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Diagnosis of MI after CABG with high-sensitivity troponin T and new ECG or echocardiogram changes: relationship with mortality and validation of the Universal Definition of MI

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Abstract

Aims: Criteria for diagnosing myocardial infarction (MI) after coronary artery bypass grafting (CABG) are controversial. Uncertainties remain around the optimal threshold for biomarker elevation and the need for associated criteria. There are no studies of high-sensitivity troponin (hs-TnT) after CABG. We assessed whether using hs-TnT to define MI after CABG was associated with 30-day and medium-term mortality and evaluated the utility of adding to the troponin criteria new Q-waves or imaging evidence of new wall motion abnormality as suggested in the Universal Definition of MI.

Methods: Isolated CABG was performed in 818 patients from July 2010 to June 2012 and hs-TnT was measured 12–24 hours after CABG. Patients with rising baseline or missing troponins (n=258) were excluded. Thresholds of 140 ng/l (10-times 99th percentile upper reference limit) and 500 ng/l (10-times coefficient of variation of 10% for fourth-generation troponin T applied to hs-TnT) were prespecified.

Results: Mean follow up was 1.8±0.6 years. On multivariate analyses, isolated hs-TnT rise >140 ng/l (n=360) or >500 ng/l (n=162) were not associated with mortality. Additional ECG and/or echocardiographic criteria plus hs-TnT >140 ng/l was associated with 30-day mortality (hazard ratio, HR, 4.92, 95% CI 1.34–18.1; p=0.017) and medium-term mortality (HR 3.44, 95% CI 1.13–10.5; p=0.030), whereas ECG and/or echocardiographic abnormalities with hs-TnT >500 ng/l was not (p=0.281 and p=0.123 for 30-day and medium-term mortality, respectively).

Conclusions: A definition for MI following CABG using hs-TnT with a cut point of 10-times 99th percentile upper reference limit and ECG and/or echocardiographic criteria predicts 30-day and medium-term mortality. These findings validate the Third Universal Definition of type 5 MI.

Keywords

Coronary artery bypass surgery, high-sensitivity troponin, myocardial infarction, Universal Definition

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Introduction

Cardiac troponins have been recommended by the Universal Definition of myocardial infarction (MI) as the preferred biomarkers for diagnosing MI after coronary artery bypass grafting (CABG),[1] due to superior sensitivity and specificity compared to traditional biomarkers such as creatine kinase MB.[2,3] Several studies have found that isolated troponin rise after CABG, measured with contemporary assays, independently predicts adverse outcomes.[3–7]

High-sensitivity troponin assays have recently been developed,[8] being more sensitive than contemporary assays at detecting lower troponin levels.[1,9] The properties and utility of these assay may be different after CABG, and

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there are no data about their use for the diagnosis of MI. The 2012 Third Universal Definition defined MI (type 5) after CABG as requiring two criteria: (1) cardiac biomarkers (with troponins preferred) rise >10-times 99% upper reference limit (URL) from a normal preoperative level; and (2) new pathological Q-waves or new left bundle branch block (LBBB) and/or imaging or angiographic evidence of new occlusion of native vessels or grafts, new regional wall motion abnormality, or loss of viable myocardium.[1]

We therefore assessed the ability of high-sensitivity troponin T (hs-TnT) to diagnose MI following CABG using several prespecified criteria including the Universal Definition and assessed its associations with mortality and morbidity.

Methods

Patient selection and data collection

Ethical approval of this study was obtained from our ethics review committee.

Patients undergoing isolated CABG without other concomitant cardiac surgery from the commencement of hs-TnT use from July 2010 to June 2012 were identified retrospectively from the cardiothoracic surgical unit database. Logistic EuroScore II, which predicts operative risk, was calculated.[10] Buckberg cold blood cardioplegia was used for on-pump CABG.

Electrocardiograms (ECGs) were performed multiple times until discharge. Transthoracic echocardiograms were performed as indicated clinically. New Q-waves or LBBB on the ECG or new regional wall motion abnormality on echocardiography were independently interpreted by two authors blinded to outcomes (TKMW and HDW), in accordance with the criteria of the Universal Definition.[1]

Mortality data were checked against New Zealand's national registry up until 31 March 2013. Thirty-day and medium-term mortality were prespecified as the primary outcomes. A composite of post-operative complications (renal failure, stroke, prolonged ventilation >24 hours, deep sternal wound infection, and return to theatre) were the secondary outcomes as determined according to the Society of Thoracic Surgeons definitions.[11]

Troponin assays and classification

The hs-TnT assay (Roche Elecsys), which is guideline compliant,[8] was introduced in July 2010. The 99th percentile URL of this assay is 14 ng/l.[8] The cut point commonly used clinically for the fourth-generation troponin T with a 10% coefficient of variation (0.03 ng/ml) when applied to the hs-TnT assay is 50 ng/l.[9] Patients routinely had hs-TnT measured 12–24 hours after surgery. The highest hs-TnT level was used for analyses.

Pre-operative troponin assays used at our hospital were the same hs-TnT. Two referral hospitals used the Abbott Architect troponin I assay with URL of 28 ng/l or the Siemens Dimension RxL troponin I assay with URL of 70 ng/l.[8] Baseline troponin levels measured >2 weeks before CABG were disregarded.

