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Aspirin in Patients With Previous Percutaneous Coronary Intervention Undergoing Noncardiac Surgery

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Background: Uncertainty remains about the effects of aspirin in patients with prior percutaneous coronary intervention (PCI) having noncardiac surgery.

Objective: To evaluate benefits and harms of perioperative aspirin in patients with prior PCI.

Design: Nonprespecified subgroup analysis of a multicenter factorial trial. Computerized Internet randomization was done between 2010 and 2013. Patients, clinicians, data collectors, and outcome adjudicators were blinded to treatment assignment. (ClinicalTrials.gov: NCT01082874)

Setting: 135 centers in 23 countries.

Patients: Adults aged 45 years or older who had or were at risk for atherosclerotic disease and were having noncardiac surgery. Exclusions were placement of a bare-metal stent within 6 weeks, placement of a drug-eluting stent within 1 year, or receipt of nonstudy aspirin within 72 hours before surgery.

Intervention: Aspirin therapy (overall trial, *n* = 4998; subgroup, *n* = 234) or placebo (overall trial, *n* = 5012; subgroup, *n* = 236) initiated within 4 hours before surgery and continued throughout the perioperative period. Of the 470 subgroup patients, 99.9% completed follow-up.

Measurements: The 30-day primary outcome was death or nonfatal myocardial infarction; bleeding was a secondary outcome.

Results: In patients with prior PCI, aspirin reduced the risk for the primary outcome (absolute risk reduction, 5.5% [95% CI, 0.4% to 10.5%]; hazard ratio [HR], 0.50 [CI, 0.26 to 0.95]; *P* for interaction = 0.036) and for myocardial infarction (absolute risk reduction, 5.9% [CI, 1.0% to 10.8%]; HR, 0.44 [CI, 0.22 to 0.87]; *P* for interaction = 0.021). The effect on the composite of major and life-threatening bleeding in patients with prior PCI was uncertain (absolute risk increase, 1.3% [CI, −2.6% to 5.2%]). In the overall population, aspirin increased the risk for major bleeding (absolute risk increase, 0.8% [CI, 0.1% to 1.6%]; HR, 1.22 [CI, 1.01 to 1.48]; *P* for interaction = 0.50).

Limitation: Nonprespecified subgroup analysis with small sample.

Conclusion: Perioperative aspirin may be more likely to benefit rather than harm patients with prior PCI.

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Noncardiac surgery is common, with more than 200 million annual procedures worldwide (1, 2). Despite the benefits of noncardiac surgery, major perioperative cardiovascular complications occur and are associated with mortality, prolonged hospitalization, and costs (3, 4). Physicians commonly encounter patients undergoing noncardiac surgery who have had a prior percutaneous coronary intervention (PCI) (5); these patients are at increased risk for major perioperative cardiovascular complications (5–9).

In the POISE-2 (PeriOperative ISchemic Evaluation-2) trial, we randomly assigned 10 010 patients having noncardiac surgery to receive aspirin or placebo and showed that aspirin did not prevent the primary composite outcome of death and nonfatal myocardial infarction but did increase the risk for major bleeding (10–12). These results influenced perioperative guidelines (13, 14).

We reported the 4 planned aspirin subgroup analyses in the main POISE-2 publication (11). When POISE-2 was designed, we did not plan a PCI subgroup analysis because we did not anticipate that physicians would enroll patients with a history of PCI. However, given that investigators enrolled 470 patients with prior PCI and the ongoing uncertainty about the effects of antiplatelet therapy for these patients (15, 16), we did this POISE-2 substudy to determine whether perioperative low-dose aspirin, compared with placebo, affected 30-day events in patients with previous PCI.

Methods

Design Overview

POISE-2 was an international, randomized controlled, factorial trial that separately evaluated the ef-

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fects of aspirin versus placebo and clonidine versus placebo in patients having noncardiac surgery. Patients were allocated in a 1:1:1:1 ratio to receive aspirin and clonidine, placebo and clonidine, aspirin and placebo, or placebo for both drugs. Full details of the trial design and results are reported elsewhere (10–12). Institutional review boards approved the trial before recruitment started at participating centers.

Setting and Participants

Patients aged 45 years or older who were having noncardiac surgery with an expected postoperative stay of at least 1 night were eligible if they had or were at risk for atherosclerotic disease. The trial excluded patients who received a bare-metal stent within 6 weeks or a drug-eluting stent within 1 year before randomization because of the risk for stent thrombosis associated with premature antiplatelet withdrawal. Patients who took nonstudy aspirin within 72 hours before surgery were also excluded to ensure unimpaired hemostasis before surgery.

Participants were recruited in 135 centers in 23 countries from July 2010 to December 2013. Eighty-two centers from 21 countries enrolled patients with a history of PCI. Research personnel enrolled patients in an initiation stratum if they were not receiving long-term aspirin and in a continuation stratum if they were receiving long-term aspirin (defined as daily aspirin for at least 1 month within the 6 weeks before surgery). Patients in the aspirin continuation stratum had to discontinue aspirin therapy at least 3 days before surgery.

Randomization and Interventions

After giving written informed consent, patients were randomly assigned before surgery by a 24-hour computerized Internet system that concealed randomization. Block randomization, stratified by center and aspirin stratum, was used. Patients received aspirin or identical-appearing placebo (200 mg) within 4 hours before surgery and continued at a dosage of 100 mg/d for 30 days in the initiation stratum and for 7 days in the continuation stratum, after which patients resumed regular aspirin dosing. Study personnel assessed study drug adherence through nursing records in the hospital and through patient reporting after discharge. Patients, clinicians, data collectors, and outcome adjudicators were blinded to study drug allocation.

Patients had a troponin measurement (or creatine kinase–MB if troponin was not available) 6 to 12 hours after surgery and on the first, second, and third days after surgery. Electrocardiography was done when an elevated troponin or creatine kinase–MB level was detected. Research personnel followed patients until 30 days after randomization, collected data, and submitted case report forms and supporting documentation directly to the data management system.

