Chapter 5. Systematic Review of Troponin as a Prognostic Factor for CHD in Women

Introduction

Patients with acute coronary syndromes (defined as myocardial infarction (MI) or unstable angina) are at increased risk for subsequent acute myocardial infarction and death. Managing patients with known or suspected acute coronary syndromes consumes a large amount of resources. Approximately five million people undergo evaluation for acute coronary syndromes in emergency departments annually in the United States at an estimated cost of over six billion dollars.[1] Several tests have been used to identify patients at high risk of a major cardiac event, including the electrocardiogram, blood tests of proteins (cardiac markers) released with myocardial injury and clinical characteristics obtained from the history and physical exam. Several characteristics were recently combined in a risk score by the Thrombolysis in Myocardial Infarction (TIMI) study group.[2] These characteristics include age of 65 or greater, known coronary artery disease, at least three risk factors for coronary artery disease (family history, hypertension, diabetes, hypercholesterolemia, current smoker), ST-segment deviation of at least 0.5 mm, recent severe angina, aspirin use in the last seven days and elevated cardiac markers (troponin, creatine kinase-MB fraction). In a recently published study based on data from Evidence Report Number 31 (Prediction of Risk for Patients with Unstable Angina),[3] we found that troponin cardiac markers indicate substantial risk for death or subsequent myocardial infarction.[4]

Cardiac troponin immunoassays (troponin T and I) were approved in 1994 by the Food and Drug Administration as markers of acute myocardial infarction and risk stratification. The troponin complex is comprised of three proteins (C, I, and T) which together regulate the contraction of striated muscle (cardiac and non-cardiac). Troponin C binds calcium and regulates contraction, troponin I inhibits actomyosin adenosine triphosphatase, and troponin T binds the troponin complex to tropomyosin. Because cardiac troponin C has the same amino acid sequence as skeletal muscle it is not a specific marker for cardiac injury. In contrast, cardiac troponins I and T are easily distinguished from skeletal troponin I and T, and the detection of cardiac troponin in serum is highly specific for cardiac injury. Both I and T have a small molecular mass and are thus released rapidly following cellular injury. They typically are detected four to six hours following injury and peak at 12 to 18 hours. Troponin I assays are produced by multiple companies and there is no standard threshold for an elevated test. Although the troponin T assay is standardized (produced by a single company), there are several generations of assays that are progressively more sensitive. The American College of Cardiology currently recommends that each lab report a positive troponin if the value is greater than the 99th percentile for normal controls.

Although all elevated troponin levels are now considered diagnostic of myocardial infarction in the appropriate clinical setting (per the American College of Cardiology and European Society of Cardiology), little is known about the prognostic value of an elevated troponin level for women. Because women with acute coronary syndromes are often older than men, they may be more likely to have congestive heart failure which often results in elevated troponin levels independent of acute coronary syndromes. Thus, the prognostic value of troponin for women may differ from the value for men.[5] One recently published study found that women suspected of acute coronary syndromes but with a negative troponin test (<0.06 ng/ml) had a very low six month risk (1 percent) of future death or myocardial infarction.[6] This was not the case for a similar group of men whose risk of events was 9 percent in those with a negative troponin test.

Thus we sought to answer the following question:

- What is the impact of troponin on risk for death or myocardial infarction for women and men with non-ST elevation acute coronary syndromes?

Women with suspected acute coronary syndromes are often older than men and are likely to have more risk factors for coronary disease.[6, 7] Thus, it is possible that the prognostic value of troponin will be different for men and women. If substantial differences between men and women exist, then different risk assessments should be considered for men and women.

Methodology

Data Sources

We used the results of a previous search of troponin articles in unstable angina (through 1999)[3] and supplemented this with a second search (through 2002) to identify gender specific rates of cardiac outcome (death or myocardial infarction) for patients with non-ST elevation acute coronary syndromes with and without elevated troponin levels. Because few published studies provided sex specific data, we also contacted a selected group of study authors directly. Peer reviewers (Appendix A) were asked to submit articles that provide evidence to address the questions.

Search Terms

We searched MEDLINE® (1966-2002) and reviewed cited references of retrieved articles to identify relevant published studies. Our search criteria were (1) the text word troponin, and (2) the text words angina or unstable or myocardial infarction or ischemia. We also performed a search of the EMBASE database from 1990-1998, but did not find any additional articles fulfilling the study criteria. We contacted experts in the field of cardiac markers to identify large unpublished cohort studies.

Inclusion and Exclusion Criteria

To be included, articles were required to fit the following inclusion criteria:
1) Clinical trial or cohort study
2) Evaluate patients with suspected myocardial ischemia
3) Evaluate the prognostic value of troponin levels in patients with non-ST elevation acute coronary syndromes
4) Published between January 1, 1966 and January 30, 2002.

We excluded studies that only included patients with myocardial infarction. We also excluded case-control studies, articles that did not report mortality, and articles with followup limited to hospitalization.