Patients were divided into three prespecified categories based on preoperative troponin levels: (1) stable baseline troponins: patients with preoperative levels below the 99th percentile URL for the assay used or with no troponin measurement and undergoing elective CABG; (2) elevated stable baseline troponins: patients with elevated preoperative troponins above the 99th percentile URL, with at least two measurements within 48 hours of each other, and the final preoperative level either lower or <20% higher than the earlier measurement; and (3) excluded: patients with elevated and rising, or no baseline troponin levels.

Two cut points for hs-TnT rise were prespecified: (1) 10-times 99th percentile URL[1] of the hs-TnT assay (i.e. 140 ng/l); and (2) 10-times the coefficient of variation of 10% for the previous cut point of the fourth-generation troponin assay of 50 ng/l[9] (i.e. 500 ng/l).

For patients with stable baseline troponins, a significant hs-TnT rise was defined as the post-operative hs-TnT being above the cut point. In patients with elevated stable baseline troponins, a significant hs-TnT rise required the post-operative hs-TnT to be above the cut point, and also a 20% rise from the preoperative level.

The prognostic significance of five prespecified potential criteria for the diagnosis of MI were: (1) hs-TnT rise >140 ng/l alone; (2) hs-TnT rise >500 ng/l alone; (3) new signs of MI on ECG and/or echocardiogram alone; (4) hs-TnT >140 ng/l plus ECG and/or echocardiographic criteria; and (5) hs-TnT rise >500 ng/l plus ECG and/or echocardiographic criteria.

Statistical analyses

Continuous and categorical variables are presented as mean±standard deviation or median (interquartile range, IQR) and *n* (%), respectively. Student t-test and Fisher's Exact test for two groups or analysis of variance (ANOVA) and chi-squared for three or more groups were used for univariate analyses. Kaplan–Meier curves and log-rank (Mantel-Cox) test were performed for longitudinal survival analysis.

Receiver operating characteristics (ROC) analysis was also used to assess how well combinations of post-operative hs-TnT levels and ECG and/or echocardiographic criteria correlated with mortality and morbidity. The areas under ROC curve (AUC) and corresponding 95% confidence intervals (CI) and *p*-values were calculated using the Wald Test for pairwise comparison with chance.

Baseline and operative variables with $p<0.10$ in univariate analyses were entered into multivariate analyses.

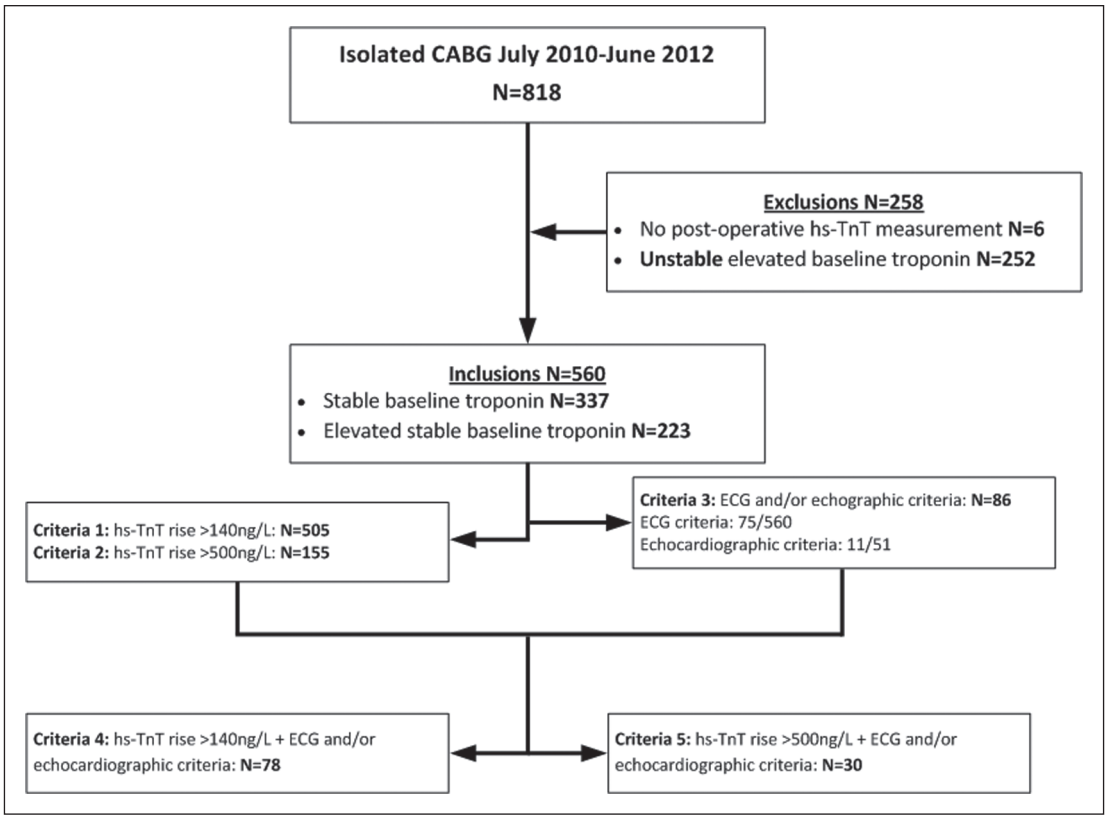

Figure 1. Study population.

