Prognostic Value of Troponins in Patients with Non-ST-segment Elevation Acute Coronary Syndromes and Chronic Kidney Disease

Address for correspondence:
Chiara Melloni, MD, MHS
Duke Clinical Research Institute
2400 Pratt St.
Durham, NC, 27705, USA
mellooo4@mc.duke.edu.

Chiara Melloni, MD, MHS, Karen P. Alexander, MD, Sarah Milford-Beland, MS, L. Kristin Newby, MD, MHS, Lynda A. Szczech, MD, Charles V. Pollack, JR, MD, MA,* J. Douglas Kirk, MD,† Robert H. Christenson, PhD,‡ Robert A. Harrington, MD, W. Brian Gibler, MD,§ E. Magnus Ohman, MD, Eric D. Peterson, MD, MPH, Matthew T. Roe, MD, MHS, for the Crusade Investigators
Division of Cardiology and Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina; *Emergency Department, Pennsylvania Hospital, Philadelphia, Pennsylvania; †University of California Davis Medical Center, Sacramento, California; ‡University of Maryland School of Medicine, Baltimore, Maryland; §Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohia, USA

ABSTRACT

Background: The prognostic value of cardiac troponins (cTn) in patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS) and chronic kidney disease (CKD) is debated.
Hypothesis: We tested the performance of cTnI and cTnT for risk stratification in patients with CKD and evaluated the prognostic significance of cTnI and cTnT elevations by their magnitude across the range of CKD severity.
Methods: We examined correlations among cTn elevation, CKD, and in-hospital mortality in 31,586 high-risk patients with NSTE ACS included in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines initiative (CRUSADE). Cardiac tropinins I and T levels were categorized as ratios of each site's upper limit of normal (ULN) for myocardial necrosis: normal (cTn ratio $\leqslant 1 \times$ ULN), mild (cTn ratio >1–$3 \times$ ULN), and major (cTn ratio $>3 \times$ ULN) elevation. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease equation. Stages of CKD were categorized as normal to mild (eGFR >60 mL/min), moderate (eGFR 30–60 mL/min), or severe (eGFR <30 mL/min).
Results: Mortality increased more steeply across CKD stages (2.0%–12.9%) than across cTn ratio categories (2.7%–5.4%). In normal or mild CKD, mortality was low regardless of cTn elevations. In moderate CKD, mortality increased incrementally with cTnI (3.3% versus 5.4% versus 7.4%) and cTnT (3.7% versus 5.3% versus 7.3%) elevation. Among severe CKD patients, only major cTn elevations further distinguished risk (cTnI: 10.1% versus 9.7% versus 14.6%; cTnT: 7.0% versus 5.7% versus 14.0%).
Conclusions: In patients with CKD, cTnI and cTnT perform equally in differentiating short-term prognosis following NSTE ACS; however, the prognostic impact of cTn is dependent upon the degree of CKD severity.

Key words: cardiac troponins, non-ST-segment, elevation acute coronary syndromes, chronic kidney disease, prognostic indicators

Introduction

Cardiac troponins (cTn) are specific markers of myocardial necrosis—are powerful tools for risk stratification and therapeutic decision-making in patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS).[1] Chronic kidney disease (CKD) is increasingly common[2] and is also an independent predictor of adverse outcomes in NSTE ACS patients.[3,4] The interpretation of cTn levels in the setting of CKD is controversial, leaving uncertainty regarding the degree of cTn elevation indicative of increased risk and the clinical significance of minor cTn elevations.[5–7]

The relative prognostic value of cTnI versus cTnT and the clinical significance of troponin elevation continue to be elusive in CKD patients.[8] Therefore, among patients with NSTE ACS enrolled in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) initiative, we tested the relative performance of cTnI and cTnT for risk stratification in patients with CKD and evaluated the prognostic significance of cTnI and cTnT elevations by their magnitude across the range of CKD severity. We sought to clarify the nature of the association between troponin elevation, CKD, and the risk of short-term death following NSTE ACS.

Methods

The CRUSADE initiative is an observational registry of patients with high-risk NSTE ACS admitted to US hospitals

Received: May 11, 2007
Accepted: June 5, 2007

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20210

since November 2001. Data collection in CRUSADE is described elsewhere.[9]

Inclusion criteria are acute ischemic symptoms at rest ⩾10 min within 24 h of hospital arrival and 1 of the following high-risk features: ST-segment depression ⩾0.5 mm, transient ST-segment elevation 0.5–1.0 mm (lasting for <10 min), and/or positive cardiac markers (elevated cTnI or T and/or creatine kinase-MB >upper limit of normal [ULN] for the local laboratory assay).

