ANESTHESIOLOGY

One-year Results of a Factorial Randomized Trial of Aspirin *versus* Placebo and Clonidine *versus* Placebo in Patients Having Noncardiac Surgery

Daniel I. Sessler, M.D., David Conen, M.D., Kate Leslie, M.D., Salim Yusuf, D.Phil., Ekaterina Popova, M.D., Michelle Graham, M.D., Andrea Kurz, M.D., Juan Carlos Villar, Ph.D., Marko Mrkobrada, M.D., Alben Sigamani, M.D., Bruce M. Biccard, Ph.D., Christian S. Meyhoff, Ph.D., Joel L. Parlow, M.D., Gordon Guyatt, M.D., Denis Xavier, M.D., Matthew T. V. Chan, Ph.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., David Torres, M.Sc., C. Y. Wang, M.B., Ch.B., Pilar Paniagua, M.D., Ph.D., Otavio Berwanger, M.D., Ph.D., Sadeesh Srinathan, M.D., Giovanni Landoni, M.D., Yannick Le Manach, M.D., Ph.D., Richard Whitlock, M.D., Ph.D., André Lamy, M.D., Kumar Balasubramanian, M.D., Ian Gilron, M.D., Alparslan Turan, M.D., Shirley Pettit, R.N., P. J. Devereaux, M.D., on behalf of the Perioperative Ischemic Evaluation-2 Trial (POISE-2) Investigators

ANESTHESIOLOGY 2020; 132:692–701

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The Perioperative Ischemic Evaluation-2 study (POISE-2) authors previously reported that neither aspirin nor clonidine reduced a 30-day composite of nonfatal myocardial infarction or death. Aspirin caused perioperative bleeding, and clonidine provoked hypotension and bradycardia.
- In a subgroup analysis of patients who had previous percutaneous coronary interventions, those given aspirin had fewer infarctions or deaths.

What This Article Tells Us That Is New

- This article reports 1-yr outcomes of the POISE-2 study. Consistent with the 30-day analysis, neither aspirin nor clonidine reduced a 1-yr composite of nonfatal myocardial infarction or death.
- In a subgroup analysis of patients who had prior percutaneous coronary interventions, those given aspirin had significantly fewer nonfatal myocardial infarctions and/or deaths.

ABSTRACT

Background: The authors previously reported that perioperative aspirin and/or clonidine does not prevent a composite of death or myocardial infarction 30 days after noncardiac surgery. Moreover, aspirin increased the risk of major bleeding and clonidine caused hypotension and bradycardia. Whether these complications produce harm at 1 yr remains unknown.

Methods: The authors randomized 10,010 patients with or at risk of atherosclerosis and scheduled for noncardiac surgery in a 1:1:1:1 ratio to clonidine/aspirin, clonidine/aspirin placebo, clonidine placebo/aspirin, or clonidine placebo/aspirin placebo. Patients started taking aspirin or placebo just before surgery; those not previously taking aspirin continued daily for 30 days, and those taking aspirin previously continued for 7 days. Patients were also randomly assigned to receive clonidine or placebo just before surgery, with the study drug continued for 72 h.

Results: Neither aspirin nor clonidine had a significant effect on the primary 1-yr outcome, a composite of death or nonfatal myocardial infarction, with a 1-yr hazard ratio for aspirin of 1.00 (95% CI, 0.89 to 1.12; $P = 0.948$; 586 patients [11.8%] *vs.* 589 patients [11.8%]) and a hazard ratio for clonidine of 1.07 (95% CI, 0.96 to 1.20; $P = 0.218$; 608 patients [12.1%] *vs.* 567 patients [11.3%]), with effect on death or nonfatal infarction. Reduction in death and nonfatal myocardial infarction from aspirin in patients who previously had percutaneous coronary intervention at 30 days persisted at 1 yr. Specifically, the hazard ratio was 0.58 (95% CI, 0.35 to 0.95) in those with previous percutaneous coronary intervention and 1.03 (95% CI, 0.91to 1.16) in those without (interaction $P = 0.033$). There was no significant effect of either drug on death, cardiovascular complications, cancer, or chronic incisional pain at 1 yr (all $P > 0.1$).

Conclusions: Neither perioperative aspirin nor clonidine have significant long-term effects after noncardiac surgery. Perioperative aspirin in patients with previous percutaneous coronary intervention showed persistent benefit at 1 yr, a plausible sub-group effect.

(ANESTHESIOLOGY 2020; 132:692–701)

Intraoperative mortality is now rare,[1,2] but postoperative mortality and morbidity remain common.[3,4] Major bleeding and myocardial infarction are leading attributable causes of mortality in the 30 days after noncardiac surgery.[5]

Currently, there is no known safe way to prevent postoperative myocardial infarction.[6,7] β-Blockers prevent myocardial infarction after noncardiac surgery but increase the risk of stroke and death.[6] Avoiding nitrous oxide is ineffective.[7] Both clonidine and aspirin were attractive candidates to reduce perioperative myocardial infarction because they either reduce sympathetic nervous system activation and lower heart rate, or block platelet activation and clot formation. However, the large randomized Perioperative Ischemic Evaluation-2 (POISE-2) trial failed to confirm these hypotheses, as neither aspirin[9] nor clonidine[8] prevented myocardial infarction or death within 30 days of randomization. We did, however, demonstrate that a subgroup of patients, those with previous percutaneous coronary interventions, benefit from

perioperative aspirin through a reduction in nonfatal myocardial infarction: 30-day hazard ratio for death or myocardial infarction 0.50 [95% CI, 0.26 to 0.95].[8]

Both aspirin and clonidine caused adverse effects. Clonidine provoked clinically important bradycardia and hypotension,[9] whereas aspirin increased the risk of major bleeding.[10] Both hypotension[11,12] and bleeding[13,14] are related to the risk of long-term complications, but it remains unclear whether perioperative treatment with either aspirin or clonidine causes long-term harm or benefit. We therefore evaluated the effect of aspirin or placebo and clonidine on the 1-yr risk of a composite outcome of death or nonfatal myocardial infarction in POISE-2 patients. Secondary and tertiary outcomes that were evaluated at 30 days were also considered at 1 yr.

