Supplemental Digital Content 1

Variable definitions

Age – the patient's age in years, calculated as the difference between their birthdate and the date of surgery and rounded down to the nearest year.

Requires assistance with Activities of Daily Living – patient requires assistance from **another person** with **any** of the following activities: dressing, eating, ambulating, toileting, hygiene**.** If a patient has suffered an acute injury leading to the need for surgery (e.g., hip fracture) the assessment for requirement of help for ADLs was based upon their condition prior to their acute injury.

Congestive heart failure – A physician diagnosis of a current or prior episode of congestive heart failure or prior radiographic evidence of vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema.

Coronary artery disease – A current or prior history of **any one** of the following:
i. angina
ii. myocardial infarction or acute coronary syndrome
iii. a segmental cardiac wall motion abnormality on echocardiography or a segmental fixed defect on radionuclide imaging
iv. a positive radionuclide exercise, echocardiographic exercise, or pharmacological cardiovascular stress test demonstrating cardiac ischemia
v. coronary angiographic or CT coronary angiographic evidence of atherosclerotic stenosis ≥50% of the diameter of any coronary artery
vi. ECG with pathological Q waves in two contiguous leads

Recent high risk coronary artery disease – Diagnosis ≤ 6 months prior to noncardiac surgery of: a myocardial infarction, acute coronary syndrome, Canadian Cardiovascular Society Class (CCSC) III angina or CCSC IV angina.
CCSC III angina – angina occurring with level walking of 1-2 blocks or climbing ≤ 1 flight of stairs at a normal pace
CCSC IV – inability to perform any physical activity without the development of angina

Cerebral vascular event – A physician diagnosis of stroke, CT or MRI evidence of a prior stroke, or physician diagnosis of a prior transient ischemic attack (TIA).

Peripheral vascular disease – A current or prior history of: physician diagnosed intermittent claudication, vascular surgery for atherosclerotic disease, an ankle/arm systolic blood pressure ratio ≤ 0.90 in either leg at rest, or angiographic or doppler study demonstrating ≥ 70% stenosis in a noncardiac artery.

Chronic Obstructive Pulmonary Disease (COPD) – If the chart or a physician has ever indicated that a patient has chronic bronchitis, we accepted this as a patient having COPD. If there is no mention of this but the patient reported they have had daily production of sputum for at least 3

months in 2 consecutive years then they were marked as having COPD. Likewise, if a physician has ever indicated that a patient has emphysema or if a patient's Pulmonary Function Tests (PFT) state fixed or irreversible airflow limitation and/or emphysema then they were marked as having COPD.

Diabetes requiring preoperative insulin – Patient states they have been diagnosed with diabetes or a physician has previously recorded that the patient has diabetes. This includes current gestational diabetes, but not past gestational diabetes that has resolved. The patient was also taking insulin prior to surgery.

Active cancer – the patient has a current diagnosis of cancer or is undergoing surgery for cancer.

History of atrial fibrillation – the patient has been diagnosed with atrial fibrillation by a physician.

Preoperative eGFR – Glomerular Filtration Rate estimated using the CKD-EPI equation using the most recent serum creatinine concentration measured before surgery.

Preoperative systolic blood pressure – most recent systolic blood pressure measured before induction of anesthesia.

Outcome definitions

Primary outcome

A composite outcome defined as any one of the following:

1. Death from any cause within 30 days of surgery.

2. MINS – any peak non-high sensitivity cardiac troponin T (cTnT) value $\geq$ 0.03 ng/mL resulting from myocardial ischemia (i.e. without evidence of a non-ischemic etiology) that occurred with the first 30 days after surgery.

3. Stroke within 30 days – a new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours.

Secondary outcomes

Intraoperative hypotension – systolic blood pressure (sBP) <90 mmHg for any duration for which intervention was initiated (including initiation or intensification of intravenous fluids, use of vasopressors or inotropes, blood transfusion, or intra-aortic balloon pump therapy) that occurred during surgery.

Postoperative hypotension – systolic blood pressure (sBP) <90 mmHg for any duration for which intervention was initiated (including initiation or intensification of intravenous fluids, use of vasopressors or inotropes, blood transfusion, or intra-aortic balloon pump therapy) that occurred during surgery during postoperative days 0 to 3.

Tracer outcomes

Intraoperative clinically significant bleeding – bleeding leading to transfusion of blood products during surgery.

Postoperative clinically significant bleeding – transfusion of blood products or reoperation for reasons of bleeding within 30 days after surgery.

Exploratory outcome

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:
i. ischemic signs or symptoms (i.e., chest, arm, neck or jaw discomfort; shortness of breath; pulmonary edema), **OR**
ii. development of pathologic Q waves present in any two contiguous leads that are ≥ 30 milliseconds, **OR**
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**
iv. coronary artery intervention (i.e., PCI or CABG surgery), **OR**
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.

Type of surgery performed

If patient underwent more than one surgery, all performed surgeries were included. If patients underwent any of the major surgical procedures, they were not classified as undergoing a 'low risk surgery'.

Major Vascular Surgery
1. Thoracic aorta reconstructive vascular surgeries (thoracic aortic aneurysm repair, repair of supra-aortic trunks not requiring total cardiopulmonary bypass, thoracoabdominal aortic aneurism repair with or without aorto-femoral bypass)
2. Aorto-iliac reconstructive vascular surgery (open abdominal aortic aneurysm repair, aorto-femoral bypass, iliac-femoral bypass, renal artery revascularization, celiac artery revascularization, superior mesenteric artery revascularization)
3. Peripheral vascular reconstruction without aortic cross-clamping (axillo-femoral bypass, femoral-femoral bypass, femoro-infragenicular bypass, profundoplasty, or other angioplasties of the infrainguinal arteries)
4. Extracranial cerebrovascular surgery (carotid endarterectomy, carotid-subclavian bypass)
5. EVAR – endovascular abdominal aortic aneurysm repair

