Perioperative Aspirin for Prevention of Venous Thromboembolism

The PeriOperative ISchemia Evaluation-2 Trial and a Pooled Analysis of the Randomized Trials

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ABSTRACT

Background: The *P*eri*O*perative *IS*chemia *E*valuation-2 (POISE-2) trial compared aspirin with placebo after noncardiac surgery.

Methods: The authors randomly assigned 10,010 patients undergoing noncardiac surgery to receive 200 mg aspirin or placebo 2 to 4 h before surgery and then 100 mg aspirin daily or placebo daily for up to 30 days after surgery. Herein, the authors report the effect of aspirin on venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, as well as an updated pooled analysis of randomized trials of antiplatelet therapy for VTE prevention in noncardiac surgery patients.

Results: Six thousand five hundred forty-eight patients (65.4%) received anticoagulant prophylaxis. VTE occurred in 53 patients (1.1%) allocated to aspirin and in 60 patients (1.2%) allocated to placebo (hazard ratio, 0.89; 95% CI, 0.61 to 1.28). Major or life-threatening bleeding occurred in 312 patients (6.3%) allocated to aspirin and in 256 patients (5.1%) allocated to placebo (hazard ratio, 1.22; 95% CI, 1.04 to 1.44). Concomitant use of anticoagulant prophylaxis did not modify the effect of aspirin on VTE or bleeding. Pooled analysis of the POISE-2 and Pulmonary Embolism Prevention trials demonstrated that symptomatic VTE occurred in 173 (1.3%) of 13,724 patients allocated to aspirin and in 246 (1.8%) of 13,730 patients allocated to placebo (odds ratio, 0.71; 95% CI, 0.56 to 0.89; heterogeneity $P = 0.27$; $I^2 = 17\%$); the impact of aspirin was very similar in those who did and did not receive pharmacologic prophylaxis. Pooled estimates for symptomatic VTE were similar to the pooled estimates for any deep vein thrombosis and pulmonary embolism from the POISE-2 trial, Pulmonary Embolism Prevention trial, and the Antiplatelet Trialists' Collaboration meta-analysis.

Conclusions: Aspirin in the POISE-2 trial did not reduce VTE, but two thirds of patients received anticoagulant prophylaxis, there were few VTE events, and results were consistent with a wide range of aspirin effects. A pooled analysis of the randomized trials demonstrates evidence for the efficacy of aspirin for VTE prevention in hospitalized surgical patients.
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PATIENTS having noncardiac surgery without routine thromboprophylaxis have a 1 to 5% incidence of symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) at 30 days,[1,2] collectively referred to as venous thromboembolism (VTE). Many physicians routinely prescribe anticoagulants for VTE prevention after surgery,[3] but some prefer aspirin because it is inexpensive and is already being taken by about one third of patients scheduled for surgery.[4] The 1994 Antiplatelet Trialists' Collaboration (APTC) meta-analysis involving 8,400 patients enrolled in 53 trials showed that antiplatelet therapy given for an average of 2 weeks compared with no pharmacologic prophylaxis reduces the risk of any (symptomatic or asymptomatic) DVT and PE by about one half in a broad range of hospitalized patients.[5] The Pulmonary Embolism Prevention (PEP) trial involving 17,444 patients demonstrated that

What We Already Know about This Topic

- Perioperative venous thromboembolism (VTE) prophylaxis is important because noncardiac surgical patients without routine thromboprophylaxis have a 1 to 5% incidence of symptomatic thrombotic complications at 30 days.
- Although heparin and other direct, oral anticoagulants are often administered for VTE prevention postoperatively, aspirin is still preferred by some clinicians because it is inexpensive and is already being taken by many patients preoperatively.

What This Article Tells Us That Is New

- From a large database of 10,010 patients undergoing noncardiac surgery who received 200 mg aspirin or placebo 2 to 4 h before surgery and then daily 100 mg aspirin or placebo for up to 30 days postoperatively, it was found that aspirin did not reduce VTE.
- However, two thirds of the patients also received anticoagulant prophylaxis, and there were few VTE events overall.

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160 mg aspirin once daily started preoperatively and continued postoperatively for 35 days compared with placebo reduced the risk of symptomatic VTE by about one third in patients undergoing hip fracture surgery, with similar effects in those who did or did not receive anticoagulant prophylaxis.[6]

The *P*eri*O*perative *I*Schemia *E*valuation-2 (POISE-2) trial was conducted to determine the effects of perioperative aspirin and clonidine on a broad range of cardiovascular outcomes in patients having noncardiac surgery.[7] Aspirin compared with placebo did not reduce the risk of nonfatal myocardial infarction or death at 30 days (primary outcome). We now report the effects of aspirin on VTE in POISE-2 and present an updated pooled analysis combining the POISE-2 results with those of the PEP trial[6] for symptomatic VTE and with those of the PEP trial[6] and the APTC meta-analysis[5] for any DVT or PE.