Outcomes and Follow-up

Outcomes evaluated in this PCI substudy included the primary outcome (a composite of death and nonfatal myocardial infarction) and secondary outcomes (myocardial infarction, all-cause mortality, vascular mortality, stroke, congestive heart failure, composite of major and life-threatening bleeding, major bleeding, life-threatening bleeding, and clinically important hypotension) at 30 days after randomization. Outcome definitions are reported in the **Supplement** (available at Annals.org). Blinded outcome adjudicators evaluated the events reported in this substudy, except for congestive heart failure and clinically important hypotension. Their decisions were used in the analyses.

Statistical Analysis

A statistical analysis plan was finalized before these substudy analyses were begun (**Supplement**). We expected aspirin to have a greater beneficial effect in patients with a history of PCI than in those without. We analyzed patients in the groups to which they were allocated, according to the intention-to-treat principle. Patients lost to follow-up before day 30 after randomization with no event reported were censored on the last day their status was known. All statistical analyses were done using SAS, version 9.4 (SAS Institute).

For the primary and secondary outcomes, we did subgroup analyses based on whether patients had prior PCI (prior PCI vs. no prior PCI). For these subgroup analyses, we used Cox proportional hazards models that incorporated tests of interaction. These models adjusted for clonidine allocation. For the primary outcome, we tested for the proportional hazards assumption by including a time–aspirin allocation interaction term in the Cox proportional hazards model (time log-transformed). We found no evidence that the proportional hazards assumption had been violated; all P values were at least 0.55.

We considered a P value for interaction less than 0.05 to be significant and to provide some evidence of a subgroup effect. In instances where the test for interaction was not significant, we considered the overall trial result (with the larger sample size) the likely best estimate of effect for all patients, including those within the subgroups.

Estimates of the hazard ratios (HRs) and 2-sided 95% CIs were calculated using the Cox proportional hazards models. We also determined the Kaplan–Meier estimates of 30-day cumulative risk. We report between-group differences in proportions between the treatment groups as absolute risk reductions (ARRs) and increases (ARIs). We determined the 95% CIs for these differences.

Among patients with a history of PCI, we did subgroup analyses based on the type of stent (bare-metal vs. drug-eluting), timing of PCI (≤1 year vs. >1 year before surgery), and preoperative use of an antiplatelet medication (use within 7 days vs. no use within 7 days before surgery) for the primary outcome. We used the same analytic approach as in the analyses comparing the prior-PCI versus no-prior-PCI subgroups.

Role of the Funding Source

POISE-2 was supported by grants from the Canadian Institutes of Health Research, the Australian National Health and Medical Research Council, and the Spanish Ministry of Health and Social Policy. Bayer

Pharmaceuticals provided the aspirin used in the study, and Boehringer Ingelheim provided the clonidine and some funding. No donor or funder had a role in the design, conduct, data collection, data analyses, or manuscript preparation. The Population Health Research Institute (McMaster University, Hamilton, Ontario, Canada) was the trial coordinating center. The investigators and members of key committees and groups are reported in the **Supplement**.

RESULTS

Figure 1 is the study flow diagram; 99.9% of the patients randomly assigned to a treatment group completed the 30-day follow-up. POISE-2 enrolled 470 patients with prior PCI (255, 119, 53, 41, and 2 patients had a bare-metal stent, drug-eluting stent, unknown type of stent, no stent, and uncertainty about whether a stent was used, respectively), of whom 234 were randomly assigned to receive aspirin and 236 placebo. The allocation to receive clonidine was similar between patients with prior PCI (233 patients [49.6%]) and those without (4776 patients [50.1%]) (P = 0.84). The median time from stent placement to noncardiac surgery was 64.0 months (interquartile range, 34.0 to 113.0 months).

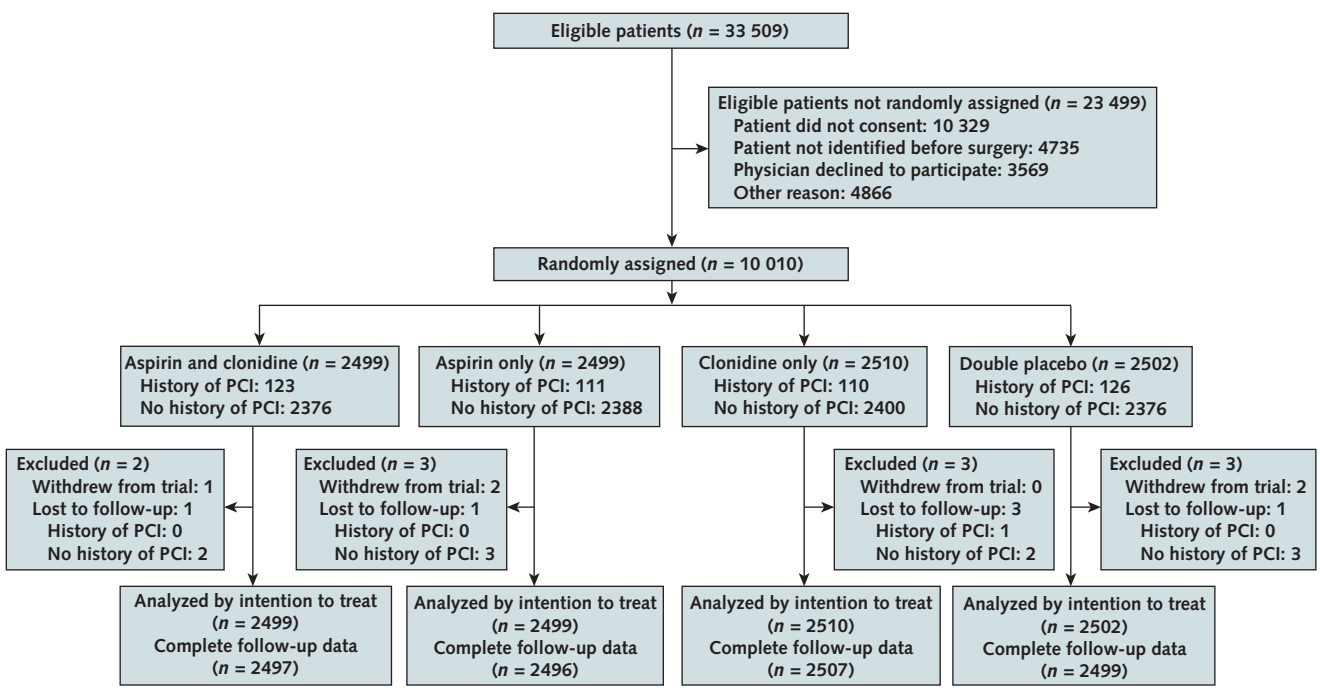
Table 1 presents the baseline characteristics, medication use, and aspirin strata of patients with and without a history of PCI, by treatment group. Patients with prior PCI had more known coronary artery disease, more commonly took antiplatelet and anticoagulant medications in the 7 days before surgery (nonstudy aspirin, thienopyridine, or direct thrombin or factor Xa inhibitors), and were more commonly in the aspirin continuation stratum than patients without prior PCI. Patients who had not had PCI before surgery were older; were more commonly female; more commonly had major surgery and urgent or emergent surgery; and were more likely to have a history of treated diabetes, hypertension, and smoking in the 2 years before surgery.