Thirty-day pain was not assessed in the trial's analyses of 30-day postoperative outcomes. Therefore, assessing 1-yr postoperative pain adds a new longer-term outcome that was not assessed in the short-term in the POISE-2 analyses of 30-day outcomes. Chronic postoperative pain after surgery is defined by pain that persists longer than natural healing and is not associated with other apparent causes. Typically, incision pain lasting more than 3 to 6 months is considered persistent. Chronic postoperative pain reduces patient function, and associated long-term opioid use can lead to abuse and addiction. It is therefore reasonable to consider preventive strategies. Aspirin is an effective analgesic and anti-inflammatory drug used for acute pain. Clonidine has been used in chronic pain and acute pain with varying degree of success.[15,16] Aspirin has yet to be tested for prevention of persistent pain, and there are only a few inconsistent studies of clonidine. We therefore also evaluated chronic pain 1 yr after surgery.

Materials and Methods

The POISE-2 Trial was an international, randomized, controlled trial with a 2-by-2 factorial design to assess the individual efficacy and safety of both clonidine and aspirin among patients having noncardiac surgery. We previously published detailed information about ethics approvals, registration, trial objectives, and methods.[17] In brief, we recruited 10,010 patients from 135 hospitals in 23 countries between July 2010 and December 2013. Eligible patients were at least 45 yr of age, having inpatient noncardiac surgery, and had either established vascular disease or multiple risk factors. The main exclusion criteria were systolic blood pressure less than 105 mm Hg, heart rate less than 55 beats per minute, consumption of aspirin within 72 h before surgery, or having a recent episode of major bleeding (Supplemental Digital Content, table 1, http://links.lww.com/ALN/C227).

Protocol

Patients were randomized through a computerized web randomization system using block randomization (n = 4) stratified by center and whether they were taking aspirin chronically (*i.e.*, the continuation stratum if they were taking aspirin chronically or the initiation stratum if they were not taking aspirin chronically). Using a factorial approach, patients were assigned in a 1:1:1:1 fashion to clonidine/aspirin, clonidine/aspirin placebo, clonidine placebo/aspirin, or clonidine placebo/ aspirin placebo. Patients, health care providers, data collectors, and outcome adjudicators were blinded to treatment allocation.

Centers were encouraged to instruct their patients to hold usual antihypertensive medications on the morning of surgery. Study personnel reviewed participants' vital signs in the presurgical area, and in consultation with the attending anesthesiologist determined which antihypertensive medications should be given, and in what doses. Patients were given 200 mg of aspirin or aspirin placebo just before surgery and took 100 mg daily for 30 days if they were in the aspirin initiation stratum, or 7 days if they were in the aspirin continuation stratum, with their regular aspirin thereafter. Two to four hours before surgery, patients fulfilling

This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a visual abstract available in the online version.

Submitted for publication January 23, 2019. Accepted for publication December 20, 2019. Published online first on February 3, 2020. From the Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio (D.I.S., A.K., A.T.); Population Health Research Institute (D.I.S., D.C., S.Y., Y.L.M., A.L., K.B., S.P., P.J.D.), Department of Medicine (D.C., S.Y., G.G., P.J.D.), Department of Health Research Methods, Evidence, and Impact (D.C., S.Y., G.G., Y.L.M., A.L., P.J.D.), Faculty of Health Sciences, Department of Anesthesia (Y.L.M.), and Department of Surgery (R.W., A.L.), McMaster University, Hamilton, Ontario, Canada; Department of Anaesthesia and Pain Management, Royal Melbourne Hospital and Centre for Integrated Critical Care, University of Melbourne, Melbourne, Australia (K.L.); Public Health and Clinical Epidemiology-Iberoamerican Cochrane Centre, Barcelona, Spain (E.P.); University of Alberta and Mazankowski Alberta Heart Institute, Edmonton, Alberta, Canada (M.G.); Department of Research, Foundation for Pediatric Cardiology, Institute of Cardiology and Faculty of Health Sciences (Departamento de Investigaciones, Fundación Cardioinfantil—Instituto de Cardiología and Facultad de Ciencias de la Salud), Universidad Autónoma de Bucaramanga, Colombia (J.C.V.); University of Western Ontario, London, Ontario, Canada (M.M.); Department of Clinical Research, Narayana Hrudayalaya Limited, Bangalore, India (A.S.); University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa (B.M.B.); Department of Anaesthesia and Intensive Care, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark (C.S.M.); Department of Anesthesiology and Perioperative Medicine, Kingston Health Sciences Centre and Queen's University, Kingston, Canada (J.L.P., I.G.); St. John's Medical College and Research Institute, Bangalore, Karnataka, India (D.X.); Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong (M.T.V.C.); University of North Carolina School of Medicine, Chapel Hills, North Carolina (P.A.K.); NHS Grampian and the University of Aberdeen, Aberdeen, United Kingdom (P.F.); Knowledge and Evidence Unite (Unidad de Conocimiento y Evidencia), Universidad Peruana Cayetano Heredia, Lima, Peru (G.M.); Department of Anaesthesia, Intensive Care, and Pain Medicine, Medical University of Vienna, Vienna, Austria (E.F.); Shifa International Hospitals, Islamabad, Pakistan (M.A.); University of the Andes and Santa Maria Clinic (Universidad de Los Andes and Clinica Santa María), Santiago, Chile (D.T.); Department of Anesthesiology, University of Malaya, Kuala Lumpur, Malaysia (C.Y.W.); Biomedical Research Institute (IIB – Sant Pau), Barcelona, Spain (P.P.); Hospital Israelita Albert Einstein, São Paulo, Brazil (O.B.); Department of Surgery, University of Manitoba, Winnipeg, Manitoba, Canada (S.S.); Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute and Vita-Salute University, Milan, Italy (G.L.).

hemodynamic requirements also received 0.2 mg of oral clonidine or placebo and had a transdermal clonidine patch (which releases 0.2 mg per day and has physiologic effects within 24 h)[18] or placebo patch applied to their upper arm or chest until 72 h after surgery.

Measurements

All sites were trained in person or by video conference before enrollment started. Training included detailed definitions of outcomes, and case-report forms included specific definitions for each field. Major outcomes were centrally adjudicated to improve consistency.

Blood pressure and heart rate were measured 1 h after starting study drugs and every 4 h for the first 96 h after surgery. If a patient developed clinically important hypotension or bradycardia that did not respond to initial treatment (*e.g.*, fluid bolus), then study personnel encouraged clinicians to remove the patient's clonidine study patch. All decisions were left to the attending physicians, including the discontinuation of study drugs.