Materials and Methods

POISE-2 was an international, randomized, controlled trial with a 2 × 2 factorial design[7] comparing aspirin with placebo,[8] and clonidine with placebo,[9] in patients having noncardiac surgery. The institutional review board in Hamilton (Hamilton Integrated Research Board, Hamilton, Ontario, Canada) and the boards at participating centers approved the protocol, and all participants provided informed consent. The trial was registered at ClinicalTrials.gov (identifier: NCT01082874; principal investigator: P.J. Devereaux, Ph.D.; registered on March 8, 2010) before patient enrollment.

Eligibility

Noncardiac surgical inpatients at least 45 yr of age were eligible for inclusion if they were expected to stay in the hospital at least one night and had one or more additional criteria identifying them as being at a high risk for an atherothrombotic event. Patients were excluded if they had taken aspirin, a thienopyridine, or ticagrelor within 72 h before surgery; they were hypersensitive or allergic to aspirin or clonidine; they were at high risk of developing hypotension; they were at high risk of bleeding; or there was a plan to use a thienopyridine, ticagrelor, or therapeutic dose anticoagulation within 3 days of surgery.

Randomization

For the aspirin randomization, patients were enrolled in one of two strata. Patients taking aspirin chronically were enrolled in the aspirin "continuation stratum"; these patients stopped aspirin at least 3 days before surgery. Patients not taking aspirin chronically were enrolled in the aspirin "initiation stratum." Chronic aspirin use was defined as daily aspirin for at least 1 month in the 6 weeks before surgery.

Randomization was performed by a 24-h computerized system. Patients in both aspirin strata received 200 mg aspirin or matching placebo 2 to 4 h before surgery followed by 100 mg aspirin daily or matching placebo for 30 days in the initiation stratum and for 7 days in the continuation stratum (after which they resumed their regular aspirin).

Outcomes

We prespecified DVT and PE at 30 days as tertiary study outcomes. Screening for the presence of asymptomatic DVT or PE was not part of the study design because asymptomatic events are common but mostly resolve without treatment and are much less important for patients than symptomatic events.[10] However, we anticipated that investigators would detect and treat some asymptomatic thrombi (*e.g.*, when performing computerized tomographic [CT] scanning of the chest for another indication), and we therefore asked investigators to report whether DVT and PE events were symptomatic or not. We provided objective criteria for the diagnosis of DVT and PE in the protocol.[7] Diagnosis of DVT required any one of the following: noncompressibility of one or more venous segments on B mode compression ultrasonography or a clearly defined intraluminal filling defect on contrast-enhanced CT or ascending venography. Diagnosis of PE required any one of the following: an intraluminal filling defect of a segmental or larger artery on helical CT scan or pulmonary angiography, high-probability ventilation/perfusion lung scan, or a positive diagnostic test for DVT and either a nondiagnostic ventilation/perfusion lung scan (low or intermediate probability) or a nondiagnostic helical CT scan (subsegmental defects or technically inadequate study).

Safety outcomes were life-threatening bleeding and major bleeding. Life-threatening bleeding was defined as bleeding that was fatal or that led to hypotension that required inotrope or vasopressor therapy or urgent surgery within 24 h (other than superficial vascular repair), or intracranial hemorrhage. Major bleeding was defined as bleeding not meeting the criteria for life-threatening bleeding that resulted in one of the following: hemoglobin less than or equal to 70 g/L and transfusion of more

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than or equal to 2 units of red blood cells; a hemoglobin drop of more than or equal to 50 g/L and transfusion of more than or equal to 2 units of red blood cells; transfusion of more than or equal to 4 units of red blood cells within a 24-h period; or any one of the following interventions: embolization, superficial vascular repair, nasal packing; or retroperitoneal, intraspinal, or intraocular bleeding (confirmed clinically or on imaging).

A central committee blinded to treatment allocation adjudicated all VTE and bleeding outcomes.

Statistical Analysis

All analyses were based on the intention-to-treat principle. Patients who were lost to follow-up were censored on the last day that their outcome status was known. We used Cox proportional hazard models stratified by aspirin strata and clonidine allocation to estimate the effects of aspirin compared with placebo on VTE outcomes and used the Kaplan-Meier estimator to present the time of the first occurrence of VTE. For the subgroup analyses, we used Cox proportional hazards models that incorporated tests of interaction.

We performed subgroup analyses to explore prespecified hypotheses that aspirin would have a bigger effect on VTE in patients who were aged less than 75 yr *versus* more than or equal to 75 yr, had diabetes *versus* did not have diabetes, underwent orthopedic *versus* nonorthopedic surgery, did not receive regional anesthesia *versus* received regional anesthesia, and did not receive prophylactic anticoagulants during the first 3 days after surgery *versus* those who did. We also explored prespecified hypotheses that aspirin would have a larger effect in the aspirin continuation *versus* aspirin initiation stratum, in patients having nonmajor *versus* major surgery, and in those who did not *versus* those who did receive any antithrombotic therapy (prophylactic or therapeutic) during the trial (excluding antithrombotic treatment for VTE). We expected that the effects of aspirin compared with those of placebo on VTE would be consistent in other prespecified subgroups that we examined, including men and women, smokers and nonsmokers, and those with or without a history of heart failure.

