

ORIGINAL ARTICLE

Aspirin in Patients Undergoing Noncardiac Surgery

P.J. Devereaux, M. Mrkobrada, D.I. Sessler, K. Leslie, P. Alonso-Coello, A. Kurz, J.C. Villar, A. Sigamani, B.M. Biccadd, C.S. Meyhoff, J.L. Parlow, G. Guyatt, A. Robinson, A.X. Garg, R.N. Rodseth, F. Botto, G. Lurati Buse, D. Xavier, M.T.V. Chan, M. Tiboni, D. Cook, P.A. Kumar, P. Forget, G. Malaga, E. Fleischmann, M. Amir, J. Eikelboom, R. Mizera, D. Torres, C.Y. Wang, T. VanHelder, P. Paniagua, O. Berwanger, S. Srinathan, M. Graham, L. Pasin, Y. Le Manach, P. Gao, J. Pogue, R. Whitlock, A. Lamy, C. Kearon, C. Baigent, C. Chow, S. Pettit, S. Chrolavicius, and S. Yusuf, for the POISE-2 Investigators*

ABSTRACT

BACKGROUND

There is substantial variability in the perioperative administration of aspirin in patients undergoing noncardiac surgery, both among patients who are already on an aspirin regimen and among those who are not.

METHODS

Using a 2-by-2 factorial trial design, we randomly assigned 10,010 patients who were preparing to undergo noncardiac surgery and were at risk for vascular complications to receive aspirin or placebo and clonidine or placebo. The results of the aspirin trial are reported here. The patients were stratified according to whether they had not been taking aspirin before the study (initiation stratum, with 5628 patients) or they were already on an aspirin regimen (continuation stratum, with 4382 patients). Patients started taking aspirin (at a dose of 200 mg) or placebo just before surgery and continued it daily (at a dose of 100 mg) for 30 days in the initiation stratum and for 7 days in the continuation stratum, after which patients resumed their regular aspirin regimen. The primary outcome was a composite of death or nonfatal myocardial infarction at 30 days.

RESULTS

The primary outcome occurred in 351 of 4998 patients (7.0%) in the aspirin group and in 355 of 5012 patients (7.1%) in the placebo group (hazard ratio in the aspirin group, 0.99; 95% confidence interval [CI], 0.86 to 1.15; $P=0.92$). Major bleeding was more common in the aspirin group than in the placebo group (230 patients [4.6%] vs. 188 patients [3.8%]; hazard ratio, 1.23; 95% CI, 1.01, to 1.49; $P=0.04$). The primary and secondary outcome results were similar in the two aspirin strata.

CONCLUSIONS

Administration of aspirin before surgery and throughout the early postsurgical period had no significant effect on the rate of a composite of death or nonfatal myocardial infarction but increased the risk of major bleeding. (Funded by the Canadian Institutes of Health Research and others; POISE-2 ClinicalTrials.gov number, NCT01082874.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Devereaux at the Population Health Research Institute, David Braley Cardiac, Vascular, and Stroke Research Institute, Rm. C1-116, Perioperative Medicine and Surgical Research Unit, Hamilton General Hospital, 237 Barton St. East, Hamilton, ON L8L 2X2, Canada, or at philipj@mcmaster.ca.

*A complete list of the investigators in the Perioperative Ischemic Evaluation 2 (POISE-2) trial is provided in the Supplementary Appendix, available at NEJM.org.

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MYOCARDIAL INFARCTION IS THE MOST common major vascular complication that occurs after noncardiac surgery.¹⁻³ Noncardiac surgery is associated with platelet activation,⁴ and coronary-artery thrombus may be a mechanism of perioperative myocardial infarction.^{5,6} Aspirin inhibits platelet aggregation,⁷ and the perioperative administration of aspirin may prevent major vascular complications by inhibiting thrombus formation.⁸

In a meta-analysis of data from large, randomized trials involving more than 110,000 patients who were not undergoing surgery, the use of aspirin was shown to prevent myocardial infarction and major vascular events.⁹ High-dose aspirin has not been shown to be superior to low-dose aspirin in preventing vascular complications,^{10,11} and low-dose aspirin has been associated with a lower incidence of gastric toxic effects.¹²

Although there is strong evidence that aspirin prevents venous thromboembolism after noncardiac surgery,^{13,14} physicians more commonly use anticoagulant therapy for the prevention of venous thromboembolism.¹⁵ Nevertheless, one third of patients undergoing noncardiac surgery who are at risk for major vascular complications receive perioperative aspirin.¹⁶ Among patients undergoing noncardiac surgery, there is variability in the use of perioperative aspirin both among patients who are not already taking aspirin and among those who are on long-term aspirin regimens.¹⁷ Uncertainty regarding the risks and benefits of aspirin underscores the need for a large perioperative trial.^{18,19}

We conducted the Perioperative Ischemic Evaluation 2 (POISE-2) trial to evaluate the effect of low-dose aspirin, as compared with placebo, on the 30-day risk of a composite of death or nonfatal myocardial infarction among patients who were undergoing noncardiac surgery.

METHODS

STUDY DESIGN

POISE-2 was an international, randomized, controlled trial with a 2-by-2 factorial design to separately evaluate the effects of aspirin versus placebo (reported here) and clonidine versus placebo (reported elsewhere in the *Journal*)²⁰ in patients undergoing noncardiac surgery. Details of the trial objectives, design, and methods have been reported previously.²¹ All centers obtained ethics approval before starting recruitment.

