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Association of Preoperative Growth Differentiation Factor-15 Concentrations and Postoperative Cardiovascular Events after Major Noncardiac Surgery

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ABSTRACT

Background: The association between growth differentiation factor-15 concentrations and cardiovascular disease has been well described. The study hypothesis was that growth differentiation factor-15 may help cardiac risk stratification in noncardiac surgical patients, in addition to clinical evaluation.

Methods: The objective of the study was to determine whether preoperative serum growth differentiation factor-15 is associated with the composite primary outcome of myocardial injury after noncardiac surgery and vascular death at 30 days and can improve cardiac risk prediction in noncardiac surgery. This is a prospective cohort study of patients 45 yr or older having major noncardiac surgery. The association between preoperative growth differentiation factor-15 and the primary outcome was determined after adjusting for the Revised Cardiac Risk Index. Preoperative N-terminal-pro hormone brain natriuretic peptide was also added to compare predictive performance with growth differentiation factor-15.

Results: Between October 27, 2008, and October 30, 2013, a total of 5,238 patients were included who had preoperative growth differentiation factor-15 measured (median, 1,325; interquartile range, 880 to 2,132 pg/ml). The risk of myocardial injury after noncardiac surgery and vascular death was 99 of 1,705 (5.8%) for growth differentiation factor-15 less than 1,000 pg/ml, 161 of 1,332 (12.1%) for growth differentiation factor-15 1,000 to less than 1,500 pg/ml, 302 of 1476 (20.5%) for growth differentiation factor-15 1,500 to less than 3,000 pg/ml, and 247 of 725 (34.1%) for growth differentiation factor-15 concentrations 3,000 pg/ml or greater. Compared to patients who had growth differentiation factor-15 concentrations less than 1,000 pg/ml, the corresponding adjusted hazard ratio for each growth differentiation factor-15 category was 1.93 (95% CI, 1.50 to 2.48), 3.04 (95% CI, 2.41 to 3.84), and 4.8 (95% CI, 3.76 to 6.14), respectively. The addition of growth differentiation factor-15 improved cardiac risk classification by 30.1% (301 per 1,000 patients) compared to Revised Cardiac Risk Index alone. It also provided additional risk classification beyond the combination of preoperative N-terminal-pro hormone brain natriuretic peptide and Revised Cardiac Risk Index (16.1%; 161 per 1,000 patients).

Conclusions: Growth differentiation factor-15 is strongly associated with 30-day risk of major cardiovascular events and significantly improved cardiac risk prediction in patients undergoing noncardiac surgery.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Increased serum growth differentiation factor-15 concentrations are associated with significantly higher rates of adverse cardiovascular events and mortality when assessed in ambulatory cohorts and in cardiac surgical cohorts.
- Whether increased preoperative serum growth differentiation factor-15 concentrations associate with significantly higher rates of postoperative adverse events has not been clearly assessed.

What This Article Tells Us That Is New

- This study used clinical data and serum samples from 5,238 patients enrolled in a multisite cohort study (Vascular Events in Noncardiac Surgery Evaluation study; VISION). The authors assessed the association between increased preoperative serum growth differentiation factor-15 and the primary study outcome of 30-day risk of myocardial injury after noncardiac surgery and vascular death.
- A preoperative growth differentiation factor-15 concentration 1,500 pg/ml or greater was associated with a 24.9% risk of myocardial injury after noncardiac surgery and vascular death.
- In the subset of patients who had preoperative N-terminal-pro hormone brain natriuretic peptide results available (n = 4,246), the incidence of myocardial injury after noncardiac surgery and vascular death was 606 patients (14.3%). In a multivariable model that included preoperative Revised Cardiac Risk Index score and preoperative N-terminal-pro hormone brain natriuretic peptide categories, both preoperative growth differentiation factor-15 and N-terminal-pro hormone brain natriuretic peptide remained independently associated with myocardial injury after noncardiac surgery and vascular death and vascular mortality at 30 days.

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Mortality associated with surgery is a major health burden, representing the third greatest contributor to deaths globally.[1] In adults having noncardiac surgery, cardiac events are among the leading causes of poor prognosis at 30 days, with 16% of deaths attributable to myocardial injury after noncardiac surgery.[2] Identifying patients at high risk of postoperative cardiac events is a central component of preoperative evaluation of patients having major noncardiac surgery. Most national perioperative guidelines recommend using clinical risk scores for cardiac risk stratification.[3–6]

Among the most commonly used cardiac risk stratification measures is the Revised Cardiac Risk Index, which is also among the most studied risk scores for noncardiac surgical patients and is recommended by guidelines for perioperative cardiac stratification.[3,7–9] Albeit having undergone extensive external validation and shown predictive utility for cardiac risk prediction, it was found to have only moderate ability to discriminate patients at high risk of perioperative cardiac events.[7] Biomarkers can add incremental information to clinical risk scores in noncardiac surgery.[10] N-terminal pro B-type natriuretic peptide (NT-proBNP) has the largest literature supporting its use in this setting, and brain natriuretic peptide or NT-proBNP are currently the only biomarkers recommended for preoperative cardiovascular risk prediction.[3,6,9] Others have probed the use of high-sensitivity cardiac troponin.[11,12]

Growth differentiation factor-15 (GDF-15) is a member of the transforming growth factor-β cytokine superfamily. Its expression is significantly increased in response to inflammation[13] and tissue injury.[14] It is produced by various cells including cardiomyocytes, endothelial cells, and vascular smooth muscle cells.[15] GDF-15 has been strongly associated with mortality across various patient populations, including those with stable coronary artery disease,[16] acute coronary syndrome,[17] atrial fibrillation,[18] and heart failure.[19] In cardiac surgery, GDF-15 was independently associated with postoperative morbidity and mortality and significantly improved risk stratification in addition to preoperative risk score and NT-proBNP.[20,21] The study hypotheses were that GDF-15 could also have incremental predictive value when added to a preoperative risk score and NT-proBNP in a noncardiac surgery population. The aim of this study was to determine in patients undergoing noncardiac surgery if GDF-15 was associated with postoperative cardiovascular events and improved risk stratification in addition to Revised Cardiac Risk Index and NT-proBNP. In addition, the study aimed to identify thresholds of GDF-15 that were associated with a significant change in 30-day risk of myocardial injury after noncardiac surgery and vascular death.