Major General Surgery
1. Complex visceral resection (surgery involving the liver, esophagus, pancreas, or multiple organs)
2. Partial or total colectomy or stomach surgery
3. Other intra-abdominal surgery (gallbladder, appendix, adrenals, spleen, regional lymph node dissection)
4. Major head and neck resection for non-thyroid tumor

Thoracic Surgery
1. Pneumonectomy
2. Lobectomy
3. Other thoracic (wedge resection of lung, resection of mediastinal tumor, major chest wall resection)

Major Urogenital Surgery
1. Visceral resection (nephrectomy, ureterectomy, bladder resection, retroperitoneal tumor resection, exenteration [i.e. radical procedure for cancer to remove pelvic organs])
2. Cytoreductive surgery "debulking" done when cancer has spread in the pelvic/abdominal area, to remove as much of the tumor as possible
3. Radical hysterectomy is surgery to remove the uterus, cervix and part of the vagina
4. Hysterectomy is surgery to remove the uterus and usually the cervix
5. Radical prostatectomy is surgery to remove entire prostate gland and surrounding tissue
6. Transurethral prostatectomy to remove overgrowth of prostate tissue

Major Orthopedic Surgery
1. Major hip or pelvic surgery (hemi or total hip arthroplasty, internal fixation of hip, pelvic arthroplasty)
2. Internal fixation of femur
3. Knee arthroplasty
4. Above knee amputations
5. Lower leg amputation (amputation below knee but above foot)

Major Neurosurgery
1. Craniotomy
2. Major spine surgery is surgery involving multiple levels of the spine.

Low Risk Surgeries (parathyroid, thyroid, breast, hernia, local anorectal procedure, oopherectomy, salpingectomy, endometrial ablation, peripheral nerve surgery, ophthalmology, ears/nose/throat surgery, vertebral disc surgery, hand surgery, cosmetic surgery, arterio-venous access surgery for dialysis, other surgeries).

Urgent or emergency surgeries: surgeries performed within 72 hours of acute event that led to need for surgery.

Table S1. Full cohort characteristics.

	All patients				Only patients who took ACEi/ARB at baseline			
Patient characteristics	**Overall**	**No death or primary vascular event**	**Death or primary vascular event**	**p-value**	**ACEi/ARB at baseline**	**ACEi/ARB continued preop.**	**ACEi/ARB withheld preop.**	**p-value**
N	14687	13278	1409	--	4802	3557	1245	--
Demographics								
Age, y				<0.001				0.22
45-64	7490 (51.0%)	7077 (53.3%)	413 (29.3%)		1708 (35.6%)	1270 (35.7%)	438 (35.2%)	
65-79	5395 (36.7%)	4839 (36.4%)	556 (39.5%)		2282 (47.5%)	1705 (47.9%)	577 (46.3%)	
≥80	1802 (12.3%)	1362 (10.3%)	440 (31.2%)		812 (16.9%)	582 (16.4%)	230 (18.5%)	
Women	7570 (51.5%)	6948 (52.3%)	622 (44.1%)	<0.001	2398 (49.9%)	1804 (50.7%)	594 (47.7%)	0.07
Clinical characteristics								
Preop. systolic BP, mmHg				<0.001				0.001
<111	1500 (10.2%)	1351 (10.2%)	149 (10.6%)		337 (7.0%)	239 (6.7%)	98 (7.9%)	
111-120	1815 (12.4%)	1685 (12.7%)	130 (9.2%)		474 (9.9%)	350 (9.8%)	124 (10.0%)	
121-140	4896 (33.3%)	4491 (33.8%)	405 (28.7%)		1553 (32.3%)	1139 (32.0%)	414 (33.3%)	
141-160	3898 (26.5%)	3510 (26.4%)	388 (27.5%)		1372 (28.6%)	995 (28.0%)	377 (30.3%)	
161-180	1761 (12.0%)	1551 (11.7%)	210 (14.9%)		700 (14.6%)	530 (14.9%)	170 (13.7%)	
>180	817 (5.6%)	690 (5.2%)	127 (9.0%)		366 (7.6%)	304 (8.5%)	62 (5.0%)	
Preop. eGFR, mL/min/1.73m^2				<0.001				0.22
<15 or dialysis	230 (1.6%)	84 (0.6%)	146 (10.4%)		82 (1.7%)	56 (1.6%)	26 (2.1%)	
15-29	259 (1.8%)	149 (1.1%)	110 (7.8%)		126 (2.6%)	82 (2.3%)	44 (3.5%)	
30-44	751 (5.1%)	564 (4.2%)	187 (13.3%)		400 (8.3%)	294 (8.3%)	106 (8.5%)	
45-59	1502 (10.2%)	1286 (9.7%)	216 (15.3%)		706 (14.7%)	524 (14.7%)	182 (14.6%)	
60-89	6525 (44.4%)	6025 (45.4%)	500 (35.5%)		2252 (46.9%)	1689 (47.5%)	563 (45.2%)	
90-109	4782 (32.6%)	4566 (34.4%)	216 (15.3%)		1134 (23.6%)	834 (23.4%)	300 (24.1%)	
≥110	638 (4.3%)	604 (4.5%)	34 (2.4%)		102 (2.1%)	78 (2.2%)	24 (1.9%)	
Body Mass Index, kg/m^2				<0.001				0.67
<18	460 (3.1%)	365 (2.7%)	95 (6.7%)		74 (1.5%)	55 (1.5%)	19 (1.5%)	
18-24.9	5374 (36.6%)	4769 (35.9%)	605 (42.9%)		1293 (26.9%)	964 (27.1%)	329 (26.4%)	
25-29.9	5015 (34.1%)	4590 (34.6%)	425 (30.2%)		1698 (35.4%)	1248 (35.1%)	450 (36.1%)	
30-39.9	3343 (22.8%)	3093 (23.3%)	250 (17.7%)		1481 (30.8%)	1091 (30.7%)	390 (31.3%)	
≥40	495 (3.4%)	461 (3.5%)	34 (2.4%)		256 (5.3%)	199 (5.6%)	57 (4.6%)	
Requires assistance with ADLs	822 (5.6%)	573 (4.3%)	249 (17.7%)	<0.001	315 (6.6%)	222 (6.2%)	93 (7.5%)	0.13
History of COPD	1233 (8.4%)	1021 (7.7%)	212 (15.0%)	<0.001	510 (10.6%)	375 (10.5%)	135 (10.8%)	0.77
History of CHF	681 (4.6%)	487 (3.7%)	194 (13.8%)	<0.001	405 (8.4%)	297 (8.3%)	108 (8.7%)	0.72
History of CAD				<0.001				0.17
No CAD	12915 (87.9%)	11864 (89.4%)	1051 (74.6%)		3723 (77.5%)	2780 (78.2%)	943 (75.7%)	
Not recent high risk	1599 (10.9%)	1301 (9.8%)	298 (21.1%)		969 (20.2%)	695 (19.5%)	274 (22.0%)	
Recent high risk CAD	173 (1.2%)	113 (0.9%)	60 (4.3%)		110 (2.3%)	82 (2.3%)	28 (2.2%)	
History of CVE	1066 (7.3%)	819 (6.2%)	247 (17.5%)	<0.001	528 (11.0%)	399 (11.2%)	129 (10.4%)	0.41
History of PVD	776 (5.3%)	556 (4.2%)	220 (15.6%)	<0.001	432 (9.0%)	327 (9.2%)	105 (8.4%)	0.42
History of AF	968 (6.6%)	749 (5.6%)	219 (15.5%)	<0.001	500 (10.4%)	369 (10.4%)	131 (10.5%)	0.88
History of diabetes				<0.001				0.37
No diabetes	11827 (80.5%)	10859 (81.8%)	968 (68.7%)		3147 (65.5%)	2315 (65.1%)	832 (66.8%)	
No preop. insulin	1505 (10.2%)	1339 (10.1%)	166 (11.8%)		872 (18.2%)	662 (18.6%)	210 (16.9%)	
Preop. insulin	1355 (9.2%)	1080 (8.1%)	275 (19.5%)		783 (16.3%)	580 (16.3%)	203 (16.3%)	
Active cancer	3904 (26.6%)	3521 (26.5%)	383 (27.2%)	0.59	1194 (24.9%)	906 (25.5%)	288 (23.1%)	0.10