Logistic regression was used to calculate odds ratios (OR) or Cox proportional hazards regression for hazard ratio (HR) and 95% CI. Independent predictors of five potential MI criteria as well as 30-day mortality, medium-term mortality, and composite morbidity were determined. Each potential MI criteria was individually added to the models of post-operative outcomes to see whether they predicted these outcomes.

All tests were two tailed and *p*-values less than 0.05 were deemed statistically significant. SAS version 9.1 (SAS Institute, Cary, NC, USA) and Prism version 5 (GraphPad Software, San Diego, CA, USA) were used for analyses.

Results

Study population

Figure 1 describes the study population. A total of 818 patients underwent isolated CABG during the 2-year study period. There were 258 patients excluded: six without post-operative hs-TnT measurements and 252 with elevated and rising preoperative troponins or lack of troponin measurements. There were 560 patients included: 337 having stable baseline troponins and 223 having elevated stable baseline troponins. Hs-TnT was measured on average 18.4±3.5 hours after beginning surgery. Mean follow up was 1.8±0.6 years, with all patients having at least 9 months follow up. New Q-waves or new LBBB were documented in 75 patients. Echocardiograms were performed in 51 patients, 11 of which showed new regional wall motion abnormalities. Only one post-operative coronary angiogram was performed, showing patent grafts and unchanged native vessels.

Clinical characteristics

Table 1 shows the baseline characteristics categorized by post-operative hs-TnT levels of ≤140, 141–500, and >500 ng/l. The medians (IQR) of hs-TnT in these groups were 116 (99–129), 282 (225–375), and 730 (603, 1100) ng/l respectively. There was no association between the time from operation to post-operative hs-TnT measurement and hs-TnT level (Pearson coefficient r=0.01, p=0.37).

Post-operative outcomes

Table 2 shows operative and post-operative variables according to post-operative hs-TnT levels. Thirty-day mortality, medium-term mortality, and composite morbidity were 1.8, 2.9, and 16.3% respectively.

Figure 2 shows the Kaplan–Meier survival curves for the five potential MI criteria. Isolated hs-TnT >140 ng/l was not associated with mortality (Figure 2a; p=0.521).

Table 1. Baseline characteristics.

Post-operative high-sensitivity troponin T levels (ng/L)	≤140 (n=38)	141-500 (n=360)	>500 (n=162)	P-value
Demographics				
Age (years)	61.4 (9.9)	64.2 (9.9)	65.1 (9.6)	0.105
Male (%)	76.3% (29)	80.8% (291)	80.2% (130)	0.800
Ethnicity (%)				0.150
Caucasian	57.9% (22)	58.3% (210)	46.3% (75)	
Maori/Pacific Islander	23.7% (9)	20.8% (75)	25.3% (41)	
Other	23.7% (9)	20.8% (75)	28.4% (46)	
Body mass index (kg/m^2)	29.6 (5.8)	29.4 (5.4)	28.4 (4.9)	0.102
Presentation				
Canadian Cardiovascular Society Class IV angina (%)	39.5% (15)	35.0% (126)	39.5% (64)	0.571
New York Heart Association Class IV dyspnoea (%)	5.3% (2)	2.5% (9)	6.2% (10)	0.109
Recent myocardial infarction within 6 weeks (%)	36.8% (14)	43.1% (155)	50.6% (82)	0.163
Pre-operative intra-aortic balloon pump (%)	7.9% (3)	5.8% (21)	10.5% (17)	0.166
Urgent operation (%)	71.1% (27)	70.3% (253)	73.5% (119)	0.759
Past medical history				
Myocardial infarction (%)	55.3% (21)	63.3% (228)	66.7% (108)	0.405
Percutaneous coronary intervention (%)	13.2% (5)	9.2% (33)	14.2% (23)	0.209
Coronary artery bypass grafting (%)	2.6% (1)	0.6% (2)	3.7% (6)	0.026
Congestive heart failure (%)	5.3% (2)	4.1% (15)	4.9% (8)	0.897
Atrial fibrillation (%)	2.6% (1)	6.7% (24)	7.4% (12)	0.565
Diabetes (%)	36.8% (14)	35.0% (126)	43.2% (70)	0.200
Diabetes on insulin (%)	10.5% (4)	7.5% (27)	14.2% (23)	0.055
Hypercholesterolemia	92.1% (35)	91.7% (330)	90.7% (147)	0.930
Hypertension	63.2% (24)	71.1% (256)	59.9% (109)	0.464
Current smoker (%)	15.8% (6)	13.6% (49)	12.3% (20)	0.837
Stroke (%)	5.3% (2)	5.6% (20)	4.9% (8)	0.959
Peripheral vascular disease (%)	0.0% (0)	10.3% (37)	13.0% (21)	0.062
Chronic respiratory disease (%)	13.2% (5)	17.8% (64)	19.8% (32)	0.622
Dialysis (%)	0.0% (0)	0.6% (2)	8.0% (13)	<0.001
Investigations				
Left main stem stenosis >50% (%)	55.3% (21)	39.2% (141)	48.1% (78)	0.044
Three-vessel disease (%)	71.1% (27)	77.2% (278)	87.0% (141)	0.014
Ejection fraction (%)				0.432
Normal (>50%)	73.7% (28)	74.7% (269)	67.3% (109)	
Mild impairment (40-50%)	13.2% (5)	14.2% (51)	14.8% (24)	
Moderate impairment (30-40%)	7.9% (3)	6.4% (23)	12.3% (20)	
Severe impairment (<30%)	5.3% (2)	4.6% (17)	5.6% (9)	
Estimated glomerular filtration rate (mL/min)	95 (34)	82 (25)	74 (35)	<0.001
Pre-operative troponin groups				<0.001
Normal (%)	84.2% (32)	62.2% (224)	50.0% (81)	
Stable elevated (%)	15.8% (6)	37.8% (136)	50.0% (81)	
EuroScore II[10]	1.8% (1.0%)	2.2% (3.1%)	2.7% (3.5%)	0.046