Pooled Analysis

To obtain more reliable estimates of the effect of aspirin for VTE prevention, we pooled the POISE-2 data with those of the PEP trial for symptomatic VTE using the Mantel–Haenszel method and a random effects model and explored the effect of aspirin compared with that of placebo according to whether patients also received anticoagulant prophylaxis. We also pooled the POISE-2 data with those of the PEP trial and the APTC meta-analysis for any DVT (asymptomatic or symptomatic) and for any PE (asymptomatic or symptomatic) and examined the consistency of the results in POISE 2 *versus* PEP *versus* the APTC meta-analysis. We were unable to pool data for VTE from the APTC meta-analysis because the investigators did not report this outcome. We explored heterogeneity with the Cochran Q test and calculated the I^2 statistic to address consistency among trials.

We assessed the risk of bias in POISE-2 and PEP using a modified form of the Cochrane risk of bias tool and confidence in estimates of effect (quality of evidence) using the Grades of Recommendation, Assessment, Development, and Evaluation approach.[11]

Results

POISE-2 included 10,010 patients (5,628 in the starting aspirin stratum and 4,382 in the continuation aspirin stratum) from 135 hospitals in 23 countries, of whom 4,998 were randomized to aspirin and 5,012 to placebo. The 30-day follow-up was complete for 99.9% of participants.

Table 1 shows that baseline patient characteristics, type of surgery, use of regional anesthesia, and postoperative use of antithrombotic therapies and nonsteroidal antiinflammatory drugs were well balanced between randomized groups. Baseline characteristics of patients in the aspirin continuation and aspirin-naive groups have been previously reported. Prophylactic dose anticoagulation was received by 65.4% of the patients during the first 30 days after surgery.

Table 2 shows the VTE outcomes, and figure 1 presents the Kaplan-Meier estimates for VTE. VTE occurred in 53 patients (1.1%) allocated to aspirin and in 60 patients (1.2%) allocated to placebo (hazard ratio [HR] for the aspirin group, 0.89; 95% CI, 0.61 to 1.28). DVT occurred in 25 patients (0.5%) allocated to aspirin and in 35 patients (0.7%) allocated to placebo (HR, 0.72; 95% CI, 0.43 to 1.20), whereas PE occurred in 33 patients (0.7%) allocated to aspirin and in 31 patients (0.6%) allocated to placebo (HR, 1.07; 95% CI, 0.65 to 1.74). Results were similar irrespective of whether patients received anticoagulant prophylaxis.

Aspirin reduced proximal leg (calf trifurcation or above) DVT (10/4,998 [0.2%] *vs.* 22/5,012 [0.4%]; HR, 0.46; 95% CI, 0.22 to 0.96) but did not appear to reduce distal (below calf trifurcation) DVT (12/4,998 [0.2%] *vs.* 10/5,012 [0.2%]; HR, 1.20; 95% CI, 0.52 to 2.78). Aspirin was associated with a favorable point estimate for symptomatic DVT (17/4,998 [0.3%] *vs.* 29/5,012 [0.6%]; HR, 0.59; 95% CI, 0.32 to 1.07) but not for asymptomatic DVT (9/4,998 [0.2%] *vs.* 6/5,012 [0.1%]; HR, 1.51; 95% CI, 0.54 to 4.23).

Table 3 shows bleeding outcomes. Major or life-threatening bleeding occurred in 312/4,998 patients (6.3%) allocated to aspirin and in 256/5,012 patients (5.1%) allocated to placebo (HR, 1.22; 95% CI, 1.04 to 1.44). Most bleeding (78.3%) was at surgical sites. The HRs for major or life-threatening bleeding were similar irrespective of whether patients received anticoagulant prophylaxis (heterogeneity P = 0.49), but bleeding rates were higher in those who received both aspirin and anticoagulant prophylaxis than in those who received aspirin alone (7.4% *vs.* 4.1%).

Aspirin did not reduce death from any cause (1.3% *vs.* 1.2%; HR, 1.05; 95% CI, 0.74 to 1.49).

