Period-dependent Associations between Hypotension during and for Four Days after Noncardiac Surgery and a Composite of Myocardial Infarction and Death

A Substudy of the POISE-2 Trial

Daniel I. Sessler, M.D., Christian S. Meyhoff, M.D., Ph.D., Nicole M. Zimmerman, M.S., Guangmei Mao, M.P.H., Kate Leslie, M.B.B.S., Skarlet M. Vásquez, M.Sc., Packianathaswamy Balaji, M.D., Jesús Alvarez-Garcia, M.D., Ph.D., Alexandre B. Cavalcanti, M.D., Ph.D., Joel L. Parlow, M.D., Prashant V. Rahate, M.D., Manfred D. Seeberger, M.D., Bruno Gossetti, M.D., S. A. Walker, M.B.Ch.B., Rajendra K. Premchand, M.D., Rikke M. Dahl, M.D., Emmanuelle Duceppe, M.D., Reitze Rodseth, M.B.Ch.B., Fernando Botto, M.D., P. J. Devereaux, M.D., Ph.D.

ABSTRACT

Background: The relative contributions of intraoperative and postoperative hypotension to perioperative morbidity remain unclear. We determined the association between hypotension and a composite of 30-day myocardial infarction and death over three periods: (1) intraoperative, (2) remaining day of surgery, and (3) during the initial four postoperative days.

Methods: This was a substudy of POISE-2, a 10,010-patient factorial-randomized trial of aspirin and clonidine for prevention of myocardial infarction. Clinically important hypotension was defined as systolic blood pressure less than 90 mmHg requiring treatment. Minutes of hypotension was the exposure variable intraoperatively and for the remaining day of surgery, whereas hypotension status was treated as binary variable for postoperative days 1 to 4. We estimated the average relative effect of hypotension across components of the composite using a distinct effect generalized estimating model, adjusting for hypotension during earlier periods.

Results: Among 9,765 patients, 42% experienced hypotension, 590 (6.0%) had an infarction, and 116 (1.2%) died within 30 days of surgery. Intraoperatively, the estimated average relative effect across myocardial infarction and mortality was 1.08 (98.3% CI, 1.03, 1.12; $P < 0.001$) per 10-min increase in hypotension duration. For the remaining day of surgery, the odds ratio was 1.03 (98.3% CI, 1.01, 1.05; $P < 0.001$) per 10-min increase in hypotension duration. The average relative effect odds ratio was 2.83 (98.3% CI, 1.26, 6.35; $P = 0.002$) in patients with hypotension during the subsequent four days of hospitalization.

Conclusions: Clinically important hypotension—a potentially modifiable exposure—was significantly associated with a composite of myocardial infarction and death during each of three perioperative periods, even after adjustment for previous hypotension. **(Anesthesiology 2018; 128:317-27)**

PLAQUE rupture and thrombosis, along with supply–demand mismatch, are believed to be the dominant mechanisms of postoperative myocardial infarction.[1,2] Patients are often hemodynamically unstable (*e.g.*, tachycardia, bradycardia, hypotension) in the perioperative period, which may lead to supply–demand mismatch. The potential contribution of hypotension is illustrated by an analysis of 104,000 patients who had noncardiac surgery at the Cleveland Clinic (Cleveland, Ohio). Time-weighted average intraoperative mean arterial pressure (MAP) was strongly related to 30-day mortality, which more than tripled as time-weighted average MAP decreased from 80 to 50 mmHg.[3] Even a few minutes of a MAP less than 55 mmHg was associated with acute kidney injury and myocardial infarction risk—both of which increased markedly when hypotension was prolonged.[4] Intraoperative reductions in MAP from preoperative values are also predictive, with decreases of more than 25% increasing the risk of mortality. However, absolute thresholds (*e.g.*, less than 65 mmHg) were equally predictive

What We Already Know about This Topic

- Predictors of perioperative myocardial infarction and death have been extensively evaluated. However, nearly all substantial predictors of serious postoperative morbidity and mortality relate to patient baseline characteristics or the surgical procedure and are thus largely unmodifiable.

What This Article Tells Us That Is New

- This study determined the association between hypotension and a composite of 30-day myocardial infarction and death over three periods: (1) intraoperative, (2) remaining day of surgery, and (3) during the initial four postoperative days.
- Clinically important hypotension was significantly associated with a composite of myocardial infarction and death during each of three perioperative periods, even after adjustment for previous hypotension.

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).

Submitted for publication March 16, 2017. Accepted for publication October 17, 2017. From the Departments of Outcomes Research (D.I.S., N.M.Z., G.M.) and Quantitative Health Sciences (N.M.Z., G.M.), Cleveland Clinic, Cleveland, Ohio; the Department of Anaesthesia and Intensive Care, Bispebjerg Hospital (C.S.M.) and the Department of Anaesthesiology, Herlev Hospital (C.S.M., R.M.D.), University of Copenhagen, Copenhagen,

 Anesthesiology 2018; 128:317-27

<zdoi;10.1097/ALN.0000000000001985>

and are easier to use because accurate preoperative pressures are often unavailable.[5]

Hypotension is common both during and after surgery, but hypotension on surgical wards lasts much longer than during surgery. For example, in the PeriOperative ISchemic Evaluation trial (POISE-1), perioperative β-blockers increased clinically important hypotension (systolic blood pressure less than 90 mmHg requiring intervention): β-blockers 15% *versus* placebo 9.7%. Moreover, clinically important hypotension had the largest population-attributable risk for perioperative death and perioperative stroke.[6] Hypotension was also independently associated with myocardial infarction, and a composite of infarction, stroke, and death in the Vascular events In noncardiac Surgery patients cOhort evaluatioN (VISION) population.[7] Postoperative hypotension is thus common and at times prolonged and severe during the initial postoperative days (PODs), which is just when myocardial infarctions are most common.[8]

Predictors of perioperative myocardial infarction and death have been extensively evaluated.[9–15] However, nearly all substantial predictors of serious postoperative morbidity and mortality relate to patient baseline characteristics or the surgical procedure and are thus largely unmodifiable. Blood pressure is an exception in that it is clearly linked to myocardial infarction, stroke, and death and can usually be controlled both intraoperatively and postoperatively. It is thus of considerable interest to evaluate the association between perioperative hypotension and cardiovascular outcomes. Understanding the temporal change in risk at various perioperative times could guide interventions targeted at periods of increased risk of myocardial infarction after noncardiac surgery, stroke, and death. We therefore used the PeriOperative ISchemic Evaluation 2 (POISE-2, a trial of aspirin and clonidine on perioperative myocardial infarction and death) study cohort[16,17] to evaluate the relationships between hypotension within various perioperative periods and cardiovascular outcomes in patients having noncardiac surgery.

