

SUPPLEMENTAL DIGITAL CONTENT

Supplemental Digital Content 1. Outcome definitions

	Outcome definition
Myocardial injury after noncardiac surgery	A typical rise of troponin or a typical fall of an elevated troponin detected at its peak post-surgery in a patient after surgery that was adjudicated as due to an ischemic etiology (i.e., no evidence of a non-ischemic etiology like pulmonary embolism, and sepsis).
Myocardial infarction (MI)	Myocardial infarction (MI) will be defined according to the Third Universal Definition of MI.
Vascular death	Vascular death is defined as any death with a vascular cause and includes those deaths following a myocardial infarction, cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention or coronary artery bypass graft surgery), pulmonary embolus, hemorrhage, or deaths due to an unknown cause.
Stroke	Stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours.
New clinically important atrial fibrillation	New clinically important atrial fibrillation is defined as new atrial fibrillation that results in angina, congestive heart failure, symptomatic hypotension, or that requires treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.
Non-fatal cardiac arrest	Non-fatal cardiac arrest is defined as successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.
Congestive heart failure	Congestive heart failure is defined at least one of the following clinical signs (i.e. any of the following signs: elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) and at least one of the following radiographic findings (i.e., vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).

Supplemental Digital Content 2. Baseline and operative characteristics according to GDF-15 categories

	Preoperative GDF-15 (pg/mL) n=5238			
	< 1000 n=1705	1000 to <1500 n=1332	1500 to <3000 n=1476	≥3000 n=725
Age – n (%), years				
45-64	1344 (78.8)	642 (48.2)	498 (33.7)	233 (32.1)
65-74	288 (16.9)	476 (35.7)	538 (36.4)	217 (29.9)
≥ 75	73 (4.3)	214 (16.1)	440 (29.8)	275 (37.9)
Males – n (%)	782 (45.9)	669 (50.2)	817 (55.4)	429 (59.2)
History of – n (%)				
Diabetes	144 (6.7)	195 (14.5)	374 (25.3)	298 (41.1)
Hypertension	675 (39.6)	737 (55.3)	967 (65.5)	522 (72.0)
Congestive heart failure	13 (0.8)	27 (2.0)	57 (3.9)	60 (8.3)
Coronary artery disease	115 (6.7)	179 (13.4)	313 (21.2)	205 (28.3)
Peripheral vascular disease	35 (2.1)	62 (4.7)	147 (10.0)	99 (13.7)
Cerebrovascular disease	42 (2.5)	76 (5.7)	134 (9.1)	91 (12.6)
Chronic pulmonary obstructive disease	69 (4.0)	96 (7.2)	188 (12.7)	106 (14.6)
Active cancer – n (%)	375 (22.0)	358 (26.9)	463 (31.4)	278 (38.3)
Preoperative estimated glomerular filtration rate* – n (%), ml/min				
> 60	1561 (91.6)	1151 (86.4)	1086 (73.6)	363 (50.1)
45-60	54 (3.2)	126 (9.5)	237 (16.1)	137 (18.9)
30-44	4 (0.2)	14 (1.1)	113 (7.7)	101 (13.9)
<30 or dialysis	7 (0.4)	9 (0.7)	20 (1.4)	102 (14.1)
Type of Surgery – n (%)				
Vascular	44 (2.6)	74 (5.6)	121 (8.2)	75 (10.3)
General	269 (15.8)	262 (19.7)	340 (23.0)	181 (25.0)
Thoracic	64 (3.8)	68 (5.1)	81 (5.5)	24 (3.3)
Major Urology/Gynecology	219 (12.8)	151 (11.3)	173 (11.7)	91 (12.6)
Major Orthopedics	532 (31.2)	410 (30.8)	410 (27.8)	164 (22.6)
Major Neurosurgery	192 (11.3)	106 (8.0)	107 (7.2)	38 (5.2)
Low risk surgeries	455 (26.7)	308 (23.1)	307 (20.8)	177 (24.4)
Urgent/emergent surgery – n (%)	47 (2.8)	35 (2.6)	47 (3.2)	38 (5.2)

Revised Cardiac Risk Index score – n (%)	1236 (72.5)	782 (58.7)	665 (45.1)	231 (31.9)
0	410 (24.0)	427 (32.1)	557 (37.7)	277 (38.2)
1	55 (3.2)	101 (7.6)	195 (13.2)	137 (18.9)
2	4 (0.2)	22 (1.7)	59 (4.0)	80 (11.0)
≥3				

GDF-15 = Growth differentiation factor 15.

Revised Cardiac Risk Index score includes the following risk factors, worth 1 point each: ischemic heart disease, congestive heart failure, preoperative insulin use, preoperative creatinine >2 mg/dL (177 μmol/L), cerebrovascular disease, and high-risk surgery (i.e., intrathoracic, intraperitoneal, and suprainguinal vascular).