Among patients with prior PCI, the baseline characteristics, medications, and aspirin strata were similar in the aspirin and placebo groups. Most patients (>85%) with PCI before surgery were in the continuation stratum; aspirin was withdrawn a median of 6 days (interquartile range, 4 to 8 days) before surgery. Among patients with prior PCI, 80.3% of the aspirin group and 83.0% of the placebo group took at least 80% of the study drug (**Appendix Table 1**, available at Annals.org).

Table 2 reports the results of the primary and secondary outcomes in the overall trial and in the no-prior-PCI and prior-PCI subgroups. Among patients with prior PCI, fewer patients had the primary outcome with aspirin than placebo (14 patients [6.0%] vs. 27 patients [11.5%]; ARR, 5.5% [95% CI, 0.4% to 10.5%]; HR, 0.50 [CI, 0.26 to 0.95]); however, in the no-prior-PCI subgroup, the aspirin and placebo groups did not differ in the primary outcome (337 patients [7.1%] vs. 328 patients [6.9%]; ARI, 0.2% [CI, −0.8% to 1.2%]; HR, 1.03 [CI, 0.89 to 1.20]) (P for interaction = 0.036 for the prior-PCI vs. no-prior-PCI subgroup effects). **Figure 2** shows the Kaplan–Meier curves for the primary end point of death or nonfatal myocardial infarction at 30 days among patients with prior PCI.

Aspirin compared with placebo did not affect myocardial infarction in the no-prior-PCI subgroup (297 pa-

Figure 1. Study flow diagram.



PCI = percutaneous coronary intervention.

Table 1. Baseline Characteristics, Medications, and Aspirin Strata Among Patients With and Without Prior PCI, by Treatment Group*

Variable	Prior PCI		No Prior PCI	
	Aspirin (*n* = 234)	Placebo (*n* = 236)	Aspirin (*n* = 4764)	Placebo (*n* = 4776)
Mean age (SD), *y*	67.3 (8.7)	68.0 (8.9)	68.6 (10.4)	68.6 (10.3)
Female	53 (22.6)	52 (22.0)	2348 (49.3)	2274 (47.6)
Patients fulfilling eligibility criteria				
History of coronary artery disease	234 (100.0)	235 (99.6)	919 (19.3)	880 (18.4)
History of peripheral arterial disease	25 (10.7)	20 (8.5)	413 (8.7)	407 (8.5)
History of stroke	8 (3.4)	16 (6.8)	242 (5.1)	276 (5.8)
History of vascular disease†	234 (100.0)	235 (99.6)	1402 (29.4)	1400 (29.3)
Undergoing major vascular surgery	18 (7.7)	12 (5.1)	226 (4.7)	233 (4.9)
Met 3 of the following 9 risk criteria	125 (53.4)	106 (44.9)	4036 (84.7)	4033 (84.4)
Undergoing major surgery‡	139 (59.4)	140 (59.3)	3767 (79.1)	3756 (78.6)
Required urgent/emergent surgery	8 (3.4)	8 (3.4)	349 (7.3)	358 (7.5)
Age ≥70 y	103 (44.0)	96 (40.7)	2535 (53.2)	2507 (52.5)
Diabetic and receiving medical treatment	69 (29.5)	72 (30.5)	1805 (37.9)	1839 (38.5)
Preoperative creatinine level >175 μmol/L (>2.0 mg/dL)	9 (3.8)	4 (1.7)	155 (3.3)	152 (3.2)
History of congestive heart failure	14 (6.0)	7 (3.0)	169 (3.5)	147 (3.1)
History of transient ischemic attack	7 (3.0)	11 (4.7)	174 (3.7)	171 (3.6)
History of hypertension	180 (76.9)	194 (82.2)	4100 (86.1)	4161 (87.1)
History of smoking ≤2 y before surgery	54 (23.1)	32 (13.6)	1241 (26.0)	1230 (25.8)
History of PCI				
Bare-metal stent	128 (54.7)	127 (53.8)	–	–
Drug-eluting stent	54 (23.1)	65 (27.5)	–	–
Unknown stent type	29 (12.4)	24 (10.2)	–	–
No stent	22 (9.4)	19 (8.1)	–	–
Uncertain whether a stent was used	1 (0.4)	1 (0.4)	–	–
Drugs received ≤7 d before surgery				
Nonstudy aspirin	108 (46.2)	108 (45.8)	1010 (21.2)	1059 (22.2)
Thienopyridine	11 (4.7)	8 (3.4)	28 (0.6)	31 (0.6)
Nonthienopyridine ADP antagonist	0 (0)	0 (0)	5 (0.1)	3 (0.1)
Warfarin	1 (0.4)	5 (2.1)	98 (2.1)	82 (1.7)
Direct thrombin or factor Xa inhibitor	3 (1.3)	2 (0.8)	6 (0.1)	8 (0.2)
NSAID medication	23 (9.8)	20 (8.5)	642 (13.5)	671 (14.0)
Aspirin strata				
Continuation	201 (85.9)	202 (85.6)	1990 (41.8)	1989 (41.6)
Initiation	33 (14.1)	34 (14.4)	2774 (58.2)	2787 (58.4)