Isolated hs-TnT >500 ng/l was associated with mortality (HR 2.60, 95% CI 1.03–7.08; p=0.046; Figure 2b). ECG and/or echocardiographic criteria alone were also associated with mortality (HR 3.32, 95% CI 1.21–9.15; p=0.020; Figure 2c). When the ECG and/or echocardiographic criteria for MI were added to hs-TnT rise, the associations with mortality were strengthened. One-year survival rates for those with and without hs-TnT >140 ng/l and ECG and/or echocardiographic criteria were 92.% and 97.9% (HR 3.76, 95% CI 1.37–10.4; p=0.010; Figure 2d) and for hs-TnT >500 ng/l and ECG and/or echocardiographic criteria were 86.7 and 97.7% (HR 6.08, 95% CI 1.96–18.9; p=0.002; Figure 2e).

Receiver operating characteristics analyses

Table 3 lists the results from the ROC analyses. Dual criteria were best at detecting 30-day mortality (AUC

Table 2. Operative and post-operative variables.

Post-operative high-sensitivity troponin T levels (ng/L)	≤140 (n=38)	141-500 (n=360)	>500 (n=162)	P-value
Operation details				
Off-pump (%)	13.2% (5)	1.7% (6)	2.5% (4)	<0.001
Number of distal anastomoses				0.002
1	5.3% (2)	1.1% (4)	0.6% (1)	
2	28.9% (11)	16.1% (58)	10.5% (17)	
3	44.7% (17)	47.2% (170)	55.6% (90)	
4	18.4% (7)	31.9% (115)	23.5% (38)	
5	2.6% (1)	3.3% (12)	9.3% (15)	
6	0.0% (0)	0.3% (1)	0.6% (1)	
Left internal mammary artery graft (%)	94.7% (36)	98.3% (354)	96.3% (156)	0.204
Right internal mammary artery graft (%)	2.6% (1)	3.9% (14)	10.5% (17)	0.008
Radial artery graft (%)	18.4% (7)	26.1% (94)	19.1% (31)	0.164
Saphenous vein grafts (%)	86.8% (33)	93.3% (336)	95.7% (155)	0.129
Cardiopulmonary bypass time (minutes)	85 (32)	89 (23)	97 (33)	0.004
Aortic cross-clamp time (minutes)	54 (25)	59 (19)	63 (23)	0.080
Post-operative Outcomes				
ECG (new Q wave or left bundle branch block %)	18.4% (7/38)	13.1% (47/358)	13.3% (21/158)	0.630
Echocardiogram (new regional wall motion abnormalities %)	0.0% (0/1)	8.7% (2/23)	33.3% (9/27)	0.094
ECG and/or echocardiographic criteria (%)	18.4% (7/38)	13.7% (49/358)	19.0% (30/158)	0.271
Composite morbidity (%)	15.8% (6)	10.6% (38)	29.0% (47)	<0.001
Stroke (%)	0.0% (0)	1.1% (4)	1.9% (3)	0.603
Renal failure (%)	5.3% (2)	1.1% (4)	1.9% (3)	0.147
Prolonged ventilation >24hours (%)	10.5% (4)	6.7% (24)	22.8% (37)	<0.001
Deep sternal wound infection (%)	0.0% (0)	0.3% (1)	0.0% (0)	0.757
Reoperation (%)	2.6% (1)	3.9% (14)	6.2% (10)	0.430
Operation to discharge (days)	6.7 (2.8)	7.8 (5.6)	8.9 (5.7)	0.028
Re-admit to hospital within 30 days (%)	26.3% (10)	19.7% (71)	20.4% (33)	0.631
30-day mortality (%)	2.6% (1)	1.1% (4)	3.1% (5)	0.266
Discharge medications				
Aspirin (%)	97.3% (36/37)	98.9% (353/357)	98.7% (155/157)	0.716
Statin (%)	94.6% (35/37)	89.9% (321/357)	86.0% (135/157)	0.227
Beta-blocker (%)	89.2% (33/37)	78.7% (281/357)	73.9% (116/157)	0.113
Angiotensin converting enzyme blockers or Angiotensin II receptor blocker (%)	32.4% (12/37)	30.0% (107/357)	29.3% (46/157)	0.932

0.693, 95% CI 0.521–0.865; p=0.036) and medium-term mortality (AUC 0.682, 95% CI 0.521–0.844; p=0.027). Hs-TnT >140 ng/l and ECG and/or echocardiographic data were the only criteria predicting 30-day mortality (AUC 0.683, 95% CI 0.519–0.857; p=0.029) and medium-term mortality (AUC 0.621, 95% CI 0.507–0.743; p=0.045). For predicting composite morbidity, hs-TnT alone had the highest AUC (AUC 0.658, 95% CI 0.589–0.726; p<0.001), although dual criteria were nearly as good (AUC 0.645, 95% CI 0.577–0.714; p=0.002). Of the single criteria, the cut point of hs-TnT >500 ng/l had the highest AUC (AUC 0.603, 95% CI 0.548–0.658; p>0.001).