Study Population

Overall, 31,586 patients of the 38,331 CRUSADE patients admitted at 404 hospitals from 3/2003 through 3/2005 were included. We excluded 696 patients who transferred out, 2,952 who transferred in from another hospital, 1,038 with inadequate troponin data, and 2,059 with missing data for variables (age, sex, race, creatinine level) used to calculate estimated glomerular filtration rate (eGFR) with the Modification of Diet in Renal Disease (MDRD) formula.

Categorization of Troponin Data

The CRUSADE initiative collects cTn data including assay type (I or T), ULN for determining definite myocardial necrosis, and absolute cTn value. Sites document cTn values at baseline (first troponin sample drawn after presentation) and peak troponin level (maximum value recorded during hospitalization). Troponin values were categorized according to multiples of the ULN defined by the maximum troponin ratio (highest recorded troponin value/ULN) as follows: ⩽1 × ULN (normal), >1–3× ULN (minor troponin elevation), and >3 × ULN (major troponin elevation). If the peak troponin value was captured >24 h from hospital presentation, the baseline value was used for determining maximum troponin ratios.

Categorization of Chronic Kidney Disease

The abbreviated MDRD formula was used to calculate the eGFR ([mL/min/1.73 m^2 of body surface area] = 186 × [serum creatinine in mg/dL]$^{-1.154}$ × [age in years]$^{-0.203}$ × [0.742 if female] × [1.210 if African-American]).[10] Patients were divided into groups: stage 1–2 (eGFR >60 mL/min, normal and mild CKD), stage 3 (eGFR 30–60 mL/min, moderate CKD), and stage 4–5 (eGFR <30 mL/min, severe CKD and end-stage renal disease).[11]

Statistical Methods

Baseline characteristics, medication and procedure use, hospital features, and in-hospital outcomes were compared across troponin ratio categories for each assay type (I and T). Because trends were similar regardless of assay type, the overall population was also characterized by troponin elevation category. Continuous variables are described as medians (with 25th and 75th percentiles) and categorical variables as frequencies. Continuous variables were compared using Jonckheere-Terpstra tests, and categorical variables using Cochran-Armitage Trend tests.

Unadjusted mortality rates were calculated for each troponin category and assay type across renal function groups. A subgroup analysis excluding patients receiving dialysis at hospital presentation was performed to eliminate any confounding effect of dialysis on the relationship between troponin elevation and mortality. Mortality estimates were adjusted for demographics, baseline characteristics, and hospital features that may influence the risk of in-hospital mortality.[12] Because patients within a hospital were more likely to be similar, all adjusted analyses were performed using generalized estimating equation models to account for correlations among clustered responses (e.g., within-hospital correlations).[13] All odds ratios were reported with the troponin ratio of ⩽1 ×ULN as the reference group. A p-value <0.05 was considered statistically significant. All analyses were performed using SAS software (version 8.2, SAS Institute, Cary, NC, USA).

Results

Categories of Troponin Elevation and Chronic Kidney Disease

Most patients (80.4%) were evaluated with cTnI assays. Overall, 5,529 patients (17.5%) had normal troponin values, 5,214 (16.5%) had mild values, and 20,843 (66.0%) had major troponin elevations. A total of 17,743 patients (56.2%) had normal or mild CKD, 10,273 patients (32.5%) had moderate CKD, and 3,570 patients (11.3%) had severe CKD, of which 896 (2.8%) were on dialysis.

Patient Characteristics, In-hospital Treatment, and Clinical Outcomes by Troponin Ratio Categories

Compared with those without troponin elevation, patients with troponin elevation were older, more likely to have signs of heart failure at presentation, and more likely to have moderate and severe CKD (Table 1).

Treatment differences during the hospital phase of care were noted across troponin ratio categories (Table 2).

The incidence of in-hospital adverse clinical outcomes increased substantially across all categories of troponin elevation, with the highest incidence in patients with major troponin elevations (Table 3).

