Relationship between perioperative cardiovascular events and perioperative hypotension in patients with coronary artery disease undergoing major noncardiac surgery

**Supplemental Digital Content 1**

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## Details of eligibility criteria

Patients were eligible if they were ≥45 years of age, undergoing elective vascular, orthopedic, thoracic, or abdominal surgery that required at least overnight admission after surgery, and had a history or risk factors for atherosclerotic disease or history of congestive heart failure.

The study excluded patients with planned invasive coronary angiography for preoperative investigation before surgery, history of coronary artery stent implantation, creatinine clearance <35 mL/min, known contrast reaction, current pregnancy, persistent atrial fibrillation or frequent premature beats, heart rate ≥70 beats/min (at centers with single source scanners) or ≥90 beats/min (at centers with dual source scanners) despite drugs to control heart rate just before scheduled coronary computed tomographic angiography, weight >300 lb (136 kg), more than four non-evaluable segments on coronary computed tomographic angiography (non-diagnostic scan), did not undergo noncardiac surgery within six months after coronary computed tomographic angiography, surgery that did not require at least an overnight stay in hospital, or results of coronary computed tomographic angiography were unblinded because of suspected left main stenosis and patient underwent preoperative coronary revascularization.

## Primary outcome definition

The primary outcome was a composite outcome defined as any one of the following:

1. Death from cardiovascular cause within 30 days of surgery was defined as death thought to be due to myocardial infarction, asystole, ventricular fibrillation, pulseless electrical activity, other sudden or arrhythmic death, sustained ventricular tachycardia, cardiogenic shock, congestive heart failure, stroke, peripheral vascular disease, aortic dissection, pulmonary embolism, bleeding, or other cardiovascular causes.

2. Non-fatal myocardial infarction within 30 days was defined as any one of the following criteria (A, B or C):

A. A typical rise of troponin or a typical fall of an elevated troponin detected at its peak post surgery in a patient without a documented alternative explanation for an elevated troponin (e.g., pulmonary embolism). This criterion also required **that 1 of the following** must also exist:

1. ischemic signs or symptoms (i.e., chest, arm, neck or jaw discomfort; shortness of breath; pulmonary edema), **OR**
2. development of pathologic Q waves present in any two contiguous leads that are ≥ 30 milliseconds, **OR**
3. iii. ECG changes indicative of ischemia (i.e., ST segment elevation [≥ 2 mm in leads V1, V2, or V3 OR ≥ 1 mm in the other leads], ST segment depression [≥ 1 mm], or symmetric inversion of T waves ≥ 1 mm) in at least two contiguous leads, **OR**
4. iv. coronary artery intervention (i.e., PCI or CABG surgery), **OR**
5. v. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging.

B. Pathologic findings of an acute or healing myocardial infarction.

C. Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event.

## Figure S1. Kaplan-Meier event-free survival estimates across four subgroups with CCTA findings re-categorized



Footnote: The primary outcome occurred in 3.7% (19/518) of patients with less than extensive obstructive coronary disease on CCTA and no hypotension compared to 11.2% (10/89) in patients with extensive obstructive coronary disease and no hypotension (hazard ratio, 3.15; 95% CI, 1.46 to 6.77; p=0.003), 11.0% (32/291) in patients with hypotension but less than extensive obstructive coronary disease (hazard ratio, 3.57; 95% CI, 2.02 to 6.30; p<0.001), and 22.8% (13/57) in patients with extensive obstructive coronary disease and hypotension (hazard ratio, 7.76 ; 95% CI, 3.83 to 15.71; p<0.001). Abbreviations: CCTA, coronary computer tomographic angiography; CAD, coronary artery disease.