Table 1. Baseline Characteristics, Type of Surgery, Anesthesia/Analgesia, and Medications

Characteristics	Aspirin Group (n = 4,998)	Placebo Group (n = 5,012)
Age, yr, mean [± SD]	68.6 ± 10.3	68.6 ± 10.3
Age, ≥ 75 yr, n (%)	1,551 (31.0)	1,554 (31.0)
Sex, male, n (%)	2,597 (52.0)	2,687 (53.6)
Medical history, n (%)		
Smoking within 2 yr of surgery	1,295 (25.9)	1,262 (25.2)
Diabetes taking medical treatment	1,874 (37.5)	1,911 (38.1)
Congestive heart failure	184 (3.7)	155 (3.1)
eGFR calculated by CKD-EPI, ml/min		
0–29	189 (3.8)	207 (4.2)
30–44	355 (7.2)	334 (6.8)
45–59	686 (13.9)	725 (14.7)
60+	3,690 (75.0)	3,654 (74.3)
Surgery		
Major	3,806 (76.9)	3,832 (77.0)
Surgery type, n (%)		
Orthopedic	1,891 (38.2)	1,953 (39.2)
General	1,327 (26.6)	1,337 (26.7)
Other	1,821 (36.8)	1,777 (35.7)
Intraoperative anesthesia, n (%)		
Any neuroaxial (epidural, spinal, or combined)	2,183 (44.1)	2,185 (43.9)
General alone	2,708 (54.7)	2,732 (54.9)
Other	61 (1.2)	62 (1.2)
Medications taken within 24 hr before surgery, n (%)		
Prophylactic dose anticoagulant	630 (12.6)	652 (13.0)
Nonsteroidal antiinflammatory drug	472 (9.4)	470 (9.4)
Statin	1,822 (36.5)	1,856 (37.0)
Medications taken during first 3 d after surgery, n (%)		
Prophylactic dose anticoagulant	3,235 (65.0)	3,223 (64.5)
Therapeutic dose anticoagulant	240 (4.8)	220 (4.4)
Nonsteroidal antiinflammatory drug	1,582 (31.8)	1,592 (31.8)
Medications taken during first 30 d after surgery, n (%)		
Prophylactic dose anticoagulant	3,276 (65.5)	3,272 (65.3)
Therapeutic dose anticoagulant	381 (7.6)	358 (7.1)
Nonsteroidal antiinflammatory drug	1,815 (36.3)	1,813 (36.2)

CKD-EPI = chronic kidney disease epidemiology collaboration equation; eGRF, estimated glomerular filtration rate.

There was no impact of clonidine on any of the results comparing aspirin with placebo ($P \geq 0.11$ for all interactions).

Figure 2 shows the results of key subgroup analyses. Event rates for VTE were similar in patients treated with aspirin compared with placebo irrespective of whether patients received anticoagulant prophylaxis, and there was no significant interaction for any of the subgroups examined.

Table 4 shows the results of the pooled analysis of the POISE-2 and PEP trials for symptomatic VTE. These estimates are based on 27,454 hospitalized surgical patients and 419 events. Symptomatic VTE occurred in 173 (1.3%) of 13,724 patients allocated to aspirin and in 246 (1.8%) of 13,730 patients allocated to placebo (odds ratio [OR], 0.70; 95% CI, 0.57 to 0.85; heterogeneity $P = 0.27$; $I^2 = 17\%$). We judged both trials to be at low risk of bias, and when considering the narrow CIs around the pooled estimates, the consistency of the results in the two trials, that neither trial screened for asymptomatic VTE, and no publication bias, we rated the confidence in the estimates as high.

The PEP trial also reported the results in hip fracture patients who did or did not receive anticoagulant prophylaxis. Pooled data from POISE-2 and PEP according to the use of anticoagulant prophylaxis (23,588 patients and 376 events) demonstrated similar results in those who received anticoagulant prophylaxis (80/6,244 [1.3%] *vs.* 112/6,160 [1.8%]; OR, 0.72; 95% CI, 0.50 to 0.94) and in those who did not receive anticoagulant prophylaxis (73/5,433 [1.3%] *vs.* 111/5,751 [1.9%]; OR, 0.69; 95% CI, 0.51 to 0.93), with no statistical evidence of heterogeneity ($P = 0.95$; $I^2 = 0$).

Figure 3 shows the results for relative effects of antiplatelet therapy compared with no antiplatelet therapy or placebo for any DVT and PE from POISE-2, PEP, and the APTC. The pooled estimates for DVT are based on 32,108 hospitalized surgical patients and 1,675 events, and the pooled estimates for PE are based on 36,345 hospitalized surgical patients and