The hs-TnT levels with maximum sensitivity × specificity for detecting 30-day and medium-term mortality were 580 ng/l alone or 200 ng/l as dual criteria. Corresponding figures for detecting composite morbidity were 410 and 200 ng/l.

Multivariate analyses

Table 4 shows on multivariate analyses that the features associated with patients having hs-TnT >140 ng/l and ECG and/or echocardiographic criteria for MI (n=78/560, 13.9%) were Canadian Cardiovascular Society class 4 angina (p=0.017), and longer cardiopulmonary bypass time (p=0.048). The features associated with patients having hs-TnT >500 ng/l and ECG and/or echocardiographic criteria for MI (n=30/560, 5.4%) were dialysis (p=0.032) and longer cardiopulmonary bypass time (p=0.006).

Table 5 shows the variables predictive for 30-day and medium-term mortality. Both hs-TnT >140 ng/l with ECG

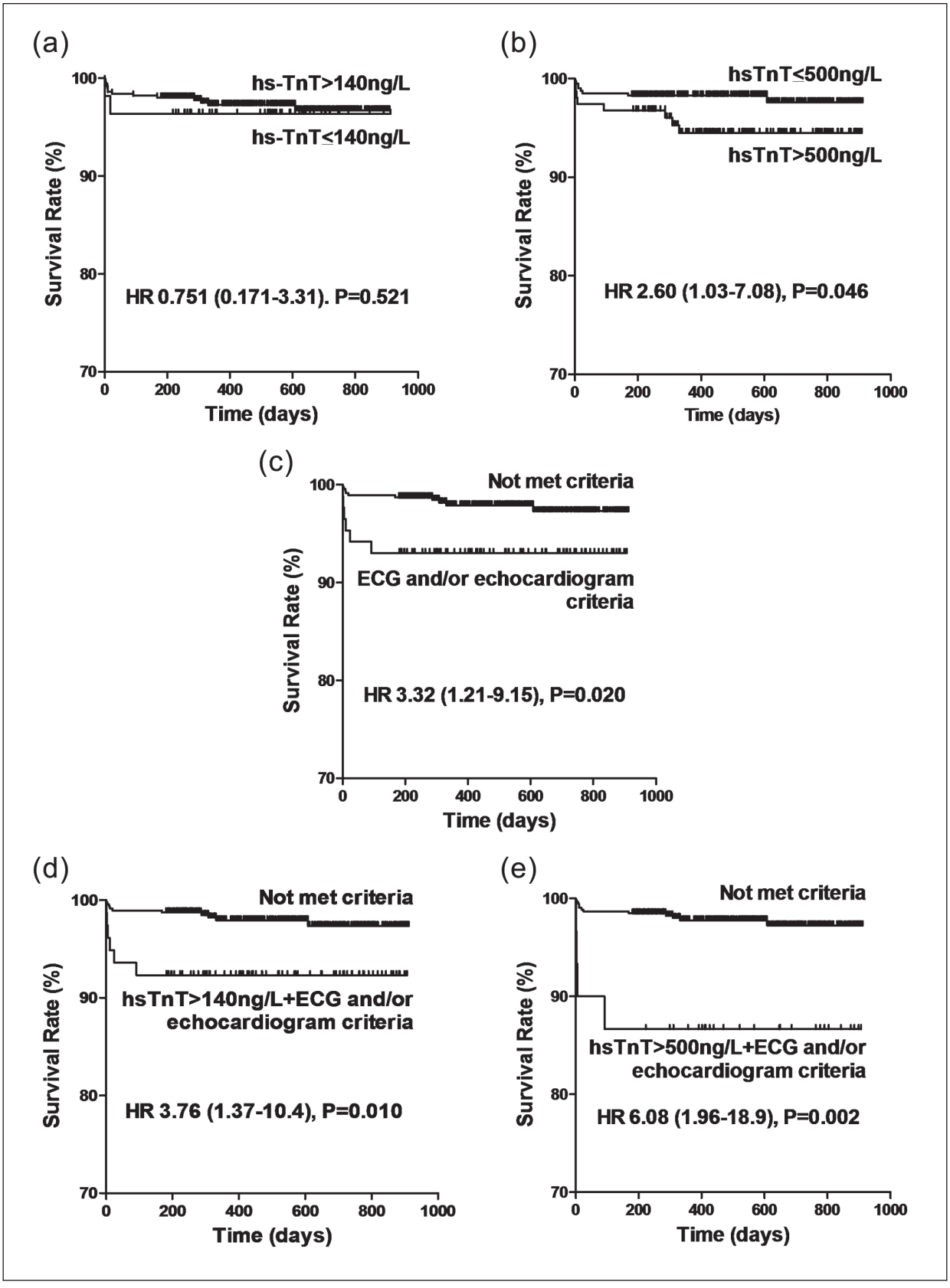

Figure 2. Kaplan–Meier survival curves for five MI criteria: (a) hs-TnT >140 ng/l; (b) hs-TnT >500 ng/l; (c) ECG and/or echocardiographic criteria; (d) hs-TnT >140 ng/l and ECG and/or echocardiographic criteria; (e) hs-TnT >500 ng/l and ECG and/or echocardiographic criteria.
Results of log-rank test are shown.

