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. Biccard, 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 ±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≥0.12 for all interactions).

The effect of aspirin was consistent across subgroups (P≥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 composite 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)	Placebo (N=5012)	Hazard Ratio (95% CI)†	P Value
	no. (%)			
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.

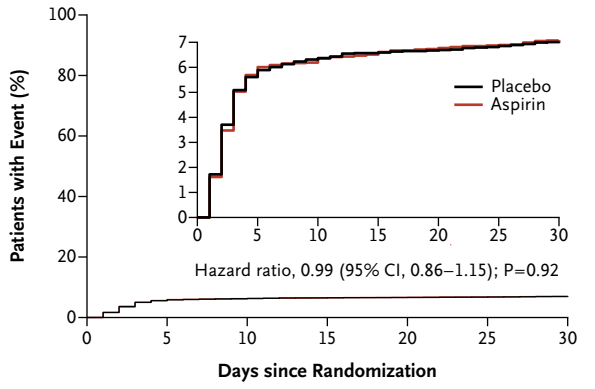

Figure 1. Kaplan–Meier Estimates of the Primary Composite Outcome of Death or Nonfatal Myocardial Infarction at 30 Days.
The inset shows the same data on an enlarged y axis.

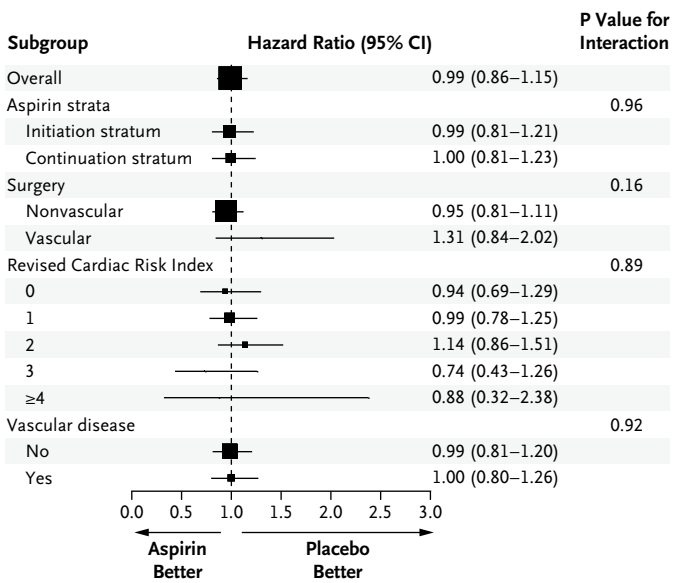

Figure 2. Subgroup Analyses of the Primary Outcome.
The primary composite outcome was death or nonfatal myocardial infarction at 30 days. The area of each square is proportional to the size of the corresponding subgroup. The Revised Cardiac Risk Index ranges from 0 to 6, with higher scores indicating greater risk.

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.

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

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 coronary 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 Mizera, 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 Coracão), 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.).

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ORIGINAL ARTICLE

Clonidine in Patients Undergoing Noncardiac Surgery

P.J. Devereaux, D.I. Sessler, K. Leslie, A. Kurz, M. Mrkobrada, P. Alonso-Coello, J.C. Villar, A. Sigamani, B.M. Biccard, 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. Chow, S. Pettit, S. Chrolavicius, and S. Yusuf, for the POISE-2 Investigators*

ABSTRACT

BACKGROUND

Marked activation of the sympathetic nervous system occurs during and after noncardiac surgery. Low-dose clonidine, which blunts central sympathetic outflow, may prevent perioperative myocardial infarction and death without inducing hemodynamic instability.

METHODS

We performed a blinded, randomized trial with a 2-by-2 factorial design to allow separate evaluation of low-dose clonidine versus placebo and low-dose aspirin versus placebo in patients with, or at risk for, atherosclerotic disease who were undergoing noncardiac surgery. A total of 10,010 patients at 135 centers in 23 countries were enrolled. For the comparison of clonidine with placebo, patients were randomly assigned to receive clonidine (0.2 mg per day) or placebo just before surgery, with the study drug continued until 72 hours after surgery. The primary outcome was a composite of death or nonfatal myocardial infarction at 30 days.

RESULTS

Clonidine, as compared with placebo, did not reduce the number of primary-outcome events (367 and 339, respectively; hazard ratio with clonidine, 1.08; 95% confidence interval [CI], 0.93 to 1.26; P=0.29). Myocardial infarction occurred in 329 patients (6.6%) assigned to clonidine and in 295 patients (5.9%) assigned to placebo (hazard ratio, 1.11; 95% CI, 0.95 to 1.30; P=0.18). Significantly more patients in the clonidine group than in the placebo group had clinically important hypotension (2385 patients [47.6%] vs. 1854 patients [37.1%]; hazard ratio 1.32; 95% CI, 1.24 to 1.40; P<0.001). Clonidine, as compared with placebo, was associated with an increased rate of nonfatal cardiac arrest (0.3% [16 patients] vs. 0.1% [5 patients]; hazard ratio, 3.20; 95% CI, 1.17 to 8.73; P=0.02).