Patient characteristics	Overall	No death or primary vascular event	Death or primary vascular event	p-value	ACEi/ARB at baseline	ACEi/ARB continued preop.	ACEi/ARB withheld preop.	p-value
Preoperative medications								
All preop. antihypertensives								
Any taken at baseline	6856 (46.7%)	5975 (45.0%)	881 (62.5%)	<0.001	--	--	--	--
Any held on day of surgery	1794 (26.2%)	1539 (25.8%)	255 (28.9%)	0.05	--	--	--	--
Any started on day of surgery	110 (1.4%)	94 (1.3%)	16 (3.0%)	0.001	--	--	--	--
ACEi/ARB preop.								
Taken at baseline	4802 (32.7%)	4193 (31.6%)	609 (43.2%)	<0.001	--	--	--	--
Held on day of surgery	1245 (25.9%)	1095 (26.1%)	150 (24.6%)	0.43	--	--	--	--
Started on day of surgery	82 (0.8%)	70 (0.8%)	12 (1.5%)	0.03	--	--	--	--
Beta-blocker preop.								
Taken at baseline	2512 (17.1%)	2127 (16.0%)	385 (27.3%)	<0.001	1316 (27.4%)	985 (27.7%)	331 (26.6%)	0.45
Held on day of surgery	405 (16.1%)	333 (15.7%)	72 (18.7%)	0.13	199 (15.1%)	55 (5.6%)	144 (43.5%)	<0.001
Started on day of surgery	38 (0.3%)	31 (0.3%)	7 (0.7%)	0.03	19 (0.4%)	10 (0.3%)	9 (0.7%)	0.04
Rate controlling CCB preop.								
Taken at baseline	484 (3.3%)	407 (3.1%)	77 (5.5%)	<0.001	253 (5.3%)	194 (5.5%)	59 (4.7%)	0.33
Held on day of surgery	102 (21.1%)	84 (20.6%)	18 (23.4%)	0.59	50 (19.8%)	23 (11.9%)	27 (45.8%)	<0.001
Started on day of surgery	5 (<0.1%)	3 (<0.1%)	2 (0.2%)	0.02	4 (0.1%)	4 (0.1%)	0 (0.0%)	0.23
Dihydropyridine CCB preop.								
Taken at baseline	2020 (13.8%)	1739 (13.1%)	281 (19.9%)	<0.001	1096 (22.8%)	803 (22.6%)	293 (23.5%)	0.49
Held on day of surgery	382 (18.9%)	315 (18.1%)	67 (23.8%)	0.02	221 (20.2%)	66 (8.2%)	155 (52.9%)	<0.001
Started on day of surgery	70 (0.6%)	56 (0.5%)	14 (1.2%)	0.001	30 (0.6%)	20 (0.6%)	10 (0.8%)	0.34
Alpha-2 agonist preop.								
Taken at baseline	88 (0.6%)	70 (0.5%)	18 (1.3%)	<0.001	39 (0.8%)	32 (0.9%)	7 (0.6%)	0.25
Held on day of surgery	19 (22%)	16 (23%)	3 (17%)	0.57	6 (15.4%)	2 (6.3%)	4 (57.1%)	<0.001
Started on day of surgery	12 (0.1%)	12 (0.1%)	0 (0.0%)	0.26	6 (0.1%)	5 (0.1%)	1 (0.1%)	0.60
Long-acting nitrate preop.								
Taken at baseline	358 (2.4%)	272 (2.0%)	86 (6.1%)	<0.001	202 (4.2%)	152 (4.3%)	50 (4.0%)	0.70
Held on day of surgery	67 (18.7%)	48 (17.6%)	19 (22.1%)	0.36	29 (14.4%)	10 (6.6%)	19 (38.0%)	<0.001
Started on day of surgery	11 (<0.1%)	7 (<0.1%)	4 (0.3%)	0.002	5 (0.1%)	3 (0.1%)	2 (0.2%)	0.47
ASA preop.								
Taken at baseline	2149 (14.6%)	1817 (13.7%)	332 (23.6%)	<0.001	1277 (26.6%)	906 (25.5%)	371 (29.8%)	0.003
Held on day of surgery	1320 (61.4%)	1139 (62.7%)	181 (54.5%)	0.01	802 (62.8%)	496 (54.7%)	306 (82.5%)	<0.001
Started on day of surgery	23 (0.2%)	20 (0.2%)	3 (0.3%)	0.45	11 (0.2%)	9 (0.3%)	2 (0.2%)	0.61
Ticlopidine/clopidogrel preop.								
Taken at baseline	244 (1.7%)	193 (1.5%)	51 (3.6%)	<0.001	159 (3.3%)	108 (3.0%)	51 (4.1%)	0.07
Held on day of surgery	180 (73.8%)	145 (75.1%)	35 (68.6%)	0.35	115 (72.3%)	70 (64.8%)	45 (88.2%)	0.002
Started on day of surgery	3 (<0.1%)	2 (<0.1%)	1 (<0.1%)	0.16	3 (<0.1%)	2 (0.1%)	1 (0.1%)	0.76
OAC preop.								
Taken at baseline	494 (3.4%)	405 (3.1%)	89 (6.3%)	<0.001	273 (5.7%)	183 (5.1%)	90 (7.2%)	0.01
Held on day of surgery	469 (94.9%)	390 (96.3%)	79 (88.8%)	0.003	260 (95.2%)	172 (94.0%)	88 (97.8%)	0.17
Started on day of surgery	3 (<0.1%)	3 (<0.1%)	0 (0.0%)	0.58	2 (<0.1%)	2 (<0.1%)	0 (0.0%)	0.41
Prophylactic subc antithrombotic preop.								
Taken at baseline	1263 (8.6%)	992 (7.5%)	271 (19.2%)	<0.001	515 (10.7%)	378 (10.6%)	137 (11.0%)	0.71
Held on day of surgery	481 (38.1%)	351 (35.4%)	130 (48.0%)	<0.001	210 (40.8%)	151 (39.9%)	59 (43.1%)	0.52
Started on day of surgery	1801 (13.4%)	1643 (13.4%)	158 (13.9%)	0.63	682 (14.2%)	513 (14.4%)	169 (13.6%)	0.49
Therapeutic subc/IV antithrombotic preop.								