STUDY OVERSIGHT

The study was funded by the Canadian Institutes of Health Research and others. The Population Health Research Institute was the study coordinating center and was responsible for the randomization design, maintenance of the database, data validation, analyses, and study-center coordination. Bayer Pharma provided the aspirin used in the study, and Boehringer Ingelheim provided the clonidine and some research funding; both companies were provided with the first draft of the manuscript. However, no donor or funder had a role in the design or conduct of the study, the collection or analyses of the data, or the preparation of the manuscript. The operations committee designed the trial, prespecified the statistical analysis plan, and vouches for the completeness and accuracy of the data and analyses and the adherence of the study to the protocol (available with the full text of this article at NEJM.org). The first author wrote the first draft of the manuscript, and the writing committee made revisions and made the decision to submit the manuscript for publication.

PATIENTS

We recruited patients from July 2010 through December 2013 at 135 hospitals in 23 countries. Eligibility criteria are reported in Section 1 in the Supplementary Appendix, available at NEJM.org. Patients were then stratified according to whether they were not taking aspirin before study enrollment (initiation stratum) or they were already on an aspirin regimen (which was defined as daily use for at least 1 month within 6 weeks before surgery) (continuation stratum). Patients in the continuation stratum were required to stop taking aspirin at least 3 days before surgery to participate in the trial.

PROCEDURES

After providing written informed consent before surgery, patients underwent randomization by means of a 24-hour computerized Internet system that used block randomization stratified according to study center and aspirin stratum. Patients were assigned in a 1:1:1:1 ratio to receive aspirin and clonidine, aspirin placebo and clonidine, aspirin and clonidine placebo, or aspirin placebo and clonidine placebo. Patients, clinicians, data collectors, and outcome adjudicators were all unaware of study-group assignments.

Patients started taking aspirin or placebo (at

a dose of 200 mg) just before surgery and continued it (at a dose of 100 mg per day) for 30 days in the initiation stratum and for 7 days in the continuation stratum, after which patients resumed their regular aspirin regimen. Patients also started clonidine (0.2 mg per day) or placebo just before surgery and continued it for 72 hours. If a patient had life-threatening or major bleeding, the aspirin study drug was to be stopped. (Details regarding the follow-up process are provided in Section 2 in the Supplementary Appendix.)

STUDY OUTCOMES

The primary outcome was a composite of death or nonfatal myocardial infarction 30 days after

randomization. Details regarding the two secondary composite outcomes, the tertiary outcomes, and the safety outcomes at 30 days are provided in Section 3 in the Supplementary Appendix, outcome definitions are provided in Section 4 in the Supplementary Appendix, and events evaluated by outcome adjudicators, which were used in the analyses, are provided in Section 5 in the Supplementary Appendix.

STATISTICAL ANALYSIS

We determined that enrollment of 10,000 patients would give the study a power of 84% to detect a hazard ratio of 0.75 in the aspirin group, at a two-sided alpha level of 0.05, on the assump-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Aspirin (N=4998)	Placebo (N=5012)
Age — yr	68.6±10.3	68.6±10.3
Male sex — no. (%)	2597 (52.0)	2686 (53.6)
Eligibility criteria met — no. (%)		
History of vascular disease	1636 (32.7)	1635 (32.6)
Coronary artery disease	1153 (23.1)	1115 (22.2)
Peripheral arterial disease	438 (8.8)	427 (8.5)
Stroke	250 (5.0)	292 (5.8)
Undergoing major vascular surgery	244 (4.9)	245 (4.9)
Risk criteria†	4161 (83.3)	4139 (82.6)
Undergoing major surgery‡	3906 (78.2)	3896 (77.7)
Requiring emergency surgery	357 (7.1)	366 (7.3)
Age ≥70 yr	2638 (52.8)	2603 (51.9)
Diabetes requiring medication	1874 (37.5)	1911 (38.1)
Preoperative serum creatinine >2.0 mg/dl (175 μmol/liter)	164 (3.3)	156 (3.1)
History of congestive heart failure	183 (3.7)	154 (3.1)
History of transient ischemic attack	181 (3.6)	182 (3.6)
History of hypertension	4280 (85.6)	4355 (86.9)
History of smoking within 2 yr before surgery	1295 (25.9)	1262 (25.2)
Other medical history — no. (%)		
History of coronary-artery bypass grafting	241 (4.8)	240 (4.8)
History of percutaneous coronary intervention	234 (4.7)	236 (4.7)
Bare-metal stent	128 (2.6)	127 (2.5)
Drug-eluting stent	54 (1.1)	65 (1.3)
Unknown stent type	29 (0.6)	24 (0.5)
No stent	22 (0.4)	19 (0.4)
Missing data	1 (<0.1)	1 (<0.1)
Dialysis in week before randomization	69 (1.4)	58 (1.2)
Median preoperative hemoglobin (IQR) — g/liter	133 (121–144)	133 (120–144)
Time from randomization to surgery — no. (%)		
≤24 hr	4777 (95.6)	4795 (95.7)
>24–48 hr	45 (0.9)	49 (1.0)
≥48 hr	176 (3.5)	168 (3.4)

Table 1. (Continued.)