## Table S1. Sensitivity analyses with angiographic findings of coronary artery disease categorized as extensive obstructive disease versus less than extensive obstructive disease (i.e. no, non-obstructive, or obstructive disease)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | | Association between hypotension and CV events | | |  | |  | |  |
|  | **CV events/patients with hypotension (%)** | | **aHR** | **(95% CI)** | **p-value** | **Interaction aHR** | | **(95% CI)** | | **p-value for interaction** |
| Any hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 45/348 | (12.9%) | 3.18 | (1.99-5.07) | <0.001 |  | | |  |  |
| In patients with less than extensive obstructive disease | 32/291 | (11.0%) | 3.57 | (2.02-6.30) | <0.001 | 1.00 | Reference | | | 0.469 |
| In patients with extensive obstructive disease | 13/57 | (22.8%) | 2.47 | (1.08-5.62) | 0.032 | 0.69 | (0.25-1.88) | | |
| Intraoperative hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 25/161 | (15.5%) | 2.48 | (1.53-4.02) | <0.001 |  | | |  |  |
| In patients with less than extensive obstructive disease | 17/133 | (12.8%) | 2.52 | (1.40-4.51) | 0.002 | 1.00 | Reference | | | 0.926 |
| In patients with extensive obstructive disease | 8/28 | (28.6%) | 2.40 | (1.01-5.66) | 0.046 | 0.95 | (0.34-2.69) | | |
| Postoperative hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 28/236 | (11.9%) | 2.25 | (1.40-3.61) | 0.001 |  | | |  |  |
| In patients with less than extensive obstructive disease | 20/198 | (10.1%) | 2.40 | (1.36-4.23) | 0.002 | 1.00 | Reference | | | 0.676 |
| In patients with extensive obstructive disease | 8/38 | (21.1%) | 1.93 | (0.82-4.56) | 0.134 | 0.80 | (0.29-2.24) | | |

Abbreviations: CV, cardiovascular; aHR, adjusted hazard ratio; CI, confidence interval.

## Table S2. Sensitivity analyses with postoperative hypotension that occurred before the day of the outcome event

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | | Association between hypotension and CV events | | |  | |  | | |  |
|  | **CV events/patients with hypotension (%)** | | **aHR** | **(95% CI)** | **p-value** | **Interaction aHR** | | **(95% CI)** | | | **p-value for interaction** |
| Any hypotension |  |  |  |  |  |  | | |  | |  |
| In all patients | 40/343 | (11.7%) | 3.42 | (2.14-5.46) | <0.001 |  | | | |  |  |
| In patients with less than obstructive disease | 12/157 | (7.6%) | 3.79 | (1.63-8.82) | 0.002 | 1.00 | Reference | | | | 0.778 |
| In patients with obstructive or extensive obstructive disease | 28/186 | (15.1%) | 3.28 | (1.88-5.70) | <0.001 | 0.87 | (0.32-2.36) | | | |
| Intraoperative hypotension |  |  |  |  |  |  | | |  | |  |
| In all patients | 25/161 | (15.5%) | 2.51 | (1.55-4.07) | <0.001 |  | | | |  |  |
| In patients with less than obstructive disease | 7/70 | (10.0%) | 2.67 | (1.09-6.56) | 0.032 | 1.00 | Reference | | | | 0.895 |
| In patients with obstructive or extensive obstructive disease | 18/91 | (19.8%) | 2.49 | (1.40-4.42) | 0.002 | 0.93 | (0.32-2.70) | | | |
| Postoperative hypotension |  |  |  |  |  |  | | |  | |  |
| In all patients | 16/224 | (7.1%) | 1.94 | (1.05-3.58) | 0.034 |  | | | |  |  |
| In patients with less than obstructive disease | 6/102 | (5.9%) | 3.07 | (1.16-8.10) | 0.024 | 1.00 | Reference | | | | 0.262 |
| In patients with obstructive or extensive obstructive disease | 10/122 | (8.2%) | 1.58 | (0.75-3.30) | 0.229 | 0.51 | (0.16-1.64) | | | |

Abbreviations: CV, cardiovascular; aHR, adjusted hazard ratio; CI, confidence interval.

