Outcomes associated with small changes in normal-range cardiac markers

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100.02.12

Data collection

- Patients were included
  - older than 18 years
  - suspected of having ACS
  - between June 1999 and August 2001
  - 12-lead electrocardiogram (ECG) or cardiac biomarkers
  - cardiac marker (troponin I, troponin T, or CK-MB) measured twice within 6 hours of presentation

Predictor variables

- 15%: change in concentration of the institutional upper limit of normal was selected
- Patients was divided into 3 groups
  - Decreasing cardiac markers>15%
  - stable markers: no absolute change greater than 15%
  - increasing markers>15%

Table 1 Site-specific marker cutpoints, with calculation of 15% change relative to the institutional upper limit of normal, that defined moving marker results

	CK-MB		Troponin	
	Institutional upper limit of normal	Minimum change not to be considered stable	Institutional upper limit of normal	Minimum change not to be considered stable
Site 1	3.50	0.53		
Site 2	5.80	0.87	0.25	0.04
Site 3	5.80	0.87	0.25	0.04
Site 4	5.80	0.87	0.25	0.04
Site 5	5.00	0.75	2.00	0.30
Site 6a*	7.00	1.05	0.20	0.03
Site 6b	5.00	0.75	1.50	0.23
Site 7	5.00	0.75	0.20	0.03
Site 8	8.00	1.20	2.00	0.30
Site 9	5.00	0.75	2.00	0.30

* Site 6 used 2 different assays during the study period.

- The institutional upper limit of normal for troponin was a factor of 10 lower than other sites; troponin levels at this site were not included in analysis.

- positive testing
  - during their hospital visit
  - within 30 days of the ED visit
  - greater than 70% stenosis
  - positive myocardial perfusion imaging
  - positive noninvasive provocative test for ischemia

- Of 17713 patient visits included in i*trACS
  - 2623 had either 2 troponins or 2 CK-MB assays performed within 6 hours
    - 85 had a positive troponin
    - 186 had a positive CK-MB
    - 164 had both a positive troponin and a positive CK-MB
    - 26 additional subjects with only 1 troponin at site 2
- these were also excluded

Table 2 Demographics, risk factors, and outcomes for patients with rising, falling, or stable troponin

	Change in Troponin (n = 2021)		
	Decreasing	Stable	Increasing
Age (y)	60.4 (15.7)	55.1 (14.6)	56.8 (15.3)
Female	22 (59.5)	1016 (52.3)	15 (60.0)
Male	15 (40.5)	925 (47.7)	10 (40.0)
White	20 (54.1)	822 (42.3)	12 (48.0)
African American	7 (18.9)	711 (36.6)	9 (36.0)
Other	10 (27.0)	408 (21.0)	4 (16.0)
Diabetes	8 (25.0)	404 (29.3)	10 (45.5)
Hypertension	26 (81.3)	1031 (74.8)	17 (77.3)
Hyperlipidemia	9 (28.1)	483 (35.1)	6 (27.3)
Angina	11 (34.4)	217 (15.7)	7 (31.8)
CAD	13 (40.6)	478 (34.7)	8 (36.4)
CHF	2 (6.3)	156 (11.3)	3 (13.6)
Current smoker	5 (27.8)	643 (46.8)	7 (41.2)
Recent smoker	2 (11.1)	135 (9.8)	4 (23.5)
ECG diagnostic category			
Acute MI	0 (0.0)	13 (0.7)	0 (0.0)
Acute ischemia	1 (2.8)	95 (5.2)	2 (8.7)
Early repolarization	1 (2.8)	47 (2.6)	0 (0.0)
Nondiagnostic	27 (75.0)	992 (54.7)	16 (69.6)
Normal	7.0 (0.2)	665.0 (0.4)	5.0 (0.2)
ACI-TIPI* (n = 1577)	35.9 (19.2)	27.6 (16.3)	33.0 (16.6)
ACS	11 (29.7)	275 (14.2)	8 (32.0)

Data are given as means and SDs for continuous variables, and frequencies and percents for categorical variables.
CAD, coronary artery disease; CHF, congestive heart failure.
* The ACI-TIPI could not be computed for all subjects due to missing data.