Article Identification

Study selection was performed initially by title review (PAH). Candidate abstracts were then reviewed and selected for data retrieval.

Data Abstraction

Two independent reviewers abstracted data for each article on standardized electronic data forms. A third reviewer compared their results and settled any differences. At least one reviewer of the pair had clinical cardiology expertise and one had experience in critical appraisal. We recorded the outcomes of nonfatal myocardial infarction and death. These were combined to form the outcome of death or myocardial infarction. If outcomes at more than one time period were reported, we used the value closest to 30 days following presentation.

Obtaining Unpublished Results

A number of eligible studies included women in the study population, but did not report findings separately by sex. In these instances we attempted to contact authors of all large studies (defined as >300 patients or >10 deaths during followup) to obtain this data. We contacted ten authors regarding nine studies[8-17] and received data from five studies.[8-10, 12, 13, 16]

Quality Assessment

We performed double abstractions for each article. For data obtained directly from authors we asked for confirmation of the data we received. We determined if the following quality indicators were present for the studies: clear listing of exclusion criteria, statement of whether providers were or were not blinded to the troponin results (for clinical trials), clear definition of myocardial infarction, classification of death outcome as cardiac death or total death. If less than three of these indicators (or the two applicable to cohort studies) were present, a study was classified as poor; otherwise it was considered to be good quality.

Data Management and Archive

All abstracted and author provided data were entered and stored electronically (EXCEL, Microsoft® Corporation). A citation of each article reviewed was archived using EndNote® (Niles Software Inc.).

Data Analysis

We used standard random (DerSimonian-Laird) and fixed (Peto) effects methods to estimate summary odds ratios for the outcomes of death and myocardial infarction.[18, 19] Because both fixed and random-effects summary estimates were similar, we report only the random-effects results. For studies with no events in a patient group, we added 0.5 to each cell of the study for the random-effects calculation. We tested homogeneity of study effect size using a standard Chi-square test with the Q statistic.[19] Summary estimates for men and women were compared using the z statistic. Data are presented as summary odds ratios with 95% confidence intervals, with two-tailed P-values and statistical significance set at $P < 0.05$.

Results

Results of study identification

A total of 1,049 articles were identified with the MEDLINE® and EMBASE databases and citation reviews. We excluded 878 articles based on title or abstract because they did not evaluate the prognostic value of troponin in patients with non-ST elevation acute coronary syndromes. The remaining 171 articles were retrieved and reviewed, and 78 of these articles met all of the inclusion/exclusion criteria.

Eligible articles were then reviewed to determine whether they reported relevant data for women. Only three of the 78 articles reported sex and troponin specific outcomes of death or myocardial infarction following hospitalization. The three included studies reported data for 407 women and 774 men.

Since so few studies reported data for an analysis of prognostic value of troponin by sex, we contacted the authors of the nine largest of the 78 studies to request outcomes data partitioned by sex and troponin test results. We obtained unpublished gender specific

data for 2,762 women and 3,296 men from the authors of five of the nine large studies. [8-10, 12, 13, 16] Two investigators reported on different topics for the same population.[10, 16]

Patient Characteristics

Patient characteristics are displayed by sex in Evidence Table 13. Women were consistently older than men. Women were less likely to be smokers and have a history of myocardial infarction, but were more likely to have hypertension and diabetes than men.

Study Report Characteristics

Evidence Table 14 shows characteristics of the studies and the source of data used in the analysis (i.e., abstraction of data from publication or supplied directly by a study author). Most studies used the highest troponin value to determine if the threshold was reached. The thresholds used for troponin T ranged from 0.1 to 0.2 ng/ml. The majority of studies were clinical trials where the troponin evaluation was a sub-study.

Quality of Study Reports

All eight included studies were rated as "good" quality. One study did not clearly list exclusion criteria.[20] All trials noted that health care providers were blinded to the troponin results. All studies stated how myocardial infarction was defined and all reported whether deaths referred to total or cardiac deaths.

Findings

Troponin Values

The frequency of elevated troponin and outcomes for women and men for each study are listed in Evidence Tables 15 and 16. Among 3,169 women, troponin was elevated in 1,118 (35 percent). This value ranged from 18 percent in the 1998 study report by Antman[9] to 49 percent for the study by Safstrom.[6] Among 4,070 men, the troponin was elevated in 1,571 (39 percent). This value ranged from 18 percent in the study by Galvani[21] to 64 percent for the study by Safstrom.[6]

Death

There were 103 deaths among 3,169 women (3.3 percent). Among 2,051 women with a negative troponin, 42 died (2.0 percent) compared to 61 (5.5 percent) who died following a positive troponin value (Figure 1). There were 129 deaths among 4,070 men (3.2 percent). Among 2,499 men with a negative troponin, 47 died (1.9 percent) compared to 82 (5.2 percent) who died following a positive troponin value (Figure 2). The summary odds ratio for death with an elevated troponin was 2.63 (95 % CI 1.75-3.95) for women and 2.83 (95% CI 1.92-4.17) for men (p=0.8 for difference in odds ratio between men and women).