Patient characteristics	Overall	No death or primary vascular event	Death or primary vascular event	p-value	ACEi/ARB at baseline	ACEi/ARB continued preop.	ACEi/ARB withheld preop.	p-value
Taken at baseline	187 (1.3%)	139 (1.0%)	48 (3.4%)	<0.001	92 (1.9%)	65 (1.8%)	27 (2.2%)	0.45
Held on day of surgery	85 (45.5%)	67 (48.2%)	18 (37.5%)	0.20	42 (45.7%)	29 (44.6%)	13 (48.1%)	0.76
Started on day of surgery	61 (0.4%)	48 (0.4%)	13 (1.0%)	0.001	26 (0.5%)	20 (0.6%)	6 (0.5%)	0.75
Statin preop.								
Taken at baseline	3549 (24.2%)	3125 (23.5%)	424 (30.1%)	<0.001	2117 (44.1%)	1543 (43.4%)	574 (46.1%)	0.10
Held on day of surgery	1028 (29.0%)	905 (29.0%)	123 (29.0%)	0.98	611 (28.9%)	283 (18.3%)	328 (57.1%)	<0.001
Started on day of surgery	22 (0.2%)	20 (0.2%)	2 (0.2%)	0.97	10 (0.2%)	7 (0.2%)	3 (0.2%)	0.71
Type of surgery								
Major general surgery	2975 (20.3%)	2644 (19.9%)	331 (23.5%)	0.001	831 (17.3%)	585 (16.4%)	246 (19.8%)	0.01
Major thoracic surgery	364 (2.5%)	324 (2.4%)	40 (2.8%)	0.36	102 (2.1%)	84 (2.4%)	18 (1.4%)	0.05
Major urogenital surgery	1813 (12.3%)	1680 (12.7%)	133 (9.4%)	<0.001	557 (11.6%)	435 (12.2%)	122 (9.8%)	0.02
Major vascular surgery	479 (3.3%)	376 (2.8%)	103 (7.3%)	<0.001	270 (5.6%)	212 (6.0%)	58 (4.7%)	0.09
Major neurosurgery	874 (6.0%)	779 (5.9%)	95 (6.7%)	0.19	273 (5.7%)	209 (5.9%)	64 (5.1%)	0.33
Major orthopedic surgery	2968 (20.2%)	2564 (19.3%)	404 (28.7%)	<0.001	1268 (26.4%)	930 (26.1%)	338 (27.1%)	0.49
Low risk surgery	5341 (36.4%)	5025 (37.8%)	316 (22.4%)	<0.001	1536 (32.0%)	1129 (31.7%)	407 (32.7%)	0.54
Urgent/emergent surgery	2090 (14.2%)	1696 (12.8%)	394 (28.0%)	<0.001	602 (12.5%)	422 (11.9%)	180 (14.5%)	0.02
Primary outcome and components								
Death, MINS, or stroke	1409 (9.6%)	--	--	--	609 (12.7%)	459 (12.9%)	150 (12.0%)	0.43
Death from any cause	302 (2.1%)	--	--	--	99 (2.1%)	74 (2.1%)	25 (2.0%)	0.88
MINS	1160 (7.9%)	--	--	--	531 (11.1%)	399 (11.3%)	132 (10.6%)	0.52
Stroke	90 (0.6%)	--	--	--	34 (0.7%)	26 (0.7%)	8 (0.6%)	0.75
Exploratory outcomes								
Death, MI, or stroke	745 (5.1%)	†27 (0.2%)	718 (51.0%)	<0.001	299 (6.2%)	221 (6.2%)	78 (6.3%)	0.95
MI	446 (3.0%)	†27 (0.2%)	419 (29.7%)	<0.001	205 (4.3%)	148 (4.2%)	57 (4.6%)	0.53
Hypotension								
Intraoperative hypotension	4162 (28.3%)	3698 (27.9%)	464 (32.9%)	<0.001	1307 (27.2%)	1017 (28.6%)	290 (23.3%)	<0.001
Postoperative hypotension	2728 (18.6%)	2289 (17.2%)	439 (31.2%)	<0.001	961 (20.0%)	719 (20.2%)	242 (19.4%)	0.56