Blood was drawn for a troponin measurement 6 to 12 h after surgery and daily for the next 3 days. Electrocardiography was performed when an elevated cardiac biomarker was detected. Research personnel followed patients until 1 yr after randomization and submitted the case report forms and supporting event documentation directly to the web-based data management system. The primary, secondary, and tertiary outcomes were documented 1 yr after randomization. The primary outcome was a composite of death or nonfatal myocardial infarction, with details previously reported.[9,10] Outcomes are defined in Supplemental Digital Content, table 2 (http://links. lww.com/ALN/C227). Adjudicators evaluated key outcomes, and their decisions were used in the statistical analyses.

A preplanned secondary outcome was persistent incisional pain. Patients were asked whether they experienced any pain at their surgical site. Those who did were further asked to complete a Modified Brief Pain Inventory[19] and Neuropathic Pain Inventory short form.[20]

Data Analyses

A statistical analysis plan was finalized and date-stamped in the investigators' files before accessing data. The plan defined primary, secondary, and tertiary outcomes (Supplemental Digital Content, http://links.lww.com/ALN/C228). Statistical analyses were performed using SAS version 9.4 according to a prespecified analysis plan. Patients were analyzed according to the intention-to-treat principle, and those lost to follow-up were censored on the last day that outcome status was known. Outcomes were analyzed using Cox proportional hazards models, stratified by the alternative factorial allocation and whether participants took aspirin chronically.

For the primary outcome, we performed prespecified subgroup analyses based on neuraxial anesthesia, vascular surgery, vascular disease, and the number of revised cardiac risk index criteria.[21] We also did a subgroup analysis based on the aspirin stratum within the aspirin factorial. In the statistical analysis plan, we prespecified the expected direction of effects in the subgroups. We performed one *post hoc* subgroup analysis.

When POISE-2 was designed, we did not plan a percutaneous coronary intervention subgroup analysis because we did not anticipate that physicians would enroll patients with a history of percutaneous coronary intervention. However, given that investigators randomized 470 patients with previous percutaneous coronary intervention, and given the ongoing uncertainty regarding the effects of antiplatelet therapy in these patients, we also undertook a percutaneous coronary intervention subgroup analysis for the aspirin factorial. We used Cox proportional hazards models that incorporated tests of interaction for all subgroup analyses. A P value less than 0.05 was prespecified to indicate statistical significance.

Trial Organization

The Population Health Research Institute was the Sponsor and Coordinating Center for POISE-2 and was responsible for the randomization scheme, database, data validation, analyses, and trial center coordination. No POISE-2 funding source had a role in the trial design, conduct, data collection, analyses, or manuscript preparation or review. The Operations Committee designed the trial, prespecified the statistical analysis plan, and vouched for the data and analyses.

Results

A total of 10,010 patients were randomized. Overall, more than 80% of the patients took at least 80% of the doses of the aspirin study drug, more than 97% of patients took the clonidine study drug before surgery, and more than 90% of patients kept the transdermal study patch on for at least 80% of the targeted duration of application.[9,10] Supplemental Digital Content figure 1 (http://links.lww.com/ALN/C229) and Supplemental Digital Content figure 2 (http://links.lww.com/ALN/C230) show the trial diagram for each treatment; only 47 (0.5%) patients did not complete the 1-yr follow-up and their data were included until the time of censoring. Baseline patient characteristics were similar in each treatment group, as shown in table 1. The mean age of patients was 69 yr, and 53% were male.

Aspirin had no effect on the primary outcome at 1 yr: hazard ratio = 1.00 (95% CI, 0.89–1.12; fig. 1). Aspirin had no effect on the incidence of new or recurrent cancer or chronic incisional pain. Aspirin had no effect on secondary or tertiary outcomes, as shown in table 2.

Clonidine had no significant effect on the primary outcome at 1 yr: hazard ratio = 1.07 (95% CI, 0.96–1.20, $P = 0.218$; fig. 2). Clonidine had no effect on the incidence of

Table 1. Baseline Characteristics

	Clonidine Placebo (n = 5,001)	Clonidine (n = 5,009)	Aspirin Placebo (n = 5,012)	Aspirin (n = 4,998)
Age, yr	69 ± 10	68 ± 10	69 ± 10	69 ± 10
Male sex	2,650 (53)	2,633 (53)	2,686 (54)	2,597 (52)
History of CAD	1,114 (22.3)	1,154 (23.0)	1,115 (22.3)	1,153 (23.1)
History of PCI	237 (4.7)	233 (4.7)	236 (4.7)	234 (4/7)
History of PVD	440 (8.8)	425 (8.5)	427 (8.5)	438 (8.8)
History of stroke	263 (5.3)	279 (5.6)	292 (5.8%)	250 (5.0)
History of transient ischemic attack	202 (4.0)	161 (3.2)	182 (3.6)	181 (3.6)
Undergoing major vascular surgery	245 (4.9)	244 (4.9)	245 (4.9)	244 (4.9)
Undergoing major surgery	3,872 (77.4)	3,930 (78.5)	3,896 (77.7)	3,906 (78.2)
Requiring urgent surgery	360 (7.2)	363 (7.2)	366 (7.3)	357 (7.1)
History of heart failure	176 (3.5)	161 (3.2)	154 (3.1)	183 (3.7)
History of treated diabetes	1,869 (37.4)	1,916 (38.3)	1,911 (38.1)	1,874 (37.5)
History of hypertension	4,323 (86.4)	4,312 (86.1)	4,355 (86.9)	4,280 (85.6)
Creatinine >175 μmol/l	162 (3.2)	158 (3.2)	156 (3.1)	164 (3.3)
History of smoking	1,299 (26.0)	1,258 (25.1)	1,262 (25.2)	1,295 (25.9)

Data are number (percentages) or means ± SDs.

CAD, coronary artery disease; PCI, percutaneous coronary angiography and stenting; and PVD, peripheral vascular disease.