CONCLUSIONS

Administration of low-dose clonidine in patients undergoing noncardiac surgery did not reduce the rate of the composite outcome of death or nonfatal myocardial infarction; it did, however, increase the risk of clinically important hypotension and nonfatal cardiac arrest. (Funded by the Canadian Institutes of Health Research and others; POISE-2 ClinicalTrials.gov number, NCT01082874.)

The authors' full names, 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.

*The 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 of surgery and is associated with substantial mortality.[1] During and after noncardiac surgery, there is marked activation of the sympathetic nervous system, which can lead to a mismatch between the supply of and demand for myocardial oxygen and to subsequent myocardial infarction.[2-4]

We previously reported that perioperative administration of a high-dose, long-acting beta-blocker (initiated 2 to 4 hours before surgery and continued after surgery) reduced the risk of myocardial infarction but increased the risk of death, stroke, and clinically important hypotension.[5] Clonidine, an α_2-adrenergic agonist, blunts central sympathetic outflow and has analgesic, anxiolytic, antishivering, and antiinflammatory effects, all of which may prevent perioperative myocardial infarction.[6-9] The results of small, randomized trials have suggested that perioperative administration of low-dose clonidine reduces the risk of myocardial ischemia without inducing hemodynamic instability and may prevent myocardial infarction and death.[6,10,11]

To further evaluate the effects of perioperative clonidine, we conducted the Perioperative Ischemic Evaluation 2 (POISE-2) trial. We tested the hypothesis that perioperative administration of low-dose clonidine, as compared with placebo, reduces the 30-day risk of a composite of death or nonfatal myocardial infarction in at-risk patients undergoing noncardiac surgery.

Methods

Study Design

The POISE-2 trial was an international, randomized, controlled trial with a 2-by-2 factorial design that allowed separate evaluation of the efficacy and safety of clonidine versus placebo and aspirin versus placebo in patients undergoing noncardiac surgery. This article describes the results of the comparison of clonidine with placebo; the results of the comparison of aspirin with placebo are reported elsewhere in the *Journal*.[12] Details regarding the objectives, design, and methods of the study have been published previously.[13]

Study Oversight

The Population Health Research Institute was the coordinating center for the POISE-2 trial and was responsible for the randomization scheme, the database, validation and analyses of the data, and trial-center coordination. Boehringer Ingelheim donated the clonidine study drug, and Bayer Pharma the aspirin study drug; both companies were provided with a copy of the initial draft of the manuscript. However, no donor or funder of the POISE-2 trial had any role in the design or conduct of the trial, the collection or analyses of the data, or the writing of the manuscript. The operations committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) designed the trial and prespecified the statistical analysis plan, and the members of that committee vouch for the data and analyses and for the fidelity of the study to the protocol (available at NEJM.org). The first author wrote the first draft of the manuscript, and all the authors made substantive revisions and made the decision to submit the manuscript for publication.

Procedures

We recruited patients from July 2010 through December 2013. The inclusion and exclusion criteria are listed in Section 1 in the Supplementary Appendix. Ethics approval was obtained at each participating site. After providing written informed consent, patients were randomly assigned, in a 1:1:1:1 ratio, to receive clonidine and aspirin, clonidine and aspirin placebo, clonidine placebo and aspirin, or clonidine placebo and aspirin placebo. Randomization was performed in fixed blocks with the use of a computerized interactive Web-based randomization system, with stratification according to center and status with respect to long-term aspirin therapy. Patients, health care providers, data collectors, and outcome adjudicators were unaware of the study-group assignments.

The study centers were encouraged to instruct patients not to take their usual antihypertensive medications, including beta-blockers, on the morning of surgery and to have study personnel review patients' vital signs in the presurgical area, report the results to the anesthesiologist, and ask the anesthesiologist whether the patients should receive their antihypertensive medications and, if they should, what dose they should receive.

At 2 to 4 hours before surgery, patients who met the hemodynamic criteria (i.e., systolic blood pressure ≥105 mm Hg and heart rate ≥55 beats per minute) received 0.2 mg of oral clonidine or placebo and had a transdermal clonidine patch (which releases 0.2 mg per day and has physiological effects within 24 hours)[14] or a placebo

patch applied to their upper arm or chest; the patch remained there until 72 hours after surgery. Patients also received aspirin or placebo just before surgery and continued receiving it daily throughout the postoperative period.

Blood pressure and heart rate were measured 1 hour after the first dose of the study drug was administered and every 4 hours for the first 96 hours after surgery. If clinically important hypotension or bradycardia developed in a patient and did not respond to initial treatment (e.g., a fluid bolus), study personnel encouraged removal of the patient's clonidine patch. Attending physicians made all medical decisions, including decisions about discontinuing either study drug.