Relations between cTnI and cTnT Elevation, Chronic Kidney Disease, and Mortality

The unadjusted incidence of death was analyzed across the spectrum of CKD overall and by degree of cTnI and cTnT elevation. A sixfold increase in short-term mortality was observed between patients with normal to mild CKD (2.0%) and those with severe CKD (12.9%) (Figure 1). When the incidence of death was analyzed separately for cTn ratio categories, patients with normal to mild CKD had low mortality regardless of troponin elevation, both with cTnT (1% versus 2.2% versus 2.6%) and with cTnI (1.7% versus 2.1% versus 2.1%). Among patients with moderate CKD, the incidence of death increased progressively with both cTnI (3.3% versus 5.4% versus 7.4%) and cTnT (3.7% versus 5.3% versus 7.3%) elevations. Among patients with severe CKD, the mortality rate was higher only when troponin elevations were major, without appreciable differences between cTnI (10.1% versus 9.7% versus 14.6%) and cTnT (7% versus 5.7% versus 14%) elevations in predicting

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20210

TABLE 1: Patient characteristics by troponin ratio category

Characteristic	Overall (N = 31, 586)	cTn ratio ⩽ 1× ULN (n = 5, 529)	cTn ratio >1–3× ULN (n = 5, 214)	cTn ratio >3 × ULN (n = 20, 843)
Demographics (%)				
Median age (y)[a]	70 (57, 80)	66 (55, 77)	71 (58, 80)	70 (58, 81)
Male sex	58.6	59.8	55.3	59.2
White race	80.4	77.2	77.4	81.9
Medical history (%)				
Hypertension	71.7	73.4	74.7	70.5
Diabetes mellitus[b]	33.9	34.4	35.9	33.2
Current/recent smoking	24.8	23.7	22.7	25.6
Hyperlipidemia	49.5	54.0	49.2	48.4
Prior stroke	11.1	9.3	11.6	11.5
Prior myocardial infarction[b]	30.8	32.4	32.0	30.2
Prior CHF	20.1	15.9	23.3	20.4
Prior percutaneous coronary intervention	21.5	29.3	23.6	18.9
Prior coronary artery bypass grafting	20.9	24.9	22.5	19.5
Presenting characteristics (%)				
ST depression	36.0	52.5	29.2	33.3
Transient ST elevation	6.8	10.3	4.4	6.5
Signs of CHF	26.6	18.9	28.1	28.3
Heart rate (bpm)[a]	84 (71, 100)	80 (69, 95)	85 (72, 100)	86 (72, 102)
Systolic blood pressure (mmHg)[a]	145 (125, 167)	148 (129, 169)	146 (126, 168)	144 (124, 166)
Chronic kidney disease stages, eGFR mL/min (%)				
<30	11.3	7.5	12.5	12.0
30–60	32.5	29.7	33.9	32.9
>60	56.2	62.8	53.6	55.0

p-values across categories of troponin elevation are <0.0001, except where indicated. [a]Presented as median (25th, 75th percentiles). [b] p<0.01.
Abbreviations: CHF = congestive heart failure, eGFR = estimated glomerular filtration rate, Tn = troponin, ULN = upper limit of normal.

mortality. The relationship between troponin elevation and mortality in patients with severe CKD did not change substantially when dialysis patients were excluded from the analysis.

After adjustment, the level of troponin elevation was only associated with in-hospital mortality among patients with moderate CKD and major cTnI elevations (odds ratio [OR] 1.84; 95% confidence interval [CI] 1.34–2.54, p<0.0012).

Discussion

In this high-risk NSTE ACS population, 82% of patients had elevated troponins and 44% had moderate to severe CKD. Patients with major troponin elevations had a two fold absolute increase in risk of death compared with patients with normal troponin values. In contrast, patients with severe CKD had a sixfold increase in risk of death compared with patients with normal renal function. The troponin level associated with increased risk differed as a function of the severity of kidney disease.

TABLE 2: Medications and in-hospital procedures by troponin ratio category[a]

	Overall (n = 31, 586)	cTn ratio ⩽ 1× ULN (n = 5, 529)	cTn ratio >1–3× ULN (n = 5, 214)	cTn ratio >3 × ULN (n = 20, 843)
Medication (%)				
Aspirin	95.1	94.3	94.3	95.6
Heparin, any	86.6	77.1	83.8	89.9
Glycoprotein IIb/IIIa inhibitors	43.1	28.8	32.5	49.8
Beta-blockers	88.0	82.0	85.9	90.2
Clopidogrel	52.3	47.1	48.3	54.8
Angiotensin-converting enzyme inhibitors	49.9	45.3	49.8	51.2
Procedures (%)				
Cardiac catheterization	84.5	78.1	79.5	87.6
Percutaneous coronary intervention	50.3	46.7	46.9	52.2
Coronary artery bypass grafting	13.4	10.0	12.4	14.6

[a] For eligible patients without listed contraindications. p-values across categories of troponin elevation are <0.001. *Abbreviations*: Tn = troponin ULN = upper limit of normal.