Denominators for medication proportions vary: for patients who took the medication at baseline (1-7 day before surgery), the denominator includes all patients; for patients who had their medication withheld on the day of surgery, the denominator includes only patients who were taking the medication at baseline; for patients who started the medication on the day of surgery, the denominator includes only patients who were not taking the medication at baseline. Column totals comprise the denominator for all other proportions. Continuous factors are categorized here for simplicity of presentation but were kept continuous in all analyses. P-values are two-sided and based on a Pearson Chi-square statistic.

†27 patients who experienced MI were not captured by MINS. They qualified for MI based on development of new pathological Q waves on an ECG when troponin levels were not obtained or were obtained at times that could have missed the clinical event.

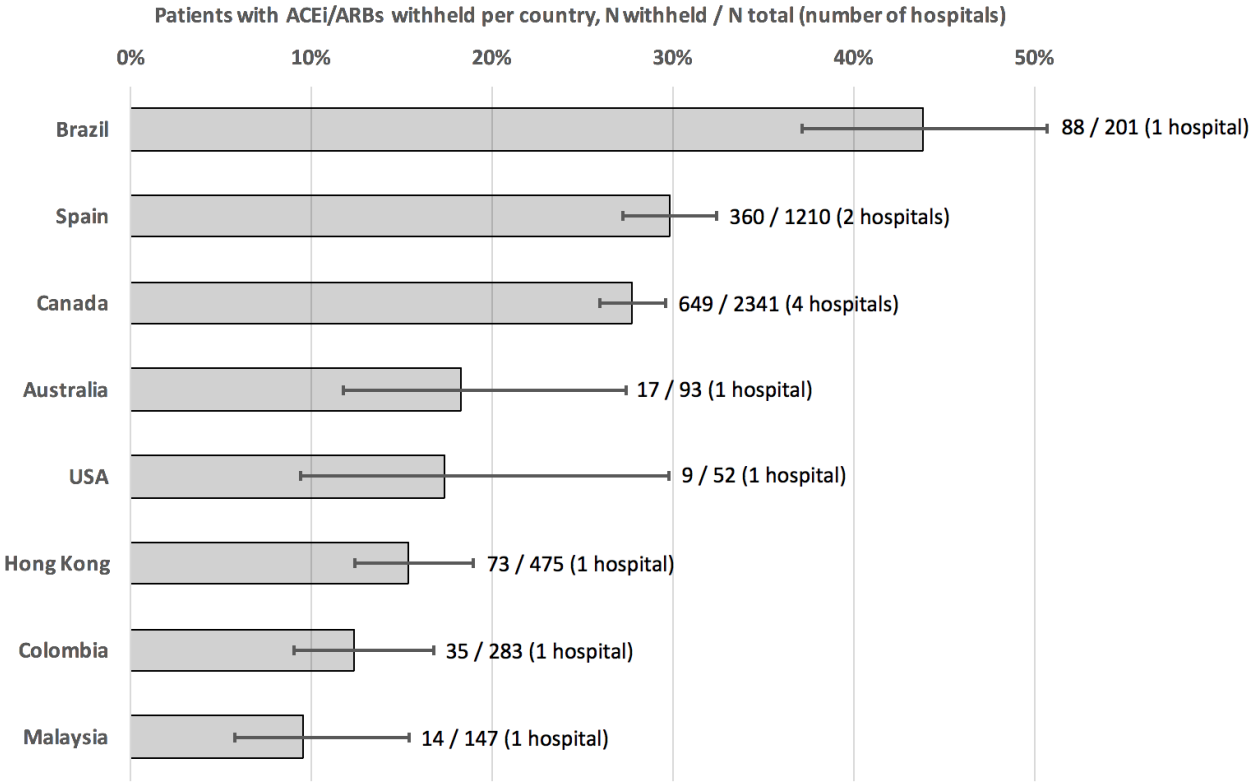
Abbreviations: MINS, myocardial injury after noncardiac surgery; MI, myocardial infarction; ADL, activities of daily living; CAD, coronary artery disease; CVE, cerebrovascular event; PVD, peripheral vascular disease; CHF, congestive heart failure; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate, ASA, acetylsalicylic acid; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; OAC, oral anticoagulant; subc, subcutaneous; IV, intravenous.

Table S2. Characteristics of excluded patients compared to included patients.