Blood was obtained for measurement of the troponin level (or the MB fraction of creatine kinase [CK-MB] if troponin was not measured) 6 to 12 hours after surgery and daily for the next 3 days. Electrocardiography was performed if the troponin level or CK-MB level was elevated. Research personnel at participating centers followed patients until 30 days after randomization, collected the data, and submitted the case-report forms and supporting documentation of events directly to the data management system (iDataFax). Data monitoring consisted of central checks for data consistency, statistical monitoring, and on-site monitoring.

OUTCOMES

The primary outcome (a composite of death or nonfatal myocardial infarction) and the secondary outcome (a composite of death, nonfatal myocardial infarction, or stroke) were documented within 30 days after randomization. The tertiary and safety outcomes are listed in Section 2 in the Supplementary Appendix, and all the outcomes are defined in Section 3 in the Supplementary Appendix. Outcome adjudicators evaluated whether a death was due to vascular or nonvascular causes and whether a patient had a myocardial infarction, nonfatal cardiac arrest, pulmonary embolism, deep-vein thrombosis, stroke, or peripheral arterial thrombosis (Section 4 in the Supplementary Appendix); the findings as determined by the adjudicators were used in the statistical analyses.

STATISTICAL ANALYSIS

We estimated that with a sample of 10,000 patients, the study would have 84% power to detect a hazard ratio with clonidine of 0.75, at a two-sided alpha level of 0.05, assuming a 30-day rate of 6.1% for the primary outcome in the placebo group.[5] An external data and safety monitoring committee conducted prespecified interim analyses when 25%, 50%, and 75% of the 30-day follow-up data were available.

Statistical analyses were performed with the use of SAS software, version 9.1. We evaluated patients according to the study group to which they had been assigned, and data from patients who were lost to follow-up were censored on the last day that their outcome status was known. Outcomes were analyzed with the use of Cox proportional-hazards models, with stratification according to assignment to aspirin or to aspirin placebo and status with respect to long-term aspirin therapy; the only exceptions were the outcome of acute kidney injury with receipt of dialysis, for which we used a logistic-regression analysis, and the length-of-stay outcomes, for which we used the log-rank test.

We also performed prespecified analyses of the primary outcome in subgroups defined according to type of anesthesia (neuraxial vs. other), type of surgery (vascular vs. nonvascular), use or no use of beta-blockers during the 24 hours before surgery, and the number of criteria for the Revised Cardiac Risk Index that the patient met.[15] We stated a priori the expected direction of effects in the subgroups. For the subgroup analyses, we used Cox proportional-hazards models that incorporated tests of interaction, for which P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

PATIENTS

The POISE-2 study included 10,010 patients at 135 hospitals in 23 countries; 5009 patients were randomly assigned to clonidine and 5001 to placebo. The 30-day follow-up was complete for 99.9% of the participants (Fig. S1 in the Supplementary Appendix). The baseline characteristics of the participants, the type of surgery they underwent, the anesthesia used, and the medications they received are shown in Table 1. The mean age of the patients was 68.6 years, and 47.2% were women. More than 97% of the patients received the study drug before surgery, and in more than 90%, the transdermal study patch remained in place for at least 80% of the targeted

duration of application (Table S1 in the Supplementary Appendix).

OUTCOMES

The effect of clonidine on 30-day outcomes is shown in Table 2. Clonidine did not significantly affect the primary outcome of death or nonfatal myocardial infarction (hazard ratio with clonidine, 1.08; 95% confidence interval [CI], 0.93 to 1.26; P=0.29) (Fig. 1). Myocardial infarction occurred in 329 patients (6.6%) assigned to clonidine and in 295 patients (5.9%) assigned to placebo (hazard ratio, 1.11; 95% CI, 0.95 to 1.30; P=0.18). A greater number of patients in the clonidine group than in the placebo group had a nonfatal cardiac arrest (16 patients [0.3%] vs. 5 patients [0.1%]; hazard ratio, 3.20; 95% CI, 1.17 to 8.73; P=0.02) (Fig. S2 in the Supplementary Appendix). Asystole and pulseless electrical activity accounted for 85.7% of the nonfatal cardiac arrests (Table S2 in the Supplementary Appendix). The median length of stay in the hospital was 4 days (interquartile range, 3 to 7) for both the clonidine group and the placebo group (P=0.97). There was no significant between-group difference in the mean number of nights spent in the intensive care unit or the cardiac care unit (P=0.48). Status with respect to receipt of the aspirin study drug had no significant effect on the results of the comparison of clonidine with placebo (P≥0.12 for all interactions).