Table 3. Receiver-operating characteristics analysis and areas under curve with corresponding 95% confidence interval.

Criteria	Operative mortality	Medium-term mortality	Composite morbidity
hs-TnT (continues)	0.606 (0.379–0.832)	0.634 (0.465–0.804)	0.658 (0.589–0.726)
ECG and/or echocardiographic criteria	0.676 (0.512–0.840)	0.613 (0.490–0.737)	0.540 (0.494–0.586)
hs-TnT (continues) + ECG and/or echocardiographic criteria	0.693 (0.521–0.865)	0.682 (0.521–0.844)	0.645 (0.577–0.714)
hs-TnT >140ng/L	0.551 (0.420–0.683)	0.513 (0.429–0.598)	0.520 (0.483–0.558)
hs-TnT >500ng/L	0.565 (0.404–0.726)	0.617 (0.489–0.745)	0.603 (0.548–0.658)
hs-TnT >140ng/L + ECG and/or echocardiographic criteria	0.683 (0.519–0.857)	0.641 (0.527–0.763)	0.549 (0.503–0.594)
hs-TnT>500ng/L + ECG and/or echocardiographic criteria	0.625 (0.475–0.775)	0.601 (0.491–0.711)	0.561 (0.522–0.599)

All figures are areas under receiver-operative characteristics curve and 95% confidence intervals, hs-TnT = high-sensitivity troponin T.

Table 4. Multivariate predictors of troponin rise and criteria for myocardial infarction.

Predictors	OR	95%CI	P-value
hs-TnT >140ng/L (n=505)			
Peripheral vascular disease	11.5	0.74–179	0.082
Estimated glomerular filtration rate (per 10ml/min decrease)	1.15	1.04–1.27	0.024
Off-pump	0.10	0.04–0.32	<0.001
hs-TnT >500ng/L (n=155)			
Body mass index (per 1 kg/m^2)	0.96	0.92–1.00	0.075
Dialysis	8.78	1.79–43.1	0.008
Previous coronary artery bypass grafting	4.37	1.02–18.6	0.047
Three-vessel disease	1.75	0.97–3.15	0.063
Cardiopulmonary bypass time (per 10 minutes)	1.08	1.00–1.17	0.038
ECG and/or echocardiographic criteria (n=86)			
None			
hs-TnT >140ng/L + ECG and/or echocardiographic criteria (n=78)			
Canadian Cardiovascular Society Class IV angina	1.94	1.13–3.33	0.017
Cardiopulmonary bypass time (per 10 minutes)	1.09	1.00–1.18	0.048
hs-TnT >500ng/L + ECG and/or echocardiographic criteria (n=30)			
Diabetes on insulin	2.46	0.91–6.71	0.078
Dialysis	4.58	1.14–18.4	0.032
EuroScore II[10]	1.11	1.00–1.22	0.061
Cardiopulmonary bypass time (per 10 minutes)	1.17	1.05–1.31	0.006

OR = odds ratio, 95% CI = 95% confidence interval, hs-TnT high sensitivity troponin T.

and/or echocardiographic criteria and ECG and/or echocardiographic criteria alone predicted 30-day mortality (OR 6.12, 95% CI 1.50–25.0, p=0.012; OR 5.93, 95% CI 1.46–24.2, p=0.013, respectively). Other predictors of 30-day mortality were NYHA class 4 dyspnoea (p=0.016), not using left internal mammary grafts, (p=0.008), and return to theatre (p=0.049).

Factors predicting medium-term mortality were estimated glomerular filtration rate (p=0.021), not using left internal mammary grafts (p=0.006), and level of post-operative hs-TnT (p=0.045). Levels of hs-TnT >140 ng/l with ECG and/or echocardiographic criteria also predicted medium-term survival (HR 3.44, 95% CI 1.13–10.5; p=0.031) but hs-TnT >500 ng/l with ECG and/or echocardiographic criteria did not (p=0.125).

Table 6 shows the predictors of post-operative composite morbidity. These included Maori or Pacific Island ethnicity (p=0.021) use of an intra-aortic balloon pump (p<0.001), previous CABG (p=0.037), and cardiopulmonary bypass time (p=0.002).

The level of post-operative troponins was also predictive of composite morbidity (p=0.014). Isolated levels of hs-TnT >500 ng/l were predictive (p=0.005) as well as hs-TnT levels >500 ng/l and ECG and/or echocardiographic criteria for MI (p=0.022).

Table 5. Multivariate predictors of mortality.