Characteristic	Aspirin (N = 4998)	Placebo (N = 5012)
Surgery — no./total no. (%)§		
Any procedure	4953/4998 (99.1)	4979/5012 (99.3)
Orthopedic	1891/4953 (38.2)	1953/4979 (39.2)
General	1327/4953 (26.8)	1337/4979 (26.9)
Urologic or gynecologic	827/4953 (16.7)	835/4979 (16.8)
Vascular	309/4953 (6.2)	296/4979 (5.9)
Thoracic	293/4953 (5.9)	298/4979 (6.0)
Other	428/4953 (8.6)	392/4979 (7.9)
No procedure performed	42/4998 (0.8)	31/5012 (0.6)
Missing data	3/4998 (0.1)	2/5012 (<0.1)
Medications taken within 24 hr before surgery — no./total no. (%)		
Prophylactic-dose anticoagulant	626/4952 (12.6)	650/4978 (13.1)
Nonsteroidal antiinflammatory drug	470/4952 (9.5)	468/4978 (9.4)
COX-2 inhibitor	162/4951 (3.3)	165/4978 (3.3)
Statin	1815/4952 (36.7)	1842/4978 (37.0)
Beta-blocker	1153/4951 (23.3)	1206/4977 (24.2)
P2Y ₁₂ inhibitor	3/4952 (0.1)	1/4978 (<0.1)
Perioperative antifibrinolytic agent — no./total no. (%)	73/4951 (1.5)	80/4977 (1.6)
Medications taken during first 3 days after surgery — no./total no. (%)		
Prophylactic-dose anticoagulant	3230/4948 (65.3)	3220/4976 (64.7)
Therapeutic-dose anticoagulant	225/4947 (4.5)	206/4976 (4.1)
Nonsteroidal antiinflammatory drug	1581/4947 (32.0)	1590/4976 (32.0)
COX-2 inhibitor	263/4947 (5.3)	270/4976 (5.4)
Statin	2071/4948 (41.9)	2100/4975 (42.2)
Beta-blocker	1428/4947 (28.9)	1498/4976 (30.1)
P2Y ₁₂ inhibitor	59/4947 (1.2)	60/4976 (1.2)

* Plus-minus values are means \pm SD. There were no significant differences between the two groups for any of the variables. IQR denotes interquartile range.

† Meeting this eligibility criterion involved meeting at least three of the nine risk criteria listed here.

‡ Major surgery was defined as intraperitoneal, intrathoracic, retroperitoneal, or major orthopedic surgery.

§ Patients may have undergone more than one type of surgery.

tion that the rate of the primary outcome in the placebo group would be 6.1%.¹⁶ An external data and safety monitoring committee reviewed the data when 25%, 50%, and 75% of the 30-day data were available.

We evaluated patients according to the group to which they were assigned, censoring the data for patients who were lost to follow-up on the last day that their status was known. Outcomes were analyzed with the use of Cox proportional-hazards models, stratified according to the aspirin stratum and status with respect to receipt of clonidine, except for the outcome of acute kidney injury with receipt of dialysis, for which we used logistic-regression analysis, and outcomes

with respect to the length of the hospital stay, for which we used the log-rank test.

For the primary outcome, we performed subgroup analyses that were based on the aspirin stratum, type of surgery (vascular vs. nonvascular), and the number of criteria of the Revised Cardiac Risk Index that the patient met.²² We also performed subgroup analyses, according to the aspirin stratum, for one of the secondary composite outcomes and for the tertiary outcomes. In a prespecified analysis, we predicted the direction of potential subgroup effects. For the subgroup analyses, we used Cox proportional-hazards models that incorporated tests of interaction, with a P value of less than 0.05 indicating

statistical significance. All analyses were performed with the use of SAS software, version 9.1.

RESULTS

PATIENTS

A total of 10,010 patients were enrolled (5628 in the initiation stratum and 4382 in the continuation stratum). Of these patients, 4998 were assigned to receive aspirin and 5012 to receive placebo. The 30-day follow-up was complete for 99.9% of the patients (Fig. S1 in the Supplementary Appendix).

The baseline characteristics were similar in the aspirin and placebo groups (Table 1). The mean age was 68.6 years; 52.8% of the patients were men, 32.7% had a history of vascular disease, and 4.3% had undergone previous coronary stenting. Among patients in the continuation stratum, aspirin was stopped a median of 7 days (interquartile range, 4 to 8) before surgery. In the first 3 days after surgery, 65.0% of the patients received prophylactic anticoagulation. Overall, 80.4% of the patients in the aspirin group and 82.4% of those in the placebo group took at least 80% of the doses of the study drug (Table S1 in the Supplementary Appendix).

STUDY OUTCOMES

The primary outcome (death or nonfatal myocardial infarction) occurred in 351 of 4998 patients (7.0%) in the aspirin group and in 355 of 5012 patients (7.1%) in the placebo group (hazard ratio in the aspirin group, 0.99; 95% confidence interval [CI], 0.86 to 1.15; $P=0.92$) (Table 2 and Fig. 1). The use of aspirin did not significantly affect the secondary composite or tertiary outcomes. Myocardial infarction occurred in 309 patients (6.2%) in the aspirin group and in 315 patients (6.3%) in the placebo group (hazard ratio, 0.98; 95% CI, 0.84 to 1.15; $P=0.85$). Aspirin increased the risk of major bleeding, as compared with placebo, with major bleeding occurring in 230 patients (4.6%) versus 188 patients (3.8%) (hazard ratio, 1.23; 95% CI, 1.01 to 1.49; $P=0.04$) (Table 2, and Fig. S2 in the Supplementary Appendix). The most common sites of bleeding were the surgical site (78.3%) and gastrointestinal tract (9.3%). Stroke occurred in 16 patients (0.3%) in the aspirin group and in 19 patients (0.4%) in the placebo group (hazard ratio, 0.84; 95% CI, 0.43 to 1.64; $P=0.62$). The median length of hospital stay was 4 days (interquartile range, 3 to 7) in both the

aspirin and placebo groups ($P=0.79$). There was no significant difference between the study groups in the length of stay in the intensive care unit or cardiac care unit ($P=0.23$). There was no significant effect of clonidine on the results comparing aspirin with placebo ($P\geq 0.12$ for all interactions).

The effect of aspirin was consistent across subgroups ($P\geq 0.16$ for all interactions) (Fig. 2). The subgroup analysis of the secondary composite outcome also showed no significant heterogeneity ($P=0.72$ for interaction).