Clinically important hypotension occurred in significantly more patients in the clonidine group than in the placebo group (2385 patients [47.6%] vs. 1854 patients [37.1%]; hazard ratio, 1.32; 95% CI, 1.24 to 1.40; P<0.001). Clinically important bradycardia occurred in 600 patients (12.0%) in the clonidine group as compared with 403 patients (8.1%) in the placebo group (hazard ratio, 1.49; 95% CI, 1.32 to 1.69; P<0.001).

PRESPECIFIED SUBGROUP ANALYSES

Results of the subgroup analyses of the primary outcome are shown in Figure 2. Of the 605 patients who underwent vascular surgery, 83 had a primary outcome event, but there was no significant difference between the two study groups. There were, however, two significant P values for interaction; the direction of the interactions was inconsistent with our a priori hypotheses. The results suggest that clonidine may increase the risk of the primary composite outcome in patients who do not undergo neuraxial anesthesia and in patients with a score of 3 on the Revised Cardiac Risk Index (on which scores range from 0 to 6, with higher scores indicating greater risk).

POST HOC ANALYSES

Table 3 shows the results of the post hoc multivariable analysis of factors associated with perioperative myocardial infarction. Clinically important hypotension was an independent predictor of subsequent myocardial infarction (hazard ratio, 1.37; 95% CI, 1.16 to 1.62). Table S3 in the Supplementary Appendix shows the rate and duration of clinically important hypotension at different time points. Although more patients had clinically important hypotension during surgery than afterward, the duration of hypotension was considerably longer after patients left the postanesthesia care unit. For example, in the clonidine group, the median duration of clinically important hypotension during surgery was 15 minutes, whereas on the first postoperative day it was 180 minutes.

DISCUSSION

The POISE-2 trial showed that low-dose clonidine, as compared with placebo, did not reduce the composite outcome of death or nonfatal myocardial infarction in adults undergoing noncardiac surgery. Moreover, clonidine increased the risk of clinically important hypotension, clinically important bradycardia, and nonfatal cardiac arrest.

A systematic review of perioperative use of α_2-adrenergic agonists (i.e., clonidine, dexmedetomidine, and mivazerol) included 12 trials involving patients who were undergoing noncardiac surgery; outcomes were reported separately for patients who were undergoing vascular surgery and those who were undergoing nonvascular surgery.[16] Meta-analyses showed that among patients who were undergoing vascular surgery, administration of a fixed dose of an α_2-adrenergic agonist, as compared with a placebo or standard care, significantly reduced the risks of both death (13 events vs. 26 events; relative risk, 0.47; 95% CI, 0.25 to 0.90) and myocardial infarction (45 events vs. 65 events; relative risk, 0.66; 95% CI, 0.46 to 0.94). Among the patients undergoing nonvascular surgery, however, there was no significant effect of α_2-adrenergic agonists on the risk of death (16 events and 15 events, respectively; relative risk, 1.05; 95% CI, 0.52 to

2.09) or of myocardial infarction (36 events and 26 events, respectively; relative risk, 1.25; 95% CI, 0.83 to 2.21).

Results of the six trials in the systemic review that included data on hypotension suggested that the use of α_2-adrenergic agonists in patients undergoing noncardiac surgery did not increase the risk of hypotension (relative risk, 1.03; 95% CI, 0.89 to 1.21).[16] In contrast, the POISE-2 trial showed that low-dose clonidine increased the risk of clinically important hypotension.

In our trial, only 605 patients underwent vascular surgery, of whom 83 had a primary outcome event. The lack of a subgroup effect for vascular surgery (P=0.34 for interaction) suggests that the best estimate of the effect of clonidine with respect to the primary outcome in patients undergoing vascular surgery is likely to be similar to the effect in the overall study population (i.e., hazard ratio, 1.08; 95% CI, 0.93 to 1.26).

Several previous trials of perioperative cloni-

Table 1. Baseline Characteristics, Type of Surgery and Anesthesia, and Perioperative Medications.*