Materials and Methods

Study Design

We undertook a prospective nested biobank cohort study that was part of the Vascular Events in Noncardiac Surgery Evaluation (VISION) study. VISION was a large, international prospective cohort study evaluating cardiovascular outcomes in patients undergoing noncardiac surgery with overnight hospital stay and who were followed for 30 days.[22,23]

The primary objective of this study was to determine the relationship between preoperative growth differentiation factor-15 (GDF-15) and the risk of myocardial injury after noncardiac surgery and vascular death at 30 days, and to evaluate whether it improves risk prediction in addition to the Revised Cardiac Risk Index score and N-terminal-pro hormone brain natriuretic peptide (NT-proBNP). Additional objectives included identifying thresholds of GDF-15 that were associated with a significant change in 30-day risk of myocardial injury after noncardiac surgery and vascular death.

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Population

Participants in this study were enrolled in the VISION and VISION biobank studies. Participants were 45 yr or older, underwent noncardiac surgery with overnight hospital stay, and had regional or general anesthesia. Participants included in this analysis also provided preoperative serum samples for the biobank, allowing for biomarker analyses. Written informed consent was obtained for participation in the main VISION study and the biobank. Ethics approval was obtained from the local ethics review board at all participating centers before study initiation, and ethics approval was also obtained before assay analysis on the stored biobank samples (Hamilton Integrated Research Ethics Board, Hamilton Health Sciences, Hamilton, Canada).

Patients were enrolled before surgery and followed during their hospital stay and contacted by phone at 30 days for outcome assessment. If patients or their next-of-kin reported an outcome, source documentation was obtained by research personnel, anonymized, and sent to the project office (Population Health Research Institute, Hamilton, Canada) for independent event adjudication.

Patients enrolled in the VISION study had troponin measured (either troponin T or high-sensitivity troponin T) for the first 3e days after surgery, or until discharge. Participating centers were encouraged to obtain a postoperative electrocardiogram for all patients with a postoperative troponin elevation at or above the respective cutoffs for fourth generation and fifth generation troponin T assays (*i.e.*, 0.03 ng/l for troponin T and 14 ng/l for high-sensitivity troponin T, which represents the 99th percentile cutoff). These elevations were sent for outcome adjudication.

GDF-15 and NT-proBNP Measurements

Participants had preoperative blood samples collected and refrigerated within 2 h of collection. Samples were then centrifuged, divided into aliquots, frozen, and shipped to the Clinical Research Laboratory and Biobank (Hamilton, Canada). Samples were then stored at −80°C and −165°C. The average time between sample storage and analysis was 6 yr. GDF-15 (Roche Diagnostics, Switzerland) was measured in batch by enzyme-linked immunosorbent assay on thawed serum samples of all patients enrolled in this study. We excluded patients enrolled in the VISION biobank without sufficient serum sample left to allow for GDF-15 analysis (n = 102). As per the manufacturer's measurement range, GDF-15 values below the limit of detection were reported as less than 400 pg/ml (limit of quantification = 400 pg/ml), and values above the measuring range were reported as greater than 20,000 pg/ml. Preoperative NT-proBNP (Roche Diagnostics) concentrations were available in a subset of patients who had this assay measured as part of another study.[24] Patients who participated in both studies (*i.e.*, VISION NT-proBNP and biobank studies) and had a GDF-15 measured were included in the secondary analysis. The limit of detection and limit of quantification for NT-proBNP are 5 pg/ml and 50 pg/ml, respectively. GDF-15 and NT-proBNP were measured on samples that were collected at the same preoperative time. According to the manufacturer's specification, GDF-15 and NT-proBNP have long-term stability at −80°C or colder. Clinicians were blinded to both GDF-15 and NT-proBNP results.

Outcomes

The primary outcome was the composite of myocardial injury after noncardiac surgery and vascular death. Myocardial injury after noncardiac surgery was defined as a troponin elevation, with or without criteria for myocardial infarction (MI),[25] occurring within 30 days of noncardiac surgery, and that is believed not to be due to a nonischemic etiology (*e.g.*, pulmonary embolism, sepsis, or a chronic elevation). Troponin T and high-sensitivity troponin T thresholds identified in previous VISION studies were used to define myocardial injury after noncardiac surgery.[23,26] Vascular death included deaths after an MI, cardiac arrest, stroke, cardiac revascularization procedure, pulmonary embolus, hemorrhage, or deaths due to an unknown cause. Secondary outcomes include the composite of MI and all-cause mortality, major cardiovascular events (*i.e.*, the composite of MI, nonfatal cardiac arrest, stroke, congestive heart failure, new clinically important atrial fibrillation, and vascular mortality), and individual components of the composite outcomes. Outcome definitions are provided in Supplemental Digital Content 1 (https://links.lww.com/ALN/D97).

Statistical Analysis

A Cox proportional hazard model was used to determine the association between preoperative GDF-15 and the primary composite outcome of myocardial injury after noncardiac surgery and vascular death at 30 days, adjusted for Revised Cardiac Risk Index score (*i.e.*, 0, 1, 2, and 3 or greater). The Revised Cardiac Risk Index score includes the following risk factors, worth one point each: ischemic heart disease, congestive heart failure, preoperative insulin use, preoperative creatinine greater than 2 mg/dl (177 μmol/l), cerebrovascular disease, and high-risk surgery (*i.e.*, intrathoracic, intraperitoneal, and suprainguinal vascular). Patients were censored at their last assessment if they did not complete 30-day follow-up.

Upon confirmation of an association between GDF-15 as a continuous variable and the primary outcome, an iterative analysis was undertaken to identify GDF-15 thresholds that correspond to important changes in the risk of myocardial injury after noncardiac surgery and vascular death. This was performed by utilizing a Cox proportional hazard model adjusted for Revised Cardiac Risk Index and identifying the model that yielded the lowest *P* value from a chi-square test based on the log likelihood comparing the model

with and without various predefined GDF-15 thresholds.[27] Thresholds explored were by increments of 500 pg/ml until 4,000 pg/ml, then by increments of 1,000 pg/ml until 6,000 pg/ml. We did not explore for thresholds higher than 6,000 pg/ml due to the small number of patients and the recommendation to avoid exploring for candidate cut points in the extremes when performing an iterative minimal *P* value approach, to reduce multiple testing in areas less of interest for prognosis.[28] The same approach was used to explore the possibility of more than one significant threshold and repeated until the model did not show significant improvement on the likelihood ratio test ($P > 0.01$), the adjusted hazard ratios for the GDF-15 thresholds were not significantly associated with the primary outcome, or the c-statistic did not show improvement in risk discrimination.