Predictors	OR or HR	95%CI	P-value
30-day mortality			
Female	3.74	1.03–13.6	0.045
Maori/Pacific Islander	*3.25*	*0.82–13.0*	0.095
New York Heart Association Class IV dyspnoea	11.4	2.58–50.8	0.001
Left internal mammary artery graft	0.06	0.01–0.63	0.02
Post-operative hs-TnT (per 100ng/L)	1.07	0.93–1.23	0.36
hs-TnT >140ng/L	0.37	0.06–2.23	0.277
hs-TnT >500ng/L	0.84	0.21–3.34	0.803
ECG and/or echocardiographic criteria	4.68	1.28–17.2	0.020
hs-TnT >140ng/L + ECG and/or echocardiographic criteria	4.92	1.34–18.1	0.017
hs-TnT>500ng/L + ECG and/or echocardiographic criteria	2.59	0.46–14.6	0.281
Medium-term mortality	HR		
Estimated glomerular filtration rate (per 10ml/min decrease)	1.34	1.03–1.73	0.021
Left internal mammary artery graft	0.11	0.02–0.53	0.006
Post-operative hs-TnT (per 100ng/L)	1.04	1.00–1.08	0.045
hs-TnT >140ng/L	1.03	0.20–5.41	0.970
hs-TnT >500ng/L	1.51	0.51–4.42	0.456
ECG and/or echocardiographic criteria	3.28	1.08–9.98	0.036
hs-TnT >140ng/L + ECG and/or echocardiographic criteria	3.44	1.13–10.5	0.030
hs-TnT >500ng/L + ECG and/or echocardiographic criteria	2.73	0.76–9.80	0.123

OR = odds ratio, HR = hazards ratio, 95%CI = 95% confidence interval, hs-TnT = high-sensitivity troponin T.

Table 6. Multivariate predictors of composite morbidity.

Predictor	OR	95%CI	P-value
Maori/Pacific Islander	1.86	1.02–3.40	0.043
Pre-operative intra-aortic balloon pump	5.39	2.29–12.7	<0.001
Previous coronary artery bypass grafting	7.12	1.13–44.7	0.037
Ejection fraction (<40%)	1.95	0.95–4.01	0.072
EuroScore II[10]	1.09	1.01–1.16	0.035
Cardiopulmonary bypass time (per 10 minutes)	1.16	1.06–1.27	0.002
Post-operative hs-TnT (per 100ng/L)	1.06	1.01–1.10	0.014
hs-TnT >140ng/L	0.91	0.36–2.32	0.846
hs-TnT >500ng/L	2.20	1.27–3.82	0.005
ECG and/or echocardiographic criteria	1.64	0.84–3.21	0.151
hs-TnT >140ng/L + ECG and/or echocardiographic criteria	1.75	0.89–3.46	0.098
hs-TnT >500ng/L + ECG and/or echocardiographic criteria	3.02	1.18–7.76	0.022

OR = odds ratio, 95%CI = 95% confidence interval, hs-TnT = high-sensitivity troponin.

Discussion

There are several novel findings of this study. Firstly, using a guideline-compliant high-sensitivity assay,[8] dual criteria of hs-TnT levels >140 ng/l associated with ECG and/or echocardiographic criteria were predictive of 30-day and medium-term mortality after CABG. A higher cut point of >500 ng/l associated with ECG and/or echocardiographic changes was not associated with mortality.

Secondly, the finding of elevated hs-TnT >10-times the URL and associated ECG and/or echocardiographic evidence of MI validates the recommendation of Third Universal Definition of MI with hs-TnT.[1] Thirdly, higher hs-TnT levels predicted post-operative morbidity.

Prognostic value of isolated high-sensitivity troponin T rise

Post-operative hs-TnT alone as a continuous parameter independently predicted medium-term mortality and composite morbidity. Previous studies with various contemporary troponin T and troponin I assays have reported similar

findings.[3–6,12] The level of post-operative hs-TnT >140 ng/l (10-times the URL) was found in 90% of patients, whereas hs-TnT >500 ng/l (36-times the URL) were found in 29% of patients.

Isolated hs-TnT >140 ng/l was not associated with mortality or composite morbidity. Isolated hs-TnT >500 ng/l was associated with medium-term mortality on univariate analysis and predicted composite morbidity. These findings of a requirement of a high cut point are similar to the findings of other studies with various assays, including point of care, none of which are guideline compliant,[13] using cut points 7.8–170-times URL.[4,7,14,15] However, we found on multivariate analysis that isolated hs-TnT >500 ng/l was not related to mortality.

Hs-TnT >500 ng/l was an independent predictor of composite morbidity, consistent with elevation of hs-TnT being a marker of myocardial injury due to multiple causes and not restricted to ischaemia (e.g. heart failure, sepsis, renal failure).[16]

ECG and/or echocardiographic features of MI

This study shows that new signs of infarction on the ECG and/or evidence of new wall motion abnormality on echocardiography are important predictors of post-CABG mortality. The prevalence of ECG signs of infarction was relatively uniform across the three thresholds of hs-TnT rise, including below 140 ng/l. This suggests that if an isolated hs-TnT threshold is set too high, some patients with poor prognosis will be missed. ECG and/or echocardiographic criteria however did not predict composite post-operative morbidity, showing their specificity for MI.