Characteristic	Clonidine (N=5009)	Placebo (N=5001)
Age — yr	68.5±10.4	68.6±10.3
Male sex — no. (%)	2633 (52.6)	2650 (53.0)
Eligibility criteria met — no. (%)†		
History of coronary artery disease	1154 (23.0)	1114 (22.3)
History of peripheral arterial disease	425 (8.5)	440 (8.8)
History of stroke	279 (5.6)	263 (5.3)
History of any vascular disease‡	1630 (32.5)	1641 (32.8)
Undergoing major vascular surgery	244 (4.9)	245 (4.9)
Risk criteria§	4167 (83.2)	4133 (82.6)
Undergoing major surgery	3930 (78.5)	3872 (77.4)
Need for urgent or emergency surgery	363 (7.2)	360 (7.2)
Age ≥70 yr	2643 (52.8)	2598 (51.9)
Current diabetes for which medication is required	1916 (38.3)	1869 (37.4)
Preoperative serum creatinine >175 μmol/liter (2.0 mg/dl)	158 (3.2)	162 (3.2)
History of congestive heart failure	161 (3.2)	176 (3.5)
History of transient ischemic attack	161 (3.2)	202 (4.0)
History of hypertension	4312 (86.1)	4323 (86.4)
History of smoking within 2 years before surgery	1258 (25.1)	1299 (26.0)
Other medical history — no. (%)		
History of coronary-artery bypass grafting	244 (4.9)	237 (4.7)
History of percutaneous coronary intervention	233 (4.7)	237 (4.7)
Need for dialysis in week before randomization	70 (1.4)	57 (1.1)
Time from randomization to surgery — no. (%)		
≤24 hr	4815 (96.1)	4757 (95.1)
>24–48 hr	38 (0.8)	56 (1.1)
>48 hr	156 (3.1)	188 (3.8)
Surgery — no./total no. (%)¶		
Underwent surgery	4972/5009 (99.3)	4960/5001 (99.2)
Orthopedic	1950/4972 (39.2)	1894/4960 (38.2)
General	1334/4972 (26.8)	1330/4960 (26.8)
Urologic or gynecologic	809/4972 (16.3)	853/4960 (17.2)
Vascular	310/4972 (6.2)	295/4960 (5.9)
Thoracic	301/4972 (6.1)	290/4960 (5.8)
Other	398/4972 (8.0)	422/4960 (8.5)
Did not undergo surgery	36/5009 (0.7)	37/5001 (0.7)
Data not available‖	1/5009 (<0.1)	4/5001 (0.1)

Table 1. (Continued.)

Characteristic	Clonidine (N = 5009)	Placebo (N = 5001)
Intraoperative anesthesia — no./total no. (%)		
General	2353/4972 (47.3)	2356/4960 (47.5)
Neuraxial		
Lumbar epidural	94/4972 (1.9)	103/4960 (2.1)
Spinal	1224/4972 (24.6)	1224/4960 (24.7)
Combined spinal and epidural	92/4972 (1.9)	104/4960 (2.1)
General and epidural		
General and thoracic epidural	298/4972 (6.0)	313/4960 (6.3)
General and lumbar epidural	57/4972 (1.1)	58/4960 (1.2)
Nerve block	40/4972 (0.8)	38/4960 (0.8)
General and nerve block	211/4972 (4.2)	183/4960 (3.7)
Spinal and nerve block	212/4972 (4.3)	204/4960 (4.1)
Other combination	392/4972 (7.9)	377/4960 (7.6)
Medications taken <7 days to >24 hr before surgery — no./total no. (%)		
Beta-blocker	1454/4971 (29.2)	1399/4958 (28.2)
Rate-controlling calcium-channel blocker	249/4972 (5.0)	270/4958 (5.4)
Statin	2288/4972 (46.0)	2257/4958 (45.5)
α_2-Adrenergic agonist	10/4972 (0.2)	13/4958 (0.3)
Medications taken ≤24 hr before surgery — no./total no. (%)		
Beta-blocker**	1198/4972 (24.1)	1161/4957 (23.4)
Rate-controlling calcium-channel blocker	198/4972 (4.0)	209/4958 (4.2)
Statin	1858/4972 (37.4)	1799/4958 (36.3)
α_2-Adrenergic agonist	5/4972 (0.1)	0/4958
Medications taken sometime during first 3 days after surgery — no./total no. (%)		
Beta-blocker††	1453/4969 (29.2)	1473/4954 (29.7)
Rate-controlling calcium-channel blocker	220/4969 (4.4)	251/4954 (5.1)
Statin	2108/4968 (42.4)	2063/4955 (41.6)

* Plus–minus values are means ±SD. There were no significant differences between the groups in any of the baseline characteristics listed here, with the exception of a history of transient ischemic attack (P=0.03) and an interval between randomization and surgery of 24 hours or less (P=0.01).
† Patients were eligible for enrollment in the study if they met one or more of the eligibility criteria.
‡ "Any vascular disease" was defined as coronary artery disease, peripheral arterial disease, or stroke. Patients may have had a history of more than one vascular disease.
§ Meeting this eligibility criterion involved meeting at least three of the nine risk criteria listed here.
¶ Patients may have had more than one type of surgery.
‖ Data were not available because the patients withdrew from the study.
** A total of 81.2% of the patients in the clonidine group and 81.7% of those in the placebo group who received a beta-blocker within 7 days to more than 24 hours before surgery also received a beta-blocker within 24 hours before surgery.
†† A total of 88.6% of the patients in the clonidine group and 90.9% in the placebo group who received a beta-blocker within 24 hours before surgery also received a beta-blocker during the first 3 days after surgery.

dine have suggested that low-dose clonidine reduces the risk of myocardial ischemia without inducing hemodynamic compromise and that it may prevent myocardial infarction and death.[10,11,17-19] In contrast to the POISE-2 trial, these trials were small (<300 patients in each trial) and included few events.