ADP = adenosine diphosphate; NSAID = nonsteroidal anti-inflammatory drug; PCI = percutaneous coronary intervention.
* Values are numbers (percentages) unless otherwise indicated.
† Coronary artery disease, peripheral arterial disease, or stroke.
‡ Defined as intraperitoneal, intrathoracic, retroperitoneal, or major orthopedic surgery.

tients [6.3%] vs. 289 patients [6.1%]; ARI, 0.2% [CI, −0.8% to 1.1%]; HR, 1.03 [CI, 0.88 to 1.21]); however, in the prior-PCI subgroup, fewer patients in the aspirin group than the placebo group had myocardial infarction (12 patients [5.1%] vs. 26 patients [11.0%]; ARR, 5.9% [CI, 1.0% to 10.8%]; HR, 0.44 [CI, 0.22 to 0.87]) (*P* for interaction = 0.021). The effect of aspirin on mortality was as follows: In the no-prior-PCI subgroup, ARI was 0.1% (CI, −0.4% to 0.5%) and HR was 1.07 (CI, 0.75 to 1.53); in the prior-PCI subgroup, ARR was 0.4% (CI, −1.4% to 2.3%) and HR was 0.65 (CI, 0.11 to 3.91); and in the overall trial population, ARI was 0.1% (CI, −0.4% to 0.5%) and HR was 1.05 (CI, 0.74 to 1.49).

In the overall trial population, more major or life-threatening bleeding events occurred in the aspirin group than the placebo group (312 events [6.3%] vs. 257 events [5.1%]; ARI, 1.1% [CI, 0.2% to 2.0%]; HR, 1.22 [CI, 1.03 to 1.44]). Results in the PCI subgroup were uncertain, with wide CIs. The interaction *P* value for the prior-PCI and no-prior-PCI subgroups was not significant (*P* for interaction = 0.86). For the outcome of major bleeding in the overall trial population, risk increased with aspirin (230 patients [4.6%] vs. 189 patients [3.8%] with placebo; ARI, 0.8% [CI, 0.1% to 1.6%]; HR, 1.22 [CI, 1.01 to 1.48]) and the no-prior-PCI and prior-PCI subgroup interaction *P* value was not significant (*P* for interaction = 0.50). **Figure 3** shows the Kaplan–Meier curves for major bleeding at 30 days among patients with prior PCI. The effect of aspirin on life-threatening bleeding was as follows: In the no-prior-PCI subgroup, ARI was 0.2% (CI, −0.3% to 0.7%) and HR was 1.14 (CI, 0.83 to 1.57); in the prior-PCI sub-

group, ARI was 1.7% (CI, −0.3% to 3.7%) and HR was 5.08 (CI, 0.59 to 43.56); and in the overall trial population, ARI was 0.3% (CI, −0.2% to 0.8%) and HR was 1.20 (CI, 0.88 to 1.63). The results did not support an effect of aspirin on all other secondary outcomes in the overall trial population and in the PCI subgroups.

Among patients with prior PCI, the subgroup analyses based on the type of stent, time since PCI, and preoperative use of an antiplatelet medication for the primary outcome are reported in the Appendix Figure (available at Annals.org). We did a post hoc subgroup analysis based on the presence or absence of a history of coronary artery disease to assess whether the PCI subgroup effect simply reflected coronary artery disease. In contrast to the PCI subgroup analyses, the coronary artery subgroup analyses did not support a subgroup effect (Appendix Table 2, available at Annals.org).

Discussion

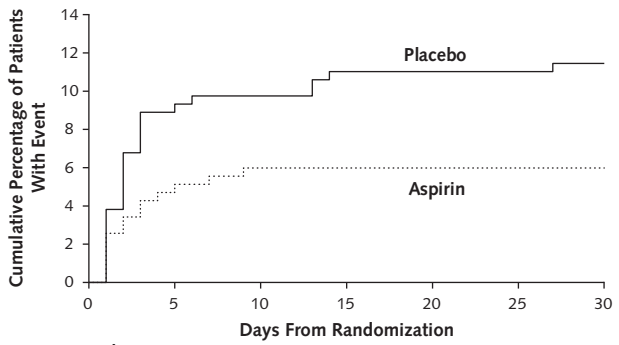
In this POISE-2 substudy of 470 patients with prior PCI, we found that use of low-dose perioperative aspirin compared with placebo reduced the risk for the pri-