The relationship between the identified GDF-15 thresholds and the 30-day risk of the composite of MI and all-cause mortality, myocardial injury after noncardiac surgery, MI, and major cardiovascular events was then determined utilizing Cox proportional models adjusted for Revised Cardiac Risk Index. The adjusted hazard ratio with corresponding 95% CI for each model and outcome incidence with 95% CI are reported according to GDF-15 categories. For each model, internal validation was performed using bootstrapping to calculate a c-statistic corrected for optimism[29] and bias-corrected calibration curve (*i.e.*, locally weighted polynomial regression with Locally Weighted Scatterplot Smoothing). The incremental predictive value of identified preoperative GDF-15 thresholds in addition to the Revised Cardiac Risk Index was determined for the prediction of 30-day myocardial injury after noncardiac surgery and vascular death using the Net Absolute Reclassification Index using risk categories (*i.e.*, less than 5%, 5 to 15%, greater than 15 to 30%, greater than 30%) and 25% relative change in risk. We assessed potential interaction between preoperative GDF-15 and estimated glomerular filtration rate, sex, and cancer in the Cox proportional model to predict myocardial injury after noncardiac surgery and vascular death at 30 days. Proportional hazards assumptions were tested using scaled Schoenfeld residuals.

In the subset of patients with preoperative NT-proBNP available, the predictive performances of GDF-15 and NT-proBNP were compared, alone or in combination, in addition to Revised Cardiac Risk Index using c-statistics comparison and Net Absolute Reclassification. NT-proBNP thresholds identified in previous VISION analyses were used (*i.e.*, less than 100 pg/ml, 100 to less than 200 pg/ml, 200 to less than 1,500 pg/ml, and 1,500 pg/ml or greater).[24]

Analyses were performed using R (version 4.1.0, The R Foundation for Statistical Computing, Austria) and SPSS (IBM SPSS Statistics 27, USA). A statistical analysis plan was written, date-stamped, and recorded in the investigator's files before data were accessed and any statistical analysis was performed.

Results

A total of 5,238 patients were included in this study, enrolled from nine centers in four countries (Canada, United Kingdom, United States, and Hong Kong) between October 27, 2008, and October 30, 2013. Half of the patients were male (51.5%), and the mean age was 64.8 yr (SD, 10.7). Baseline characteristics, cardiovascular risk factors, Revised Cardiac Risk Index score, and surgical characteristics are reported in table 1. The median growth differentiation factor-15 (GDF-15) was 1,325 pg/ml (interquartile range, 880 to 2,132). The primary composite outcome of myocardial injury after noncardiac surgery or vascular death occurred in 15.4% (809 of 5,238) of patients at 30 days, and 4.8% (252 of 5,238) had the composite of MI and all-cause death. Major cardiovascular events occurred in 6.2% of patients (325 of 5,238). Outcome incidences at 30 days are reported in table 2. Vital status at 30 days could not be confirmed in 0.3% of patients, who were censored at the day of last of contact for the statistical analysis.

The Cox proportional hazards iterative process adjusted for Revised Cardiac Risk Index to predict myocardial injury after noncardiac surgery and vascular mortality at 30 days yielded three significant GDF-15 thresholds: 1,000, 1,500, and 3,000 pg/ml. Baseline characteristics according to GDF-15 categories are reported in Supplemental Digital Content 2 (https://links.lww.com/ALN/D97). The patients with higher GDF-15 values were older and had more severe comorbidities than those with lower values. The risk of myocardial injury after noncardiac surgery and vascular death was 5.8% (95% CI, 4.8 to 7.0%) for GDF-15 less than 1,000 pg/ml, 12.1% (95% CI, 10.4 to 14.0%) for GDF-15 less than 1,000 to 1,500 pg/ml, 20.5% (95% CI, 18.5 to 22.6%) for GDF-15 1,500 to less than 3,000 pg/ml, and 34.1% (95% CI, 30.7 to 37.6) for GDF-15 3,000 pg/ml or greater (table 3). For the same GDF-15 categories, the risk of MI and all-cause death was 1.6% (95% CI, 1.1 to 2.4%), 3.4% (95% CI, 2.5 to 4.5%), 6.4% (95% CI, 5.3 to 7.8), and 11.6% (95% CI, 9.5 to 14.1%), respectively. Figure 1 shows the cumulative risk of myocardial injury after noncardiac surgery or vascular death at 30 days according to GDF-15 thresholds. The Cox proportional hazards model including preoperative GDF-15 thresholds and Revised Cardiac Risk Index demonstrated that, compared to a preoperative GDF-15 less than 1,000 pg/ml, patients with GDF-15 1,000 to less than 1,500 pg/ml had a hazard ratio of 1.93 (95% CI, 1.50 to 2.48) of myocardial injury after noncardiac surgery or vascular death at 30 days, patients with GDF-15 1,500 to less than 3,000 pg/ml a hazard ratio of 3.04 (95% CI, 2.41 to 3.84), and patients with GDF-15 3,000 pg/ml or greater a hazard ratio of 4.8 (95% CI, 3.76 to 6.14; table 3). GDF-15 added to Revised Cardiac Risk Index in multivariable analysis was also significantly associated with MI and vascular death, and major cardiovascular events. We did not find at interaction between preoperative GDF-15 and estimated glomerular filtration rate (*P* value, 0.36), sex (*P* value, 0.91), or cancer (*P* value, 0.44).

Table 1. Baseline and Operative Characteristics of Patients Who Suffered a Myocardial Injury after Noncardiac Surgery or Vascular Death at 30 Days