- 2162 patient visits were included, 2021 patient visits had 2 troponin assays

Table 3 Demographics, risk factors, and outcomes for patients with rising, falling, or stable CK-MB

	Change in CK-MB (n=1311)		
	Decreasing	Stable	Increasing
Age (y)	52.7 (13.5)	54.0 (14.6)	57.9 (16.8)
Female	33 (36.3)	601 (50.6)	18 (54.5)
Male	58 (63.7)	586 (49.4)	15 (45.5)
White	42 (46.2)	540 (45.5)	20 (60.6)
African American	43 (47.3)	515 (43.4)	11 (33.3)
Other	6 (6.6)	133 (11.2)	2 (6.1)
Diabetes	23 (33.8)	235 (28.6)	13 (54.2)
Hypertension	52 (76.5)	609 (74.0)	19 (79.2)
Hyperlipidemia	26 (38.2)	312 (37.9)	8 (33.3)
Angina	16 (23.5)	160 (19.4)	6 (25.0)
CAD	28 (41.2)	261 (31.7)	10 (41.7)
CHF	8 (11.8)	75 (9.1)	3 (12.5)
Current smoker	29 (44.6)	430 (48.0)	6 (25.0)
Recent smoker	8 (12.3)	87 (9.7)	5 (20.8)
ECG diagnostic category			
Acute MI	0 (0.0)	6 (0.5)	0 (0.0)
Acute ischemia	4 (4.7)	53 (4.8)	2 (6.7)
Early repolarization	3 (3.5)	28 (2.5)	0 (0.0)
Nondiagnostic	50 (58.8)	605 (54.9)	20 (66.7)
Normal	28 (32.9)	410 (37.2)	8 (26.7)
ACI-TIPI* (n = 1125)	28.0 (17.0)	27.2 (16.1	28.2 (20.1
ACS	14 (15.4)	174 (14.6)	8 (24.2)

Data are given as means and SDs for continuous.
CAD, coronary artery disease; CHF, congestive heart failure.
* The ACI-TIPI could not be computed for all subjects due to missing data variables and frequencies and percents for categorical variables.

- 1311 patient visits had 2CK-MB assays

Table 4 Outcomes stratified by marker changes and compared with 30-day adverse events

	Change in troponin				Change in CK-MB			
	Stable or decreasing		Increasing		Stable or decreasing		Increasing	
	n	%	n	%	n	%	n	%
Positive testing	224	12.1	6	31.6	169	13.2	6	18.2
Revascularization	70	3.8	4	21.1	49	3.8	3	9.1
MI	27	1.5	0	0.0	15	1.2	1	3.0
Death	7	0.4	0	0.0	2	0.2	0	0.0

Positive testing was defined as greater than 70% stenosis in any vessel at cardiac catheterization, positive myocardial perfusion imaging, or a positive noninvasive provocative test for ischemia. Revascularization was defined as documentation of any percutaneous coronary intervention, or a DRG code indicating revascularization. Myocardial infarction was defined based on documented evidence or a DRG code of acute MI.

- raw outcomes associated with changing troponin and CK-MB.

Table 5 Logistic regression models showing the odds ratios for predicting ACS given increasing or decreasing cardiac markers compared with stable cardiac markers

		OR	95% CI
Decreasing troponin	Versus stable	1.03	0.30-3.51
Increasing troponin	troponin	3.59	1.40-9.21
Decreasing troponin	Versus stable	1.19	0.33-4.23
Increasing troponin	troponin	4.81	1.60-14.46
ACI-TIPI		1.03	1.02-1.04
Decreasing CK-MB	Versus stable	1.06	0.59-1.92
Increasing CK-MB	CK-MB	1.87	0.83-4.20
Decreasing CK-MB	Versus stable	1.13	0.59-2.18
Increasing CK-MB	CK-MB	1.37	0.49-3.85
ACI-TIPI		1.03	1.02-1.05

Unadjusted models and models adjusted for probability of ischemia defined by ACI-TIPI are shown. OR indicates odds ratio.

- Patients with both increasing and decreasing troponin had greater odds of ACS than patients with stable troponin
- Patients with decreasing CK-MB had lower odds of ACS than those with stable CK-MB
- Those with increasing CK-MB had similar odds of ACS to those with a stable CK-MB.

Discussion

- **small changes in troponin** not exceeding the institutional upper limit of normal are associated with **increased risk of ACS**
- a **decreasing troponin** did not portend ACS despite the fact that theoretically it could be the result of a resolving MI, which could also **be associated with ACS**

- Because the odds of adverse events are more than **tripled** when marker troponin was increasing, this suggests that even the **smallest increases in troponin are clinically significant**
- We found **no differences** between those with **a stable CK-MB** and those with either an **increasing or decreasing CK-MB**
- The significance of this finding is unclear but may reflect the **lower specificity of CK-MB**

- the **ECG was normal** or nondiagnostic in approximately **90% of all patients**
- **Small changes in troponin** identify a cohort of patients at risk for ACS **not** otherwise **detected by the ECG**

Conclusions

- Any **increase in troponin** concentration **within 6 hours of ED evaluation**, is associated with an **increased risk of ACS**
- it will hopefully prompt further research into how patients, with troponin changes below the upper limit of normal, should be managed

Thank you for attention