Denmark; the Department of Anaesthesia and Pain Management, Royal Melbourne Hospital, Melbourne, Australia (K.L.); the Department of Research, Grupo de Cardiología Preventiva Universidad Autónoma de Bucaramanga, Fundación CardioInfantil Instituto de Cardiología, Bucaramanga, Colombia (S.M.V.); the Anaesthetic Department, Hull and East Yorkshire Hospitals, National Health Service Trust, Hull, East Yorkshire, United Kingdom (P.B.); Department of Cardiology, Hospital de la Santa Creu i Sant Pau, IIB-SantPau, Universidad Autónoma de Barcelona, Barcelona (J.A.-G.); the Research Institute, Hospital do Coração, São Paulo, Brazil (A.B.C.); the Department of Anesthesia, Queen's University and Kingston General Hospital, Kingston, Canada (J.L.P.); Rahate Surgical Hospital, Nagpur, Maharashtra, India (P.V.R.); the Department of Anesthesia and Intensive Care Medicine, University Hospital Basel, University of Basel, Basel, Switzerland (M.D.S.); the Department of Vascular Surgery, Sapienza University of Rome, Rome, Italy (B.G.); Counties Manukau District Health, Aukland, New Zealand (S.A.W.); the Krishna Institute of Medical Sciences, Hyderbad, India (R.K.P.); the Department of Pediatrics, Hvidovre Hospital, Copenhagen, Denmark (R.M.D.); the Department of Anaesthetics, University of KwaZulu-Natal, Pietermaritzburg, South Africa (R.R.), the Hypertension and Vascular Aging Center, Hospital Universitario Austral, Pilar, Argentina (F.B.); the Departments of Health Research Methods, Evidence, and Impact and Medicine, McMaster University, Hamilton, Canada (P.J.D.); and the Population Health Research Institute, Hamilton, Canada (E.D., P.J.D., D.I.S.).

Our primary goal was to determine the association between clinically important hypotension and a 30-day composite of myocardial infarction and death during three periods: (1) intraoperative, (2) remaining day of surgery, and (3) during the initial four PODs. As a sensitivity analysis, we explored the relationship between the lowest systolic blood pressure (at any time preceding an outcome event within the first four days after surgery) and a composite of 30-day myocardial infarction and death.

Materials and Methods

The full protocol for the POISE-2 trial (Clinical Trial NCT01082874) has been published.[18] Enrollment was restricted to patients with or at risk for cardiovascular disease who had systolic pressure of at least 105 mmHg and heart rate of at least 55 beats/min. With institutional review board approval and written informed consent, 10,010 patients were factorially randomized to placebo or aspirin 100 mg/day *and* to placebo or clonidine 200 μg orally followed by a patch, which released 200 μg/day. Thirty-day follow-up was 99.9% complete. Study medications were started shortly before surgery. Aspirin/placebo continued for seven PODs in patients taking aspirin chronically or 30 days in those who were not taking it chronically; clonidine/placebo patches were removed after 72 h.

The study centers generally instructed patients to avoid taking their usual antihypertensive medications, including β-blockers, on the morning of surgery. Instead, study personnel reviewed patients' vital signs in the presurgical area and asked the anesthesiologists to determine whether the patients should receive their antihypertensive medications and at what dose.

Anesthetic management was not controlled and could include general and/or neuraxial approaches, as well as peripheral nerve blocks or local anesthesia. When patients developed clinically important hypotension or bradycardia that did not respond to initial treatment (*e.g.*, fluid bolus), the clonidine/placebo study patch could be removed. 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 72 h target.

The POISE-2 trial main results demonstrated that aspirin did not reduce major cardiovascular outcomes but significantly increased major bleeding from 3.7 to 4.6% (hazard ratio 1.2 [95% CI, 1.0 to 1.5]; $P = 0.04$); aspirin had no direct effect on blood pressure or heart rate.[16] Clonidine increased the risk of bradycardia and hypotension (1.32 [95% CI, 1.24 to 1.40]) but did not reduce the incidence of myocardial infarction.[17] There was no interaction between aspirin and clonidine.

Measurements

Blood pressure and heart rate were measured per local routine, typically at 1- to 5-min intervals intraoperatively, at 5- to 15-min intervals in the postanesthesia care unit, and

every 4 to 6 h thereafter for the first 96 h after surgery or until hospital discharge. Patients admitted to critical care units were included in the analysis. For analysis purposes, we considered the following intervals: (1) intraoperative, (2) postanesthesia care unit and the remaining day of surgery, and (3) PODs 1 to 4 while patients remained hospitalized.

During each interval, we recorded the duration of clinically important hypotension, the lowest systolic blood pressure, the cumulative duration of systolic pressure less than 90 mmHg, and the cumulative duration of systolic blood pressure between 90 and 99 mmHg. Blood pressures were assumed to be maintained at the previous value until a new one was recorded. Clinically important hypotension was defined as systolic blood pressure less than 90 mmHg requiring fluid resuscitation, intraaortic balloon pump, inotropic or vasopressor treatment, or study drug discontinuation.

Blood was drawn for troponin assessment 6 to 12 h after surgery and once daily for the next 3 days while patients remained hospitalized. Patients with elevated troponin concentrations were evaluated for clinical symptoms and electrocardiographic changes. Some were also evaluated with Doppler echocardiography. Myocardial infarction was diagnosed based on the Third Universal Definition of Myocardial Infarction criteria,[19] as determined and verified by central adjudication. Strokes were similarly centrally adjudicated. The earliest clear diagnostic feature was considered to be the onset time. We considered the 30-day occurrence of adjudicated myocardial infarctions and death to be our primary composite outcome. Individual secondary outcomes included: stroke, myocardial infarction after noncardiac surgery, nonfatal cardiac arrest, serious adverse events, along with the separate occurrences of the primary composite components, myocardial infarction and death.

Life-threatening bleeding was defined by bleeding that was fatal, led to clinically important hypotension that required inotrope therapy, required urgent (within 24 h) surgery other than major vascular repair, or was intracranial. Major bleeding was defined by bleeding that did not meet the criteria for life-threatening bleeding but (1) resulted in a postoperative hemoglobin level of at most 70 g/l and transfusion of at most 2 units of red blood cells; (2) resulted in a hemoglobin reduction of at least 50 g/l and transfusion of at least 2 units of red blood cells; (3) resulted in transfusion of at least 4 units of red blood cells within a 24-h period; (4) led to embolization, minor vascular repair, or nasal packing; or (5) was retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging). Clinically important bradycardia was defined by a heart rate of less than 55 beats/min requiring a temporary pacemaker, administration of a sympathomimetic agent or atropine, or study drug discontinuation.

Data Analyses

Analyses was based on an *a priori* detailed protocol and statistical analyses plan. We summarized the study population on potentially confounding patient characteristics using appropriate summary statistics. Variables included the following preoperative factors: age, sex, race/ethnicity, body mass index, current smoking status, history of hypertension, treated diabetes, coronary artery disease, peripheral vascular disease, history of stroke or transient ischemic attack, congestive heart failure, baseline heart rate, systolic blood pressure, estimated glomerular filtration rate of less than 60 ml/min, any use of each of individual cardiovascular drugs in the 24 h before surgery (*i.e.*, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, calcium channel blocker, β-blocker, statin), surgery urgency rating (*i.e.*, urgent, emergent, elective), and duration and type of surgery (*i.e.*, vascular, orthopedic, intraperitoneal, or other). Perioperative factors included new clinically important atrial fibrillation, important bradycardia, and major or life-threatening bleeding.