## Table S3. Sensitivity analyses with outcome limited to non-fatal myocardial infarction

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | | Association between hypotension and CV events | | |  | |  | |  |
|  | **CV events/patients with hypotension (%)** | | **aHR** | **(95% CI)** | **p-value** | **Interaction aHR** | | **(95% CI)** | | **p-value for interaction** |
| Any hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 39/348 | (11.2%) | 2.93 | (1.79-4.79) | <0.001 |  | |  | |  |
| In patients with less than obstructive disease | 12/159 | (7.5%) | 3.27 | (1.34-8.01) | 0.009 | 1.00 | Reference | | | 0.770 |
| In patients with obstructive or extensive obstructive disease | 27/189 | (14.3%) | 2.79 | (1.55-5.02) | 0.001 | 0.85 | (0 .29-2.48) | | |
| Intraoperative hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 20/161 | (12.4%) | 2.08 | (1.23-3.53) | 0.007 |  | |  | |  |
| In patients with less than obstructive disease | 5/70 | (7.1%) | 1.90 | (0.69-5.23) | 0.213 | 1.00 | Reference | | | 0.798 |
| In patients with obstructive or extensive obstructive disease | 15/91 | (16.5%) | 2.22 | (1.19-4.13) | 0.012 | 1.17 | (0.36-3.83) | | |
| Postoperative hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 24/236 | (10.2%) | 2.04 | (1.23-3.37) | 0.006 |  | |  | |  |
| In patients with less than obstructive disease | 9/106 | (8.5%) | 3.42 | (1.42-8.27) | 0.006 | 1.00 | Reference | | | 0.167 |
| In patients with obstructive or extensive obstructive disease | 15/130 | (11.5%) | 1.60 | (0.86-2.98) | 0.140 | 0.47 | (0.16-1.37) | | |

Abbreviations: CV, cardiovascular; aHR, adjusted hazard ratio; CI, confidence interval.

## Table S4. Sensitivity analyses with categorization of obstructive and extensive obstructive disease based on ≥70% stenosis

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | | Association between hypotension and CV events | | |  | |  | |  |
|  | **CV events/patients with hypotension (%)** | | **aHR** | **(95% CI)** | **p-value** | **Interaction aHR** | | **(95% CI)** | | **p-value for interaction** |
| Any hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 45/348 | (12.9%) | 3.14 | (1.97-5.01) | <0.001 |  | |  | |  |
| In patients with less than obstructive disease | 17/201 | (8.5%) | 3.72 | (1.70-8.14) | 0.001 | 1.00 | Reference | | | 0.587 |
| In patients with obstructive or extensive obstructive disease | 28/147 | (19.0%) | 2.84 | (1.59-5.09) | 0.001 | 0.76 | (0.29-2.02) | | |
| Intraoperative hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 25/161 | (15.5%) | 2.44 | (1.50-3.95) | <0.001 |  | |  | |  |
| In patients with less than obstructive disease | 9/89 | (10.1%) | 2.59 | (1.16-5.78) | 0.020 | 1.00 | Reference | | | 0.847 |
| In patients with obstructive or extensive obstructive disease | 16/72 | (22.2%) | 2.34 | (1.28-4.23) | 0.006 | 0.91 | (0.33-2.47) | | |
| Postoperative hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 28/236 | (11.9%) | 2.25 | (1.40-3.61) | 0.001 |  | |  | |  |
| In patients with less than obstructive disease | 12/140 | (8.6%) | 2.98 | (1.39-6.34) | 0.005 | 1.00 | Reference | | | 0.363 |
| In patients with obstructive or extensive obstructive disease | 16/96 | (16.7%) | 1.90 | (1.04-3.48) | 0.038 | 0.64 | (0.24-1.68) | | |

Abbreviations: CV, cardiovascular; aHR, adjusted hazard ratio; CI, confidence interval.