	All Patients (n = 5,238)	No Nonfatal Myocardial Injury after Noncardiac Surgery or Vascular Death (n = 4,429)	Nonfatal Myocardial Injury after Noncardiac Surgery or Vascular Death (n = 809)
Age, n (%)			
45–64 yr	2,717 (51.9)	2,494 (56.3)	223 (27.5)
65–74 yr	1,519 (29.0)	1,253 (28.3)	266 (32.9)
≥ 75 yr	1,002 (19.1)	682 (15.4)	320 (39.6)
Male, n (%)	2,697 (51.5)	2,219 (50.1)	478 (59.1)
Baseline medication, n (%)*			
Acetylsalicylic acid	902 (17.2)	673 (15.2)	229 (28.3)
β-Blocker	1,083 (20.7)	817 (18.4)	266 (32.9)
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker	1,898 (36.2)	1,529 (34.5)	369 (45.6)
Statin	1,889 (36.1)	1,516 (34.2)	373 (46.1)
History of the following, n (%)			
Diabetes	981 (18.7)	751 (17.0)	230 (28.4)
Hypertension	2,901 (55.4)	2,331 (52.6)	570 (70.5)
Congestive heart failure	157 (3.0)	93 (2.1)	64 (7.9)
Coronary artery disease	812 (15.5)	570 (12.9)	242 (29.9)
Peripheral vascular disease	343 (6.5)	218 (4.9)	125 (15.5)
Cerebrovascular disease	343 (6.5)	251 (5.7)	92 (11.4)
Chronic pulmonary obstructive disease	459 (8.8)	332 (7.5)	127 (15.7)
Active cancer, n (%)	1,474 (28.1)	1,217 (27.5)	257 (31.8)
Preoperative estimated glomerular filtration rate†, n (%), ml/min			
> 60	4,161 (79.4)	3,663 (82.7)	498 (61.6)
45–60	554 (10.6)	413 (9.3)	141 (17.4)
30–44	232 (4.4)	146 (3.3)	86 (10.6)
< 30 or dialysis	138 (2.6)	70 (1.6)	68 (8.4)
Type of surgery, n (%)			
Vascular	314 (6.0)	216 (4.9)	98 (12.1)
General	1,052 (20.1)	884 (20.0)	168 (20.8)
Thoracic	237 (4.5)	177 (4.0)	60 (7.4)
Major urology/gynecology	634 (12.1)	548 (12.4)	86 (10.6)
Major orthopedics	1,516 (28.9)	1,267 (28.6)	249 (30.8)
Major neurology	443 (8.5)	387 (8.7)	56 (6.9)
Low-risk surgeries	1,247 (23.8)	1,124 (25.4)	123 (15.2)
Urgent/emergent surgery, n (%)	167 (3.2)	138 (3.1)	29 (3.6)
Preoperative growth differentiation factor-15, median (interquartile range), pg/ml	1,325 (880–2,132)	1,233 (839–1,925)	2,056 (1,283–3,406)
Revised Cardiac Risk Index score, n (%)			
0	2,914 (55.6)	2,631 (59.4)	283 (35.0)
1	1,671 (31.9)	1,367 (30.9)	304 (37.6)
2	488 (9.3)	348 (7.9)	140 (17.3)
≥3	165 (3.2)	83 (1.9)	82 (10.1)

*Eleven missing for acetylsalicylic acid, six missing for angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, seven missing for β-blocker, and five missing for statin. †Ten values missing for estimated glomerular filtration rate. Revised Cardiac Risk Index score includes the following risk factors, worth one point each: Ischemic heart disease, congestive heart failure, preoperative insulin use, preoperative creatinine greater than 2 mg/dl (177 μmol/l), cerebrovascular disease, and high-risk surgery (*i.e.*, intrathoracic, intraperitoneal, and suprainguinal vascular). The type of procedures that are included in each type of surgery category are listed in Supplemental Digital Content 8 (https://links.lww.com/ALN/D97).

Preoperative GDF-15 improved risk classification compared to Revised Cardiac Risk Index alone in 5.6% of patients with events and 34.6% in patients without events, corresponding to an improved risk stratification in 301 out of a sample of 1,000 patients (30.1%) when using risk categories of myocardial injury after noncardiac surgery and vascular death. Reclassification tables are reported in table 4. The net absolute reclassification also showed improvement using a 25% relative change in risk (Supplemental Digital Content 3, https://links.lww.com/ALN/D97). GDF-15 also improved discrimination when comparing c-statistics using Revised Cardiac Risk Index only (c-statistic, 0.649) to the model with added GDF-15 categories (c-statistic, 0.722) to predict 30-day risk of

Table 2. Outcome Incidence at 30 Days

Outcome	N	% (95% CI)
Composite of myocardial injury after noncardiac surgery and vascular death	809	15.4 (14.5–16.5)
MI and death	252	4.8 (4.3–5.4)
Major cardiovascular events	325	6.2 (5.6–6.9)
Myocardial injury after noncardiac surgery	797	15.2 (14.3–16.2)
MI	223	4.3 (3.7–4.8)
Nonfatal cardiac arrest	6	0.1 (0.05–0.3)
Stroke	21	0.4 (0.3–0.6)
Congestive heart failure	51	1.0 (0.7–1.3)
New clinically significant atrial fibrillation	64	1.2 (1.0–1.6)
Vascular mortality	21	0.4 (0.3–0.6)
All-cause mortality	40	0.8 (0.6–1.0)

N = 5,238. "Major cardiovascular events" is a composite of MI, nonfatal cardiac arrest, stroke, congestive heart failure, new clinically important atrial fibrillation, and vascular mortality.
MI, myocardial infarction.

myocardial injury after noncardiac surgery and vascular death. The model combining GDF-15 and Revised Cardiac Risk Index also showed good calibration as evaluated using the bias-corrected calibration curve (fig. 2).

Comparison between Preoperative GDF-15 and NT-proBNP

In the subset of patients who had preoperative N-terminal-pro hormone brain natriuretic (NT-proBNP) results available (n = 4,246), the incidences of myocardial injury after noncardiac surgery and vascular death (606 patients, 14.3%) and MI and all-cause death (210 patients, 4.9%) were similar to the overall cohort. In the multivariable model that included preoperative Revised Cardiac Risk Index score and NT-proBNP categories, both GDF-15 and NT-proBNP remained independently associated with myocardial injury after noncardiac surgery and vascular mortality at 30 days (table 5). The c-statistic for the model with NT-proBNP and Revised Cardiac Risk Index improved from 0.723 to 0.751 when adding GDF-15 categories. Preoperative GDF-15 also improved risk stratification in addition to preoperative NT-proBNP and Revised Cardiac Risk Index, with a net absolute reclassification index of 161 patients in 1,000 patients (16.1%; Supplemental Digital Content 4, https://links.lww.com/ALN/D97). NT-proBNP concentrations 200 pg/ml or greater and GDF-15 1,500 pg/ml or greater were both independently associated with the risk of MI and all-cause mortality (Supplemental Digital Content 5, https://links.lww.com/ALN/D97). GDF-15 and NT-proBNP showed the same improvement in risk discrimination when added to Revised Cardiac Risk Index separately to predict MI or all-cause death (c-statistic, 0.723 for both biomarkers) but further improved risk discrimination when added in combination with Revised Cardiac Risk Index (c-statistic, 0.744).