Primary Outcome. Our primary outcome was a composite of 30-day mortality and myocardial infarction. Minutes of hypotension was used as the exposure variable for the intraoperative period and for the period extending from entry into the postanesthesia care unit through the remaining day of surgery, whereas hypotension status was treated as binary variable for PODs 1 to 4 because only 7.6% patients had clinically important hypotension in that period. If a patient had a second myocardial infarction, we only considered the first occurrence.

To assess the associations between hypotension during each period and the composite outcome, all analyses adjusted for duration of hypotension occurring before the exposure period of interest (if applicable), clinically important bradycardia and major or life-threatening bleeding that occurred before or during the exposure period of interest, and the other previously mentioned potential confounding factors (except for baseline systolic blood pressure) by including these variables as terms in our multivariable models. Patients who had a myocardial infarction or death during or before the exposure period of interest were excluded from that particular analysis (fig. 1).

For each exposure, we estimated the average relative effect of hypotension across the two components of the composite outcome using a generalized estimating equation "distinct effect" model with unstructured correlation among components.[20,21] This method captures complete information on each component for each patient and is not driven by components with the highest frequency. The heterogeneity of the hypotension effect on myocardial infarction and death was evaluated by testing the hypotension-by-outcome interaction. Regardless of the existence of the interaction, we estimated the individual associations of hypotension with myocardial infarction and death adjusting for the same confounders. The multicollinearity of hypotension variables for different periods was assessed by variance inflation factor. Linearity of hypotension duration was evaluated graphically and by considering quadratic and cubic spine analyses.

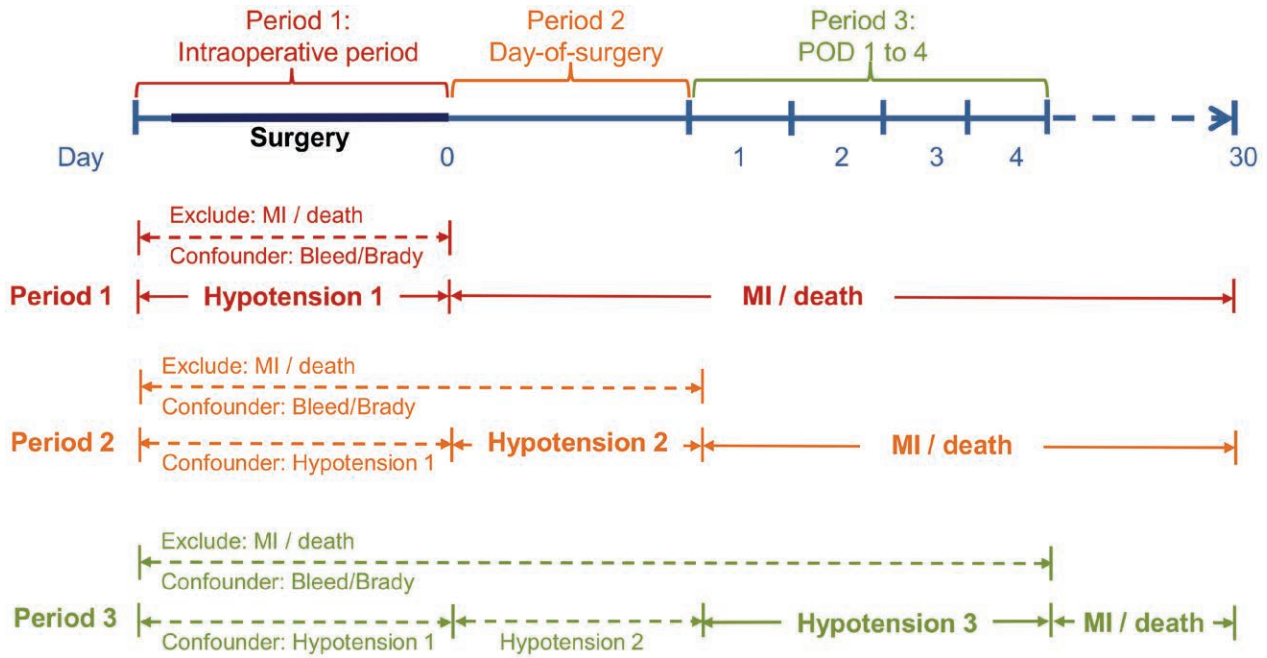

Fig. 1. Analysis method for three perioperative periods. The association between hypotension and the primary composite of 30-day myocardial infarction (MI) and mortality was adjusted for hypotension before the exposure period of interest (if applicable), clinically important bradycardia, whether the major or life-threatening bleeding occurred before or during the exposure period of interest, and the other potential confounders in table 1. Patients with MI and mortality before or during the exposure period of interest were excluded. POD = postoperative day.

We assessed whether the relationship between duration of hypotension and the composite differed by POISE-2 randomization assignment by testing for the hypotension-by-clonidine and hypotension-by-aspirin interactions using a significance criterion of $P < 0.10$. Aspirin and clonidine were not otherwise included in our statistical models because we previously reported that neither significantly influences death, myocardial infarction, or stroke.[16,17]

Sensitivity Analysis. We performed a sensitivity analysis assessing the association between lowest systolic blood pressure and the composite outcome of myocardial infarction and mortality in three perioperative periods, using analogous generalized estimating equation models to the primary analysis. Because the lowest systolic pressure was only reported for patients with some amount of hypotension, we conservatively considered the lowest systolic pressure to be 90 mmHg in patients without reported hypotension. The lowest systolic pressures were used as the exposure variable for the first and second periods, whereas hypotension status was considered a dichotomous variable for the third period.

With an overall α of 0.05 for the analyses, we used a significance criterion of 0.0167 for each primary analysis (*i.e.*, 0.05/3, Bonferroni correction) corresponding to 98.3% CIs. Analyses assessing the separate associations between hypotension and each component of the composite used a significance criterion of 0.008 (*i.e.*, 0.05/6), corresponding to 99.2% CIs. SAS version 9.4 (SAS Institute, USA) was used for all analyses.

Sample Size and Power. The POISE-2 trial included 10,010 patients, of whom about 7% had a perioperative myocardial infarction or death. *A priori*, we assumed that duration of hypotension was log-normally distributed with a mean of 1 min and a SD of 2.3 min based on a database query of a similar patient population. We expected to have more than 95% power at the 0.0167 significance level to detect an odds ratio as small as 1.02 per 5-min increase in hypotension. Given that observed hypotension was log-normally distributed with a mean of 2.5 min and a SD of 1 min for the intraoperative period, we had 89% empirical power at the 0.0167 significance level for detecting an odds ratio as small as 1.08 per 10-min increase in hypotension based on 9,776 patients with complete data.

Results

Among the 10,010 POISE-2 study patients, 9,772 with complete hemodynamic data were analyzed in this study. After excluding patients with myocardial infarction before a given exposure period, the total sample sizes were 9,765 intraoperatively, 9,592 in the postanesthesia care unit and remaining initial surgical day, and 9,186 for PODs 1 to 4 (fig. 2).