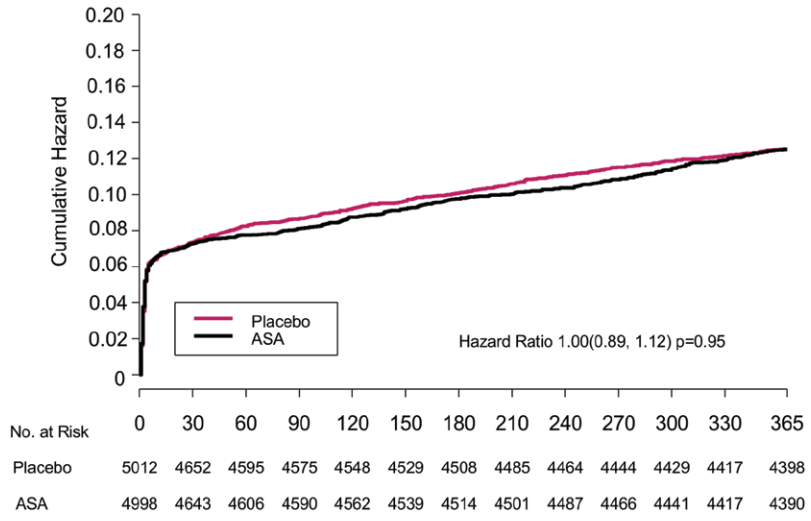

Fig. 1. Primary efficacy outcome, death or myocardial infarction, at 365 days for aspirin (ASA) and placebo.

new or recurrent cancer or chronic incisional pain. Clonidine significantly increased the risk of congestive heart failure: 1.8 *vs.* 1.1%, hazard ratio = 1.54 (95% CI, 1.10–2.15, $P = 0.012$) but none of the other secondary or tertiary outcomes (table 3).

Figures 3 and 4 present subgroup analyses for the 1-yr primary outcome. Three of the prespecified subgroup effects were nominally significant; however, none was in the direction prespecified in the analysis plan. Specifically, aspirin reduced risk in patients who had a previous percutaneous coronary intervention, clonidine worsened risk in patients who did not have a neuraxial block, and clonidine worsened risk in patients with Revised Cardiac Risk scores of 3. The previously reported reduction in the 30-day risk of death and nonfatal myocardial infarction in the subgroup of patients who previously had percutaneous coronary intervention persisted at 1 yr: hazard ratio = 0.58 (95% CI, 0.35–0.95) in those with percutaneous coronary intervention *versus* hazard ratio = 1.03 (95% CI, 0.91–1.16) in those without previous percutaneous coronary intervention; *P* for interaction 0.033 (fig. 5 and Supplemental Digital Content, table 3, http://links. lww.com/ALN/C227). Reduced risk in the percutaneous coronary intervention subgroup was

Table 2. Effects of Aspirin at 1 Yr

	Aspirin (N = 4,998)	Placebo (N = 5,012)	Hazard Ratio (95% CI)	*P* Value
Primary outcome, N (%)				
Death or nonfatal myocardial infarction	586 (11.8)	589 (11.8)	1.00 (0.89–1.12)	0.95
Secondary outcomes, N (%)				
Death, nonfatal myocardial infarction, or nonfatal stroke	611 (12.3)	611 (12.2)	1.00 (0.89–1.12)	0.99
New diagnosis of cancer or diagnosis of recurrent cancer	257 (5.1)	238 (4.8)	1.09 (0.91–1.30)	0.36
Chronic incisional pain	258 (5.2)	273 (5.5)	0.94 (0.79–1.13)	0.52
New diagnosis of cancer	136 (2.7)	112 (2.2)	1.22 (0.95–1.58)	0.12
Recurrent cancer	129 (2.6)	136 (2.7)	0.95 (0.74–1.21)	0.68
Death, nonfatal myocardial infarction, cardiac revascularization, nonfatal pulmonary embolism or nonfatal deep venous thrombosis	675 (13.5)	672 (13.4)	1.01 (0.90–1.12)	0.91
Tertiary outcomes, N (%)				
Total death	304 (6.1)	312 (6.3)	0.97 (0.83–1.14)	0.75
Death from vascular causes	108 (2.2)	122 (2.5)	0.89 (0.68–1.15)	0.36
Myocardial infarction	340 (6.8)	342 (6.9)	1.00 (0.86–1.16)	0.97
Nonfatal cardiac arrest	12 (0.2)	18 (0.4)	0.67 (0.32–1.39)	0.28
Cardiac revascularization	42 (0.9)	48 (1.0)	0.88 (0.58–1.32)	0.53
Pulmonary embolism	55 (1.1)	47 (1.0)	1.17 (0.79–1.73)	0.42
Deep venous thrombosis	56 (1.1)	59 (1.2)	0.95 (0.66–1.37)	0.78
New clinically important atrial fibrillation	141 (2.8)	133 (2.7)	1.06 (0.84–1.35)	0.61
Peripheral arterial thrombosis	24 (0.5)	21 (0.4)	1.14 (0.64–2.05)	0.65
Amputation	37 (0.8)	39 (0.8)	0.95 (0.60–1.49)	0.82
Rehospitalization for vascular reasons	263 (5.4)	235 (4.8)	1.12 (0.94–1.34)	0.20
Congestive heart failure	77 (1.6)	65 (1.3)	1.19 (0.85–1.65)	0.31
Acute kidney injury requiring dialysis*	68 (1.4%)	50 (1.0)	1.38 (0.95–1.99)	0.09

*For this outcome we report the odds ratio instead of the hazard ratio, because we did not collect the actual date patients first started dialysis.

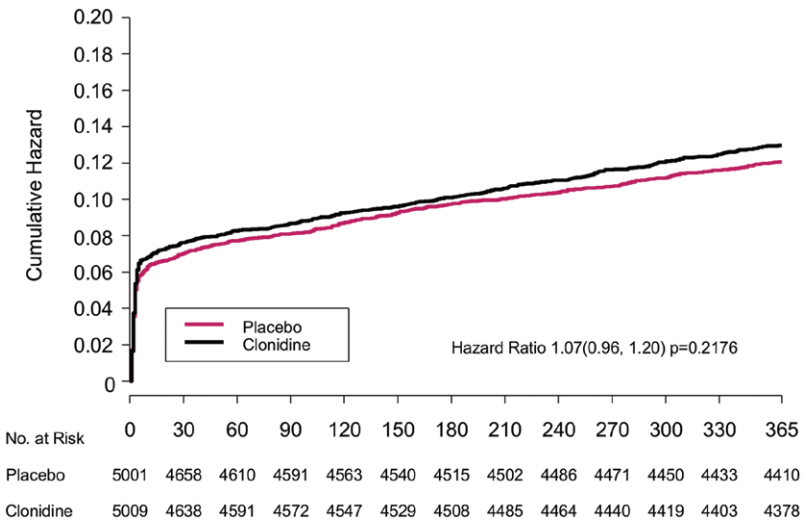

Fig. 2. Primary efficacy outcome, death or myocardial infarction, at 365 days for clonidine and placebo.

mainly attributable to a reduction in nonfatal myocardial infarction rather than death.