	All patients			Only patients who took ACEi/ARB at baseline		
Patient characteristics	**Included**	**Excluded**	**p-value**	**Included**	**Excluded**	**p-value**
N	14687	1392	--	4802	401	--
Demographics						
Age, y, mean (SD)	64.8 (11.8)	64.8 (12.3)	0.77	68.8 (10.8)	68.8 (10.8)	0.96
Women	7570 (51.5%)	746 (53.6%)	0.14	2398 (49.9%)	202 (50.4%)	0.87
Preoperative characteristics						
ACEi/ARB withheld	--	--	--	1245 (25.9%)	96 (23.9%)	0.38
Preop. systolic BP, mmHg, mean (SD)	139.7 (23.7)	140.0 (24.3)	0.63	143.9 (24.0)	143.7 (25.8)	0.85
Preop. eGFR, mL/min/1.73m^2, mean (SD)	79.0 (22.7)	77.3 (24.1)	0.01	72.5 (22.9)	70.5 (24.3)	0.09
BMI, kg/m^2, mean (SD)	27.1 (6.0)	26.6 (6.1)	0.002	28.8 (6.3)	28.7 (6.8)	0.81
Requires assistance with ADLs	822 (5.6%)	110 (7.9%)	<0.001	315 (6.6%)	25 (6.2%)	0.80
History of COPD	1233 (8.4%)	104 (7.5%)	0.23	510 (10.6%)	47 (11.7%)	0.49
History of CHF	681 (4.6%)	80 (5.7%)	0.06	405 (8.4%)	35 (8.7%)	0.84
History of CAD			0.86			0.90
No CAD	12915 (87.9%)	1217 (87.4%)		3723 (77.5%)	307 (76.6%)	
Not recent high risk	1599 (10.9%)	158 (11.4%)		969 (20.2%)	84 (20.9%)	
Recent high risk CAD	173 (1.2%)	17 (1.2%)		110 (2.3%)	10 (2.5%)	
History of CVE	1066 (7.3%)	107 (7.7%)	0.56	528 (11.0%)	50 (12.5%)	0.37
History of PVD	776 (5.3%)	82 (5.9%)	0.34	432 (9.0%)	37 (9.2%)	0.88
History of AF	968 (6.6%)	91 (6.5%)	0.94	500 (10.4%)	38 (9.5%)	0.55
History of diabetes			0.08			0.01
No diabetes	11827 (80.5%)	1099 (79.0%)		3147 (65.5%)	241 (60.1%)	
No preop. insulin	1505 (10.2%)	139 (10.0%)		872 (18.2%)	70 (17.5%)	
Preop. insulin	1355 (9.2%)	154 (11.1%)		783 (16.3%)	90 (22.4%)	
Active cancer	3904 (26.6%)	319 (22.9%)	0.003	1194 (24.9%)	78 (19.5%)	0.02
Type of surgery						
Major general surgery	2975 (20.3%)	235 (16.9%)	0.003	831 (17.3%)	63 (15.7%)	0.42
Major thoracic surgery	364 (2.5%)	34 (2.4%)	0.93	102 (2.1%)	6 (1.5%)	0.40
Major urogenital surgery	1813 (12.3%)	165 (11.9%)	0.59	557 (11.6%)	56 (14.0%)	0.16
Major vascular surgery	479 (3.3%)	42 (3.0%)	0.62	270 (5.6%)	21 (5.2%)	0.75
Major neurosurgery	874 (6.0%)	56 (4.0%)	0.003	273 (5.7%)	12 (3.0%)	0.02
Major orthopedic surgery	2968 (20.2%)	298 (21.4%)	0.29	1268 (26.4%)	115 (28.7%)	0.32
Low risk surgery	5341 (36.4%)	575 (41.3%)	<0.001	1536 (32.0%)	130 (32.4%)	0.86
Urgent/emergent surgery	2090 (14.2%)	223 (16.0%)	0.07	602 (12.5%)	51 (12.7%)	0.92
Postoperative outcomes						
Death within 30d postop	302 (2.1%)	13 (0.9%)	0.004	99 (2.1%)	4 (1.0%)	0.14
Stroke within 30d postop.	90 (0.6%)	2 (0.1%)	0.03	34 (0.7%)	0 (0.0%)	0.09
MI within 30d postop.	446 (3.0%)	38 (2.7%)	0.52	205 (4.3%)	9 (2.2%)	0.05
Intraoperative hypotension	4162 (28.3%)	438 (31.5%)	0.01	1307 (27.2%)	120 (29.9%)	0.24

P-values are two-sided and based on Pearson Chi-square tests for proportions and t-tests for continuous variables. Column totals comprise the denominator for all proportions. Data on MINS, postoperative hypotension, and preoperative medications (other than ACEi/ARBs) are not shown because their absence was the reason for exclusion. Abbreviations: MINS, myocardial injury after noncardiac surgery; MI, myocardial infarction; ADL, activities of daily living; CAD, coronary artery disease; CVE, cerebrovascular event; PVD, peripheral vascular disease; CHF, congestive heart failure; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate, ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure.

Figure S1. The percentage of patients who had their ACEi/ARBs withheld preoperatively in study hospitals in each country.