Table 2. Effects of Aspirin on 30-day Venous Thromboembolism Outcomes

	Aspirin (n = 4,998)	Placebo (n = 5,012)	Hazard Ratio (95% CI)	*P* Value
VTE (DVT or PE), n (%)*	53 (1.1)	60 (1.2)	0.89 (0.61–1.28)	0.52
Symptomatic	45 (0.9)	53 (1.1)	0.85 (0.57–1.27)	0.42
Asymptomatic	11 (0.2)	9 (0.2)	1.23 (0.51–2.96)	0.65
DVT, n (%)*	25 (0.5)	35 (0.7)	0.73 (0.42–1.20)	0.20
Symptomatic	17 (0.3)	29 (0.6)	0.59 (0.32–1.07)	0.08
Asymptomatic	9 (0.2)	6 (0.1)	1.51 (0.54–4.23)	0.44
PE, n (%)	33 (0.7)	31 (0.6)	1.07 (0.65–1.74)	0.79
Symptomatic	31 (0.6)	28 (0.6)	1.11 (0.67–1.85)	0.69
Asymptomatic	2 (0.0)	3 (0.1)	0.67 (0.11–4.00)	0.66
DVT location, n (%)				
Leg	22 (0.4)	32 (0.6)	0.69 (0.40–1.19)	0.18
Femoral or more proximal	3 (0.1)	14 (0.3)	0.21 (0.06–0.75)	0.02
Calf trifurcation or more proximal	10 (0.2)	22 (0.4)	0.46 (0.22–0.96)	0.04
Distal	12 (0.2)	10 (0.2)	1.20 (0.52–2.78)	0.67
Arm	4 (0.1)	2 (0.1)	2.01 (0.37–10.95)	0.42
Insertion of IVC filter, n (%)	4 (0.1)	0 (0.0)	—	—
PE severity, n (%)				
RV dysfunction	1 (0.0)	3 (0.1)	0.33 (0.03–3.21)	0.34
Elevated biomarker	4 (0.1)	11 (0.2)	0.36 (0.12–1.14)	0.08
Requiring ICU/CCU admission	3 (0.1)	6 (0.1)	0.50 (0.13–2.00)	0.33
Treated with thrombolytic therapy	2 (0.0)	3 (0.1)	0.67 (0.11–4.00)	0.66
Fatal	1 (0.1)	1 (0.1)	1.00 (0.06–16.05)	0.99
Any of the above	9 (0.2)	13 (0.3)	0.69 (0.30–1.62)	0.40

*Some patients experienced both DVT and PE, and one patient experienced both leg and arm DVT.

CCU = coronary care unit; DVT = deep vein thrombosis; ICU = intensive care unit; IVC = inferior vena cava; PE = pulmonary embolism; RV = right ventricular; VTE = venous thromboembolism.

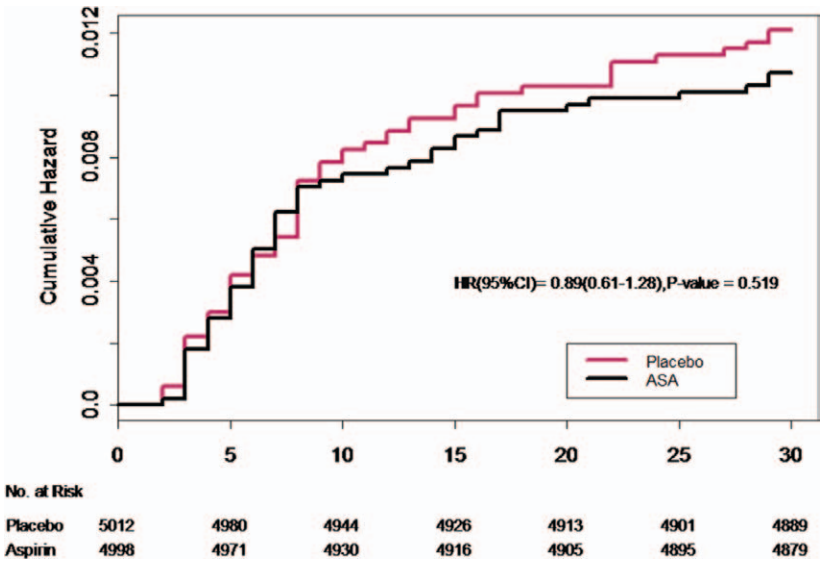

Fig. 1. Kaplan-Meier estimates of venous thromboembolism. HR = hazard ratio.

375 events. DVT occurred in 710 (4.4%) of 16,039 patients allocated to antiplatelet therapy and in 965 (6.0%) of 16,069 patients allocated to placebo (OR, 0.66; 95% CI, 0.59 to 0.74; heterogeneity $P = 0.33$; $I^2 = 12$), whereas PE occurred in 132 (0.7%) of 18,165 patients allocated to antiplatelet therapy and in 243 (1.3%) of 18,180 patients allocated to placebo (OR, 0.52; 95% CI, 0.33 to 0.80; heterogeneity $P = 0.005$; $I^2 = 73\%$).

Discussion

Our prespecified analyses of the POISE-2 trial did not demonstrate that aspirin reduces the risk of VTE in noncardiac

Table 3. Effects of Aspirin on 30-day Bleeding Outcomes*

	Aspirin (n = 4,998)	Placebo (n = 5,012)	Hazard Ratio (95% CI)	*P* Value
Bleeding, n (%)				
Major or life threatening	312 (6.3)	256 (5.1)	1.22 (1.04–1.44)	0.02
Major	230 (4.6)	188 (4.2)	1.23 (1.01–1.49)	0.04
Life threatening	87 (1.7)	73 (1.5)	1.19 (0.88–1.63)	0.26

*Among patients who also received anticoagulant prophylaxis, major or life-threatening bleeding occurred in 242 (7.4%) of 3,276 patients allocated to aspirin and 204 (6.2%) of 3,272 patients allocated to placebo (hazard ratio [HR], 1.18; 95% CI, 0.98 to 1.43), whereas among patients who did not receive anticoagulant prophylaxis, major of life-threatening bleeding occurred in 70 (4.1%) of 1,722 patients allocated to aspirin and 52 (3.0%) of 1,740 patients allocated to placebo (HR, 1.36; 95% CI, 0.95 to 1.95; heterogeneity *P* = 0.49).