Supplemental Digital Content 3. Risk reclassification table for the addition of GDF-15 to Revised Cardiac Risk Index using 25% relative change in predicted risk of myocardial injury after noncardiac surgery or vascular death at 30 days

	Patients with events n= 809/5238	Patients without events n= 4429/5238
Appropriate risk reclassification – n	301	1998
Inappropriate risk reclassification – n	131	1140
Proportion reclassification (%)	170/809 (21.0)	858/4429 (19.4)
Net Absolute Reclassification Index	196 per 1000 patients (19.6%)	

GDF-15 = Growth differentiation factor 15.

Predicted probability determined using logistic regression. A relative change in predicted probability of 25% is considered a significant change in risk prediction. For patients with events, a 25% relative increase in predicted probability was considered improved risk classification and a reduction in 25% relative reduction in predicted probability was considered worse risk reclassification.

Supplemental Digital Content 4. Reclassification table for the risk reclassification for the addition of preoperative GDF-15 to preoperative NT-proBNP and Revised Cardiac Risk Index to predict myocardial injury after noncardiac surgery or vascular death at 30 days (n=4246)

Patients with events n = 606/4246					
	Revised Cardiac Risk Index + NT-proBNP				
	Risk categories	<5%	5 to <15%	15 to <30%	≥30%
Revised Cardiac Risk Index + NT-proBNP + preop GDF-15	<5%	0	29	0	0
	5 to <15%	0	147	15	1
	15 to <30%	0	41	182	12
	≥30%	0	0	64	115
Proportion reclassification (%)	48/606 (7.9%)				
Patients without events N = 3640/4246					
	Revised Cardiac Risk Index + NT-proBNP				
	Risk categories	<5%	5 to <15%	15 to <30%	≥30%
Revised Cardiac Risk Index + NT-proBNP + preop GDF-15	<5%	0	759	0	0
	5 to <15%	0	1696	129	1
	15 to <30%	0	190	582	30
	≥30%	0	0	93	160
Proportion reclassification (%)	636/3640 (17.5%)				
Net Absolute Reclassification Index (%)	161/1000 (16.1%)				

Predicted probabilities determined using multivariable logistic regression.

Supplemental Digital Content 5. Preoperative GDF-15 and NT-proBNP in addition to Revised Cardiac Risk Index to predict MI and all-cause mortality at 30 days (n=4246)

	Adjusted Hazard Ratio (95% CI)
GDF-15 thresholds (pg/mL)	
<1000	-
1000 to <1500	1.63 (0.97-2.74)
1500 to <3000	2.47 (1.53-4.00)
≥3000	3.12 (1.85-5.3)
NT-proBNP (pg/mL)	
<100	-
100 to <200	1.17 (0.76-1.79)
200 to <1500	2.23 (1.57-3.17)
≥1500	2.56 (1.46-4.5)

C-statistic 0.744

CI = confidence interval; GDF-15 = Growth differentiation factor 15; MI = myocardial infarction; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Cox proportional hazard model adjusted for Revised Cardiac Risk Index.

Supplemental Digital Content 6. Risk of postoperative cardiac events and mortality according to elevated preoperative GDF-15 and NT-proBNP* (N=4246)

Preoperative concentrations		Myocardial injury after noncardiac surgery and vascular death N=606		MI and all-cause death (N=210)	
		N	% (95% CI)	N	% (95% CI)
No biomarker elevation	GDF-15 not elevated and NT-proBNP not elevated	145/2205	6.6 (5.6-7.7)	41/2205	1.9 (1.4-2.5)
Only one biomarker elevated	GDF-15 not elevated and NT-proBNP elevated	55/288	19.1 (14.9-23.9)	21/288	7.3 (4.7-10.7)
	GDF-15 elevated and NT-proBNP not elevated	155/1005	15.4 (13.3-17.8)	56/1005	5.6 (4.3-7.1)
	GDF-15 elevated or NT-proBNP elevated	210/1293	16.2 (14.3-18.3)	77/1293	6.0 (4.8-7.3)
Both biomarkers elevated	GDF-15 elevated and NT-proBNP elevated	251/748	33.6 (30.2-37.0)	92/748	12.3 (10.1-14.8)

*GDF-15 elevation defined as GDF-15 concentrations ≥ 1500 pg/mL. NT-proBNP elevation defined as NT-proBNP ≥ 200 pg/mL.

CI = confidence intervals; MI = myocardial infarction; GDF-15 = Growth differentiation factor 15; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Supplemental Digital Content 7. C-statistic comparison for multivariable models to predict myocardial injury after noncardiac surgery and vascular death (n=4229)

Multivariable models	C-statistic
Revised Cardiac Risk Index and age	0.740
Revised Cardiac Risk Index, age, preoperative NT-proBNP (continuous)	0.746
Revised Cardiac Risk Index, age, preoperative NT-proBNP (continuous), preoperative GDF-15 (continuous)	0.755
Revised Cardiac Risk Index, age, preoperative NT-proBNP (categorical)	0.760
Revised Cardiac Risk Index, age, preoperative NT-proBNP (categorical), preoperative GDF-15 (categorical)	0.768