Table 2. Effects of Aspirin on 30-Day Outcomes

Outcome	Patients, *n/N (%)**		Absolute Risk Difference (95% CI), %†	Hazard Ratio (95% CI)‡	*P* Value for Interaction‡
	Aspirin	Placebo			
Mortality or nonfatal myocardial infarction					0.036
Overall trial population	351/4998 (7.0)	355/5012 (7.1)	0.1 (−0.9 to 1.1)	0.99 (0.86 to 1.15)	
No-prior-PCI subgroup	337/4764 (7.1)	328/4776 (6.9)	−0.2 (−1.2 to 0.8)	1.03 (0.89 to 1.20)	
Prior-PCI subgroup	14/234 (6.0)	27/236 (11.5)	5.5 (0.4 to 10.5)	0.50 (0.26 to 0.95)	
Myocardial infarction					0.021
Overall trial population	309/4998 (6.2)	315/5012 (6.3)	0.1 (−0.8 to 1.0)	0.98 (0.84 to 1.15)	
No-prior-PCI subgroup	297/4764 (6.2)	289/4776 (6.1)	−0.2 (−1.1 to 0.8)	1.03 (0.88 to 1.21)	
Prior-PCI subgroup	12/234 (5.1)	26/236 (11.0)	5.9 (1.0 to 10.8)	0.44 (0.22 to 0.87)	
All-cause mortality					0.61
Overall trial population	65/4998 (1.3)	62/5012 (1.2)	−0.1 (−0.5 to 0.4)	1.05 (0.74 to 1.49)	
No-prior-PCI subgroup	63/4764 (1.3)	59/4776 (1.2)	−0.1 (−0.5 to 0.4)	1.07 (0.75 to 1.53)	
Prior-PCI subgroup	2/234 (0.9)	3/236 (1.3)	0.4 (−1.4 to 2.3)	0.65 (0.11 to 3.91)	
Vascular mortality					0.99
Overall trial population	35/4998 (0.7)	35/5012 (0.7)	0 (−0.3 to 0.3)	1.00 (0.63 to 1.60)	
No-prior-PCI subgroup	33/4764 (0.7)	33/4776 (0.7)	0 (−0.3 to 0.3)	1.00 (0.62 to 1.63)	
Prior-PCI subgroup	2/234 (0.9)	2/236 (0.8)	0 (−1.7 to 1.7)	1.00 (0.14 to 7.15)	
Stroke					0.90
Overall trial population	16/4998 (0.3)	19/5012 (0.4)	0.1 (−0.2 to 0.3)	0.84 (0.43 to 1.64)	
No-prior-PCI subgroup	15/4764 (0.3)	18/4776 (0.4)	0.1 (−0.2 to 0.3)	0.84 (0.42 to 1.66)	
Prior-PCI subgroup	1/234 (0.4)	1/236 (0.4)	0 (−1.2 to 1.2)	1.00 (0.06 to 16.12)	
Congestive heart failure					0.157
Overall trial population	44/4998 (0.9)	39/5012 (0.8)	−0.1 (−0.5 to 0.3)	1.13 (0.74 to 1.74)	
No-prior-PCI subgroup	43/4764 (0.9)	35/4776 (0.7)	−0.2 (−0.5 to 0.2)	1.23 (0.79 to 1.93)	
Prior-PCI subgroup	1/234 (0.4)	4/236 (1.7)	1.3 (−0.6 to 3.1)	0.22 (0.02 to 1.96)	
Major or life-threatening bleeding					0.86
Overall trial population	312/4998 (6.3)	257/5012 (5.1)	−1.1 (−2.0 to −0.2)	1.22 (1.03 to 1.44)	
No-prior-PCI subgroup	299/4764 (6.3)	247/4776 (5.2)	−1.1 (−2.0 to −0.2)	1.21 (1.03 to 1.44)	
Prior-PCI subgroup	13/234 (5.6)	10/236 (4.2)	−1.3 (−5.2 to 2.6)	1.26 (0.55 to 2.88)	
Major bleeding					0.50
Overall trial population	230/4998 (4.6)	189/5012 (3.8)	−0.8 (−1.6 to −0.1)	1.22 (1.01 to 1.48)	
No-prior-PCI subgroup	222/4764 (4.7)	180/4776 (3.8)	−0.9 (−1.7 to −0.1)	1.24 (1.02 to 1.51)	
Prior-PCI subgroup	8/234 (3.4)	9/236 (3.8)	0.4 (−3.0 to 3.8)	0.85 (0.33 to 2.20)	
Life-threatening bleeding					0.174
Overall trial population	87/4998 (1.7)	73/5012 (1.5)	−0.3 (−0.8 to 0.2)	1.20 (0.88 to 1.63)	
No-prior-PCI subgroup	82/4764 (1.7)	72/4776 (1.5)	−0.2 (−0.7 to 0.3)	1.14 (0.83 to 1.57)	
Prior-PCI subgroup	5/234 (2.1)	1/236 (0.4)	−1.7 (−3.7 to 0.3)	5.08 (0.59 to 43.56)	
Clinically important hypotension					0.44
Overall trial population	2144/4998 (42.9)	2099/5012 (41.9)	−1.0 (−3.0 to 0.9)	1.03 (0.97 to 1.09)	
No-prior-PCI subgroup	2048/4764 (43.0)	1997/4776 (41.8)	−1.2 (−3.2 to 0.8)	1.03 (0.97 to 1.10)	
Prior-PCI subgroup	96/234 (41.0)	102/236 (43.2)	2.2 (−6.7 to 11.1)	0.92 (0.70 to 1.22)	

PCI = percutaneous coronary intervention.
* Kaplan-Meier estimates of 30-d cumulative risk.
† The difference in the proportion of outcome between the aspirin active and placebo groups.
‡ From a Cox model that adjusted for clonidine allocation.

Figure 2. Effect of aspirin on risk for composite of death and nonfatal myocardial infarction among patients with a history of percutaneous coronary intervention.