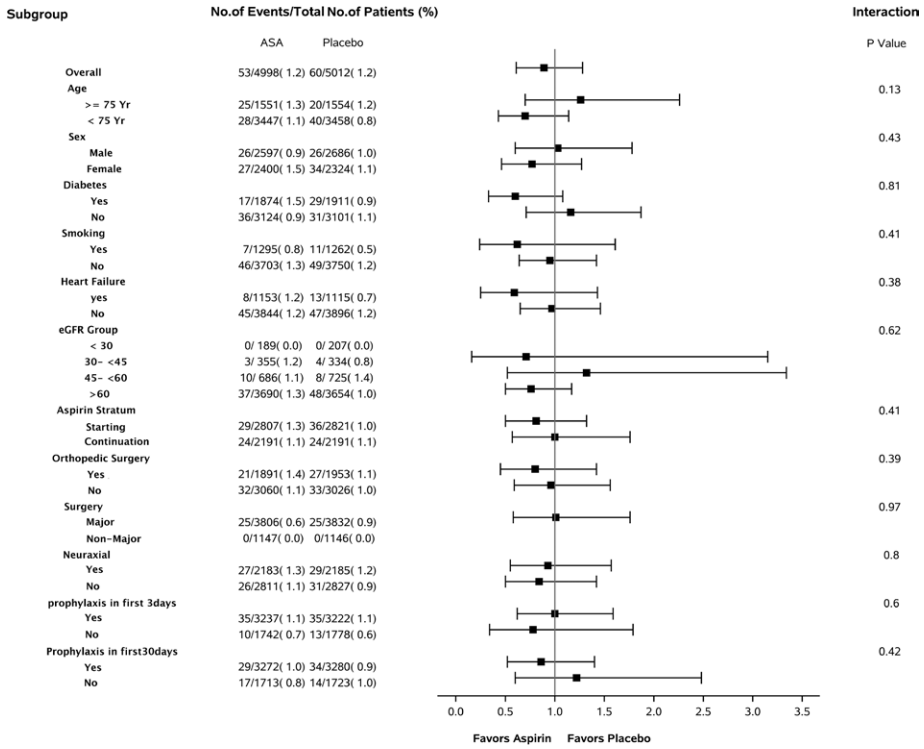

Fig. 2. Subgroup analyses for venous thromboembolism. ASA = aspirin; eGFR = estimated glomerular filtration rate (ml/min).

Table 4. Pooled Estimate of the Effects of Antiplatelet Therapy Compared with No Antiplatelet Therapy on Symptomatic VTE from the POISE-2 and PEP Trials

Outcome	Aspirin, n (%)	Placebo, n (%)	Odds Ratio (95% CI)	Heterogeneity *P* Value	I^2, %
Symptomatic VTE					
POISE-2	45/4,998 (0.9)	53/5,012 (1.1)	0.85 (0.57–1.27)		
PEP	128/8,726 (1.5)	193/8,718 (2.2)	0.66 (0.52–0.82)		
Combined	173/13,724 (1.3)	246/13,730 (1.8)	0.71 (0.56–0.89)	0.27	17
Bleeding					
POISE-2	312/4,998 (6.3)	256/5,012 (5.1)	1.24 (1.04–1.47)		
PEP	261/8,726 (2.9)	232/8,718 (2.7)	1.13 (0.94–1.35)		
Combined	573/13,724 (4.2)	488/13,730 (3.6)	1.18 (1.05–1.34)	0.46	0

PEP = Pulmonary Embolism Prevention; POISE-2 = The *P*eri*O*perative *I*Schemia *E*valuation-2; VTE = venous thromboembolism.

surgical patients although there was a suggestion that it may have reduced proximal DVT. Despite including more than 10,000 patients in the trial, the very low VTE event rate (approximately 1.1%) and total number of events (113) limited the trial's power to detect a benefit of aspirin for VTE prevention.