Evidence suggests that the surgical stress response is a mechanism that can cause the mismatch between the supply of and demand for myocardial oxygen, a mismatch that can result in perioperative myocardial infarction.[4] Possible approaches to attenuating the adverse effects of the surgical stress response include treatment with a beta-blocker and treatment with an α_2-adrenergic agonist. In a previous trial evaluating perioperative use of a beta-blocker (the POISE trial), which involved 8351 patients, we found

Table 2. Effects of Clonidine on the Outcomes at 30 Days.*

Outcome	Clonidine (N=5009)	Placebo (N=5001)	Hazard Ratio (95% CI)	P Value
Primary outcome: death or nonfatal myocardial infarction — no. (%)	367 (7.3)	339 (6.8)	1.08 (0.93–1.26)	0.29
Secondary outcome: death, nonfatal myocardial infarction, or nonfatal stroke — no. (%)	380 (7.6)	352 (7.0)	1.08 (0.93–1.25)	0.30
Tertiary outcomes — no. (%)				
Death	64 (1.3)	63 (1.3)	1.01 (0.72–1.44)	0.94
Death from vascular causes	38 (0.8)	32 (0.6)	1.19 (0.74–1.90)	0.48
Myocardial infarction	329 (6.6)	295 (5.9)	1.11 (0.95–1.30)	0.18
Nonfatal cardiac arrest	16 (0.3)	5 (0.1)	3.20 (1.17–8.73)	0.02
Cardiac revascularization	19 (0.4)	11 (0.2)	1.73 (0.82–3.63)	0.15
Pulmonary embolism	32 (0.6)	32 (0.6)	1.00 (0.61–1.63)	0.99
Deep-vein thrombosis	37 (0.7)	23 (0.5)	1.61 (0.96–2.71)	0.07
New, clinically important atrial fibrillation	107 (2.1)	96 (1.9)	1.11 (0.84–1.47)	0.45
Peripheral arterial thrombosis	14 (0.3)	14 (0.3)	1.00 (0.48–2.09)	1.00
Amputation	12 (0.2)	11 (0.2)	1.09 (0.48–2.47)	0.84
Rehospitalization for vascular reasons	66 (1.3)	58 (1.2)	1.14 (0.80–1.62)	0.48
Acute kidney injury with receipt of dialysis†	29 (0.6)	23 (0.5)	1.26 (0.73–2.18)	0.41
Safety outcomes — no. (%)				
Stroke	18 (0.4)	17 (0.3)	1.06 (0.54–2.05)	0.87
Clinically important hypotension	2385 (47.6)	1854 (37.1)	1.32 (1.24–1.40)	<0.001
Clinically important bradycardia	600 (12.0)	403 (8.1)	1.49 (1.32–1.69)	<0.001
Congestive heart failure	48 (1.0)	34 (0.7)	1.41 (0.91–2.19)	0.12
Infection	478 (9.6)	505 (10.1)	0.94 (0.83–1.07)	0.34
Sepsis	233 (4.7)	268 (5.4)	0.86 (0.72–1.03)	0.10

* The percentages in this table are Kaplan–Meier estimates.
† For this outcome, we report the odds ratio instead of the hazard ratio, because we did not obtain information on the actual date that patients first started dialysis.

that metoprolol succinate in an extended-release pill (at a dose of 100 mg administered just before noncardiac surgery and 200 mg daily thereafter for 30 days), as compared with placebo, reduced the risk of myocardial infarction (176 events vs. 239 events; hazard ratio, 0.73; 95% CI, 0.60 to 0.89).[5] The POISE-2 trial showed that clonidine, which attenuates the perioperative stress response through a different mechanism, did not reduce the risk of myocardial infarction (hazard ratio, 1.11; 95% CI, 0.95 to 1.30).

We offer two potential explanations for these findings. First, enhanced control of the heart rate appears to increase protection against perioperative myocardial infarction,[20] and the results of the POISE-2 trial suggest that clinically important hypotension increases the risk of perioperative myocardial infarction. Therefore, creating a better balance between perioperative supply of and demand for myocardial oxygen may require a balance between decreasing the heart rate (thus minimizing demand) and avoiding clinically important hypotension (thus ensuring supply). Although we did not collect data on daily heart rates in the POISE-2 trial, clinically important bradycardia may act as a proxy for the overall effect on control of the heart rate. We used the same definitions of clinically important hypotension and bradycardia in the POISE and POISE-2 trials. The risk of clinically important hypotension was increased among patients who received metoprolol in the POISE trial (hazard ratio, 1.55; 95% CI, 1.38 to 1.74) and among those who received clonidine in the POISE-2 trial (hazard ratio, 1.32; 95% CI, 1.24 to 1.40).[5] The risk of clinically important bradycardia was also in-

creased with metoprolol and with clonidine; however, metoprolol had a substantially larger relative effect than did clonidine (hazard ratio with metoprolol, 2.74; 95% CI, 2.19 to 3.43; hazard ratio with clonidine, 1.49; 95% CI, 1.32 to 1.69). It is therefore possible that the balance between heart-rate control and hypotension produced the discrepant results that were observed between metoprolol and clonidine.