## Table S5. Sensitivity analyses with categorization of coronary artery disease based on complete occlusion (100% stenosis) in at least one major vessel: the right coronary artery, left anterior descending artery, or left circumflex artery

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | | Association between hypotension and CV events | | |  | |  | |  |
|  | **CV events/patients with hypotension (%)** | | **aHR** | **(95% CI)** | **p-value** | **Interaction aHR** | | **(95% CI)** | | **p-value for interaction** |
| Any hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 45/348 | (12.9%) | 3.09 | (1.94-4.94) | <0.001 |  | |  | |  |
| In patients without complete occlusion in a major vessel | 32/287 | (11.1%) | 4.32 | (2.37-7.87) | <0.001 | 1.00 | Reference | | | 0.063 |
| In patients with complete occlusion in at least one major vessel | 13/61 | (21.3%) | 1.71 | (0.79-3.70) | 0.171 | 0.40 | (0 .15-1.05) | | |
| Intraoperative hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 25/161 | (15.5%) | 2.36 | (1.45-3.85) | 0.001 |  | |  | |  |
| In patients without complete occlusion in a major vessel | 6/131 | (4.6%) | 3.41 | (1.91-6.10) | <0.001 | 1.00 | Reference | | | 0.048 |
| In patients with complete occlusion in at least one major vessel | 19/30 | (63.3%) | 1.14 | (0.46-2.85) | 0.776 | 0.33 | (0.11-0.99) | | |
| Postoperative hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 28/236 | (11.9%) | 2.19 | (1.36-3.53) | 0.001 |  | |  | |  |
| In patients without complete occlusion in a major vessel | 20/195 | (10.3%) | 2.67 | (1.50-4.75) | 0.001 | 1.00 | Reference | | | 0.280 |
| In patients with complete occlusion in at least one major vessel | 8/41 | (19.5%) | 1.53 | (0.66-3.53) | 0.322 | 0.57 | (0.21-1.58) | | |

Abbreviations: CV, cardiovascular; aHR, adjusted hazard ratio; CI, confidence interval.

## Table S6. Sensitivity analyses adjusted for unbalanced baseline characteristics, major bleeding, and use of postoperative epidural analgesia

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | | Association between hypotension and CV events | | |  | |  | |  |
|  | **CV events/patients with hypotension (%)** | | **aHR** | **(95% CI)** | **p-value** | **Interaction aHR** | | **(95% CI)** | | **p-value for interaction** |
| Any hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 45/348 | (12.9%) | 2.54 | (1.52-4.23) | <0.001 |  | |  | |  |
| In patients with less than obstructive disease | 17/201 | (8.5%) | 2.88 | (1.17-7.08) | 0.021 | 1.00 | Reference | | | 0.735 |
| In patients with obstructive or extensive obstructive disease | 28/147 | (19.0%) | 2.40 | (1.31-4.39) | 0.005 | 0.83 | (0.29-2.41) | | |
| Intraoperative hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 25/161 | (15.5%) | 2.29 | (1.33-3.94) | 0.003 |  | |  | |  |
| In patients with less than obstructive disease | 9/89 | (10.1%) | 2.59 | (1.00-6.69) | 0.050 | 1.00 | Reference | | | 0.796 |
| In patients with obstructive or extensive obstructive disease | 16/72 | (22.2%) | 2.24 | (1.29-4.21) | 0.012 | 0.87 | (0.29-2.58) | | |
| Postoperative hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 28/236 | (11.9%) | 1.69 | (1.03-2.80) | 0.039 |  | |  | |  |
| In patients with less than obstructive disease | 12/140 | (8.6%) | 2.63 | (1.10-6.31) | 0.030 | 1.00 | Reference | | | 0.239 |
| In patients with obstructive or extensive obstructive disease | 16/96 | (16.7%) | 1.39 | (0.76-2.56) | 0.287 | 0.53 | (0.18-1.53) | | |

Footnote: In addition to coronary computed tomographic angiography findings and hypotension, models were adjusted for: age, body mass index, preoperative medications (statins, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, aspirin, and beta-blockers), gender, requirement for assistance with activities of daily living, history of hypertension, duration of surgery, history of diabetes, history of coronary artery disease, history of peripheral vascular disease, type of surgery (major vascular and major orthopedic vs other), bleeding, and use of postoperative epidural analgesia. Abbreviations: CV, cardiovascular; aHR, adjusted hazard ratio; CI, confidence interval.