In patients without preoperative elevation of either biomarker (*i.e.*, NT-proBNP less than 200 pg/ml and GDF-15 less than 1,500 pg/ml), the incidence of myocardial injury after noncardiac surgery and vascular death was 6.6% (95% CI, 5.6 to 7.7). In comparison, patients with only one of both biomarkers elevated (*i.e.*, NT-proBNP 200 pg/ml or greater, or GDF-15 1,500 pg/ml or greater), the incidence

Table 3. Multivariable Models Including Preoperative Growth Differentiation Factor-15 Thresholds to Predict 30-Day Cardiovascular Events (n = 5,238)

Preoperative Growth Differentiation Factor-15 Thresholds (pg/ml)	Number of Events	Incidence % (95% CI)	Adjusted Hazard Ratio (95% CI)
Myocardial injury after noncardiac surgery and vascular death at 30 days (809 events)			
C-statistic, 0.722 (corrected for optimism, 0.719)			
< 1,000	99 of 1,705	5.8 (4.8–7.0)	—
1,000 to < 1,500	161 of 1,332	12.1 (10.4–14.0)	1.93 (1.50–2.48)
1,500 to < 3,000	302 of 1,476	20.5 (18.5–22.6)	3.04 (2.41–3.84)
≥ 3,000	247 of 725	34.1 (30.7–37.6)	4.8 (3.76–6.14)
Myocardial infarction and all-cause mortality at 30 days (252 events)			
C-statistic, 0.723 (corrected for optimism, 0.719)			
< 1,000	28 of 1,705	1.6 (1.1–2.4)	—
1,000 to < 1,500	45 of 1,332	3.4 (2.5–4.5)	1.18 (1.13–2.92)
1,500 to < 3,000	95 of 1,476	6.4 (5.3–7.8)	3.10 (2.02–4.8)
≥ 3,000	84 of 725	11.6 (9.5–14.1)	4.9 (3.10–7.6)
Major cardiovascular events at 30 days (325 events)			
C-statistic, 0.716 (corrected for optimism, 0.714)			
< 1,000	43 of 1,705	2.5 (1.9–3.4)	—
1,000 to < 1,500	63 of 1,332	4.7 (3.7–6.0)	1.77 (1.41–2.22)
1,500 to < 3,000	118 of 1,476	8.0 (6.7–9.5)	2.73 (2.22–3.37)
≥ 3,000	101 of 725	13.9 (11.6–16.6)	4.1 (3.24–5.1)

Cox proportional hazard models adjusted for Revised Cardiac Risk Index.

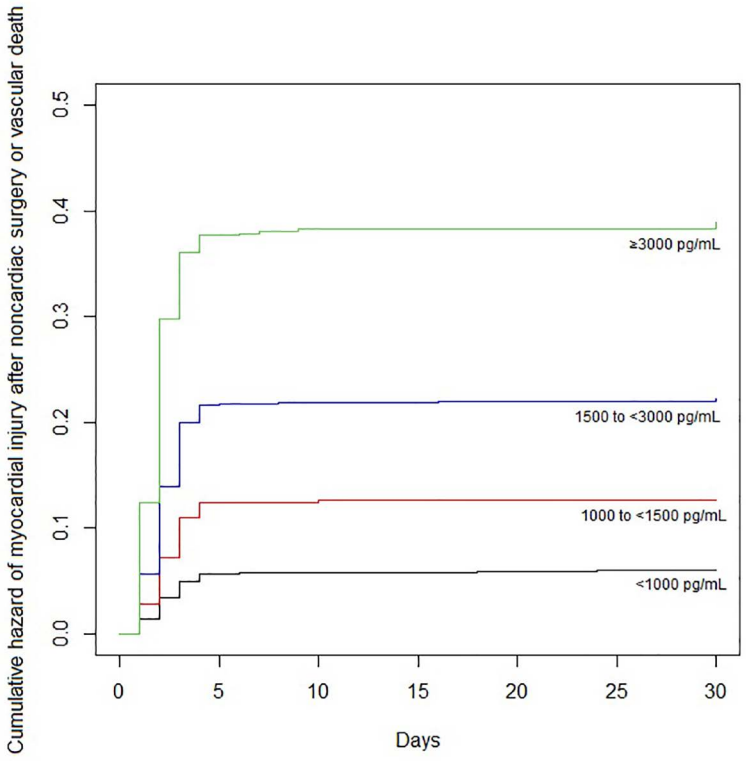

Fig. 1. Cumulative hazard for myocardial injury after noncardiac surgery or vascular death at 30 days by growth differentiation factor-15 thresholds. Probability of suffering a myocardial injury after noncardiac surgery or vascular death during a 30-day period after noncardiac surgery in patients with different concentrations of preoperative growth differentiation factor-15. Vascular death is defined as any death with a vascular cause and includes those deaths after 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.

of myocardial injury after noncardiac surgery and vascular death was 16.2% (95% CI, 14.3 to 18.3). For patients with both elevated biomarkers, the incidence rose to 33.6% (95% CI, 30.2 to 37.0). The corresponding incidences of MI and death were 1.9% (95% CI, 1.4 to 2.5), 6.0% (95% CI, 4.8 to 7.3), and 12.3% (95% CI, 10.1 to 14.8; Supplemental Digital Content 6, https://links.lww.com/ALN/D97).

Post Hoc Analyses

We performed additional analyses to explore model performance to predict myocardial injury after noncardiac surgery and vascular death when the preoperative biomarkers were both added as a continuous variable and adding age to the model. The results show that compared to the model including Revised Cardiac Risk Index, age, and preoperative NT-proBNP as a continuous variable (c-statistic, 0.746), the addition of preoperative GDF-15 expressed as a continuous variable improved model discrimination (c-statistic, 0.755). The improved discrimination was also observed when adding GDF-15 categories to the model including age, Revised Cardiac Risk Index, and NT-proBNP categories (c-statistic, 0.768 and 0.760 with and without GDF-15 categories, respectively; Supplemental Digital Content 7, https://links.lww.com/ALN/D97). The use of NT-proBNP and GDF-15 categories in the multivariable models to predict myocardial injury after noncardiac surgery and vascular death improved model calibration compared to the models including the biomarkers as continuous variables (Supplemental Digital Content 8, https://links.lww.com/ALN/D97).

