ORIGINAL ARTICLE

Clonidine in Patients Undergoing Noncardiac Surgery

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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.)

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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 ar-

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.

rests (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 bra-

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.

dycardia 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 impor-

tant 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-

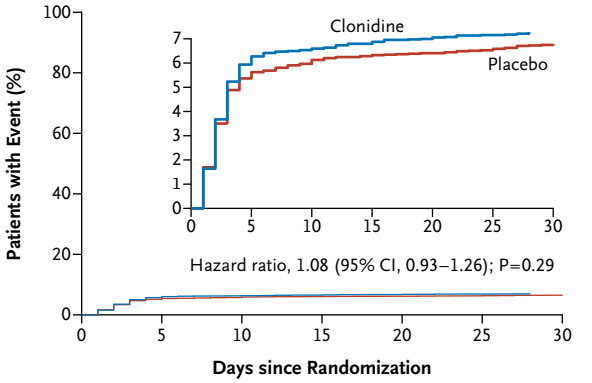

Figure 1. Kaplan–Meier Estimates of the Primary Outcome, According to Study Group.

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.

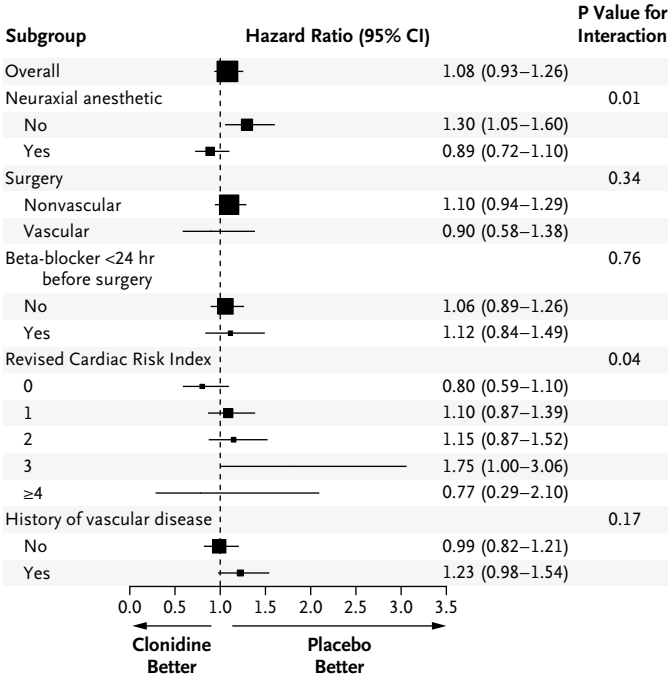

Figure 2. Subgroup Analyses of the Primary Outcome.

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.

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.

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 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.

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 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

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