A second potential explanation for the difference between the POISE trial and the POISE-2 trial with respect to the effects on myocardial infarction is that the effect on important but poorly understood determinants of myocardial ischemia and infarction differs between the sympathetic block produced by central α_2-adrenergic agonists and that produced by peripheral beta-blockers.

The POISE-2 trial revealed no significant effect of clonidine on the rate of stroke (18 strokes in the clonidine group and 17 in the placebo group; hazard ratio, 1.06; 95% CI, 0.54-2.05), whereas the POISE trial showed that metoprolol increased the risk of stroke (41 strokes vs. 19 strokes; hazard ratio, 2.17; 95% CI, 1.26 to 3.74).[5] Potential explanations for this finding include differences in the relative effects of the two agents on hypotension (hazard ratio with metoprolol, 1.55; 95% CI, 1.38 to 1.74; hazard ratio with clonidine, 1.32; 95% CI, 1.24 to 1.40) or differences in the power of the two trials.

In the POISE-2 trial, there was a significant increase in the risk of nonfatal cardiac arrest with clonidine as compared with placebo — equivalent to two additional cases per 1000 patients. The main types of nonfatal cardiac arrest were asystole and pulseless electrical activity.

Two subgroup analyses of the primary outcome showed significant P values for interaction. It is appropriate to consider with skepticism the results of the analysis of the subgroup defined according to the Revised Cardiac Risk Index because those results do not follow a linear pattern, suggesting that they may represent a chance finding (Fig. 2). The analysis of the subgroup defined according to the anesthesia suggests that among patients receiving non-neuraxial anesthesia, clonidine may increase the risk of death or nonfatal myocardial infarction. This subgroup effect was counter to the direction of our a priori hypothesis and requires cautious interpretation. Moreover, clonidine did not show a benefit in any of the subgroup analyses.

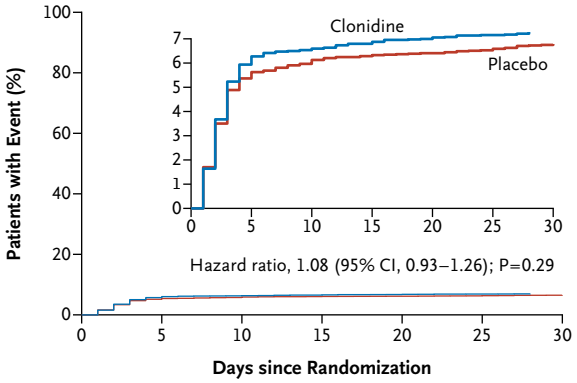

Figure 1. Kaplan–Meier Estimates of the Primary Outcome, According to Study Group.

The primary outcome was a composite of death or nonfatal myocardial infarction at 30 days. The inset shows the same data on an enlarged y axis.

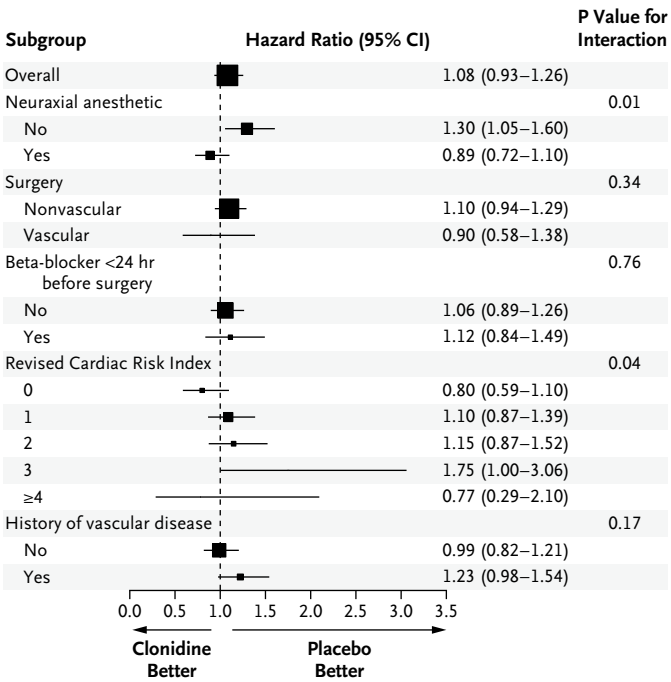

Figure 2. Subgroup Analyses of the Primary Outcome.