The amount of hypotension in each period is presented in figure 3. A large proportion of patients who had hypotension in remaining day of surgery and PODs 1 to 4 had prior hypotension. In our analyses, prior hypotension status was adjusted when assessing the association of hypotension in

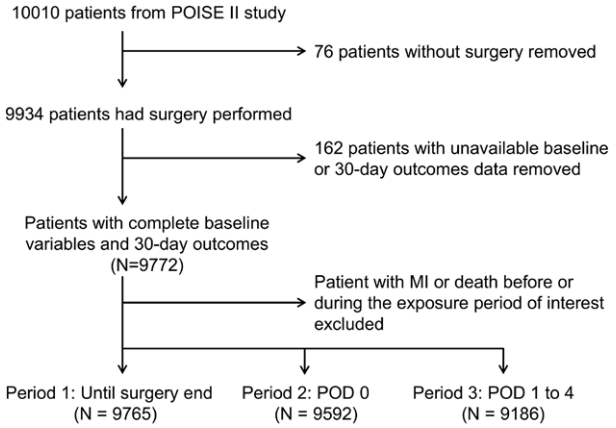

Fig. 2. Trial diagram. MI = myocardial infarction; POD = postoperative day.

the remaining day of surgery and PODs 1 to 4 to myocardial infarction/mortality. We summarized patient demographic and baseline characteristics and surgical details in table 1, divided by myocardial infarction or mortality and by period. The incidence of clinically important hypotension, major or life-threatening bleeding, and clinically important bradycardia in three periods by the composite outcome is presented in table 2.

Clinically important hypotension occurred in 42% of the patients and was significantly associated with 30-day myocardial infarction and mortality in each of the three periods (table 3 and fig. 4). Intraoperatively, the estimated average relative effect (*i.e.* average odds ratio) across myocardial infarction and mortality was 1.08 (98.3% CI, 1.03, 1.12; $P < 0.001$) per 10-min increase in hypotension; for the remaining day of surgery, the odds ratio was 1.03 (98.3% CI, 1.01, 1.05; $P < 0.001$) per 10-min increase in hypotension. The average relative effect odds ratio was 2.83 (98.3% CI, 1.26, 6.35; $P = 0.002$) for patients with clinically important hypotension in PODs 1 to 4 *versus* those without, after adjusting for hypotension in both of the previous periods and all other potential confounders.

The association across each component of the composite outcome for each period was in the same direction, although the hypotension-by-outcome component interaction was significant ($P < 0.001$). As shown in table 4, clinically important hypotension was significantly associated with higher odds of mortality in each perioperative period and higher odds of myocardial infarction for the period extending from admission to the postanesthesia care unit through the remaining day of surgery. Because the incidence in PODs 1 to 4 was low, we also estimated the impact of hypotension without adjusting for confounders to assess the robustness of the analysis. The association was still significant with an odds ratio of 4.45 (98.3% CI, 2.33, 8.48; $P < 0.001$), suggesting that the primary result was valid.

The associations between hypotension in remaining day of surgery and hypotension in PODs 1 to 4 with myocardial infarction or death that we report are both additive effects because we adjusted for hypotension that occurred before the corresponding period. Take the remaining day of surgery, for example. Because the hypotension in the remaining day of surgery could only be associated with additive risk of myocardial infarction/mortality that occurred after the day of surgery, we excluded patients who experienced a postoperative myocardial infarction or death during the day of surgery.

In our multivariable analysis, the association of hypotension in the remaining day of surgery time period was adjusted for the minutes of hypotension during the surgery and the other confounding variables. The odds ratio of 1.03 (98.3% CI, 1.01, 1.05) indicates a 10-min increase in hypotension

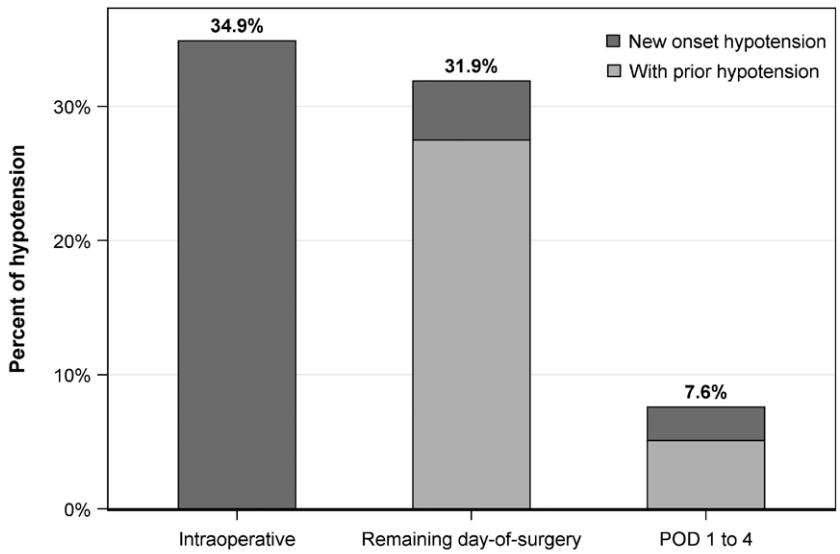

Fig. 3. The amount of hypotension observed in each postoperative analysis period. POD = postoperative day.

Table 1. Patient Characteristics by the Composite Outcome of 30-day Myocardial Infarction and Mortality after Three Perioperative Periods

	Without MI/Mortality (N = 9,098)	With MI/Mortality after Surgery (N = 667)	With MI/Mortality after Day of Surgery (N = 494)	With MI/Mortality after POD 4 (N = 88)
Age (yr)	69 ± 10	74 ± 9	74 ± 9	75 ± 9
BMI (kg/m^2)	30 ± 7	28 ± 7	28 ± 7	27 ± 7
Female	4,287 (47)	308 (46)	237 (48)	39 (44)
Race/ethnicity				
White	6,555 (72)	437 (66)	328 (66)	59 (67)
Hispanic	865 (10)	81 (12)	69 (14)	14 (16)
Asian	359 (4)	35 (5)	24 (5)	4 (5)
Black	1,185 (13)	99 (15)	63 (13)	10 (11)
Other	134 (1)	15 (2)	10 (2)	1 (1)
Smoker	2,369 (26)	140 (21)	98 (20)	19 (22)
Medical history				
Hypertension	7,838 (86)	580 (87)	433 (88)	75 (85)
Diabetes	3,465 (38)	233 (35)	170 (34)	30 (34)
CAD	2,011 (22)	197 (30)	145 (29)	28 (32)
PVD	734 (8)	103 (15)	69 (14)	11 (13)
Stroke	482 (5)	39 (6)	27 (5)	9 (10)
CHF	283 (3)	40 (6)	29 (6)	6 (7)
Preoperative condition				
SBP (mmHg)	144 ± 24	148 ± 27	147 ± 27	141 ± 25
HR (beats per min)	76 ± 13	77 ± 15	77 ± 16	80 ± 16
eGFR < 60	372 (4)	39 (6)	28 (6)	6 (7)
Preoperative medication				
ACEi or ARB	3,251 (36)	241 (36)	173 (35)	28 (32)
CCB	2,066 (23)	148 (22)	102 (21)	19 (22)
β-Blocker	2,148 (24)	174 (26)	132 (27)	23 (26)
Statin	3,357 (37)	253 (38)	189 (38)	26 (30)
Surgery information				
Emergency surgery	637 (7)	61 (9)	48 (10)	12 (14)
Duration (h)	2 [1, 3]	2 [2, 3]	2 [2, 3]	2 [2, 4]
Surgery type				
General	2,414 (27)	149 (22)	117 (24)	35 (40)
Orthopedic	3,439 (38)	285 (43)	217 (44)	23 (26)
Spinal	491 (5)	16 (2)	10 (2)	2 (2)
Thoracic	200 (2)	6 (1)	4 (1)	1 (1)
Urologic or gynecologic	527 (6)	48 (7)	31 (6)	7 (8)
Vascular	1,516 (17)	87 (13)	66 (13)	16 (18)
Other	511 (6)	76 (11)	49 (10)	4 (5)