Our pooled analysis combining the results of POISE-2 with those of the PEP trial demonstrated that aspirin is

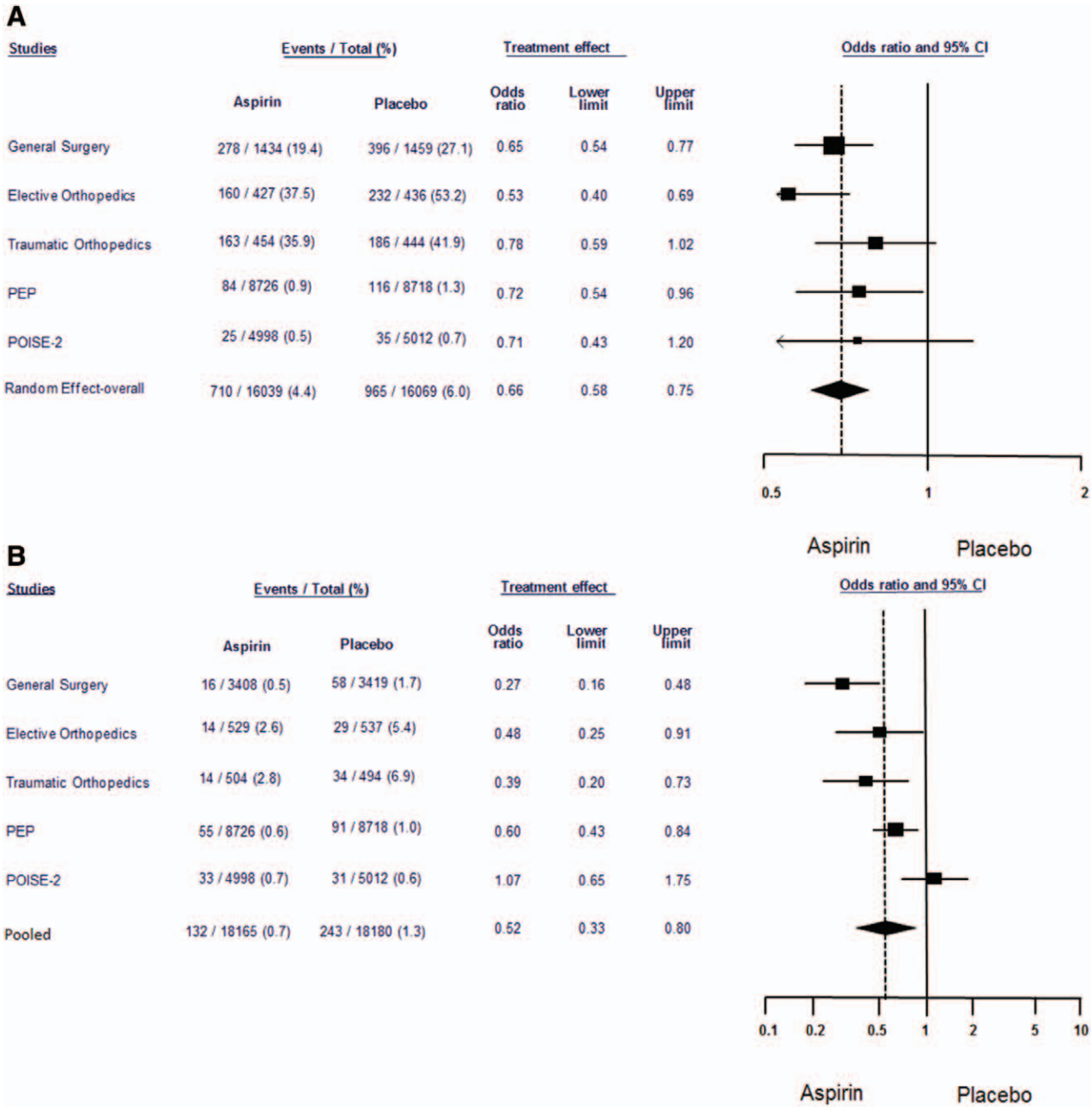

Fig. 3. Meta-analysis data from *P*eri*O*perative *I*Schemia *E*valuation-2 (POISE-2), Pulmonary Embolism Prevention (PEP), and the Antiplatelet Trialists' Collaboration. (*A*) Forest plot and pooled estimate of the effects of antiplatelet therapy compared with no antiplatelet therapy on any (asymptomatic or symptomatic) deep vein thrombosis from the POISE-2 and PEP trials and from surgical patients in the Antiplatelet Trialists Collaboration meta-analysis. Cochran *Q* test for heterogeneity, 4.80; $P = 0.44$; $I^2 = 13$. (*B*) Forest plot and pooled estimate of the effects of antiplatelet therapy compared with no antiplatelet therapy on pulmonary embolism from the POISE-2 and PEP trials and surgical patients in the Antiplatelet Trialists Collaboration meta-analysis. Cochran *Q* test for heterogeneity, 14.72; $P = 0.005$; $I^2 = 73$.

associated with a reduced risk of symptomatic VTE by about one third. Confidence in this finding is supported by the low risk of bias of the POISE-2 and PEP trials, the narrow CI, and the consistent results of the two studies. Some of the trials included in the APTC meta-analysis were of lower quality (*e.g.*, uncertain allocation concealment, lack of blinding of study personnel and patients to treatment allocation, and use of screening radiolabeled fibrinogen studies to diagnose DVT), but the consistency of the pooled results for symptomatic VTE with that of the pooled results for any DVT and PE from the analysis that combined the results of POISE-2 and PEP trials with those of the APTC meta-analysis strengthens the conclusion that aspirin is effective for VTE prevention in surgical patients.