DIFFERENCES BETWEEN STRATA

Aspirin use significantly increased the risk of major bleeding and decreased the risk of stroke in the initiation stratum ($P=0.03$ for both comparisons) and significantly increased the rate of acute kidney injury requiring dialysis in the continuation stratum ($P=0.04$) (Tables S2 and S3 in the Supplementary Appendix). However, the P value for strata interaction was significant only for stroke ($P=0.01$) (Table S4 in the Supplementary Appendix). In the initiation stratum, there were 3 strokes in the aspirin group and 12 in the placebo group (hazard ratio, 0.25; 95% CI, 0.07 to 0.89), whereas in the continuation stratum there were 13 strokes in the aspirin group and 7 in the placebo group (hazard ratio, 1.86; 95% CI, 0.74 to 4.66; $P=0.19$).

The effects of aspirin on myocardial infarction were similar in the initiation stratum and the continuation stratum (hazard ratio, 0.98; 95% CI, 0.79 to 1.22 in the initiation stratum; hazard ratio, 0.99; 95% CI, 0.79 to 1.24 in the continuation stratum; $P=0.96$ for interaction). In addition, the effects of aspirin on the composite of life-threatening or major bleeding were similar in the initiation stratum and the continuation stratum (hazard ratio, 1.24; 95% CI, 0.99 to 1.55 in the initiation stratum; hazard ratio, 1.20; 95% CI, 0.94 to 1.55 in the continuation stratum; $P=0.87$ for interaction).

BLEEDING RISK

To better understand the risk of bleeding on the basis of the timing of administration of aspirin, we undertook post hoc analyses. Among patients who were alive and did not have life-threatening or major bleeding, we determined the subsequent risk of a composite of life-threatening or major bleeding until day 30, starting on the day of surgery and then starting on each day thereafter (Table 3).

The absolute increase in the risk of a composite bleeding outcome associated with aspirin was 1.2% from the day of surgery up to 30 days and 0.9% from day 4 after surgery up to 30 days. If a patient survived without the composite bleeding outcome until day 8 after surgery, the increase in risk from day 8 to day 30 was 0.3% (3 in 1000 patients).

Table S5 in the Supplementary Appendix shows the results of the post hoc multivariable analysis investigating potential factors associated with perioperative myocardial infarction. The compos-

ite of life-threatening or major bleeding was an independent predictor of myocardial infarction (hazard ratio, 1.82; 95% CI, 1.40 to 2.36; $P < 0.001$).

DISCUSSION

In this trial, the use of low-dose perioperative aspirin, as compared with placebo, did not reduce the rate of a composite of death or nonfatal myocardial infarction (the primary outcome) or the rates of the two secondary composite out-

Table 2. Effects of Aspirin on 30-Day Outcomes.*

Outcome	Aspirin (N = 4998) no. (%)	Placebo (N = 5012) no. (%)	Hazard Ratio (95% CI) [†]	P Value
Primary composite outcome: death or nonfatal myocardial infarction	351 (7.0)	355 (7.1)	0.99 (0.86–1.15)	0.92
Secondary outcomes				
Death, nonfatal myocardial infarction, or nonfatal stroke	362 (7.2)	370 (7.4)	0.98 (0.85–1.13)	0.80
Death, nonfatal myocardial infarction, cardiac revascularization, nonfatal pulmonary embolism, or nonfatal deep venous thrombosis	402 (8.0)	407 (8.1)	0.99 (0.86–1.14)	0.90
Tertiary outcomes — no. (%)				
Death from any cause	65 (1.3)	62 (1.2)	1.05 (0.74–1.49)	0.78
Death from cardiovascular cause	35 (0.7)	35 (0.7)	1.00 (0.63–1.60)	0.99
Myocardial infarction	309 (6.2)	315 (6.3)	0.98 (0.84–1.15)	0.85
Nonfatal cardiac arrest	9 (0.2)	12 (0.2)	0.75 (0.32–1.79)	0.52
Cardiac revascularization	13 (0.3)	17 (0.3)	0.77 (0.37–1.58)	0.47
Pulmonary embolism	33 (0.7)	31 (0.6)	1.07 (0.65–1.74)	0.79
Deep-vein thrombosis	25 (0.5)	35 (0.7)	0.72 (0.43–1.20)	0.20
New clinically important atrial fibrillation	109 (2.2)	94 (1.9)	1.16 (0.88–1.53)	0.28
Peripheral arterial thrombosis	13 (0.3)	15 (0.3)	0.87 (0.41–1.83)	0.71
Amputation	10 (0.2)	13 (0.3)	0.77 (0.34–1.76)	0.54
Rehospitalization for cardiovascular reasons	70 (1.4)	54 (1.1)	1.30 (0.91–1.86)	0.15
Acute kidney injury with receipt of dialysis [‡]	33 (0.7)	19 (0.4)	1.75 (1.00–3.09)	0.05
Safety outcomes				
Life-threatening bleeding	87 (1.7)	73 (1.5)	1.19 (0.88–1.63)	0.26
Major bleeding	230 (4.6)	188 (3.8)	1.23 (1.01–1.49)	0.04
Clinically important hypotension	2143 (42.9)	2096 (41.8)	1.03 (0.97–1.09)	0.37
Stroke	16 (0.3)	19 (0.4)	0.84 (0.43–1.64)	0.62
Congestive heart failure	44 (0.9)	38 (0.8)	1.16 (0.75–1.79)	0.50
Infection	488 (9.8)	495 (9.9)	0.99 (0.87–1.12)	0.86
Sepsis	243 (4.9)	258 (5.2)	0.94 (0.79–1.13)	0.52

* Percentages were calculated with the use of the Kaplan–Meier method.