Discussion

POISE-2, a large international trial, showed that neither aspirin nor clonidine significantly reduced death or nonfatal myocardial infarction at 30 days.[9,10] The current long-term follow-up of POISE-2 confirmed the absence of benefit or harm of either drug in the overall population in terms of death, nonfatal myocardial infarction, and stroke up to 1 yr after surgery. The 1-yr data also show that neither aspirin nor clonidine has an effect on noncardiovascular outcomes

Table 3. Effects of Clonidine at 1 Yr

Outcome	Clonidine (N = 5,009)	Placebo (N = 5,001)	Hazard Ratio (95% CI)	*P* Value
Primary outcome, N (%)				
Death or nonfatal myocardial infarction	608 (12.2)	567 (11.4)	1.07 (0.96–1.20)	0.22
Secondary outcomes, N (%)				
Death, nonfatal myocardial infarction, or nonfatal stroke	633 (12.7)	589 (11.8)	1.08 (0.96–1.20)	0.20
New diagnosis of cancer or diagnosis of recurrent cancer	254 (5.1)	241 (4.8)	1.06 (0.88–1.26)	0.56
Chronic incisional pain	271 (5.4)	260 (5.2)	1.04 (0.88–1.24)	0.64
New diagnosis of cancer	131 (2.6)	117 (2.3)	1.12 (0.87–1.44)	0.38
Recurrent cancer	131 (2.6)	117 (2.3)	0.98 (0.76–1.25)	0.84
Death, nonfatal myocardial infarction, cardiac revascularization, nonfatal pulmonary embolism or nonfatal deep venous thrombosis	695 (13.9)	652 (13.1)	1.07 (0.96–1.19)	0.22
Tertiary outcomes, N (%)				
Total death	313 (6.3)	303 (6.1)	1.03 (0.88–1.21)	0.69
Death from vascular causes	118 (2.4)	112 (2.3)	1.05 (0.81–1.36)	0.70
Myocardial infarction	362 (7.3)	320 (6.4)	1.13 (0.97–1.32)	0.11
Nonfatal cardiac arrest	19 (0.4)	11 (0.2)	1.73 (0.82–3.63)	0.15
Cardiac revascularization	48 (1.0)	42 (0.9)	1.14 (0.76–1.73)	0.52
Pulmonary embolism	55 (1.1)	47 (1.0)	1.17 (0.79–1.72)	0.43
Deep venous thrombosis	68 (1.4)	47 (1.0)	1.45 (1.00–2.10)	0.05
New clinically important atrial fibrillation	139 (2.8)	135 (2.7)	1.03 (0.81–1.30)	0.82
Peripheral arterial thrombosis	24 (0.5)	21 (0.4)	1.14 (0.64–2.05)	0.66
Amputation	41 (0.8)	35 (0.7)	1.17 (0.75–1.84)	0.50
Rehospitalization for vascular reasons	258 (5.3)	240 (5.0)	1.08 (0.90–1.28)	0.41
Congestive heart failure	86 (1.8)	56 (1.1)	1.54 (1.10–2.15)	0.01
Acute kidney injury requiring dialysis*	63 (1.3)	55 (1.1)	1.15 (0.80–1.65)	0.46

*For this outcome we report the odds ratio instead of the hazard ratio, because we did not collect the actual date patients first started dialysis.

including new-onset cancer, cancer recurrence, or persistent incisional pain. Perioperative aspirin reduced the incidence of composite of death and nonfatal myocardial infarction at 1 yr in patients with previous percutaneous coronary intervention.

It was plausible that clonidine and aspirin would cause long-term harm given that they induced adverse effects around the time of surgery. Specifically, at 30 days, aspirin significantly increased the risk of major bleeding compared with placebo (230 patients [4.6%] *vs.* 188 patients [3.8%]; hazard ratio = 1.23; 95% CI, 1.01, to 1.49; $P = 0.04$), whereas clonidine increased the risk of hypotension (2385 patients [47.6%] *vs.*1854 patients [37.1%]; hazard ratio = 1.32; 95% CI, 1.24 to 1.40; $P < 0.001$) and nonfatal arrest (0.3% [16 patients] *vs.* 0.1% [5 patients]; hazard ratio = 3.20; 95% CI, 1.17 to 8.73; $P = 0.02$).[9,10] Bleeding and hypotension are both associated with organ injury and death.[11–14] Similar rates of adverse outcome events in the aspirin, clonidine, and placebo arms of the trial suggest that the hazards induced by aspirin and clonidine in the immediate perioperative period did not translate into a measurable long-term harm, with the possible exception of congestive heart failure from clonidine.

The primary 30-day results clearly showed that, in the overall population, aspirin provides no benefit but increases bleeding during the perioperative period.[10] But patients who previously had percutaneous coronary interventions are a special population. Patients who received a bare-metal stent within 6 weeks or placement of a drug-eluting stent within 1 yr were excluded from POISE-2, but 470 patients who had a remote history of percutaneous coronary intervention participated in the trial. Among those patients, we previously reported that aspirin reduced the risk of the composite of death and nonfatal myocardial infarction at 30 days.[22] We now demonstrate that the benefit of aspirin in percutaneous coronary intervention patients persists at 1 yr. These data suggest that patients with a history of percutaneous coronary intervention should continue aspirin around the time of noncardiac surgery except, presumably, in patients with special risk of bleeding or in whom the consequences might be especially severe.

There was also a significant interaction for the percutaneous coronary intervention subgroup on myocardial infarction. However, this analysis was not specified *a priori* because when POISE-2 was designed we did not anticipate that physicians would randomize patients with a history of percutaneous coronary intervention. An additional concern is that the total number of myocardial infarctions in the percutaneous coronary intervention subgroup was fewer than 70. Large effects (such as the relative reduction of approximately 50% seen here) with small numbers of events typically prove to be overestimates, and often by large amounts. Overall, the credibility of the percutaneous coronary intervention subgroup effects in POISE-2 is only moderate.