Age is expressed as a continuous variable and Revised Cardiac Risk Index as categorical (ie., 0, 1, 2, or ≥ 3) in all models. NT-proBNP categories were <100 , 100 to <200 , 200 to <1500 , and ≥ 1500 ng/L. GDF-15 categories were <1000 , 1000 to <1500 , 1500 to <3000 , and ≥ 3000 ng/L. NT-proBNP = N-terminal pro-brain natriuretic peptide, GDF-15=Growth differentiating factor 15

Supplemental Digital Content 8. Calibration curves to predict myocardial injury after noncardiac surgery and vascular death (n=4229)

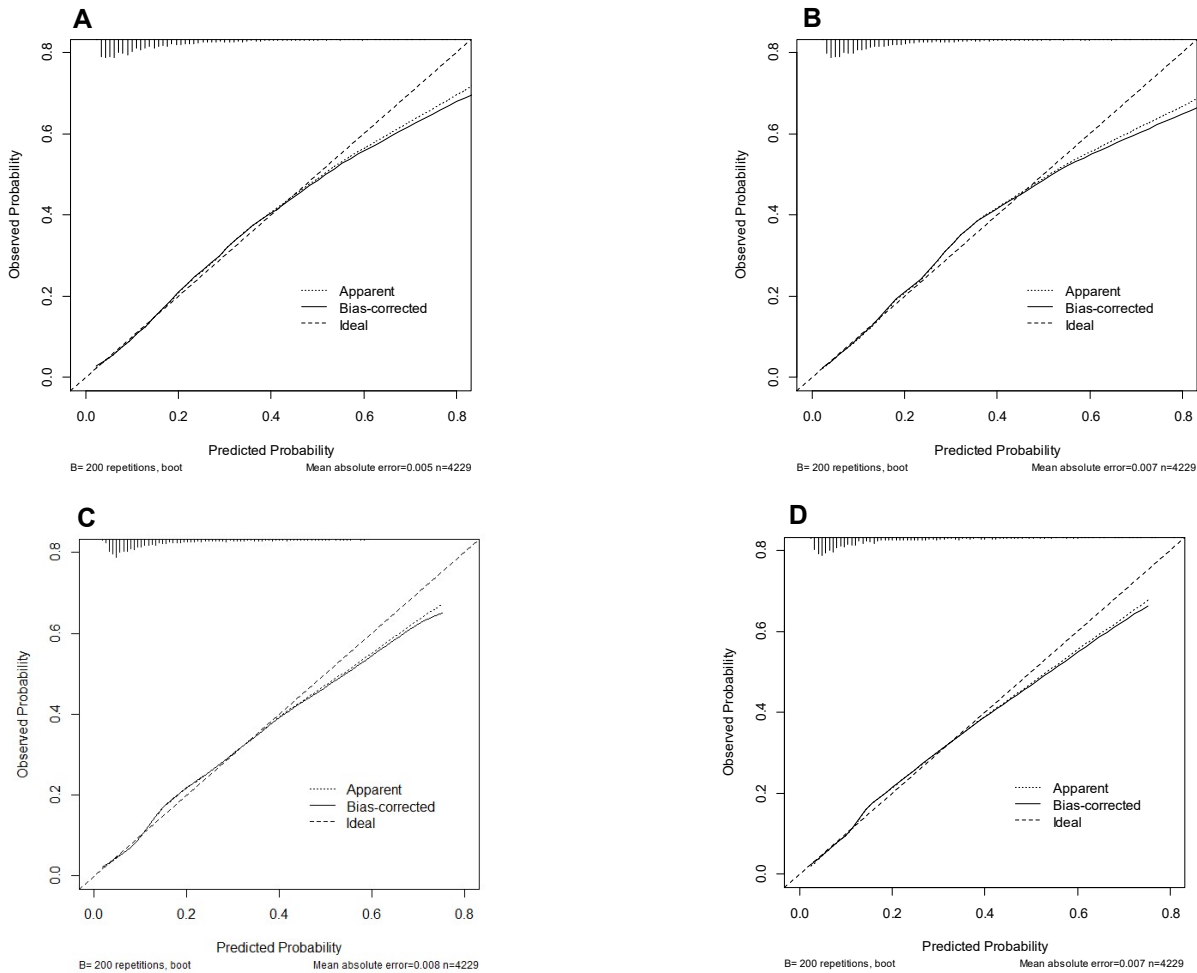


Figure A. Multivariable logistic regression model including Revised Cardiac Risk Index, age (continuous), preoperative NT-proBNP (continuous)

Figure B. Multivariable logistic regression model including Revised Cardiac Risk Index, age (continuous), preoperative NT-proBNP (continuous), preoperative GDF-15 (continuous)

Figure C. Multivariable logistic regression model including Revised Cardiac Risk Index, age (continuous), preoperative NT-proBNP (categorical)

Figure D. Multivariable logistic regression model including Revised Cardiac Risk Index, age (continuous), preoperative NT-proBNP (categorical), preoperative GDF-15 (categorical)

The 45-degree line represents perfect calibration. The lines at the top figure are histogram illustration of the proportion of patients with predicted probability on the corresponding x-axis.

Supplemental Digital Content 9. Type of procedures included in the type of surgery categories

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 aneurysm 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, oophorectomy, 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