[†] Hazard ratios are for the aspirin group, as compared with the placebo group.

[‡] For this outcome, an odds ratio is provided instead of a hazard ratio, because the date that patients first started dialysis was not known.

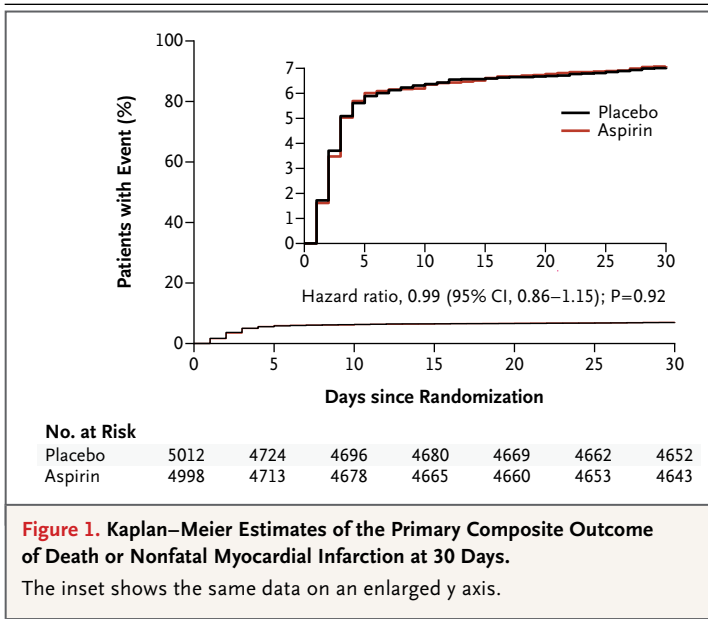


Figure 1. Kaplan–Meier Estimates of the Primary Composite Outcome of Death or Nonfatal Myocardial Infarction at 30 Days.

The inset shows the same data on an enlarged y axis.

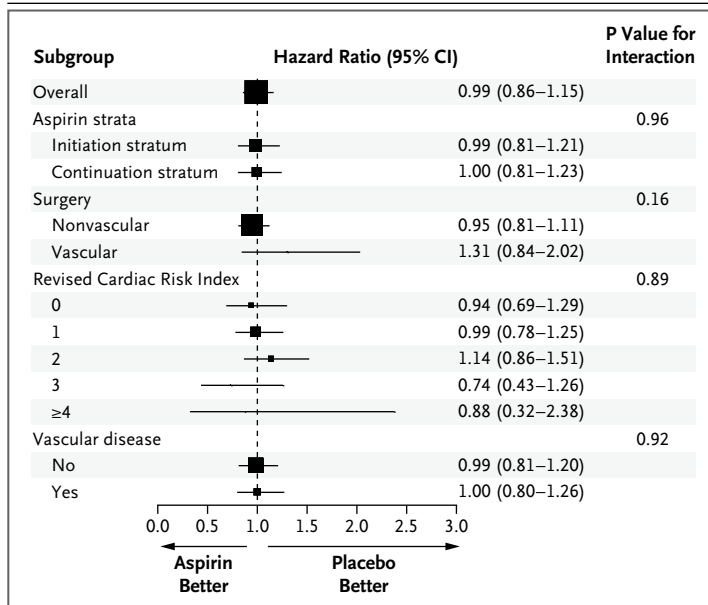


Figure 2. Subgroup Analyses of the Primary Outcome.

The primary composite outcome was death or nonfatal myocardial infarction at 30 days. The area of each square is proportional to the size of the corresponding subgroup. The Revised Cardiac Risk Index ranges from 0 to 6, with higher scores indicating greater risk.

In a meta-analysis of data from trials involving more than 110,000 patients who were not undergoing surgery, the use of aspirin, for primary and for secondary prevention, reduced the relative risk of myocardial infarction by 20% and 25%, respectively.⁹ In contrast, the Pulmonary Embolism Prevention (PEP) trial included 13,356 patients undergoing surgery for a hip fracture.¹³ Patients received 160 mg of aspirin or placebo before surgery and daily for 35 days. Aspirin was associated with an increased risk of myocardial infarction (hazard ratio, 1.33; 95% CI, 1.00 to 1.78), although the number of myocardial infarctions (184) was much lower than that in our study (624; hazard ratio with aspirin, 0.98; 95% CI, 0.84 to 1.15).

Consistent with our findings, the PEP trial and other perioperative trials have shown that aspirin significantly increases the risk of bleeding requiring a transfusion.^{13,14} In previous surgical trials with hundreds of venous thromboembolism events, the use of aspirin decreased the risk of deep-vein thrombosis and pulmonary embolism by one third.^{13,14} In our study, relatively few patients had deep-vein thrombosis (60 patients) or pulmonary embolism (64 patients), and more patients in our study than in the PEP trial received concomitant anticoagulant prophylaxis (65.0% vs. 44.4%).

Observational data suggest that the discontinuation of aspirin before surgery results in an increased thrombotic risk.^{19,23} In our study, among the 4382 patients in the continuation stratum, we found no increase in thrombotic events owing to preoperative withholding of aspirin.

In the nonoperative setting, aspirin prevents myocardial infarction in patients with or at risk for atherosclerotic disease. However, in our study, aspirin did not prevent perioperative myocardial infarction. We offer three potential explanations for this finding. First, previous studies and our post hoc multivariable analysis showed that major bleeding was associated with perioperative myocardial infarction.^{3,24} The absolute increase in bleeding risk with aspirin is greater in the perioperative setting than the nonoperative setting. It is possible that aspirin prevented some perioperative myocardial infarctions through thrombus inhibition and caused some myocardial infarctions through bleeding and subsequent mismatch between the supply of and demand for myocardial oxygen, thus resulting in

comes. The use of perioperative aspirin increased the risk of major bleeding (hazard ratio, 1.23; 95% CI, 1.01 to 1.49). The results with respect to the primary and secondary outcomes were consistent in the initiation stratum and the continuation stratum.