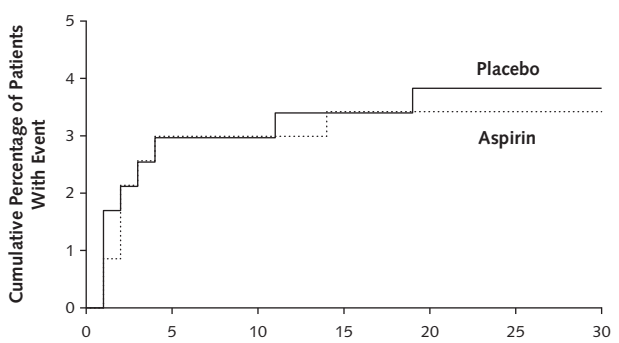


Patients at risk, *n*							
Placebo	236	215	212	209	209	209	208
Aspirin	234	223	221	221	221	221	221

P for interaction = 0.036.

mary outcome (a composite of death and nonfatal myocardial infarction). This beneficial effect, which differed from the effect found in patients without prior PCI, was driven by a reduction in myocardial infarction (ARR, 5.9% [CI, 1.0% to 10.8%]). Aspirin increased the risk for the composite of major and life-threatening bleeding in the overall trial population (ARI, 1.1% [CI, 0.2% to 2.0%]). Whereas the estimate of composite bleeding risk in patients with prior PCI was uncertain (ARI, 1.3% [CI, −2.6% to 5.2%]), the estimate in patients without prior PCI (ARI, 1.1% [CI, 0.2% to 2.0%]) was similar to that of the overall population, and the test for interaction was not significant. Of the composite's components, only major bleeding had an increased risk with aspirin in the overall trial population, and the no-prior-PCI and prior-PCI subgroup interaction *P* value was not significant (*P* for interaction = 0.50).

Figure 3. Effect of aspirin on risk for major bleeding among patients with a history of percutaneous coronary intervention.



Patients at risk, *n*							
Placebo	236	228	225	224	223	223	223
Aspirin	234	228	227	226	226	226	226

P for interaction = 0.73.

Studies have shown an increased risk for perioperative myocardial infarction in patients with a history of PCI before noncardiac surgery (9, 17, 18). Consistent with the POISE-2 PCI population, studies demonstrate that more than 90% of patients having PCI receive a coronary artery stent (19, 20). Kaluza and colleagues (6) raised concerns about patients with a bare-metal stent undergoing noncardiac surgery. They showed that among 40 consecutive patients, 17% had myocardial infarction and 20% died, with stent thrombosis accounting for most of the deaths. Almost all of the events occurred in patients who had noncardiac surgery within 14 days of PCI. Subsequent studies found an increased risk for major perioperative cardiovascular complications among patients having noncardiac surgery within 1 year of receiving a bare-metal or drug-eluting stent (9, 17, 18). Data suggest that both types of stents similarly increase risk for perioperative cardiovascular complications (7, 20–22). In POISE-2, the type of stent had no subgroup effect for the primary outcome, although this analysis had limited power.

We searched MEDLINE (search terms in the **Supplement**) to identify studies that evaluated the effects of aspirin in patients undergoing noncardiac surgery who had a prior stent. Observational studies reported inconsistent results about the effects of antiplatelet therapy for patients with prior PCI having noncardiac surgery. A case–control study of 284 matched pairs of patients with previous coronary stent implantation found no association between antiplatelet cessation at least 5 days before noncardiac surgery and major perioperative cardiovascular complications (odds ratio, 0.86 [CI, 0.57 to 1.29]) (23). In contrast, Albaladejo and colleagues (24) did a multicenter prospective cohort study of 1134 consecutive patients with prior coronary stenting who subsequently had noncardiac surgery. Multivariable analysis showed that cessation of antiplatelet therapy more than 5 days before surgery was independently associated with an increased risk for major cardiovascular complications (odds ratio, 2.11 [CI, 1.23 to 3.63]).

Mantz and colleagues (25) did a trial of patients having noncardiac surgery who received antiplatelet therapy for secondary prevention. These patients were randomly assigned to daily aspirin or placebo for the 10 days before surgery. All patients resumed their regular antiplatelet therapy after surgery as soon as the surgeon considered it safe. The trial included only 38 patients who had a bare-metal stent (21 in the aspirin group and 17 in the placebo group). No statistically significant difference was found in the occurrence of major thrombotic events between the groups (0 patients [0%] in the aspirin group and 2 patients [11.8%] in the placebo group) (25). In contrast, POISE-2 included 470 patients with a history of PCI, and the aspirin study drug was continued throughout the postoperative period.

This POISE-2 substudy suggests that in patients with prior PCI, perioperative low-dose aspirin reduces the primary composite outcome of death and nonfatal myocardial infarction; however, analyses of the component outcomes were significant only for a reduction in myocardial infarction with aspirin versus placebo (12

patients [5.1%] vs. 26 patients [11.0%]; ARR, 5.9% [CI, 1.0% to 10.8%]; HR, 0.44 [CI, 0.22 to 0.87]; *P* for interaction = 0.021). When harms were considered, aspirin increased the risk for the composite of major and life-threatening bleeding events in the overall trial population (312 patients [6.2%] vs. 257 patients [5.1%] with placebo; ARI, 1.1% [CI, 0.2% to 2.0%]; HR, 1.22 [CI, 1.03 to 1.44]). However, analyses of the component outcomes were significant only for an increased risk in major bleeding with aspirin versus placebo (230 patients [4.6%] vs. 189 patients [3.8%]; ARI, 0.8% [CI, 0.1% to 1.6%]; HR, 1.22 [CI, 1.01 to 1.48]). For major bleeding in the prior-PCI versus no-prior-PCI subgroups, the interaction *P* value was not significant (*P* for interaction = 0.50). These results, along with what we know from other trials about bleeding risks of aspirin, suggest that in this instance the overall trial results are the most reliable and are likely applicable to the PCI subgroup. The results, then, suggest that for every 1000 patients with prior PCI who have noncardiac surgery, administration of perioperative aspirin would prevent 59 myocardial infarctions (CI, 10 to 108 myocardial infarctions) and cause 8 major bleeding events (CI, 1 to 16 events).

Appendix Table 3 (available at Annals.org) reports the criteria to assess the credibility of the PCI subgroup effect for myocardial infarction (26), and most criteria were met. We did not prespecify the PCI subgroup analysis because we did not anticipate that physicians would enroll patients with prior PCI. A possible additional concern is that the total number of myocardial infarctions in the PCI subgroup was fewer than 50, which may lead to an overestimate of the effect size. Overall, these criteria suggest that evidence for a subgroup effect is moderate.