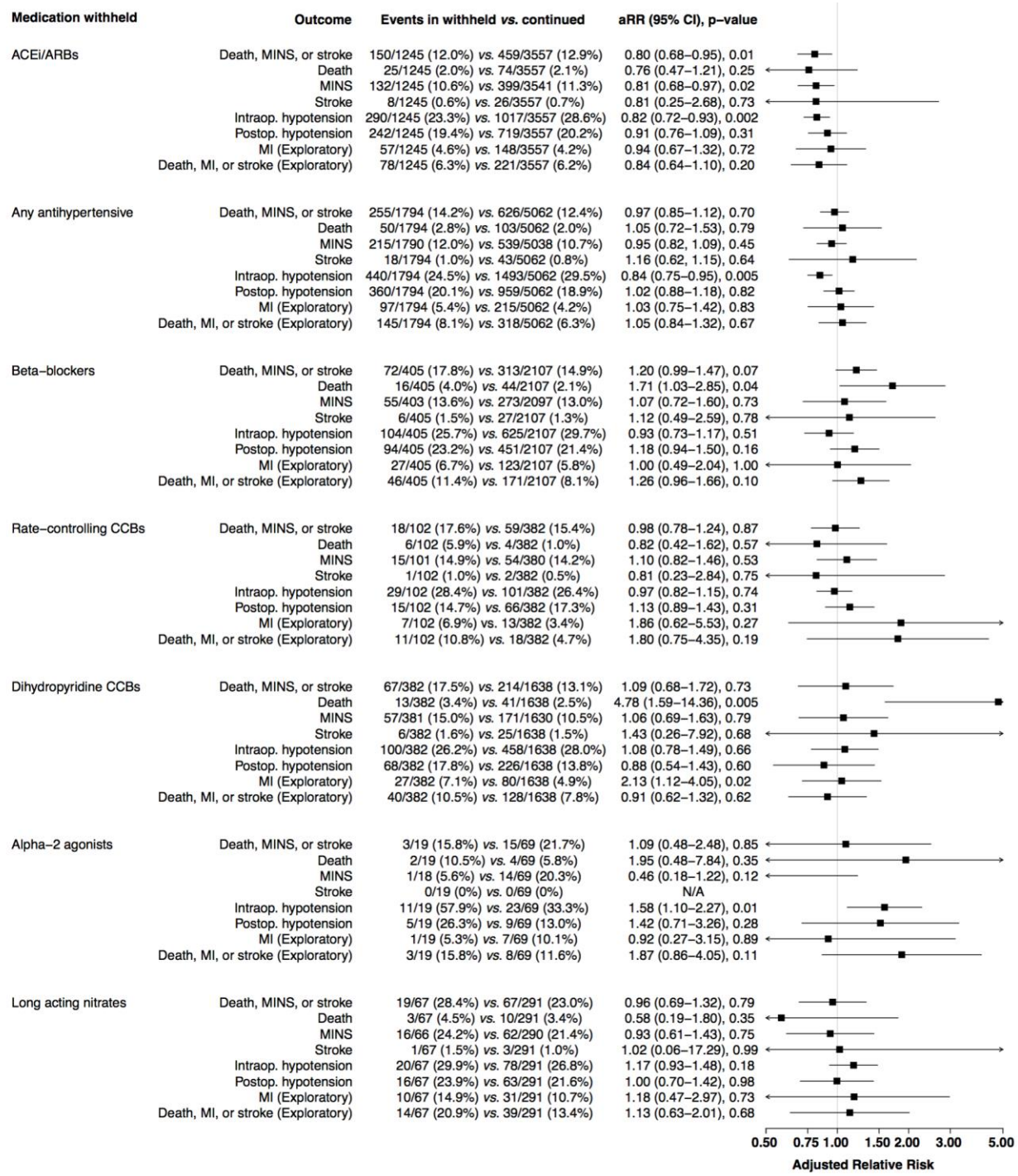
Error bars represent 95% confidence intervals. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table S3. Preoperative management of antihypertensive medications at different levels of preoperative systolic blood pressure.

	Preoperative systolic blood pressure, mmHg							
	Overall	<111	111-120	121-140	141-160	161-180	>180	Chi-sq p-value
All preop antihypertensives								
Any taken at baseline	6856 (46.7%)	499 (33.3%)	666 (36.7%)	2147 (43.9%)	1999 (51.3%)	1029 (58.4%)	516 (63.2%)	<0.001
Any held on day of surgery	1794 (26.2%)	139 (27.9%)	178 (26.7%)	578 (26.9%)	537 (26.9%)	262 (25.5%)	100 (19.4%)	0.012
Any started on day of surgery	110 (1.4%)	10 (1.0%)	5 (0.4%)	22 (0.8%)	35 (1.8%)	26 (3.6%)	12 (4.0%)	<0.001
ACEi/ARB preop								
Taken at baseline	4802 (32.7%)	337 (22.5%)	474 (26.1%)	1553 (31.7%)	1372 (35.2%)	700 (39.8%)	366 (44.8%)	<0.001
Held on day of surgery	1245 (25.9%)	98 (29.1%)	124 (26.2%)	414 (26.7%)	377 (27.5%)	170 (24.3%)	62 (16.9%)	0.001
Started on day of surgery	82 (0.8%)	6 (0.5%)	2 (0.1%)	16 (0.5%)	29 (1.1%)	20 (1.9%)	9 (2.0%)	<0.001
Beta-blocker preop								
Taken at baseline	2512 (17.1%)	205 (13.7%)	239 (13.2%)	765 (15.6%)	686 (17.6%)	388 (22.0%)	229 (28.0%)	<0.001
Held on day of surgery	405 (16.1%)	26 (12.7%)	45 (18.8%)	124 (16.2%)	123 (17.9%)	56 (14.4%)	31 (13.5%)	0.24
Started on day of surgery	38 (0.3%)	3 (0.2%)	3 (0.2%)	11 (0.3%)	12 (0.4%)	5 (0.4%)	4 (0.7%)	0.50
Rate controlling CCB preop								
Taken at baseline	484 (3.3%)	32 (2.1%)	46 (2.5%)	137 (2.8%)	133 (3.4%)	93 (5.3%)	43 (5.3%)	<0.001
Held on day of surgery	102 (21.1%)	8 (25.0%)	11 (23.9%)	28 (20.4%)	31 (23.3%)	19 (20.4%)	5 (11.6%)	0.66
Started on day of surgery	5 (<0.1%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)	1 (<0.1%)	1 (0.1%)	2 (0.3%)	0.026
Dihydropyridine CCB preop								
Taken at baseline	2020 (13.8%)	108 (7.2%)	162 (8.9%)	600 (12.3%)	658 (16.9%)	350 (19.9%)	142 (17.4%)	<0.001
Held on day of surgery	382 (18.9%)	24 (22.2%)	34 (21.0%)	114 (19.0%)	126 (19.1%)	58 (16.6%)	26 (18.3%)	0.77
Started on day of surgery	70 (0.6%)	3 (0.2%)	7 (0.4%)	17 (0.4%)	20 (0.6%)	14 (1.0%)	9 (1.3%)	0.003
Alpha-2 agonist preop								
Taken at baseline	88 (0.6%)	7 (0.5%)	6 (0.3%)	27 (0.6%)	27 (0.7%)	11 (0.6%)	10 (1.2%)	0.12
Held on day of surgery	19 (22%)	2 (29%)	2 (33%)	10 (37%)	4 (15%)	0 (0%)	1 (10%)	0.11
Started on day of surgery	12 (0.1%)	2 (0.1%)	1 (0.1%)	3 (0.1%)	2 (0.1%)	3 (0.2%)	1 (0.1%)	0.67
Long-acting nitrate preop								
Taken at baseline	358 (2.4%)	32 (2.1%)	46 (2.5%)	99 (2.0%)	102 (2.6%)	53 (3.0%)	26 (3.2%)	0.11
Held on day of surgery	67 (18.7%)	6 (18.8%)	14 (30.4%)	17 (17.2%)	16 (15.7%)	10 (18.9%)	4 (15.4%)	0.40
Started on day of surgery	11 (0.1%)	1 (0.1%)	3 (0.2%)	3 (0.1%)	1 (<1%)	1 (0.1%)	2 (0.3%)	0.25