We also explored if GDF-15 was predictive of postoperative events in patients without previous known ischemic heart disease or congestive heart failure, as estimated by a Revised Cardiac Risk Index score of 0. In the subgroup of patients with a Revised Cardiac Risk Index score of 0, a preoperative GDF-15 values of 1,000 to less than 1,500, 1,500 to less than 3,000, and 3,000 ng/l or greater were associated with a hazard ratio, 2.07 (95% CI, 0.76 to 5.5), 4.7 (95% CI, 1.74 to 12.9), and 7.1 (95% CI, 2.56 to 19.7), respectively, for the 30-day risk of myocardial injury after noncardiac surgery or vascular death. We also explored if there was an interaction in the association between preoperative GDF-15 and which troponin T cohort patients were part of (*i.e.*, fourth generation

Table 4. Risk Reclassification Table of Preoperative Growth Differentiation Factor-15 Added to Revised Cardiac Risk Index to Predict Myocardial Injury after Noncardiac Surgery and Vascular Death at 30 Days

		Patients with Events n = 809 of 5,238 (15.4%)			
		Revised Cardiac Risk Index Only			
	Predicted Risk	< 5%	5 to < 15%	15 to < 30%	≥ 30%
Revised Cardiac Risk Index and growth differentiation factor-15	< 5%	0	64	0	0
	5 to < 15%	0	170	91	0
	15 to < 30%	0	49	200	2
	≥ 30%	0	0	153	80
Proportion reclassification for patients with events		45 of 809 (5.6%)			
		Patients without Events n = 4,429 of 5,238 (84.6%)			
		Revised Cardiac Risk Index Only			
	Predicted Risk	< 5%	5 to < 15%	15 to < 30%	≥ 30%
Revised Cardiac Risk Index and growth differentiation factor-15	< 5%	0	1,172	0	0
	5 to < 15%	0	1,277	801	0
	15 to < 30%	0	182	653	2
	≥ 30%	0	0	261	81
Proportion reclassification for patients without events		1,532 of 4,429 (34.6%)			
Net absolute reclassification improvement		301 per 1,000 patients (30.1%)			

Predicted risk determined using logistic regression models. For patients with events, an improvement was considered moving up in category of predicted risk in the model with growth differentiation factor-15, compared to the model with Revised Cardiac Risk Index only, and worse classification when moving down a risk category. The opposite rationale was applied to the group of patients without events.

troponin T or fifth generation high-sensitivity troponin T) and did not find a significant interaction ($P = 0.89$).

Discussion

In patients undergoing major noncardiac surgery, preoperative growth differentiation factor-15 (GDF-15) was found to be significantly associated with postoperative major cardiovascular events and improved cardiac risk stratification in addition to Revised Cardiac Risk Index. A preoperative GDF-15 level 1,500 pg/ml or greater was associated with a 24.9% risk of myocardial injury after noncardiac surgery or vascular death and 8.1% risk of MI and death at 30 days, compared to 8.6% and 2.4% in patients with GDF-15 less than 1,500 pg/ml, respectively. GDF-15 also improved risk prediction when used in combination with preoperative N-terminal-pro hormone brain natriuretic peptide (NT-proBNP) and Revised Cardiac Risk Index and resulted in improved risk classification in one in six patients.

There is limited evidence informing on the predictive performance of GDF-15 in major noncardiac surgery, but it has been addressed in a few studies in cardiac surgery. In a cohort of 504 patients undergoing elective coronary artery bypass surgery and/or cardiac valve repair, Kazem *et al.* found that preoperative GDF-15 was associated with 1-year all-cause mortality and cardiovascular mortality.[21] The addition of GDF-15 to the European System of Cardiac Operative Risk Evaluation (EuroSCORE II; *i.e.*, a risk score used in cardiac surgery to predict postoperative mortality) improved prediction of long-term survival (*i.e.*, net reclassification improvement, 33.6%). A study by Heringlake *et al.* looked at preoperative GDF-15 in 1,458 patients undergoing cardiac surgery and found that patients who died at 30 days had significantly higher median preoperative GDF-15 than survivors (2,537 pg/ml *vs.* 1,057 pg/ml).[20] In multivariable regression models, GDF-15 improved risk discrimination compared to the EuroSCORE II alone and was an independent predictor of 30-day and 1-year mortality; in these analyses, NT-proBNP was not associated with postoperative mortality. GDF-15 was associated with a 41.4% net reclassification improvement compared to EuroSCORE II to predict 30-day mortality. Although cardiac and noncardiac surgery differ in terms of risk of postoperative mortality and cardiovascular events, these findings are consistent with this study's findings that showed that GDF-15 independently predicts adverse postoperative outcome and provides additional prognostic information beyond commonly used perioperative risk score and NT-proBNP.

These findings are similar to the results described in the nonperioperative setting, where several studies have demonstrated the association between GDF-15 and cardiovascular disease, including acute coronary syndrome,[17] stable coronary artery disease,[30] heart failure,[31] and atrial fibrillation.[18] In a substudy of the Study of Platelet Inhibition and Patient Outcomes (PLATO) trial that randomized patients (n = 16,876 patients) with acute coronary syndrome to ticagrelor or clopidogrel, higher GDF-15 concentrations were associated with a greater burden of coronary artery disease at baseline and