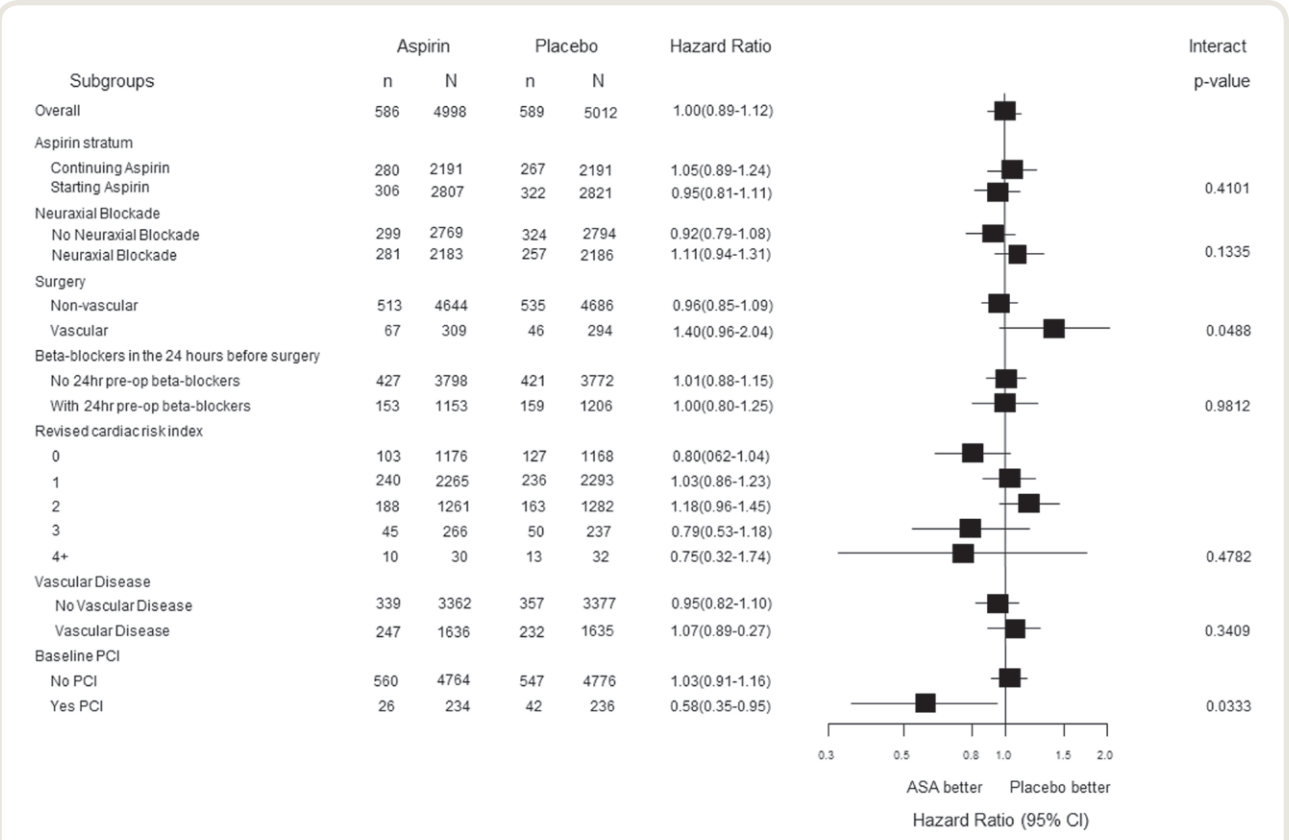

Fig. 3. Subgroup analysis for aspirin. ASA, aspirin; PCI, percutaneous coronary intervention.

A limitation of our analysis is that subgroup effects are often spurious. Indeed, we report two other *a priori* specified subgroup effects in which the interaction *P* values reach conventional levels of statistical significance: neuraxial blockade *versus* no neuraxial blockade and Revised Cardiac Risk grade 3 *versus* other grades. It nonetheless seems likely that both of these other apparent subgroup effects are spurious. Previous work suggests that neuraxial anesthesia is not protective for cardiovascular outcomes.[23]

None of the defined secondary outcomes of POISE-2 differed significantly between groups at 1 yr. The tertiary outcome of congestive heart failure was increased at the 1-yr follow-up in patients randomized to clonidine (hazard ratio = 1.54; 95% CI, 1.10 to 2.15, $P = 0.012$). Although congestive heart failure was a tertiary outcome in this study, and the observed association between clonidine and long-term congestive heart failure may be a false positive association, it is not impossible that the increased risk of nonfatal cardiac arrest associated with clonidine could play a role. Were that the case though, we would have expected a stronger signal at 30 days and not at 1 yr of follow-up. Further investigation may be warranted to determine plausible biologic mechanisms for this putative association.

Our large study shows that neither clonidine nor aspirin ameliorates development of persistent incisional pain. Furthermore, the incidence of chronic postsurgical pain (approximately 5%) was in our patients considerably lower than reported in other postsurgical cohort studies[15,24]—possibly because of variations in pain assessment measures, but more likely because we included a broad range of surgeries rather than selecting operations that are particularly susceptible to persistent pain.

Neither aspirin nor clonidine had an effect on cancer occurrence or recurrence. Previous studies have shown that aspirin may prevent incident cancer during long-term follow-up, but the beneficial effect of aspirin is observed only after two decades of follow-up.[25]

In conclusion, POISE-2 randomized 10,010 noncardiac surgical patients and did not show a significant effect of either aspirin or clonidine on prespecified outcomes, including death, cardiovascular complications, cancer, and chronic incisional pain at 1 yr of follow-up. Perioperative aspirin in patients with previous percutaneous coronary intervention reduced the composite of death and nonfatal myocardial infarction at 1 yr of follow-up, supporting the continued use of perioperative aspirin in this subgroup.