Continuous variables are presented as means ± SD or median [Q1, Q3] as appropriate; categorical variables were presented as number (percent).

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BMI = body mass index; CAD = coronary artery disease; CCB = calcium channel blocker; CHF = congestive heart failure; eGFR = estimated glomerular filtration rate; HR = heart rate; MI = myocardial infarction; POD = postoperative day; PVD = peripheral vascular disease; SBP = systolic blood pressure.

during the remaining day of surgery was associated with 1.03 higher odds of myocardial infarction or death, for patients with the same duration of intraoperative hypotension and the same level of all other confounders. Similarly for the period from PODs 1 to 4, the association of hypotension in PODs 1 to 4 to myocardial infarction or death occurred after POD 4 was adjusted for intraoperative hypotension and hypotension that occurred on the day of surgery.

We found no significant hypotension-by-clonidine or hypotension-by-aspirin interactions for any time period ($P > 0.30$ for all interactions), suggesting that the associations between hypotension and outcomes are consistent across POISE-2 treatments. The multicollinearity of hypotension variables for different periods were all negligible with a variance inflation factor less than 1.5. Figure 5 shows that the relationship between hypotension duration and the composite outcome was linear. The model was not improved by adding quadratic or spline terms.

The sensitivity analyses, which used the lowest systolic blood pressure to measure the severity of clinically important hypotension, show similar results (table 5). A decrease in the lowest systolic pressure increased the odds of 30-day myocardial infarction or mortality significantly for the remaining day of surgery and PODs 1 to 4 but only moderately intraoperatively. Specifically,

Table 2. Incidence of Hypotension, Bleeding, and Bradycardia by the Composite Outcome of 30-day Myocardial Infarction and Mortality in Three Perioperative Periods

	Intraoperative		Remaining Day of Surgery		PODs 1 to 4	
	With MI/Mortality (N = 667)	Without MI/Mortality (N = 9,098)	With MI/Mortality (N = 494)	Without MI/Mortality (N = 9,098)	With MI/Mortality (N = 88)	Without MI/Mortality (N = 9,098)
Clinically important hypotension						
Incidence	249 (37.3%)	3,155 (34.7%)	184 (37.3%)	2,876 (31.6%)	22 (25%)	675 (7.4%)
Duration for hypotensive patients (min)	15 [7, 30]	15 [5, 28]	25 [10, 83]	17 [8, 42]	175 [58, 220]	185 [60, 397]
Major/life-threatening bleeding	35 (5.3%)	135 (1.5%)	11 (2.2%)	43 (0.5%)	7 (8.0%)	175 (1.9%)
Clinically important bradycardia	55 (8.3%)	635 (7.0%)	7 (1.4%)	86 (1.0%)	1 (1.1%)	24 (0.3%)

Incidence is presented as the count (%). The duration of clinically important hypotension is presented as the median [Q1, Q3]. Clinically important hypotension was defined as systolic blood pressure less than 90 mmHg requiring fluid resuscitation, intraaortic balloon pump, inotropic or vasopressor treatment, or POISE-2 study drug (clonidine/aspirin) discontinuation. Major bleeding was defined by bleeding that did not meet the criteria for life-threatening bleeding but that (1) resulted in a postoperative hemoglobin at most 70 g/l requiring transfusion of at least 2 units of red blood cells; (2) resulted in a hemoglobin reduction of at least 50 g/l and transfusion of at least 2 units of red blood cells; (3) resulted in transfusion of at least 4 units of red blood cells within a 24-h period; (4) led to embolization, minor vascular repair, or nasal packing; or (5) was retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging). Clinically important bradycardia was defined by a heart rate less than 55 beats/min requiring a temporary pacemaker, administration of a sympathomimetic agent or atropine, or study drug discontinuation.

MI = myocardial infarction; POD = postoperative day.

Table 3. Primary Analysis: The Association between Clinically Important Hypotension and the Composite Outcome of 30-day Myocardial Infarction and Mortality

Period	Average Relative Effect OR (98.3% CI)*	*P* Value[2]
10-min increase in hypotension		
Intraoperative (N = 9,765)	1.08 (1.03, 1.12)	< 0.001‡
Remaining day of surgery (N = 9,592)	1.03 (1.01, 1.05)	< 0.001‡
Hypotension *vs.* nonhypotension: PODs 1 to 4 (N = 9,186)	2.83 (1.26, 6.35)	0.002‡

*The odds ratios (ORs) for average relative effect were estimated using generalized estimating equation distinct effects models. Each model was adjusted for potential confounders listed in table 1, duration of clinically important hypotension in previous periods if applicable, and whether the occurrence of bradycardia and major or life-threatening bleeding occurred before or during the exposure period of interest. †Significance criterion and CIs for multiple comparisons were adjusted by Bonferroni correction. Correspondingly, $P < 0.017$ (0.05/3) was considered to be significant. ‡The association is statistically significant.

POD = postoperative day.

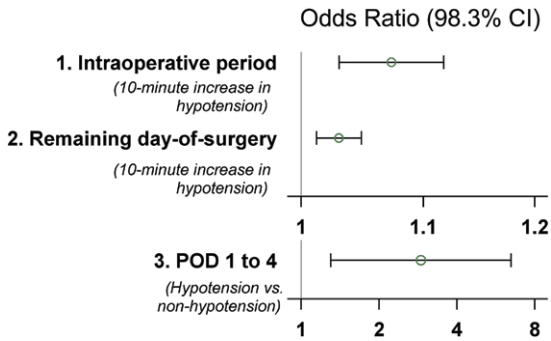

Fig. 4. Odds ratios of average relative effect on the primary composite of 30-day myocardial infarction and mortality for three perioperative periods: intraoperative, remaining day of surgery, and the initial four PODs of hospitalization. CIs for multiple comparisons were adjusted by Bonferroni correction. Correspondingly, $P < 0.017$ (0.05/3) was considered to be significant for the average relative effect. The *circles* present the odds ratios, and the *bars* present the CIs. POD = postoperative day.

the odds ratio of average relative effect per 5-mmHg decrease in the lowest systolic pressure was 1.07 (98.3% CI, 0.99, 1.14; $P = 0.029$) intraoperatively, and 1.17 (98.3% CI, 1.04, 1.32; $P = 0.002$) for remaining day of surgery. Comparing patients with clinically important hypotension in PODs 1 to 4 to those without it, the odds ratio was 3.02 (98.3% CI, 1.41, 6.45; $P < 0.001$), adjusted for the lowest systolic pressure in previous periods and other confounders.