Table 3. Absolute Increase in the Risk of a Composite of Life-Threatening or Major Bleeding with Aspirin Therapy, Starting on Each of the First 10 Postoperative Days until 30 Days after Surgery.*

Day at Start of Risk Analysis	Aspirin†	Placebo†	Absolute Increase in Risk with Aspirin	P Value
	no./total no. (%)		percentage points	
Day of surgery	311/4953 (6.3)	254/4978 (5.1)	1.2	0.01
Day 1 after surgery	191/4832 (4.0)	129/4852 (2.7)	1.3	<0.001
Day 2 after surgery	138/4779 (2.9)	92/4813 (1.9)	1.0	0.002
Day 3 after surgery	102/4741 (2.2)	59/4777 (1.2)	1.0	<0.001
Day 4 after surgery	73/4710 (1.6)	33/4748 (0.7)	0.9	<0.001
Day 5 after surgery	59/4693 (1.3)	27/4739 (0.6)	0.7	<0.001
Day 6 after surgery	43/4674 (0.9)	25/4736 (0.5)	0.4	0.03
Day 7 after surgery	39/4667 (0.8)	22/4731 (0.5)	0.3	0.03
Day 8 after surgery	20/2623 (0.8)	14/2662 (0.5)	0.3	0.29
Day 9 after surgery	15/2617 (0.6)	14/2660 (0.5)	0.1	0.82
Day 10 after surgery	14/2614 (0.5)	12/2657 (0.5)	0.0	0.67

* Among patients who were alive and had not already had life-threatening or major bleeding, we determined the risk of the composite of life-threatening or major bleeding until day 30, starting on the day of surgery and then on each subsequent day. We also determined the absolute increase in risk among patients in the aspirin group and the P value for the comparison between aspirin and placebo. This allows the inference that, for example, if aspirin is started on the day of surgery, the cumulative incremental risk of bleeding attributable to aspirin over the next 30 days is 1.2%. If aspirin had been started on day 4 after surgery, the cumulative incremental risk over the next 26 days would be 0.9%, and so forth. Starting on day 8 after surgery, the sample was restricted to patients in the initiation stratum because all patients in the continuation stratum stopped taking the study drug in the aspirin trial on day 8 after surgery and resumed their regular aspirin regimen.

† Percentages were calculated with the use of the Kaplan–Meier method.

the overall neutral effect in our study. Second, the lower boundary of the hazard ratio for myocardial infarction was 0.84, and we cannot exclude the possibility of a missed moderate effect that would be consistent with results of other aspirin trials.⁹ Third, coronary-artery thrombus may not be the dominant mechanism of perioperative myocardial infarction.^{5,6}

The results with respect to the primary and secondary outcomes were similar across the two aspirin strata. There were significant between-group differences in one tertiary outcome (acute kidney injury with receipt of dialysis) and two safety outcomes (major bleeding and stroke) in one aspirin stratum but not the other (Table S4 in the Supplementary Appendix). The interaction P value for the aspirin stratum was not significant for two of these outcomes (i.e., acute kidney injury with receipt of dialysis and major bleeding), suggesting that there is no significant difference in effect across the aspirin strata for these two outcomes and that the results in the overall population provide the most reliable effect estimates.

Our data suggest that among patients on a

long-term aspirin regimen, stopping aspirin 3 or more days before surgery may decrease the risk of major bleeding. Because we did not randomly assign patients according to the timing of aspirin cessation before surgery, we cannot determine the most effective timing to minimize bleeding risk. Studies have suggested that hemostasis is unimpaired if at least 20% of the platelets have normal COX-1 activity^{25,26} and 12% of circulating platelets are replaced every 24 hours.^{27,28} Therefore, stopping aspirin 72 or more hours before surgery may be adequate to minimize the risk of perioperative bleeding.

We observed one significant interaction: aspirin appeared to reduce the incidence of stroke in the initiation stratum but not in the continuation stratum (P=0.01 for interaction). Several considerations suggest that this is a spurious subgroup effect.²⁹ First, there were only 15 strokes in the initiation stratum, so the power to detect a change is small. Second, the effect of aspirin on reducing the risk of stroke in the initiation stratum was large (hazard ratio, 0.25), an effect that was inconsistent with the effect in the non-

operative setting on the basis of analyses of more than 1000 strokes and the perioperative data from the PEP trial with 103 strokes (hazard ratio for aspirin, 1.10; 95% CI, 0.75 to 1.62).^{9,13} Third, since this analysis was 1 of 19 tertiary or safety subgroup analyses that we performed, the results may be a chance finding. Finally, our hypothesized direction was opposite to that observed (i.e., we expected more benefit in the continuation stratum because of an aspirin-withdrawal effect). Therefore, the best estimate of the effect of aspirin on stroke is probably reflected in the overall population (hazard ratio, 0.84; 95% CI, 0.43 to 1.64).

If clinicians plan to use an anticoagulant agent for perioperative prevention of venous thromboembolism, our results suggest that starting or continuing aspirin throughout the perioperative period will provide no additional benefit but will increase the risk of major bleeding. However, our findings do not resolve the issue of the relative merits of aspirin versus other anticoagulant agents for perioperative thromboprophylaxis.³⁰ Although the POISE-2 trial is a large study by perioperative standards, the lower boundary (0.86) and upper boundary (1.15) of the hazard ratio for the primary outcome show that we have not excluded the possibility of appreciable benefit or harm.