Research Support

POISE-2 was funded through grants from the Canadian Institutes of Health Research (Ottawa, Canada), the

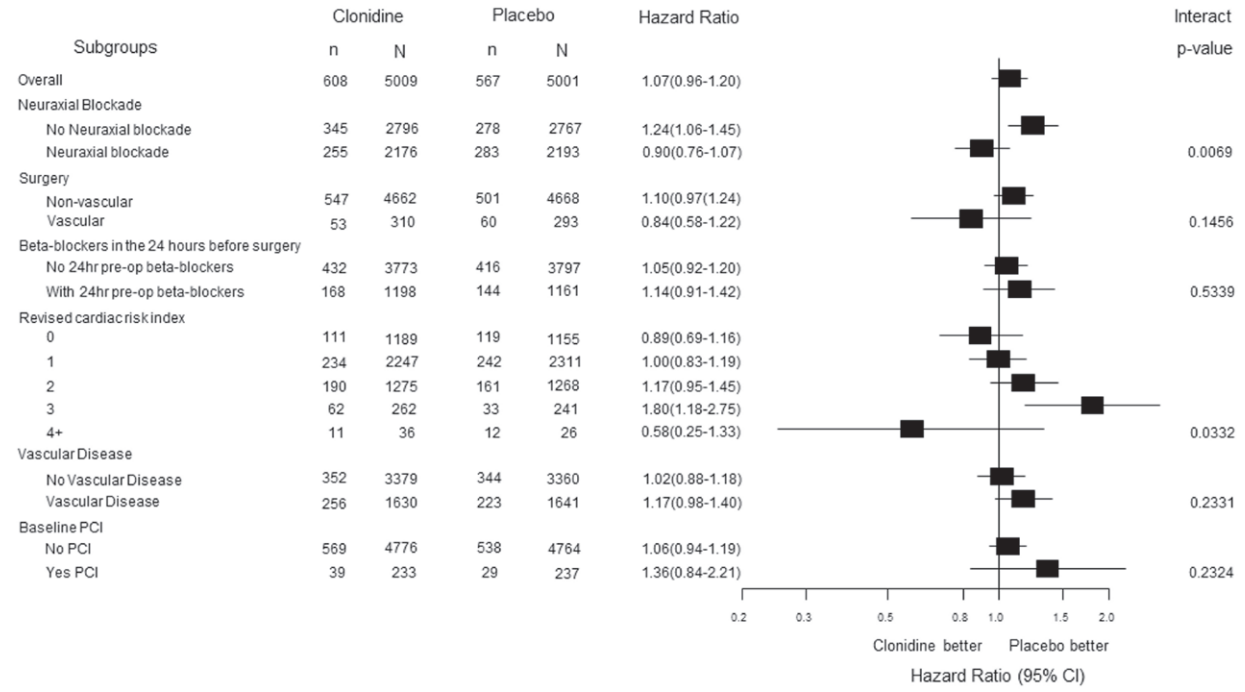

Fig. 4. Subgroup analysis for clonidine. PCI, percutaneous coronary intervention.

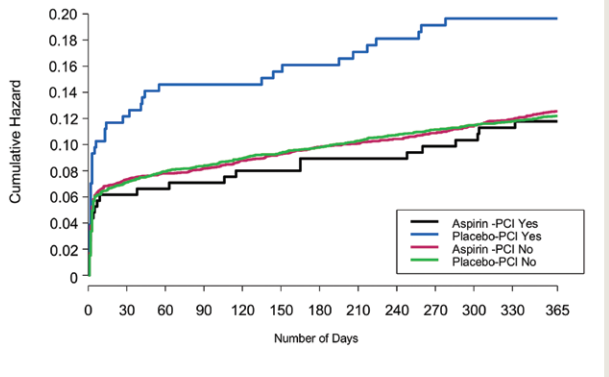

Fig. 5. Primary efficacy outcome, death or myocardial infarction, at 365 days in patients with percutaneous coronary interventions (PCI).

Commonwealth Government of Australia's National Health and Medical Research Council (Canberra, Australia), the Spanish Ministry of Health and Social Policy (Madrid, Spain), and Boehringer Ingelheim (Ingelheim am Rhein, Germany) who also provided the clonidine study drug. Bayer Pharma AG (Berlin, Germany) provided the aspirin study drug. The funding agencies had no role in study conduct, data analysis, or manuscript preparation. None of the authors has a personal financial interest in this work.

Competing Interests

Dr. Kurz reports a financial relationship with Canadian Institute of Health Research (Ottawa, Canada). Dr. Meyhoff reports that in his role as Head of Research, his department received direct and indirect research funding from Boehringer Ingelheim (Ingelheim am Rhein, Germany), Ferring Pharmaceuticals (Saint-Prex, Switzerland), and Merck, Sharp and Dohme (Kenilworth, New Jersey), all outside submitted work. Dr. Xavier reports support from Population Health Research Institute, Hamilton Health Sciences (Hamilton, Ontario, Canada), and financial relationships with AstraZeneca (Cambridge, United Kingdom), Bristol Myers Squibb (New York, New York), Cadila Pharma India (Gujarat, India), and Sanofi (Paris, France). Dr. Amir reports support from Population Health Research Institute. Mr. Torres also reports support from Population Health Research Institute and acting as a speaker for 3M (Maplewood, Minnesota), and Pfizer (New York, New York). Dr. Wang reports support from Hamilton Health Sciences Corporation through Population Health Research Institute. Dr. Paniagua reports an ongoing financial relationship with CSL Behring (King of Prussia, Pennsylvania). Dr. Devereaux reports financial relationships with Abbott Diagnostics (Abbott Park, Illinois), Phillips Healthcare (Amsterdam, The Netherlands), Roche Diagnostics (Rotkreuz, Switzerland), and Siemens (Munich, Germany). The remaining authors declare no competing interests.

Correspondence

Address correspondence to Dr. Sessler: Michael Cudahy Professor and Chair, Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, 9500 Euclid Ave — P77, Cleveland, Ohio 44195. DS@OR.org.