## Table S7. Sensitivity analyses with patients who had previous CABG and no unprotected coronary territories re-classified as having non-obstructive coronary disease

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | | Association between hypotension and CV events | | |  | |  | |  |
|  | **CV events/patients with hypotension (%)** | | **aHR** | **(95% CI)** | **p-value** | **Interaction aHR** | | **(95% CI)** | | **p-value for interaction** |
| Any hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 45/348 | (12.9%) | 3.13 | (1.96-4.99) | <0.001 |  | |  | |  |
| In patients with less than obstructive disease | 14/173 | (8.1%) | 3.16 | (1.40-7.11) | 0.006 | 1.00 | Reference | | | 0.980 |
| In patients with obstructive or extensive obstructive disease | 31/175 | (17.7%) | 3.11 | (1.76-5.52) | <0.001 | 0.99 | (0.37-2.66) | | |
| Intraoperative hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 25/161 | (15.5%) | 2.42 | (1.49-3.93) | <0.001 |  | |  | |  |
| In patients with less than obstructive disease | 7/77 | (9.1%) | 2.31 | (0.96-5.56) | 0.063 | 1.00 | Reference | | | 0.871 |
| In patients with obstructive or extensive obstructive disease | 18/84 | (21.4%) | 2.52 | (1.41-4.50) | 0.002 | 1.09 | (0.38-3.13) | | |
| Postoperative hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 28/236 | (11.9%) | 2.15 | (1.33-3.45) | 0.002 |  | |  | |  |
| In patients with less than obstructive disease | 10/116 | (8.6%) | 3.05 | (1.35-6.88) | 0.007 | 1.00 | Reference | | | 0.304 |
| In patients with obstructive or extensive obstructive disease | 18/120 | (15.0%) | 1.81 | (1.09-3.24) | 0.047 | 0.59 | (0.22-1.61) | | |

Abbreviations: CV, cardiovascular; CABG, coronary artery bypass grafting surgery; aHR, adjusted hazard ratio; CI, confidence interval.

## Table S8. Sensitivity analyses excluding 6 patients with ≥50% stenosis of the left main coronary artery (n = 949)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | | Association between hypotension and CV events | | |  | |  | |  |
|  | **CV events/patients with hypotension (%)** | | **aHR** | **(95% CI)** | **p-value** | **Interaction aHR** | | **(95% CI)** | | **p-value for interaction** |
| Any hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 45/347 | (13.0%) | 3.14 | (1.97-5.01) | <0.001 |  | |  | |  |
| In patients with less than obstructive disease | 14/159 | (8.8%) | 3.85 | (1.62-9.19) | 0.002 | 1.00 | Reference | | | 0.579 |
| In patients with obstructive or extensive obstructive disease | 31/188 | (16.5%) | 2.88 | (1.65-5.01) | <0.001 | 0.75 | (0.27-2.09) | | |
| Intraoperative hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 25/161 | (15.5%) | 2.41 | (1.49-3.92) | <0.001 |  | |  | |  |
| In patients with less than obstructive disease | 7/70 | (10.0%) | 2.67 | (1.09-6.54) | 0.032 | 1.00 | Reference | | | 0.834 |
| In patients with obstructive or extensive obstructive disease | 18/91 | (19.8%) | 2.38 | (1.34-4.23) | 0.003 | 0.89 | (0.31-2.59) | | |
| Postoperative hypotension |  |  |  |  |  |  | | |  |  |
| In all patients | 28/236 | (11.9%) | 2.16 | (1.34-3.47) | 0.001 |  | |  | |  |
| In patients with less than obstructive disease | 10/106 | (9.4%) | 3.53 | (1.52-8.18) | 0.007 | 1.00 | Reference | | | 0.176 |
| In patients with obstructive or extensive obstructive disease | 18/129 | (14.0%) | 1.75 | (0.98-3.12) | 0.058 | 0.50 | (0.18-1.37) | | |

Abbreviations: CV, cardiovascular; aHR, adjusted hazard ratio; CI, confidence interval.