Strengths of this substudy include that only 5 subgroup analyses have been done in the aspirin component of the POISE-2 data set (4 published in the original report and the PCI subgroup reported here). POISE-2 was a large, international, randomized controlled trial; among 470 patients with prior PCI, 30-day follow-up was incomplete for only 1 patient. For the PCI subgroup effect for the outcome of myocardial infarction, biological rationale is strong for the potential benefit of aspirin related to perioperative stent thrombosis, as well as coronary thrombosis at non–stent-related sites (20); we prespecified the direction of the subgroup effect; and the interaction *P* value was significant.

This substudy has several limitations. Although POISE-2 is the largest randomized trial of aspirin in patients with prior PCI undergoing noncardiac surgery, it included only 470 patients with prior PCI and they had few events, which creates imprecision in the estimates of effect. The subgroup analyses among patients with a history of PCI (based on the type of stent, timing of PCI, and preoperative use of an antiplatelet medication) had small sample sizes. These subgroup analyses were underpowered and do not exclude a potential subgroup effect. Although we excluded patients with recent stents, our results, which suggest that patients with older stents are more likely to benefit from continuing aspirin in the perioperative setting, support the current practice of continuing aspirin therapy in patients with a recent stent who are having noncardiac surgery because of concern over their high risk for myocardial infarction. Clinicians should not generalize the results of our study to alternative antiplatelet agents, such as clopidogrel, prasugrel, or ticagrelor.

Among patients with prior PCI, perioperative aspirin may be more likely to benefit rather than harm those undergoing noncardiac surgery. The risk–benefit tradeoff will likely shift on the basis of the risk for bleeding and myocardial infarction associated with the type of noncardiac surgery a patient has.

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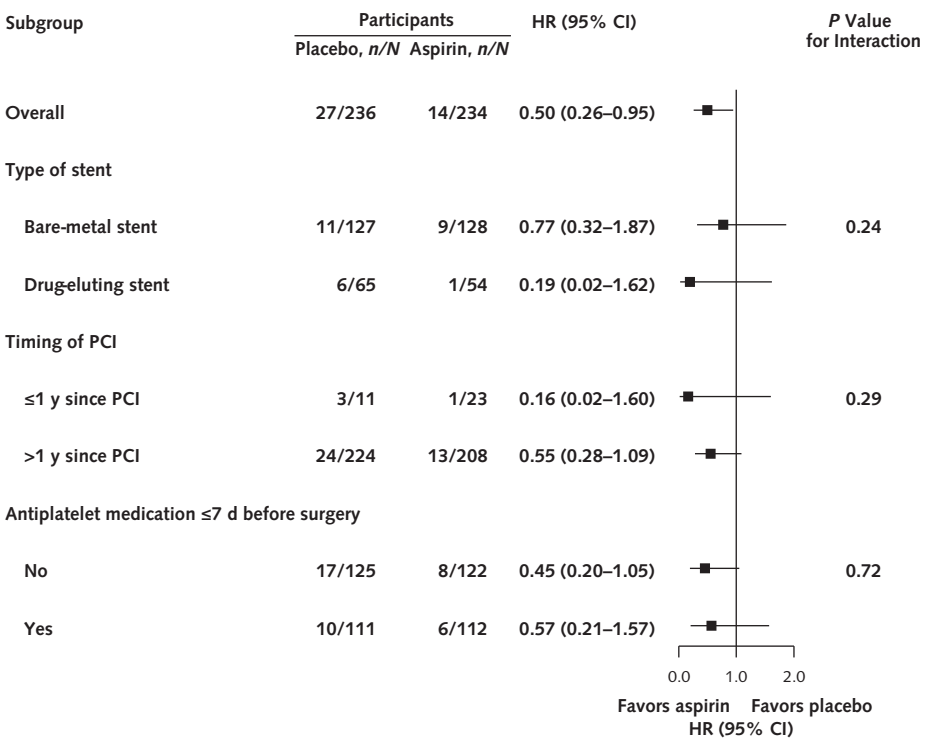
Appendix Table 1. Adherence to Trial Medication*

Adherence	Aspirin (*n* = 234)	Placebo (*n* = 236)
Took 100% of study drug	176 (75.2)	188 (80.0)
Took ≥80% of study drug	188 (80.3)	195 (83.0)

* Values are numbers (percentages).

Appendix Figure. Subgroup analyses of the primary outcome among patients with a history of PCI before surgery.



HR = hazard ratio; PCI = percutaneous coronary intervention.

Appendix Table 2. Coronary Artery Disease Subgroup Effects of Aspirin on 30-Day Outcomes*

