group	28/197			43/411			71/608
HR (95% CI)	0.51 (0.27-0.94); $P = .03$			0.86 (0.56-1.33); $P = .50$			NS
Authors' conclusions	When given after anticoagulant treatment in patients with unprovoked VTE, aspirin is effective in preventing recurrence, with no apparent increase in the risk of major bleeding.			When given after anticoagulant treatment in patients with unprovoked VTE, aspirin did not reduce VTE recurrence. Aspirin reduced the secondary composite outcome of major vascular events by 34% without increasing bleeding and resulted in a significant net clinical benefit.			ASPIRE trial, when considered together with the WARFASA trial, provides consistent evidence that low-dose aspirin is beneficial in preventing recurrent VTE and major vascular events in patients who have had a first episode of unprovoked VTE.

CI, Confidence interval; *DVT,* deep venous thrombosis; *HR,* hazard ratio; *NS,* not specified; *PE,* pulmonary embolism; *RCT,* randomized controlled trial.
[a]Reasons for premature discontinuation were consent withdrawal, new indication for aspirin, new indication for vitamin K antagonist other than VTE, lost to follow-up, adverse events, not qualifying VTE. For the WARFASA trial, the percentage was calculated for the sole purpose of this review and based on the original study design figure. For the ASPIRE trial, these data were retrieved from the supplemental web figures.
[b]Cox proportional hazards model: adjustment for age, sex, index event, and duration of initial anticoagulant treatment; includes smoking and body mass index in the ASPIRE trial.

isolated calf thrombus as well as the role of aspirin in thrombus resolution.

CONCLUSIONS

Aspirin is now recognized as a thromboprophylactic agent for prevention of DVT after hip and knee replacement in orthopedic surgery. In almost all other medical and surgical populations, lack of good-quality studies makes it difficult to define the role of aspirin, and other agents are recommended. We suggest that the current practice using aspirin to prevent thromboembolism include cautious discussion of the benefits and risks of this agent before use in a patient until precise clarification of dosage and treatment length is available. Despite inclusion of aspirin in the guidelines for orthopedic surgery, there is little evidence to support its use for primary prevention of VTE.

The pooled WARFASA and ASPIRE studies suggest that low-dose (100 mg) aspirin is a reasonable alternative

to prevent recurrence of VTE in patients who have been treated for a first episode of unprovoked VTE. Until definitive unbiased trials are published, we suggest that aspirin remain a realistic option to use for secondary prevention of VTE, especially compared with the option of using no prophylaxis.

AUTHOR CONTRIBUTIONS

Conception and design: NS, SD, AD
Analysis and interpretation: NS, EJB, AD
Data collection: NS, SD, RHK
Writing the article: NS, AD
Critical revision of the article: NS, EJB, SD, RHK, AD
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