Bleeding and its related anemia potentially negatively affect postoperative myocardial infarction/death, and bleeding is related to hypotension as well. Intraoperatively, 129 (3.8%) of the 3,404 patients with hypotension had major/life-threatening bleeding, whereas only 41 (0.6%) patients without hypotension had bleeding. Thus we adjusted for bleeding in our analyses by including a binary covariate in the generalized estimating equation models. Because it is unlikely that hypotension causes bleeding, we adjusted for bleeding that occurred both during and before the interested period for adjustment. Therefore, a delayed bleeding diagnosis will not affect our analyses.

After adjusting for bleeding, the odds ratio for hypotension in association with 30-day myocardial infarction/death in our final analyses was slightly lower, suggesting that bleeding has a confounding effect. Unfortunately, it was impossible to completely adjust for the confounding effect of bleeding because the severity of bleeding, timing of bleeding, or potential interaction effects with other factors can all influence the association between hypotension and death/myocardial infarction.

However, because only 2% of patients had bleeding during the three different periods, ignoring some detailed information about bleeding should not affect our conclusion. To provide further evidence, we assessed the association among patients without bleeding. As shown in table 6, the association

Table 4. The Association of Clinically Important Hypotension to Component of the 30-day Composite Outcome

Period	Outcome	Incidence (%)*	OR (99.2% CI)†	*P* Value‡
10-min increase in hypotension				
Intraoperative	MI	590 (6.0%)	1.03 (0.97, 1.10)	0.162
	Mortality	116 (1.2%)	1.12 (1.05, 1.20)	< 0.001§
Remaining day of surgery	MI	418 (4.4%)	1.03 (1.00, 1.05)	0.002§
	Mortality	105 (1.1%)	1.03 (1.01, 1.06)	< 0.001§
Hypotension *vs.* nonhypotension: PODs 1 to 4	MI	29 (0.3%)	2.95 (0.84, 10.4)	0.023
	Mortality	63 (0.7%)	2.72 (1.07, 6.93)	0.004§

*Incidence of myocardial infarction (MI) and death are presented as the count (%) for three perioperative periods. †The odds ratios (ORs) for MI and death were estimated using generalized estimating equation distinct effects models, adjusted for potential confounders listed in table 1, duration of clinically important hypotension in previous periods if applicable, and whether the occurrence of bradycardia and major or life-threatening bleeding occurred before or during the exposure period of interest. ‡Significance criterion and CIs for multiple comparisons were adjusted by Bonferroni correction. $P < 0.008$ (0.05/6) was considered significant for MI and death individual effect. §The association is statistically significant.

POD = postoperative day.

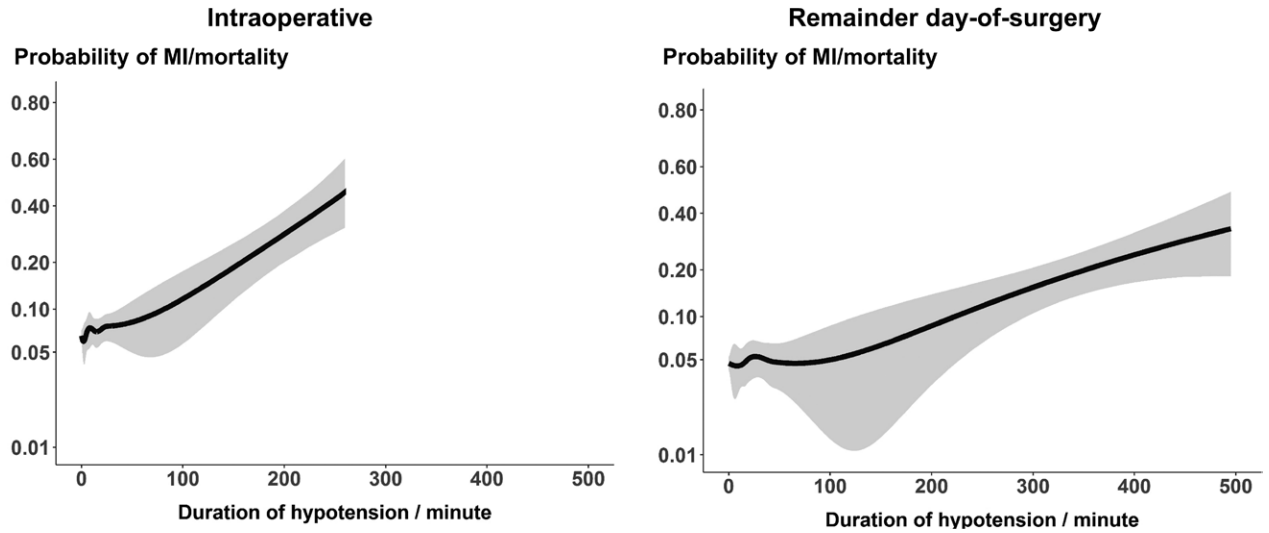

Fig. 5. Unadjusted relationship between duration of clinically important hypotension and the composite outcome. The *solid lines* represent predicted probability of the collapsed composite outcome, whereas the *shaded areas* represent the 95% CI of the predicted value. The adjusted odds ratios were 1.08 intraoperatively and 1.03 postoperatively (table 3). MI = myocardial infarction.

between hypotension and outcomes were still significant for all three periods, suggesting that our conclusion is valid.

As shown in table S1 (Supplemental Digital Content 1, http://links.lww.com/ALN/B569), the percentage of patients who were given epidural analgesia was higher in hypotensive than nonhypotensive patients for all three perioperative periods. To assess the effect of epidural analgesia on the association of hypotension and myocardial infarction/mortality, we adjusted for epidural analgesia received before any outcomes for each period. The results, as shown in table S2 (Supplemental Digital Content 2, http://links.lww.com/ALN/B570), are similar to the analyses without adjusting for epidural analgesia. The significant association between hypotension and myocardial infarction/mortality thus appears to be robust to epidural analgesia.