TABLE 3: Unadjusted in-hospital clinical outcomes by troponin ratio category

Outcome (%)	Overall (n = 31, 586)	cTn ratio ⩽ 1× ULN (n = 5, 529)	cTn ratio >1–3× ULN (n = 5, 214)	cTn ratio >3 × ULN (n = 20, 843)
Death	4.7	2.7	4.1	5.4
Cardiogenic shock	2.6	1.9	2.0	3.0
Congestive heart failure	8.7	6.1	8.5	9.5
Any red blood cell transfusion	14.9	11.4	14.1	16.1

p-values across categories of troponin elevation are <0.001. *Abbreviations*: Tn = troponin, ULN = upper limit of normal.

Risk Stratification with Troponin Levels in Patients with Chronic Kidney Disease

The prognostic significance of elevated troponin among patients with NSTE ACS and CKD has been controversial.[14,15] Previous reports demonstrated that cTnT was more frequently elevated than cTnI in patients with CKD without evidence of myocardial injury, and cTnI appeared to be a superior marker of cardiac injury in patients undergoing dialysis.[5,16]

Conversely, recent analyses report that cTnT maintains its predictive value for the short- and long-term risk of death or myocardial infarction in ACS patients across all degrees of kidney disease.[7,8,17,18] These contradictory results on the prognostic power of troponins may be explained by the use of different generations of troponin assays, as well as variability in the threshold of troponin chosen among different studies. Troponin I and T also have differences in cellular distribution, kinetics of release patterns, and biochemical modification that are not fully understood in patients with renal insufficiency.[6,7] We know that minor troponin elevations are frequently found among patients with severe CKD, but patients enrolled in CRUSADE also have symptoms thought to be attributable to ischemia. Moreover, because it would be cumbersome to analyze troponin results in a core laboratory in an observational analysis such as CRUSADE, we rely on best available data from local laboratory assays. Evaluating cTnI and cTnT as a function of each hospital's ULN, we found no substantial differences between the prognostic information from cTnI and cTnT.

We demonstrate that troponin was most prognostic among patients with moderate CKD. Owing to the high-risk nature of those with severe CKD, only major troponin elevations added any information in this group. The prognostic significance of troponin elevations in NSTE ACS may be strongly influenced by the presence of concomitant kidney disease and other baseline comorbidities. Therefore, the initial management of patient with NSTE ACS should

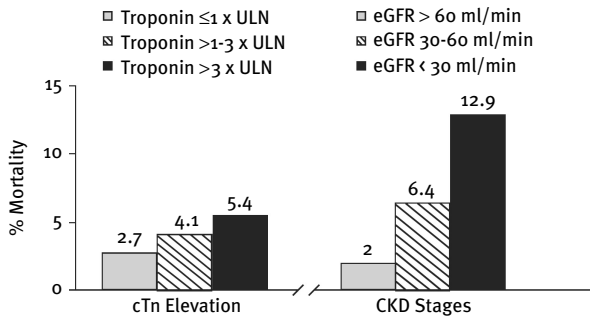

Figure 1: Unadjusted in-hospital mortality rates by troponin ratio categories (left) and degree of chronic kidney disease (right).

take into account the presence of CKD and the degree of troponin elevation equally, to ensure a balanced approach to treatment.

Limitations

Only baseline and peak troponin values were collected, so we could not assess serial troponin measurements. Furthermore, lacking information on the specific manufacturer of cTnI assay, these results represent composite findings, and we cannot exclude the possibility of variation among commercially available assays. Also, cTnT and cTnI were evaluated separately because patients who had cTnT obtained differed from those who were evaluated with cTnI. We defined the categories of troponin elevation using the maximum troponin ratio, but this technique for normalizing results from different troponin assays has not been validated in ACS populations. Finally, we did not assess long-term prognosis because CRUSADE is limited to the in-hospital period.

Conclusion

Both cTnI and cTnT are equal at prognostic differentiation in patients with CKD. However, in patients with NSTE ACS, cardiac troponin elevation increases risk two fold, while CKD increases risk sixfold from normal to a severe degree. The short-term prognostic value of cTn elevations must be considered in the context of CKD severity.