Exploratory analyses that separately examined the effects of aspirin compared with placebo on symptomatic compared with asymptomatic DVT and on proximal compared with distal DVT suggest that aspirin is more effective in preventing large than preventing small thrombi. Aspirin might also have a greater effect on PE associated with right ventricular dysfunction, elevated biomarkers and admission to a critical care unit, or requiring thrombolysis for less severe episodes of PE, but these differences were not statistically significant. Collectively, our data suggest that aspirin may be less effective for prevention of initiation than for progression of thrombus possibly because it is a relatively weak antiplatelet drug and platelets play a greater role in later stages of VTE formation.

The use of anticoagulant prophylaxis in two thirds of patients likely contributed to the low incidence of VTE in the POISE-2 trial (1.2% rate of VTE in patients allocated to placebo). Improvements in surgical and anesthetic techniques and the quality of postsurgical care (*e.g.*, intensive care unit management, transfusion, and early mobilization) also likely explain lower rates of symptomatic VTE in more recent trials[1] compared with trials conducted more than two decades ago.[5] Recent studies comparing dabigatran, rivaroxaban, or apixaban with low molecular-weight heparin for VTE prevention in patients undergoing major orthopedic surgery reported 1 to 2% rates of symptomatic VTE.[1] As a result of low event rates, the POISE-2 trial had less than 50% power to detect a significant reduction in symptomatic VTE.

The effects of aspirin compared with placebo on VTE were similar in all prespecified subgroups examined, including in patients who received anticoagulant prophylaxis and those who did not receive anticoagulant prophylaxis. Likewise, the PEP trialists reported that aspirin produced consistent proportional reductions in DVT and PE irrespective of whether patients received heparin prophylaxis. These results support the validity of testing the efficacy and safety of aspirin compared with placebo on a background of usual care, including the use of anticoagulant prophylaxis.

The POISE-2 trial is notable for randomizing a large number of patients; blinding of patients, caregivers, investigators, and outcome assessors to treatment allocation; high adherence (more than 80%) to randomized treatment allocation; and near-complete follow-up. For the assessment of aspirin's ability to prevent VTE, the most important weakness was a low VTE event rate. We did not adjudicate whether events were symptomatic, but very few patients underwent screening for VTE, and the majority of events were reported to be symptomatic. The limitation of the pooled analysis is that many of the trials included in the APTC meta-analysis were performed more than two decades ago. Rates of VTE are much lower in more recent trials, including POISE-2, whereas bleeding event rates appear to be similar, thereby potentially altering the balance between benefits and risks of antithrombotic prophylaxis.

In conclusion, the POISE-2 trial did not demonstrate a benefit of aspirin compared with placebo for VTE prevention in patients undergoing noncardiac surgery, but there were few VTE events. Combining our data with PEP provides evidence that aspirin reduces the risk of symptomatic VTE in hospitalized surgical patients by about one third. These results support the use of aspirin as a simple, inexpensive treatment for VTE prevention in hospitalized surgical patients, particularly when anticoagulant therapy is unavailable or contraindicated. In individual patients, the benefits of aspirin for the prevention of VTE will need to be weighed against the increase in bleeding risk.

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Competing Interests

Dr. Yusuf received funds for research from Boehringer Ingelheim, Germany, for the Prospective Urban and Rural Epidemiological (PURE) study (epidemiology), Management of myocardial injury After NoncArdiac surGEry (MANAGE) study (trial of antithrombotics), and RelY study (trial in atrial fibrillation). Dr. Jones received funding for travel to PeriOperative ISchemia Evaluation-2 (POISE-2) steering committee study meeting. Dr. Painter was reimbursed for travel and accommodation expenses to travel to POISE-2 investigator's meeting on March 28, 2014, Washington, D.C. Per-patient payments from Monash University, Melbourne, Victoria, Australia, paid to his institution for other concurrently run clinical trials (The BALANCED Anaesthesia Study, Aspirin and Tranexamic Acid for Coronary Artery Surgery [ATACAS], REstrictive Versus LIb-Eral Fluid Therapy in Major Abdominal Surgery [RELIEF], and Measurement of Exercise Tolerance before Surgery [METS]) to support research nursing salaries and meet trial expenses. The work by Dr. Eikelboom was supported by a personnel award from the Heart and Stroke Foundation, Ottawa, Ontario, Canada. The other authors declare no competing interests.

Reproducible Science

Full protocol available from Dr. Eikelboom: eikelbj@mcmaster.ca. Raw data available from Dr. Eikelboom: eikelbj@mcmaster.ca.

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