Outcome	Patients, *n/N (%)**		Absolute Risk Difference %†	Hazard Ratio (95% CI)‡	*P* Value	*P* Value for Interaction‡
	Aspirin	Placebo				
Mortality or nonfatal myocardial infarction						0.47
Overall trial population	351/4998 (7.0)	355/5012 (7.1)	0.1 (−0.9 to 1.1)	0.99 (0.86 to 1.15)	0.92	
No history of coronary artery disease subgroup	249/3844 (6.5)	247/3896 (6.3)	−0.1 (−1.2 to 1.0)	1.02 (0.86 to 1.22)	0.79	
History of coronary artery disease subgroup	102/1153 (8.8)	108/1115 (9.7)	0.8 (−1.5 to 3.2)	0.91 (0.70 to 1.19)	0.50	
Myocardial infarction						0.51
Overall trial population	309/4998 (6.2)	315/5012 (6.3)	0.1 (−0.8 to 1.0)	0.98 (0.84 to 1.15)	0.85	
No history of coronary artery disease subgroup	219/3844 (5.7)	219/3896 (5.6)	−0.1 (−1.1 to 1.0)	1.02 (0.84 to 1.22)	0.87	
History of coronary artery disease subgroup	90/1153 (7.8)	96/1115 (8.6)	0.8 (−1.5 to 3.1)	0.91 (0.68 to 1.21)	0.50	
All-cause mortality						0.28
Overall trial population	65/4998 (1.3)	62/5012 (1.2)	−0.1 (−0.5 to 0.4)	1.05 (0.74 to 1.49)	0.78	
No history of coronary artery disease subgroup	47/3844 (1.2)	40/3896 (1.0)	−0.2 (−0.7 to 0.3)	1.19 (0.78 to 1.82)	0.41	
History of coronary artery disease subgroup	18/1153 (1.6)	22/1115 (2.0)	0.4 (−0.7 to 1.5)	0.79 (0.42 to 1.47)	0.45	
Vascular mortality						0.40
Overall trial population	35/4998 (0.7)	35/5012 (0.7)	0.0 (−0.3 to 0.3)	1.00 (0.63 to 1.60)	0.99	
No history of coronary artery disease subgroup	23/3844 (0.6)	20/3896 (0.5)	−0.1 (−0.4 to 0.2)	1.17 (0.64 to 2.13)	0.61	
History of coronary artery disease subgroup	12/1153 (1.0)	15/1115 (1.3)	0.3 (−0.6 to 1.2)	0.77 (0.36 to 1.65)	0.50	
Stroke						0.80
Overall trial population	16/4998 (0.3)	19/5012 (0.4)	0.1 (−0.2 to 0.3)	0.84 (0.43 to 1.64)	0.62	
No history of coronary artery disease subgroup	11/3844 (0.3)	14/3896 (0.4)	0.1 (−0.2 to 0.3)	0.80 (0.36 to 1.76)	0.57	
History of coronary artery disease subgroup	5/1153 (0.4)	5/1115 (0.5)	0.0 (−0.5 to 0.6)	0.97 (0.28 to 3.34)	0.96	
Congestive heart failure						0.98
Overall trial population	44/4998 (0.9)	39/5012 (0.8)	−0.1 (−0.5 to 0.3)	1.13 (0.74 to 1.74)	0.57	
No history of coronary artery disease subgroup	31/3844 (0.8)	28/3896 (0.7)	−0.1 (−0.5 to 0.3)	1.12 (0.67 to 1.87)	0.66	
History of coronary artery disease subgroup	13/1153 (1.1)	11/1115 (1.0)	−0.1 (−1.0 to 0.7)	1.14 (0.51 to 2.54)	0.75	
Major or life-threatening bleeding						0.174
Overall trial population	312/4998 (6.3)	257/5012 (5.1)	−1.1 (−2.0 to −0.2)	1.22 (1.03 to 1.44)	0.019	
No history of coronary artery disease subgroup	245/3844 (6.4)	192/3896 (4.9)	−1.4 (−2.5 to −0.4)	1.30 (1.08 to 1.57)	0.007	
History of coronary artery disease subgroup	67/1153 (5.8)	65/1115 (5.8)	0.0 (−1.9 to 1.9)	0.99 (0.70 to 1.39)	0.96	
Major bleeding						0.111
Overall trial population	230/4998 (4.6)	189/5012 (3.8)	−0.8 (−1.6 to −0.1)	1.22 (1.01 to 1.48)	0.041	
No history of coronary artery disease subgroup	182/3844 (4.7)	139/3896 (3.6)	−1.2 (−2.1 to −0.3)	1.33 (1.07 to 1.66)	0.011	
History of coronary artery disease subgroup	48/1153 (4.2)	50/1115 (4.5)	0.3 (−1.4 to 2.0)	0.92 (0.62 to 1.37)	0.69	
Life-threatening bleeding						0.81
Overall trial population	87/4998 (1.7)	73/5012 (1.5)	−0.3 (−0.8 to 0.2)	1.20 (0.88 to 1.63)	0.26	
No history of coronary artery disease subgroup	67/3844 (1.7)	58/3896 (1.5)	−0.3 (−0.8 to 0.3)	1.17 (0.82 to 1.67)	0.38	
History of coronary artery disease subgroup	20/1153 (1.7)	15/1115 (1.3)	−0.4 (−1.4 to 0.6)	1.29 (0.66 to 2.51)	0.46	
Clinically important hypotension						0.30
Overall trial population	2144/4998 (42.9)	2099/5012 (41.9)	−1.0 (−3.0 to 0.9)	1.03 (0.97 to 1.09)	0.39	
No history of coronary artery disease subgroup	1701/3844 (44.3)	1656/3896 (42.5)	−1.7 (−4.0 to 0.5)	1.05 (0.98 to 1.12)	0.20	
History of coronary artery disease subgroup	443/1153 (38.4)	443/1115 (39.7)	1.3 (−2.7 to 5.3)	0.97 (0.85 to 1.10)	0.61	

PCI = percutaneous coronary intervention.
* Kaplan–Meier estimates of 30-d cumulative risk.
† The difference in the proportion of outcome between the aspirin active and placebo groups.
‡ Hazard ratios and PCI vs. non-PCI subgroup *P* values for interaction are from a Cox model that adjusted for clonidine allocation.

Appendix Table 3. Criteria to Assess Credibility of Subgroup Effect

Criteria	POISE-2 Subgroup for Myocardial Infarction
Design	
Was the subgroup variable a baseline characteristic?	Yes
Was the subgroup variable a stratification factor at randomization?	No
Was the subgroup hypothesis specified a priori?	No
Was the subgroup analysis 1 of a few subgroup hypotheses tested (≤5)?	Yes
Analyses	
Was the test of interaction significant (interaction $P < 0.05$)?	Yes
Was the significant interaction effect independent, if there were multiple significant interactions?	Not relevant as no other significant interactions
Context	
Was the direction of subgroup effect correctly prespecified?	Yes
Was the subgroup effect consistent with evidence from previous related studies?	Not relevant as no other trials with enough events
Was the subgroup effect consistent across related outcomes?	Somewhat (congestive heart failure went in the same direction)
Was there any indirect evidence to support the apparent subgroup effect–for example, biological rationale, laboratory tests, animal studies?	Yes (strong biological rationale and cardiac catheterization data)

POISE-2 = Perioperative Ischemic Evaluation-2.