Acknowledgments

The CRUSADE initiative is funded by Schering-Plough Corporation. Bristol-Myers Squibb/sanofi-aventis Pharmaceuticals Partnership provides additional funding support. Millennium Pharmaceuticals, Inc., also provided funding for this work. We would like to thank Amanda McMillan for her editorial assistance.

References

1. Newby LK, Goldmann BU, Ohman EM: Troponin: an important prognostic marker and risk-stratification tool in non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol* 2003;41:S31–S36
2. Al Suwaidi J, Reddan DN, Williams K, Pieper KS, Harrington RA, et al.: GUSTO-IIb, GUSTO-III, PURSUIT. Global use of strategies to open occluded coronary arteries. Platelet glycoprotein IIb/IIIa in unstable angina: Receptor suppression using integrilin therapy; PARAGON-A investigators. Platelet IIb/IIIa antagonism for the reduction of acute coronary syndrome events in a global organization network. Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. *Circulation* 2002;106(8):974–980
3. Gibson CM, Dumaine RL, Gelfand EV, Murphy SA, Morrow DA, et al., TIMI Study Group: Association of glomerular filtration rate on presentation with subsequent mortality in non-ST-segment elevation acute coronary syndrome; observations in 13,307 patients in 5 TIMI trials. *Eur Heart J* 2004;25(22):1998–2005
4. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, et al.: Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004;351(13):1285–1295
5. McLaurin MD, Apple FS, Voss EM, Herzog CA, Sharkey SW: Cardiac troponin I, cardiac troponin T, and creatine kinase MB in dialysis patients without ischemic heart disease: evidence of cardiac troponin T expression in skeletal muscle. *Clin Chem* 1997;43(6 Pt. 1):976–982
6. Freda BJ, Tang WH, Van Lente F, Peacock WF, Francis GS: Cardiac troponins in renal insufficiency: review and clinical implications. *J Am Coll Cardiol* 2002;40:2065–2071
7. Hamm CW, Giannitsis E, Katus HA: Cardiac troponin elevations in patients without acute coronary syndrome. *Circulation* 2002;106(23):2871–2872
8. Aviles RJ, Askari AT, Lindahl B, Wallentin L, Jia G, et al.: Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med* 2002;346(26):2047–2052
9. Hoekstra JW, Pollack CV Jr, Roe MT, Peterson ED, Brindis R, et al.: Improving the care of patients with non-ST-elevation acute coronary syndromes in the emergency department: the CRUSADE Initiative. *Acad Emerg Med* 2002;9(11):1146–1155
10. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, et al.: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999;130(6):461–470
11. *Am J Kidney Dis* Executive summary: K/DOQI clinical practice guidelines. 2002;39:S17–S31
12. Roe MT, Peterson ED, Li Y, Pollack CV Jr, Christenson RH, et al.: Relationship between risk stratification by cardiac troponin level and adherence to guidelines for non-ST-segment elevation acute coronary syndromes. *Arch Intern Med* 2005;165(16):1870–1876
13. Liang KY, Zeger SL: Longitudinal data analysis using generalized linear models. *Biometrika* 1986;73:13–22
14. Apple FS, Sharkey SW, Hoeft P, Skeate R, Voss E, et al.: Prognostic value of serum cardiac troponin I and T in chronic dialysis patients: A 1-year outcomes analysis. *Am J Kidney Dis* 1997;29(3):399–403
15. Van Lente F, McErlean ES, DeLuca SA, Peacock WF, Rao JS, et al.: Ability of troponins to predict adverse outcomes in patients with renal insufficiency and suspected acute coronary syndromes: a case-matched study. *J Am Coll Cardiol* 1999;33(2):471–478
16. McLaurin MD, Apple FS, Falahati A, Murakami MM, Miller EA, et al.: Cardiac troponin I and creatine kinase-MB mass to rule out myocardial injury in hospitalized patients with renal insufficiency. *Am J Cardiol* 1998;82(8):973–975
17. Ricchiuti V, Voss EM, Ney A, Odland M, Anderson PA, et al.: Cardiac troponin T isoforms expressed in renal diseased skeletal muscle will not cause false-positive results by the second generation cardiac troponin T assay by Boehringer Mannheim. *Clin Chem* 1998;44(9):1919–1924
18. Apple FS, Murakami MM, Pearce LA, Herzog CA: Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. *Circulation* 2002;106(23):2941–2945

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20210