The 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 the POISE-2 trial, we evaluated a fixed, low-dose clonidine regimen that was initiated just before surgery and was continued for 72 hours

Table 3. Independent Predictors of Myocardial Infarction.*

Independent Predictor	All Patients (N=10,010)	Patients with Myocardial Infarction ≤30 Days after Randomization (N=624)		Adjusted Hazard Ratio (95% CI)	P Value	Population Attributable Risk (95% CI)
	no. (%)	*no.*	*% (95% CI)*			
Preoperative						
History of coronary artery disease	2268 (22.7)	186	29.8 (26.2–33.4)	1.49 (1.25–1.78)	<0.001	10.3 (6.4–16.3)
History of peripheral vascular disease	865 (8.6)	100	16.0 (13.1–18.9)	2.10 (1.69–2.60)	<0.001	8.9 (6.1–12.7)
History of congestive heart failure	337 (3.4)	39	6.2 (4.4–8.1)	1.60 (1.15–2.22)	0.005	2.5 (1.1–5.7)
Estimated GFR <60 ml/min/1.73 m²†	2496 (25.4)	239	38.5 (34.7–42.4)	1.52 (1.28–1.79)	<0.001	13.9 (9.0–20.8)
Age ≥75 yr	3105 (31.0)	295	47.3 (43.4–51.2)	1.89 (1.60–2.23)	<0.001	23.5 (17.9–30.1)
Intraoperative and postoperative						
Clinically important hypotension	4217 (42.1)	319	51.1 (47.2–55.0)	1.37 (1.16–1.62)	<0.001	14.8 (8.8–23.7)
Major bleeding‡	527 (5.3)	65	10.4 (8.0–12.8)	1.82 (1.40–2.36)	<0.001	5.0 (2.9–8.4)

* We performed a multivariable logistic-regression analysis to determine the independent predictors of myocardial infarction. In this model, the dependent variable was myocardial infarction at 30 days after randomization, and we included potential independent preoperative variables that we had determined in previous studies to be independent predictors of perioperative myocardial infarction (i.e., history of stroke, hypertension, congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes for which the patient was receiving medical treatment, preoperative estimated glomerular filtration rate [GFR; <60 ml per minute per 1.73 m² of body-surface area vs. ≥60 ml/minute/1.73 m² in reference group], age ≥75 years, every increase of 10 beats per minute in baseline heart rate, and urgent or emergency surgery) and potential independent intraoperative and postoperative variables that occurred before myocardial infarction (i.e., clinically important bradycardia, clinically important hypotension, and all major bleeding episodes, which were time-dependent variables in the model).

† Data on estimated GFR were available for 9841 patients.

‡ Major bleeding was a composite of life-threatening bleeding or major bleeding.

after surgery. We selected this regimen because small trials had suggested that it might prevent myocardial infarction and death without causing hypotension,[19] because the 72-hour period after surgery is the period when catecholamine levels are elevated and most myocardial infarctions occur, and because the regimen is practical in the clinical setting.[2,21,22] Other clonidine regimens may produce different results.

The POISE-2 trial showed that a substantial problem persists, as evidenced by the fact that 7.1% of adults died or had a nonfatal myocardial infarction in the first 30 days after surgery. The data indicate that in current practice, low-dose clonidine does not minimize these complications. If decreasing the heart rate while minimizing hypotension is important in preventing perioperative myocardial infarction, the finding of the POISE-2 trial that patients had prolonged episodes of clinically important hypotension after surgery identifies a target for potential improvement.

In conclusion, administering low-dose clonidine in patients undergoing noncardiac surgery did not reduce the composite outcome of death or nonfatal myocardial infarction, and it increased the risk of clinically important hypotension. New strategies are needed to address the problem of major vascular complications after noncardiac surgery.

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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' full names and degrees are as follows: P.J. Devereaux, M.D., Ph.D., Daniel I. Sessler, M.D., Kate Leslie, M.B., B.S., M.D., Andrea Kurz, M.D., Marko Mrkobrada, M.D., Pablo Alonso-Coello, M.D., Ph.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, M.B., B.S., John Eikelboom, M.B., B.S., Richard Mizera, 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, M.Sc., Janice Pogue, Ph.D., Richard Whitlock, M.D., Ph.D., André Lamy, M.D., Clive Kearon, M.B., Ph.D., 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.

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, Australia (K.L.); Iberoamerican Cochrane Center (P.A.-C.) and the Anesthesiology Department (P.P.), Biomedical Research Institute (IIB-Sant Pau), 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 (ECLA), Instituto Cardiovascular de Buenos Aires (ICBA), Buenos Aires (F.B.); the Department of Anesthesia, University Hospital Basel, Basel, Switzerland (G.L.B.); the Department of Anaesthesia and Intensive Care, the 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 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 Coracão), São Paulo (O.B.); Anesthesia and Intensive Care, San Raffaele Scientific Institute, Milan (L.P.); and the George Institute for Global Health and the University of Sydney, Sydney (C.C.).

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