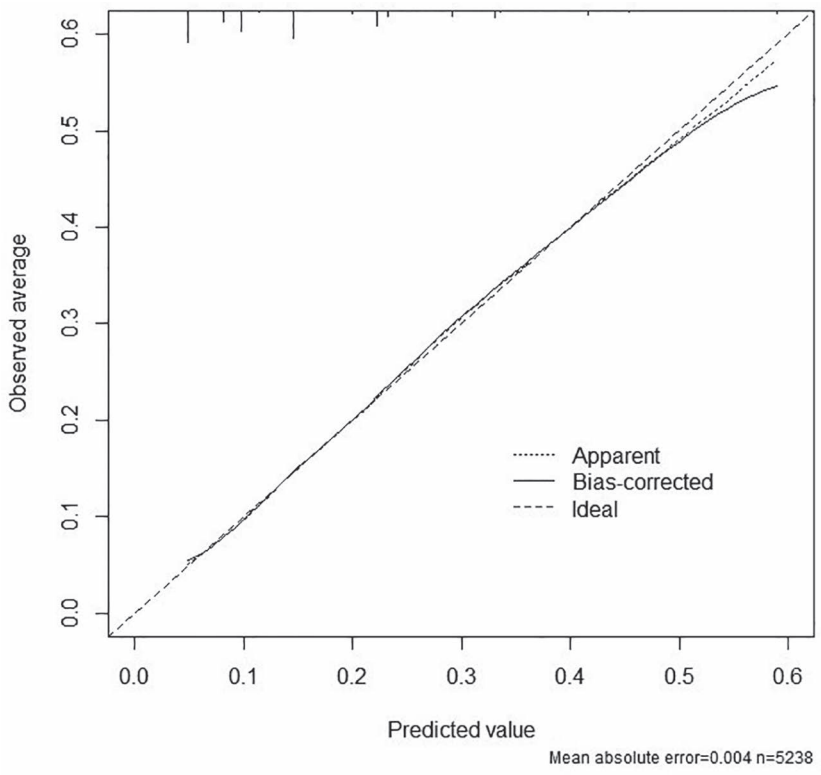

Fig. 2. Calibration curve for the model including growth differentiation factor-15 thresholds and Revised Cardiac Risk Index to predict myocardial injury after noncardiac surgery and vascular mortality at 30 days. Locally Weighted Scatterplot Smoothing calibration curve of average observed risk and predicted risk of 30-day myocardial injury after noncardiac surgery and vascular mortality. The 45° *dashed line* represents perfect calibration. The *lines* at the top of the figure are a histogram illustration of the proportion of patients with the corresponding predicted risk on x-axis. The bias-corrected calibration curve was obtained from 200 bootstrapping repetitions.

Table 5. Preoperative Growth Differentiation Factor-15 and N-terminal-pro Hormone Brain Natriuretic Peptide to Predict Myocardial Injury after Noncardiac Surgery or Vascular Death at 30 Days (n = 4,246)

	Adjusted Hazard Ratio (95% CI)
Growth differentiation factor-15 thresholds (pg/ml)	
< 1,000	—
1,000 to < 1,500	1.76 (1.32–2.36)
1,500 to < 3,000	2.27 (1.72–3.00)
≥ 3,000	3.24 (2.39–4.4)
N-terminal-pro hormone brain natriuretic peptide thresholds (pg/ml)	
< 100	—
100 to < 200	1.97 (1.56–2.48)
200 to < 1,500	2.65 (2.14–3.28)
≥ 1,500	3.72 (2.67–5.2)

C-statistic, 0.751. Cox proportional hazard model adjusted for Revised Cardiac Risk Index.

increased risk of MI, stroke, and cardiovascular mortality at 12 months.[32,33]

Increase in plasma GDF-15 can occur through various stimuli such as cellular ischemia, oxidative stress, and inflammation, which have been linked to atherosclerosis progression.[34,35] GDF-15 is not normally expressed in healthy tissue and is prominently released in response to injury and plays a role in the regulation of endothelial adaptations to vascular damage.[36] Given its pathologic implications in atherosclerosis and well-described association with cardiovascular disease,[37] GDF-15 may be a prognostic indicator of underlying cardiovascular disease at higher risk of complications in the perioperative setting, as seen in this study and in cardiac surgery. Previous studies have reported changes in GDF-15 concentrations according to sex, estimated glomerular filtration rate, and cancer, but no interaction was found between GDF-15 and any of these in our study.[33,38,39]

Another important finding of this study is that in patients with both GDF-15 and NT-proBNP elevated preoperatively (*i.e.*, GDF-15 1,500 pg/ml or greater and NT-proBNP 200

pg/ml or greater), the risk of postoperative cardiac events and death was six times higher than in patients with no biomarker elevation, and twice as high as in patients with only one of the biomarkers elevated. The combination of both biomarkers can help identify patients at high risk of postoperative cardiac complications, which could benefit from interventions targeted at prevention and early identification and management of postoperative cardiac events. This could also help move forward research efforts to identify therapies to reduce the occurrence of cardiovascular complication, by targeting the interventions to higher-risk patients with the greatest potential to benefit from such interventions.[40,41]

Study Limitations

This study has limitations. GDF-15 is expressed in concentrations that are measured as continuous values, and higher concentrations are associated with greater risk of cardiovascular events, with the distribution of risk also being continuous. From a statistical standpoint, utilizing a variable as continuous when performing analyses of association is preferred for several reasons, including the loss of statistical power that occurs when categorizing a continuous variable.[42] In the clinical setting, however, having thresholds that can help clinicians in decision-making is desirable. In fact, the vast majority of biomarkers used in daily clinical care are used with thresholds to define what should be considered abnormal, some defining the upper limit of normal by the 99th percentile in the healthy population (*e.g.*, high-sensitivity troponins in acute coronary syndrome[43]), and other biomarkers have prognosis-based estimates to define thresholds that guide management (*e.g.*, cholesterol concentrations and cardiovascular disease).[44] This study identified preoperative GDF-15 thresholds associated with a significant change in prognosis, in addition to clinical risk factors, that can be used for risk prediction in the perioperative setting.

Another limitation in dichotomization of continuous variables is that it can produce unrealistic risk estimates, with patients close below and above the threshold having drastically different predicted risks. An option to mitigate this limitation is by identifying more than one threshold, resulting in risk categories rather than dichotomous estimates. This was performed in this study by using the minimal *P*-value approach developed by Mazumdar *et al.* for multivariable settings,[27] with a modification that allows for identification of multiple prognostically important thresholds.

Another limitation in the generalizability of this study's results is regarding urgent or emergent noncardiac surgeries. Given the nested biobank design and the fact that patients had to have a preoperative serum sample collected in order to be included in the study, the proportion of patients undergoing urgent or emergent surgery is lower than in the overall Vascular Events in Noncardiac Surgery Evaluation (VISION) cohort (3.2% *vs.* 10.5%).[45] Likely some patients were sent to the operating room before preoperative samples could be collected. Only 167 patients underwent urgent or emergent surgery, and although there was not a significant interaction in the association between GDF-15 ($P = 0.18$) and the primary outcome, the statistical power is limited to detect an interaction. The generalizability of the study may also be limited in certain subtypes of surgery, in particular vascular surgery (see Supplemental Digital Content 9, https://links.lww.com/ALN/D97, for types of procedures included). Given that GDF-15 is expressed in atherosclerosis, it is possible that GDF-15 may be expressed related to the peripheral arterial disease rather than due to cardiac disease. However, vascular surgery patients commonly have higher cardiovascular disease burden, so it may also be predictive. The number of vascular surgery patients in our cohort (n = 314) limited our ability to perform sufficiently powered subgroup analyses.