References

1. Lienhart A, Auroy Y, Péquignot F, Benhamou D, Warszawski J, Bovet M, Jougla E: Survey of anesthesia-related mortality in France. Anesthesiology 2006; 105:1087–97
2. Li G, Warner M, Lang BH, Huang L, Sun LS: Epidemiology of anesthesia-related mortality in the United States, 1999-2005. Anesthesiology 2009; 110:759–65
3. Bartels K, Karhausen J, Clambey ET, Grenz A, Eltzschig HK: Perioperative organ injury. Anesthesiology 2013; 119:1474–89
4. The Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators: Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2012; 307: 2295–304
5. Writing Committee for the Vision Study Investigators, Devereaux PJ, Biccard BM, Sigamani A, Xavier D, Chan MTV, Srinathan SK, Walsh M, Abraham V, Pearse R, Wang CY, Sessler DI, Kurz A, Szczeklik W, Berwanger O, Villar JC, Malaga G, Garg AX, Chow CK, Ackland G, Patel A, Borges FK, Belley-Cote EP, Duceppe E, Spence J, Tandon V, Williams C, Sapsford RJ, Polanczyk CA, Tiboni M, Alonso-Coello P, Faruqui A, Heels-Ansdell D, Lamy A, Whitlock R, LeManach Y, Roshanov PS, McGillion M, Kavsak P, McQueen MJ, Thabane L, Rodseth RN, Buse GAL, Bhandari M, Garutti I, Jacka MJ, Schunemann HJ, Cortes OL, Coriat P, Dvirnik N, Botto F, Pettit S, Jaffe AS, Guyatt GH: Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2017; 317: 1642–51
6. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Malaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomised controlled trial. Lancet 2008; 371: 1839–47
7. Myles PS, Leslie K, Chan MT, Forbes A, Peyton PJ, Paech MJ, Beattie WS, Sessler DI, Devereaux PJ, Silbert B, Schricker T, Wallace S; ANZCA Trials Group for the ENIGMA-II investigators: The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): A randomised, single-blind trial. Lancet 2014; 384:1446–54
8. Graham MM, Sessler DI, Parlow JL, Biccard BM, Guyatt G, Leslie K, Chan MTV, Meyhoff CS, Xavier D, Sigamani A, Kumar PA, Mrkobrada M, Cook DJ, Tandon V, Alvarez-Garcia J, Villar JC, Painter TW, Landoni G, Fleischmann E, Lamy A, Whitlock R, Le Manach Y, Aphang-Lam M, Cata JP, Gao P, Terblanche NCS, Ramana PV, Jamieson KA, Bessissow A, Mendoza GR, Ramirez S, Diemunsch PA, Yusuf S, Devereaux PJ: Aspirin in patients with previous percutaneous coronary intervention undergoing noncardiac surgery. Ann Intern Med 2018; 168:237–44
9. Devereaux PJ, Sessler DI, Leslie K, Kurz A, Mrkobrada M, Alonso-Coello P, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodseth RN, Botto F, Lurati Buse G, Xavier D, Chan MT, Tiboni M, Cook D, Kumar PA, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, Vanhelder T, Paniagua P, Berwanger O, Srinathan S, Graham M, Pasin L, Le Manach Y, Gao P, Pogue J, Whitlock R, Lamy A, Kearon C, Chow C, Pettit S, Chrolavicius S, Yusuf S; POISE-2 Investigators: Clonidine in patients undergoing noncardiac surgery. N Engl J Med 2014; 370:1504–13
10. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodseth RN, Botto F, Lurati Buse G, Xavier D, Chan MT, Tiboni M, Cook D, Kumar PA, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, VanHelder T, Paniagua P, Berwanger O, Srinathan S, Graham M, Pasin L, Le Manach Y, Gao P, Pogue J, Whitlock R, Lamy A, Kearon C, Baigent C, Chow C, Pettit S, Chrolavicius S, Yusuf S; POISE-2 Investigators: Aspirin in patients undergoing noncardiac surgery. N Engl J Med 2014; 370:1494–503
11. Mascha EJ, Yang D, Weiss S, Sessler DI: Intraoperative mean arterial pressure variability and 30-day mortality in patients having noncardiac surgery. Anesthesiology 2015; 123:79–91
12. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, Kurz A: Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: A retrospective cohort analysis. Anesthesiology 2017; 126:47–65
13. Smilowitz NR, Oberweis BS, Nukala S, Rosenberg A, Zhao S, Xu J, Stuchin S, Iorio R, Errico T, Radford MJ, Berger JS: Association between anemia, bleeding, and transfusion with long-term mortality following noncardiac surgery. Am J Med 2016; 129:315–23.e2
14. Harris DG, Koo G, McCrone MP, Weltz AS, Chiu WC, Sarkar R, Scalea TM, Diaz JJ, Lissauer ME, Crawford RS: Acute kidney injury in critically ill vascular surgery

patients is common and associated with increased mortality. Front Surg 2015; 2:8
15. Deumens R, Steyaert A, Forget P, Schubert M, Lavand'homme P, Hermans E, De Kock M: Prevention of chronic postoperative pain: cellular, molecular, and clinical insights for mechanism-based treatment approaches. Prog Neurobiol 2013; 104:1–37
16. Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I: Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Database Syst Rev 2013: CD008307
17. Devereaux PJ; POISE-2 Investigators: Rationale and design of the PeriOperative ISchemic Evaluation-2 (POISE-2) trial: An international 2 × 2 factorial randomized controlled trial of acetyl-salicylic acid vs. placebo and clonidine vs. placebo in patients undergoing noncardiac surgery. Am Heart J 2014; 167:804–9.e4
18. Langley MS, Heel RC: Transdermal clonidine: A preliminary review of its pharmacodynamic properties and therapeutic efficacy. Drugs 1988; 35:123–42
19. Mendoza TR, Chen C, Brugger A, Hubbard R, Snabes M, Palmer SN, Zhang Q, Cleeland CS: The utility and validity of the modified brief pain inventory in a multiple-dose postoperative analgesic trial. Clin J Pain 2004; 20:357–62
20. Backonja MM, Krause SJ: Neuropathic pain questionnaire–short form. Clin J Pain 2003; 19:315–6
21. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100:1043–9
22. Graham MM, Sessler DI, Parlow JL, Biccard BM, Guyatt G, Leslie K, Chan MTV, Meyhoff CS, Xavier D, Sigamani A, Kumar PA, Mrkobrada M, Cook DJ, Tandon V, Alvarez-Garcia J, Villar JC, Painter TW, Landoni G, Fleischmann E, Lamy A, Whitlock R, Le Manach Y, Aphang-Lam M, Cata JP, Gao P, Terblanche NCS, Ramana PV, Jamieson KA, Bessissow A, Mendoza GR, Ramirez S, Diemunsch PA, Yusuf S, Devereaux PJ: Aspirin in patients with previous percutaneous coronary intervention undergoing noncardiac surgery. Ann Intern Med 2018; 168:237–44
23. Nash DM, Mustafa RA, McArthur E, Wijeysundera DN, Paterson JM, Sharan S, Vinden C, Wald R, Welk B, Sessler DI, Devereaux PJ, Walsh M, Garg AX: Combined general and neuraxial anesthesia *versus* general anesthesia: a population-based cohort study. Can J Anaesth 2015; 62:356–68
24. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: Risk factors and prevention. Lancet 2006; 367:1618–25
25. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW: Effect of daily aspirin on long-term risk of death due to cancer: Analysis of individual patient data from randomised trials. Lancet 2011; 377:31–41