It should be noted that we excluded patients who received a bare-metal coronary stent less than 6 weeks before surgery or a drug-eluting coro-

nary stent less than 1 year before surgery. Observational data have suggested that perioperative aspirin prevents myocardial infarction and stent thrombosis in these two groups of patients.³¹

For patients on a long-term aspirin regimen, the most effective time to restart aspirin would be 8 to 10 days after surgery, when the bleeding risk has diminished considerably. If physicians consider starting aspirin after surgery to treat a thrombotic event (e.g., stroke or myocardial infarction), they can expect an absolute increase of 1.0 to 1.3 percentage points in the risk of life-threatening or major bleeding if aspirin is administered within the first 2 days after surgery. Physicians and their patients will have to weigh this risk against the high risk of death from the thrombotic event and the potential benefits of aspirin.^{3,12,16}

In conclusion, the administration of aspirin before noncardiac surgery and throughout the early postsurgical period had no significant effect on the rate of death or nonfatal myocardial infarction but increased the risk of major bleeding. These findings apply both to patients who were not already receiving aspirin and to those who were on a long-term aspirin regimen.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors are as follows: P.J. Devereaux, M.D., Ph.D., Marko Mrkobrada, M.D., Daniel I. Sessler, M.D., Kate Leslie, M.B., B.S., M.D., M.Epi., Pablo Alonso-Coello, M.D., Ph.D., Andrea Kurz, M.D., Juan Carlos Villar, M.D., Ph.D., Alben Sigamani, M.B., B.S., M.D., Bruce M. Biccard, M.B., Ch.B., Ph.D., Christian S. Meyhoff, M.D., Ph.D., Joel L. Parlow, M.D., Gordon Guyatt, M.D., Andrea Robinson, B.Sc., Amit X. Garg, M.D., Ph.D., Reitze N. Rodseth, M.B., Ch.B., Ph.D., Fernando Botto, M.D., Giovanna Lurati Buse, M.D., Denis Xavier, M.D., Matthew T.V. Chan, M.B., B.S., Maria Tiboni, M.D., Deborah Cook, M.D., Priya A. Kumar, M.D., Patrice Forget, M.D., Ph.D., German Malaga, M.D., Edith Fleischmann, M.D., Mohammed Amir, F.R.C.S.Ed., John Eikelboom, M.B., B.S., Richard Mizer, M.D., David Torres, M.D., C.Y. Wang, M.B., Ch.B., Tomas VanHelder, M.D., Ph.D., Pilar Paniagua, M.D., Otavio Berwanger, M.D., Ph.D., Sadeesh Srinathan, M.D., Michelle Graham, M.D., Laura Pasin, M.D., Yannick Le Manach, M.D., Ph.D., Peggy Gao, Janice Pogue, Ph.D., Richard Whitlock, M.D., Ph.D., André Lamy, M.D., Clive Kearon, M.B., M.R.C.P.I., Ph.D., Colin Baigent, F.F.P.H., Clara Chow, M.B., B.S., Ph.D., Shirley Pettit, R.N., Susan Chrolavicius, B.A., R.N., and Salim Yusuf, M.D., D.Phil., for the POISE-2 Investigators.

The authors' affiliations are as follows: the Population Health Research Institute, Hamilton Health Sciences and McMaster University (P.J.D., M.M., A.R., F.B., G.L.B., J.E., Y.L.M., P.G., J.P., R.W., A.L., S.P., S.C., S.Y.), the Departments of Clinical Epidemiology and Biostatistics (P.J.D., G.G., D.C., J.E., Y.L.M., J.P., C.K., S.Y.), Medicine (P.J.D., G.G., M.T., D.C., J.E., R.M., C.K., S.Y.), Anesthesia (T.V., Y.L.M.), Surgery (R.W., A.L.), and Critical Care (R.W.), McMaster University, Hamilton, ON, the Department of Medicine, London Health Sciences Centre, London, ON (M.M.), the Department of Anesthesiology and Perioperative Medicine, Kingston General Hospital and Queen's University, Kingston, ON (J.L.P.), the Department of Medicine, Division of Nephrology, University of Western Ontario, London, ON (A.X.G.), the Department of Surgery, University of Manitoba, Winnipeg (S.S.), and the Department of Medicine, University of Alberta, Edmonton (M.G.) — all in Canada; the Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland (D.I.S., A.K.); the Department of Anaesthesia and Pain Management, Royal Melbourne Hospital, Melbourne, VIC, Australia (K.L.); Iberoamerican Cochrane Center (P.A.-C.) and the Anesthesiology Department (P.P.), Biomedical Research Institute, Barcelona; Universidad Autónoma de Bucaramanga and Fundación Cardioinfantil, Bogota, Colombia (J.C.V.); the Department of Pharmacology, Division of Clinical Research and Training, St. John's National Academy of Health Sciences, Bangalore, India (A.S., D.X.); the Department of Anaesthetics, Perioperative Research Group, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban,

South Africa (B.M.B., R.N.R.); the Department of Anesthesiology, Herlev Hospital, University of Copenhagen, Herlev, Denmark (C.S.M.); Estudios Clínicos Latino América, Instituto Cardiovascular de Buenos Aires, Buenos Aires (F.B.); the Department of Anesthesia, University Hospital Basel, Basel, Switzerland (G.L.B.); the Department of Anaesthesia and Intensive Care, Chinese University of Hong Kong, Hong Kong (M.T.V.C.); the Department of Anesthesiology, University of North Carolina, Chapel Hill (P.A.K.); Anesthesiology, Cliniques universitaires Saint-Luc, Brussels (P.F.); Universidad Peruana Cayetano Heredia, Lima, Peru (G.M.); the Department of Anesthesia and Intensive Care, Medical University of Vienna, Vienna (E.F.); the Department of Surgery, Shifa International Hospital, Islamabad, Pakistan (M.A.); the Department of Anesthesiology, Clinica Santa Maria, Santiago, Chile (D.T.); the Department of Anesthesiology, University of Malaya, Kuala Lumpur, Malaysia (C.Y.W.); Research Institute HCor (Hospital do Coração), São Paulo (O.B.); Anesthesia and Intensive Care, San Raffaele Scientific Institute, Milan (L.P.); Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford, United Kingdom (C.B.); and the George Institute for Global Health and the University of Sydney, Sydney (C.C.).