Finally, patients enrolled in the first half of the VISION study had fourth generation non–high-sensitivity troponin T measured, of whom 966 (22.8%) were included in this study; the remaining patients had postoperative monitoring with high-sensitivity troponin T. The incidence of myocardial injury after noncardiac surgery may have been underestimated in the group with troponin T measurement, as demonstrated by studies that performed postoperative monitoring with non–high-sensitivity troponins.[46] This also limits our ability to explore in this study if the addition of preoperative high-sensitivity troponin T to GDF-15 and NT-proBNP could further improve cardiac risk prediction.

In conclusion, in this large prospective cohort, preoperative GDF-15 was found to be associated with the occurrence of cardiovascular events at 30 days after noncardiac surgery. When added to clinical evaluation using the Revised Cardiac Risk Index score, it significantly improved cardiac risk stratification in one in three patients. GDF-15 has been shown to be associated with cardiovascular disease, and this study demonstrated that it may be useful to improve cardiac risk prediction in the noncardiac surgery setting. The combination of GDF-15 and preoperative NT-proBNP was found to further enhance risk stratification and identify patients at high risk of postoperative cardiovascular events. Both could be used in clinical practice in patient populations for which preoperative biomarkers are commended for risk stratification, but their use could also facilitate research progress on the topic of prevention of cardiovascular complications after noncardiac surgery, where additional studies are needed. Future studies may explore whether GDF-15 adds predictive value to other surgical risk models that were not assessed in this study (*e.g.*, American College of Surgeons National Surgical Quality Improvement Program [ACS-NSQIP] score[47]).

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The sponsor was the Population Health Research Institute in Hamilton, Canada. The sponsor originated the research idea and drafted the protocol that was submitted to Roche

Diagnostics (Rotkreuz, Switzerland) for feedback. Roche Diagnostics provided by donation-in-kind the growth differentiation factor-15, troponin T, high-sensitivity troponin T, and N-terminal-pro hormone brain natriuretic peptide assays and some funding to support this study. The Population Health Research Institute was responsible for the design and conduct of the study, the collection, analysis, and interpretation of the data, specimen collection and assay analysis, and the preparation, review, or approval of the manuscript. No funding source had a role in study design, data collection, analysis plan, statistical analyses, manuscript drafting, or decision for publication.

Competing Interests

Dr. Duceppe reports investigator-initiated research grants, lecture fees, and honoraria for advisory board participation from Roche Diagnostics and investigator-initiated research grants from Abbott Diagnostics (Lake Forest, Illinois), and is supported by a Fonds de Recherche du Quebec en Sante junior clinical research scholar award. Dr. Borges reports investigator-initiated research grants from Siemens Healthcare Diagnostics (Malvern, Pennsylvania) and Roche Diagnostics, and is a recipient of a Research Early Career Award from Hamilton Health Sciences (Hamilton, Canada). Dr. Conen reports consultancy fees from Roche Diagnostics and Trimedics (Indianapolis, Indiana) outside of the current work and speaker fees from Bristol-Myers Squibb/Pfizer (New York, New York) and Servier outside of the current work. Dr. Kavsak has received grants, reagents, consultant fees, advisor fees, and honoraria from Abbott Laboratories (Abbott Park, Illinois), Abbott Point of Care (Abbott Park, Illinois), Beckman Coulter (Brea, California), Ortho Clinical Diagnostics (Raritan, New Jersey), Randox Laboratories (London, United Kingdom), Roche Diagnostics, Quidel (San Diego, California), Siemens Healthcare Diagnostics, and Thermo Fisher Scientific (Waltham, Massachusetts). McMaster University (Hamilton, Canada) has filed patents with Dr. Kavsak listed as an inventor in the acute cardiovascular biomarker field. Dr. Pearse has received research grants and/or honoraria from Edwards Lifesciences (Irvine, California), Intersurgical (London, United Kingdom), and GlaxoSmithKline (London, United Kingdom). Dr. Jaffe reports consulting fees from Abbott, Siemens, Beckman-Coulter, Ortho Diagnostics, Roche, Radiometer (København, Denmark), ET Healthcare (Palo Alto, California), Sphingotec (Hennigsdorf, Germany), Astellas (Tokyo, Japan), RCE Technologies (Atlanta, Georgia), Amgen (Thousand Oaks, California), and Novartis (Basel, Switzerland). Dr. Devereaux is a member of a research group with a policy of not accepting honoraria or other payments from industry for their own personal financial gain. They do accept honoraria or payments from industry to support research endeavors and costs to participate in meetings. Based on study questions Dr. Devereaux has originated and grants he has written, he has received grants from Abbott Diagnostics, AstraZeneca (London, United Kingdom), Bayer (Berlin, Germany), Boehringer Ingelheim (Berlin, Germany), Bristol Myers Squibb, CloudDX (Ontario, Canada), Coviden (Dublin, Ireland), Octapharma (Lachen, Switzerland), Philips Healthcare (Amsterdam, The Netherlands), Roche Diagnostics, Siemens, and Stryker (Portage, Michigan). Dr. Devereaux has participated in advisory board meetings for GlaxoSmithKline, Boehringer Ingelheim, Bayer, and Quidel (Canada). He attended an expert panel meeting with AstraZeneca and Boehringer Ingelheim, and he was consultant for a call with Roche Pharma and performed consultant work with Trimedic (Ontario, Canada). He has also been invited as a speaker with Bayer Inc. (Germany) and Novartis Pharma Canada. The other authors declare no competing interests.

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Supplemental Digital Content

Supplemental Content, https://links.lww.com/ALN/D97

Supplemental Digital Content 1. Outcome definitions.

Supplemental Digital Content 2. Baseline characteristics by growth differentiation factor-15 categories.

Supplemental Digital Content 3. Risk reclassification for relative risk change.

Supplemental Digital Content 4. Risk reclassification using growth differentiation factor-15 and N-terminal-pro hormone brain natriuretic peptide.

Supplemental Digital Content 5. Adjusted risk of growth differentiation factor-15 and N-terminal-pro hormone brain natriuretic peptide.

Supplemental Digital Content 6. Risk prediction combining growth differentiation factor-15 and N-terminal-pro hormone brain natriuretic peptide.

Supplemental Digital Content 7. C-statistic comparison for multivariable models.

Supplemental Digital Content 8. Calibration curves.

Supplemental Digital Content 9. Type of procedures included.

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