Discussion

Death within 30 days of surgery remains common, with a U.S. incidence of about 2% among inpatients.[22] In fact, if the postoperative period were considered a distinct disease, it would be the third leading cause of death in the United States.[23] Cardiovascular events and their consequences are by far the most common cause of death in the month after surgery.[24] Myocardial infarction or injury is the leading major cardiovascular complication, with stroke being a distant second.[25] Large trials—including the one underlying the current analysis—have shown that postoperative myocardial infarction *cannot* be safely prevented by administration of β-blockers,[6] aspirin,[16] or clonidine[17] or by avoiding nitrous oxide.[26]

Postoperative myocardial infarctions are often missed clinically because few infarcted patients have any symptoms whatsoever. However, blood troponin concentration is a reliable indicator of myocardial infarction and is strongly and progressively associated with postoperative death.[25] Furthermore, mortality after troponin elevation is similar in patients who do and do not have symptoms. Consequently troponin elevation of apparently ischemic origin, with or

Table 5. Sensitivity Analysis: Associations between Lowest SBP and the Composite Outcome of 30-day Myocardial Infarction and Mortality

Period	Average Relative Effect OR (98.3% CI)*	*P* Value†
5-mmHg decrease in lowest SBP		
Intraoperative	1.07 (0.99, 1.14)	0.029
Remaining day of surgery	1.17 (1.04, 1.32)	0.002‡
Hypotension *vs.* nonhypotension: PODs 1 to 4	3.02 (1.41, 6.45)	< 0.001‡

*The odds ratios (ORs) for average relative effect were estimated using a generalized estimating equation distinct effects model, adjusted for potential confounders listed in Table 1, lowest systolic blood pressure (SBP) in previous periods if applicable, and whether the occurrence of bradycardia and major or life-threatening bleeding occurred before or during the exposure period of interest. †Significance criterion and CIs for multiple comparisons were adjusted by Bonferroni correction. Correspondingly, $P < 0.017$ (0.05/3) was considered to be significant for the average relative effect. ‡The association is statistically significant.

POD = postoperative day.

Table 6. Association between Hypotension and MI/Mortality among Patients without Major or Life-threatening Bleeding

Period	Average Relative Effect OR (98.3% CI)*	*P* Value†
Per 10-min increase in hypotension		
Intraoperative (N = 9,595)	1.09 (1.04, 1.14)	< 0.001‡
Remaining day of surgery (N = 9,379)	1.03 (1.01, 1.05)	0.002‡
Hypotension *vs.* nonhypotension: PODs 1 to 4 (N = 9,186)	3.01 (1.26, 7.23)	0.003‡

*The odds ratio (OR) for average relative effect were estimated using a generalized estimating equation distinct effects model, adjusted for potential confounders listed in table 1, lowest systolic blood pressure (SBP) in previous periods if applicable, and whether the occurrense of brachycardia occured before or suring the exposure period of interest. †Significance criterion and CIs for multiple comparisons were adjusted by Bonferroni correction. Correspondingly, $P < 0.017$ (0.05/3) was considered to be significant for the average relative effect. ‡The association is statistically significant.

MI = myocardial infarction; POD = postoperative day.

without cardiovascular symptoms or ischemic electrocardiogram changes, independently and strongly predicts death and defines myocardial infarction after noncardiac surgery.[25] All patients in the current analysis had troponin monitoring on the day of surgery and on the subsequent three postoperative mornings so long as they remained hospitalized. Furthermore, myocardial infarctions were centrally adjudicated based on the third Universal Definition of Myocardial Infarction. The infarction incidence we report is thus reliable.

A concerning finding of the POISE-1 trial was that metoprolol administration doubled the risk of stroke (hazard ratio, 2.2 [95% CI 1.3 to 3.7]; $P = 0.005$), with a consequent increase in overall 30-day mortality. Furthermore, the strokes were serious: a third of the stroke patients died within a month of surgery, and more than 50% of survivors were incapacitated or required assistance with daily activities.[6] In POISE-2, clonidine, which also causes hypotension, did not increase stroke risk.[17] Furthermore, a recent registry analysis failed to identify an association between intraoperative hypotension and stroke,[27] possibly because postoperative hypotension, which usually lasts much longer than intraoperative hypotension, may contribute more to stroke genesis.

Given that it is illogical to consider associations between hypotension and myocardial infarction when the exposure happens after the outcome, our analyses of hypotension during each perioperative period was conditional on not having a myocardial infarction before or during the exposure period of interest. For example, if a patient had a myocardial infarction after admission to the postanesthesia care unit, we only considered intraoperative hypotension. We did not consider hypotension during the period in which a myocardial infarction occurred because we could not determine the order of events, which risked reverse causation bias.

Our analyses assessed the independent contribution of hypotension at each perioperative interval. Adjusted for hypotension in previous periods, the primary results thus show the association between hypotension and 30-day myocardial infarction and/or mortality given equal hypotension duration in prior periods. The increase was highly exposure-dependent, increasing linearly on a logit scale intraoperatively and over the remaining day of surgery. The effect sizes intraoperatively and on the day of surgery were substantial considering that the odds are reported per 10 min of hypotension in patients who frequently had hypotension lasting for hours. For example, the risk of myocardial infarction or death increased 3% per just 10 min of postoperative hypotension on the day of surgery. An unfortunate consequence of differing measurement intervals and different definitions of hypotension is that there is no obvious way to compare strength of the associations across various periods.

We did not find strong collinearity among hypotension variables in the three periods, suggesting that the analysis approach was generally valid. Generally speaking, our results are consistent with a dichotomous analysis of postoperative hypotension in the VISION population, which identified a 2.0 (95% CI, 1.7, 2.3) relative risk of a 30-day composite of myocardial infarction, stroke, and death.[7] Our current analysis, in a different population, extends previous work by evaluating associations over specific time periods.

The most serious limitation of our analysis is that POISE-2 was a pragmatic trial that included relatively limited detail about blood pressure. We were thus unable to consider time-weighted average pressure under thresholds and various other quantifications of hypotensive exposure. Similarly, mean arterial pressure, which was the primary exposure in previous analyses,[3,5] was not recorded in POISE-2. Postoperatively, especially, we were restricted to nursing assessments that were typically recorded at 4- to 6-h intervals, making it difficult to estimate exposure duration. On the other hand, our primary definition of systolic pressure less than 90 mmHg requiring treatment assures that hypotension considered in our analysis was deemed clinically important

for individual patients. The results were also similar across various other definitions. The associations we observed were strong, and it is possible that they would be even stronger if hypotension had been better characterized.

An exclusion criterion for POISE-2 (the underlying trial) was preoperative hypotension, so our results are only generalizable to patients experiencing a new event of hypotension during or after surgery. An important enrollment criterion was known or suspected cardiovascular disease. All participants were thus at risk of myocardial infarction. However, the same cardiovascular disease that increased infarction risk presumably also increased the risk of hypotension.

Although our analysis was fully adjusted for a broad range of potential confounding factors, surely some of the observed association between hypotension and myocardial infarction and death was due to unobserved confounding. However, it also seems likely that at least some fraction of the association represents a causal relationship. The causal component can only be determined in a randomized trial, and given the strength of the overall association and severity of the outcome, a major trial seems well justified. For example, a study might randomize patients to routine hemodynamic control *versus* aggressive prevention and treatment of hypotension. But until trial results become available, clinicians might be prudent to assume that ward hypotension is potentially deleterious and probably well worth preventing and treating.