REFERENCES

1. Botto F, Alonso-Coello P, Chan MT, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology* 2014;120:564-78.
2. Devereaux PJ, Chan MT, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012;307:2295-304. [Erratum, *JAMA* 2012;307:2590.]
3. Devereaux PJ, Xavier D, Pogue J, et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med* 2011;154:523-8.
4. Naesh O, Friis JT, Hindberg I, Winther K. Platelet function in surgical stress. *Thromb Haemost* 1985;54:849-52.
5. Devereaux PJ, Chan M, Eikelboom J. Major vascular complications in patients undergoing non-cardiac surgery: magnitude of the problem, risk prediction, surveillance, and prevention. In: Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ, eds. *Evidence based cardiology*. 3rd ed. Chichester, England: Wiley-Blackwell, 2010:47-62.
6. Gualandro DM, Campos CA, Calderaro D, et al. Coronary plaque rupture in patients with myocardial infarction after noncardiac surgery: frequent and dangerous. *Atherosclerosis* 2012;222:191-5.
7. Reilly IA, FitzGerald GA. Inhibition of thromboxane formation in vivo and ex vivo: implications for therapy with platelet inhibitory drugs. *Blood* 1987;69:180-6.
8. Robless P, Mikhailidis DP, Stansby G. Systematic review of antiplatelet therapy for the prevention of myocardial infarction, stroke or vascular death in patients with peripheral vascular disease. *Br J Surg* 2001;88:787-800.
9. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849-60.
10. The CURRENT-OASIS 7 Investigators. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* 2010;363:930-42. [Erratum, *N Engl J Med* 2010;363:1585.]
11. Taylor DW, Barnett HJ, Haynes RB, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. *Lancet* 1999;353:2179-84.
12. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86. [Erratum, *BMJ* 2002;324:141.]
13. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000;355:1295-302.
14. Collaborative overview of randomised trials of antiplatelet therapy. III. Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994;308:235-46.
15. Cohen AT, Tapson VF, Bergmann JF, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet* 2008;371:387-94. [Erratum, *Lancet* 2008;371:1914.]
16. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008;371:1839-47.
17. Hiralal R, Guyatt G, Bhandari M, et al. A survey evaluating surgeons' perioperative usage of acetyl-salicylic acid (ASA) and their willingness to enroll their patients in a perioperative ASA randomised controlled trial. *Clin Invest Med* 2010;33:E375-E383.
18. Neilipovitz DT, Bryson GL, Nichol G. The effect of perioperative aspirin therapy in peripheral vascular surgery: a decision analysis. *Anesth Analg* 2001;93:573-80.
19. Burger W, Chemnitz JM, Kneissl GD, Rücker G. Low-dose aspirin for secondary cardiovascular prevention — cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation — review and meta-analysis. *J Intern Med* 2005;257:399-414.
20. Devereaux PJ, Sessler DI, Leslie K, et al. Clonidine in patients undergoing noncardiac surgery. *N Engl J Med* 2014;370:1504-13.
21. Devereaux PJ, Sessler DI, Mrkobra M, et al. Rationale and design of the Peri-Operative ISchemic Evaluation-2 (POISE-2) Trial: an international 2 x 2 factorial randomized controlled trial of acetylsalicylic acid versus placebo and clonidine versus placebo in patients undergoing noncardiac surgery. *Am Heart J* 2014 ([http://www.ahjonline.com/article/S0002-8703\(14\)00077-5/fulltext](http://www.ahjonline.com/article/S0002-8703(14)00077-5/fulltext)).
22. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999;100:1043-9.
23. Gerstein NS, Schulman PM, Gerstein WH, Petersen TR, Tawil I. Should more patients continue aspirin therapy perioperatively? Clinical impact of aspirin withdrawal syndrome. *Ann Surg* 2012;255:811-9.
24. Kamel H, Johnston SC, Kirkham JC, et al. Association between major perioperative hemorrhage and stroke or Q-wave myocardial infarction. *Circulation* 2012;126:207-12.
25. Bradlow BA, Chetty N. Dosage frequency for suppression of platelet function by low dose aspirin therapy. *Thromb Res* 1982;27:99-110.
26. Patrono C, Ciabattini G, Patrignani P, et al. Clinical pharmacology of platelet cyclooxygenase inhibition. *Circulation* 1985;72:1177-84.
27. Cerskus AL, Ali M, Davies BJ, McDonald JW. Possible significance of small numbers of functional platelets in a population of aspirin-treated platelets in vitro and in vivo. *Thromb Res* 1980;18:389-97.
28. O'Brien JR. Effects of salicylates on human platelets. *Lancet* 1968;1:779-83.
29. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010;340:c117.
30. Anderson DR, Dunbar MJ, Bohm ER, et al. Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. *Ann Intern Med* 2013;158:800-6.
31. Albaladejo P, Marret E, Samama CM, et al. Non-cardiac surgery in patients with coronary stents: the RECO study. *Heart* 2011;97:1566-72.

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