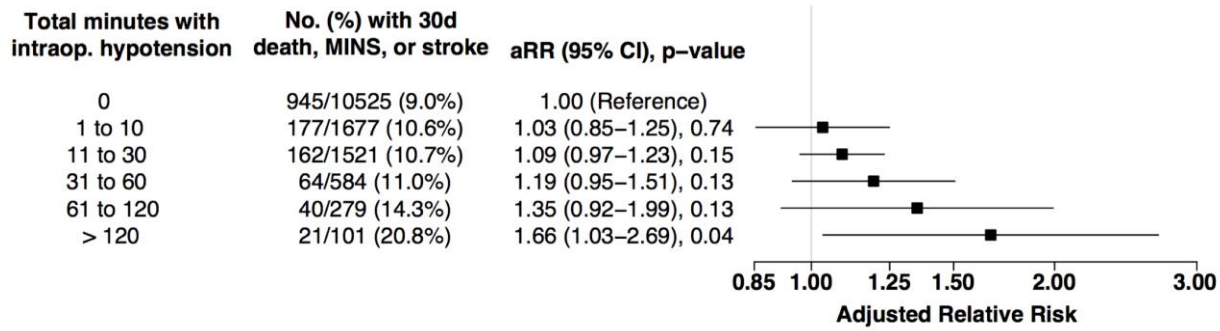
Denominators for medication proportions vary: for patients who took the medication at baseline (1-7 day before surgery), the denominator includes all patients; for patients who had their medication withheld on the day of surgery, the denominator includes only patients who were taking the medication at baseline; for patients who started the medication on the day of surgery, the denominator includes only patients who were not taking the medication at baseline. eGFR was calculated using the CKD-Epi equation. Column totals comprise the denominator for all other proportions. Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

Figure S2. Results for all antihypertensive medications in full dataset (n=14,687).



Abbreviations: MINS, myocardial injury after noncardiac surgery; MI, myocardial infarction; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; aRR, adjusted relative risk; CI, confidence interval.

Figure S3. Exploratory assessment of the relationship between the total duration of intraoperative hypotension and the primary outcome of 30 day death, MINS, or stroke (n=14,687). Test for trend p<0.001.



Abbreviations: MINS, myocardial injury after noncardiac surgery; aRR, adjusted relative risk; CI, confidence interval.

Table S4. Sensitivity analysis of prespecified outcomes using logistic regression.

Outcome	Adjusted Odds Ratio	95% Confidence Interval	p-value
ACEi/ARBs withheld versus continued (n=4802)			
Death, MINS, or stroke*	0.80	0.64-0.998	0.048
Death[†]	0.69	0.36-1.31	0.26
MINS[‡]	0.83	0.65-1.06	0.13
Stroke[§]	0.80	0.28-2.30	0.68
Intraoperative hypotension[¥]	0.73	0.64-0.84	<0.001
Postoperative hypotension[◊]	0.89	0.70-1.14	0.37
Intraoperative hypotension versus no intraoperative hypotension (n=14687)			
Death, MINS, or stroke[€]	1.18	0.99-1.39	0.06
Death[∂]	1.53	1.11-2.09	0.01
MINS[π]	1.09	0.89-1.32	0.41
Stroke[Ω]	1.14	0.82-1.58	0.44
Postoperative hypotension	2.02	1.80-2.28	<0.001
Postoperative hypotension versus no postoperative hypotension (n=14687)			
Death, MINS, or stroke[€]	2.14	1.89-2.43	<0.001
Death[∂]	2.64	2.16-3.22	<0.001
MINS[π]	1.96	1.70-2.26	<0.001
Stroke[Ω]	1.76	0.65-4.80	0.27

Footnote: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MINS, myocardial injury after noncardiac surgery. For some analyses, the logistic regression procedure did not use all observations because there were no events in some groups: *19 observations not used; [†]303 not used; [‡]22 not used; [§]555 not used; [¥]8 not used; [◊]2 not used; [€]15 not used; [∂]56 not used; [π]15 not used; [Ω]218 not used.

Sensitivity analysis for relationship between hypotension and the primary outcome

In the full dataset, intraoperative bleeding occurred in 803 of 14687 patients (5.5%) and was associated with the primary composite outcome of 30-day MINS, stroke, and all-cause mortality (aRR, 1.58; 95% CI, 1.39-1.79; p<.001), with intraoperative hypotension (2.33; 2.05-2.66, <0.001) and with postoperative hypotension, (2.23; 1.87-2.69; <0.001). Significant bleeding within 30 days occurred in 2,588 patients (17.6%) and was also associated with the primary outcome in the full dataset (2.20; 1.94-2.50; <0.001). After adjusting for intraoperative bleeding, intraoperative hypotension was not associated with 30 day bleeding (1.07; 0.96-1.19; 0.25) but postoperative hypotension was (2.01; 1.80-2.24; <0.001). After adjusting for both intraoperative and 30 day bleeding, postoperative hypotension remained significantly associated with the composite of death or vascular events (1.40; 1.28-1.54; <0.001) and the relationship between intraoperative hypotension and this outcome became weaker but overall consistent with the main results (1.07; 0.93-1.23; 0.38). These findings suggest that some residual confounding affects the relationship between hypotension and the primary outcome, but the results remained qualitatively similar after adjusting for bleeding.