Patients known to be septic at the time of surgery were excluded, but a fraction of patients may have become septic, and sepsis may have contributed to hypotension. Because the overall incidence of hypotension was 42%, it seems unlikely that sepsis was an important contributor to hypotension. However, to the extent that it was, a large randomized trial shows that targeting a higher blood pressure does not reduce mortality.[28]

Our previous studies evaluated associations between mean arterial pressure and myocardial infarction, acute kidney injury, and death. The current analysis differs in being based on systolic pressure because that is how hypotension was defined and recorded in POISE-2. Although it seems likely that the mean is the single best characterization of arterial pressure, it remains unknown whether diastolic or systolic pressures might better predict cardiovascular or renal complications. Comparisons from our current results to previous analyses of perioperative blood pressure[3,5] should be made cautiously because measurements were sparse in the current study and based on different definitions.

In summary, clinically important hypotension was significantly associated with a composite of myocardial infarction and death during each of three perioperative periods, even after adjustment for previous hypotensive episodes. The results were broadly similar for the individual components of the composite and over a range of sensitivity analyses. That intraoperative hypotension is strongly associated with myocardial infarction and death (and somewhat less so with acute kidney injury) is already well established. This analysis extends previous work by showing that postoperative hypotension is also strongly associated with a 30-day composite of myocardial infarction and death. Both intraoperative and ward hypotension are potentially modifiable factors that are strongly associated with myocardial infarction, which is the single most important cause of 30-day postoperative mortality. Clinicians should not assume that ward hypotension is benign just because it is common.

Research Support

Supported by the Canadian Institutes of Health Research (Ottawa, Ontario, Canada) and more than 40 grants to participating centers.

Competing Interests

The authors declare no competing interests.

Correspondence

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

References

1. Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH: Perioperative cardiac events in patients undergoing noncardiac surgery: A review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ 2005; 173:627–34
2. Devereaux PJ, Sessler DI: Cardiac complications in patients undergoing major noncardiac surgery. N Engl J Med 2015; 373:2258–69
3. 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
4. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI: Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: Toward an empirical definition of hypotension. Anesthesiology 2013; 119:507–15
5. 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
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. Roshanov PS, Rochwerg B, Patel A, Salehian O, Duceppe E, Belley-Côté EP, Guyatt GH, Sessler DI, Le Manach Y, Borges FK, Tandon V, Worster A, Thompson A, Koshy M, Devereaux B, Spencer FA, Sanders RD, Sloan EN, Morley EE, Paul J, Raymer KE, Punthakee Z, Devereaux PJ: Withholding *versus* continuing angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers before noncardiac surgery: An analysis of the vascular events in noncardiac surgery patients cohort evaluation prospective cohort. Anesthesiology 2017; 126:16–27

8. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Rao-Melacini P, Chrolavicius S, Yang H, Macdonald C, Avezum A, Lanthier L, Hu W, Yusuf S; POISE (PeriOperative ISchemic Evaluation) Investigators: Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: A cohort study. Ann Intern Med 2011; 154:523–8
9. Dalton JE, Glance LG, Mascha EJ, Ehrlinger J, Chamoun N, Sessler DI: Impact of present-on-admission indicators on risk-adjusted hospital mortality measurement. Anesthesiology 2013; 118:1298–306
10. Dalton JE, Kurz A, Turan A, Mascha EJ, Sessler DI, Saager L: Development and validation of a risk quantification index for 30-day postoperative mortality and morbidity in noncardiac surgical patients. Anesthesiology 2011; 114:1336–44
11. Rodseth RN, Biccard BM, Chu R, Lurati Buse GA, Thabane L, Bakhai A, Bolliger D, Cagini L, Cahill TJ, Cardinale D, Chong CP, Cnotliwy M, Di Somma S, Fahrner R, Lim WK, Mahla E, Le Manach Y, Manikandan R, Pyun WB, Rajagopalan S, Radovic M, Schutt RC, Sessler DI, Suttie S, Vanniyasingam T, Waliszek M, Devereaux PJ: Postoperative B-type natriuretic peptide for prediction of major cardiac events in patients undergoing noncardiac surgery: Systematic review and individual patient meta-analysis. Anesthesiology 2013; 119:270–83
12. Rodseth RN, Biccard BM, Le Manach Y, Sessler DI, Lurati Buse GA, Thabane L, Schutt RC, Bolliger D, Cagini L, Cardinale D, Chong CP, Chu R, Cnotliwy M, Di Somma S, Fahrner R, Lim WK, Mahla E, Manikandan R, Puma F, Pyun WB, Radović M, Rajagopalan S, Suttie S, Vanniyasingam T, van Gaal WJ, Waliszek M, Devereaux PJ: The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery: B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: A systematic review and individual patient data meta-analysis. J Am Coll Cardiol 2014; 63:170–80
13. Gupta PK, Gupta H, Sundaram A, Kaushik M, Fang X, Miller WJ, Esterbrooks DJ, Hunter CB, Pipinos II, Johanning JM, Lynch TG, Forse RA, Mohiuddin SM, Mooss AN: Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation 2011; 124:381–7
14. 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
15. Wijeysundera DN, Beattie WS, Austin PC, Hux JE, Laupacis A: Non-invasive cardiac stress testing before elective major non-cardiac surgery: Population based cohort study. BMJ 2010; 340:b5526
16. 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
17. 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
18. 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
19. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction: Third universal definition of myocardial infarction. Circulation 2012; 126:2020–35
20. Mascha EJ, Imrey PB: Factors affecting power of tests for multiple binary outcomes. Stat Med 2010; 29:2890–904
21. Mascha EJ, Sessler DI: Design and analysis of studies with binary-event composite endpoints: Guidelines for anesthesia research. Anesth Analg 2011; 112:1461–71
22. Sessler DI, Sigl JC, Manberg PJ, Kelley SD, Schubert A, Chamoun NG: Broadly applicable risk stratification system for predicting duration of hospitalization and mortality. Anesthesiology 2010; 113:1026–37
23. Bartels K, Karhausen J, Clambey ET, Grenz A, Eltzschig HK: Perioperative organ injury. Anesthesiology 2013; 119:1474–89
24. 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
25. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Investigators: Myocardial injury after noncardiac surgery: A large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. Anesthesiology 2014; 120:564–78
26. 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
27. Hsieh JK, Dalton JE, Yang D, Farag ES, Sessler DI, Kurz AM: The association between mild intraoperative hypotension and stroke in general surgery patients. Anesth Analg 2016; 123:933–9
28. Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, Mira JP, Dequin PF, Gergaud S, Weiss N, Legay F, Le Tulzo Y, Conrad M, Robert R, Gonzalez F, Guitton C, Tamion F, Tonnelier JM, Guezennec P, Van Der Linden T, Vieillard-Baron A, Mariotte E, Pradel G, Lesieur O, Ricard JD, Hervé F, du Cheyron D, Guerin C, Mercat A, Teboul JL, Radermacher P; SEPSISPAM Investigators: High *versus* low blood-pressure target in patients with septic shock. N Engl J Med 2014; 370:1583–93