There were 11 patients with new regional wall motion abnormalities out of 51 patients who had post-operative echocardiograms, all of whom had no new ECG changes but met the Universal Definition criteria for MI. The diagnosis of MI would have been missed if an echocardiogram was not performed in these patients.

Dual elevation of high-sensitivity troponin plus ECG and/or echocardiographic criteria

Our results showed that dual criteria are more prognostic of mortality than single criteria. Fourteen percent (78/560) of patients had an MI as defined by the dual criteria corresponding to the Universal Definition in our cohort, where the hs-TnT threshold was 140 ng/l (10-times 99th percentile URL). This criteria was the strongest predictor of both 30-day and medium-term mortality in both the ROC and multivariate analyses amongst the five criteria assessed. It utilises the strengths of both hs-TnT's sensitivity for myocardial injury with the specificity of new Q-waves and new LBBB on ECG for MI.

A higher threshold for hs-TnT >500 ng/l with ECG and/or echocardiographic criteria did not independently predict mortality at 30 days or medium term. This may be because the dual criteria, although very specific for adverse outcomes, compromise its sensitivity and therefore fails to capture the majority of post-operative mortality throughout the follow-up period. As the ECG and/or echocardiogram are very specific for MI after CABG, a lower threshold for hs-TnT rise for dual criteria than single criteria has better prognostic value, as shown by our results for hs-TnT >140 ng/l with ECG and/or echocardiogram criteria.

The highest AUCs for mortality we found with dual criteria were 0.64–0.70, while previous studies have reported area under ROC curves of 0.73–0.82 using single criteria with contemporary I or T troponin assays.[3,7] A potential reason for our finding of a lower area under the ROC curve may be that the superior sensitivity of the hs-TnT assay may have compromised its specificity and positive predictive value

The biomarker cut point for the Universal Definition for MI associated with CABG in the 2007 guidelines was 5-times the URL.[17] The increase to 10-times the URL threshold for biomarker elevation in the 2012 Universal Definition of MI URL was arbitrary.[1] Troponins are preferred because of their sensitivity and specificity.[1,9] Creatine kinase MB, although a proven predictor of mortality after CABG, has been shown to be inferior to troponins in predicting adverse cardiovascular outcomes.[2,3]

The importance of stable baseline troponin levels

To diagnose MI appropriately, a stable baseline of troponin is required. We thus included patients with 'normal stable baseline' and 'elevated stable baseline' troponins. Patients with elevated but rising troponin levels were excluded because post-operative troponin rises cannot be accurately distinguished from an index MI and be attributed to an MI after CABG.[18]

The Universal Definition for MI after CABG does not define the amount of rise required in patients with 'elevated stable baseline troponins'. We used the 20% elevation from baseline criteria, defined by the Universal Definition for MI with PCI.[1]

Independent predictors of MI and mortality

Unstable angina and cardiopulmonary bypass time were identified as independent predictors of MI (defined as hs-TnT >140 ng/l with ECG and/or echocardiographic criteria), both of which have been previously reported with other definitions of MI.[19]

In addition to MI, predictors of 30-day or medium term mortality were female sex, NYHA class IV dyspnoea, and reduced renal function, all of which are incorporated in the EuroScore[20] and the Society of Thoracic Surgeons score.[11] We also found, as reported by others,[21] that revascularization

with the left internal mammary artery was significantly associated with lower mortality.

Implications

The presence of predictors of MI should alert clinicians to the importance of their management. As the occurrence of MI is associated with mortality and other adverse outcomes such as inotropic requirement[5] and longer ventilation time,[19] treatments proven to improve survival after CABG, including aspirin,[22] statins,[23] and beta-blockers[24] should be administered. A lower threshold for angiography and return to theatre, in patients requiring inotropes or with prolonged ventilation should be considered.[4]

The 30-day mortality rate is similar to that reported for 2009 by the STS database; 1.8 vs. 1.9% STS.[25] However, the rate of MI we found (14%) is higher than previously reported using conservative definitions. This means that more patients will be labelled with the diagnosis. However, there is an opportunity to improve outcomes in these patients. More research is required to assess which therapies may reduce the occurrence of MI, and adverse outcomes after MI.

Study limitations

This is a retrospective observational study from one centre. About 20% of patients were excluded because of rising or missing baseline troponin levels. The timing of troponin measurements post-operatively was at 12–24 hours and not at a fixed time. The moderate cohort size means some of the outcomes might have been underpowered for analyses. A small number of patients had post-operative cardiac imaging such as echocardiography, based on clinical indications.

Conclusions

This study shows the utility of hs-TnT in detecting MI using a cut point of 10-times 99th percentile URL with ECG and/or echocardiographic findings. Diagnosis of MI with dual criteria was related to 30-day and medium-term mortality. These results validate the Third Universal Definition of MI using hs-TnT as the biomarker.

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Conflict of interest

HW has received research grants from Sanofi Aventis, Eli Lilly, Medicines Company, Pfizer, Roche, Johnson & Johnson, Schering Plough, Merck Sharpe & Dohme, Astra Zeneca, GlaxoSmithKline, Daiichi Sankyo Pharma Development, and Bristol-Myers Squibb and has served on advisory boards for Merck Sharpe & Dohme, Roche, and Regado Biosciences. TW, RS, TR, NK and GG declare that they have no conflicts of interest.

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