Death or Myocardial Infarction

There were 256 deaths or nonfatal myocardial infarctions among 3,169 women (8.1 percent). Among women with a negative troponin, 117 died or had a myocardial infarction (5.7 percent) compared to 139 (12.4 percent) who died or had a myocardial infarction following a positive troponin value (Figure 3). There were 366 deaths or myocardial infarctions among 4,070 men (9.0 percent). Among men with a negative troponin, 180 died or had a myocardial infarction (7.2 percent) compared to 186 (11.8 percent) who died or had a myocardial infarction following a positive troponin value (Figure 4). The summary odds ratio for the combined endpoint of death or MI for patients with an elevated troponin was for 2.16 (95% CI 1.65-2.81) women and 1.50 (95% CI 1.20-1.88) for men (p=0.04 for difference in odds ratio between men and women).

Nonfatal Myocardial Infarction

There were 153 nonfatal myocardial infarctions among 3,169 women (4.8 percent). Among women with a negative troponin, 75 had a nonfatal myocardial infarction (3.7 percent) compared to 78 (7.0 percent) who had a nonfatal myocardial infarction following a positive troponin value (Figure 5). There were 237 nonfatal myocardial infarctions among 4,070 men (5.8 percent). Among men with a negative troponin, 133 had a nonfatal myocardial infarction (5.3 percent) compared to 104 (6.6 percent) who had a nonfatal myocardial infarction following a positive troponin value (Figure 6). The odds ratio for death with an elevated troponin was for 1.80 (95% CI 1.28-2.54) women and 1.06 (95% CI 0.8-1.41) for men (p=0.02 for difference in odds ratio between men and women).

Comparisons Between Men and Women

The summary odds ratios for death (Figure 7), death or myocardial infarction (Figure 8) and nonfatal myocardial infarction (Figure 9) were computed separately for women and men. There was no significant heterogeneity ($p<0.05$) for any of the six summary estimates (three per gender). These results show that women and men had a similar increase in risk of death associated with a positive troponin. However, the relationship between death or myocardial infarction and elevated troponin was stronger for women (p=0.05). This was due to a stronger risk of nonfatal myocardial infarction with a positive troponin for women than for men (p=0.02).

Conclusions

Few published data are available comparing the prognostic value of troponin for men and women. Although many analyses of troponin have included a large number of women, we identified only three studies that reported sex specific outcome data. Because several of the investigators from the larger studies provided sex specific data, we were able to calculate a more robust estimate of the impact of troponin on outcome for men and women.

Our study is consistent with prior investigations that found that women with acute coronary syndromes are older and have more comorbidities (hypertension, diabetes) than men. In addition, we found that women were less likely to have a prior history of myocardial infarction and less likely to be smokers. Unlike other studies we found that the frequency of elevated troponin levels was similar for men and women.

We found that the prognostic value of troponin for predicting death was the same for both men and women (odds ratio near 3). However, for the combined outcome of death or MI, troponin had greater prognostic value in women than men. This was due to a smaller number of nonfatal myocardial infarctions in troponin negative women than troponin negative men.

How does one reconcile the similar troponin prognostic value for death but a difference in prognostic value for nonfatal MI? One possibility is that men and women are treated differently. In the study by Safstrom,[6] low risk women (troponin <0.06 ng/ml) were less likely to undergo revascularization with percutaneous coronary interventions or bypass grafting than men (22 percent vs. 46 percent, $p<0.01$). However for higher levels of troponin, the rate of revascularization in men and women was similar. In fact, revascularization was more common for women than for men (though not significantly) with a troponin value >= 0.2 ng/ml (39 percent vs. 36 percent). If revascularization is frequently complicated by small myocardial infarctions, there will be more nonfatal myocardial infarctions in men than in women due to higher rates of revascularization in men, yet fatal events would be similar. Unfortunately, we do not have data on revascularization by gender and troponin level for most of the included studies.

Another possibility is that men are at an increased risk for nonfatal myocardial infarction (but not fatal infarction) compared to women. Men are known to have more severe coronary artery disease than women among those presenting with chest pain. Men may be more likely to develop myocardial infarction at a site unrelated to the culprit lesion responsible for the initial coronary syndrome. These infarctions would not be preceded by a positive troponin level. Our findings could be explained if these new infarctions are more likely to be survived than the initial coronary syndrome. If men are simply at higher risk of events in general, we would have expected to observe similar gender specific risk with elevated troponin for death and nonfatal myocardial infarction.

Our ability to observe differences between men and women in their risk associated with an elevated troponin would not have been possible without the data provided directly from authors of past studies. Less than a third of the patients' data used in the analysis were available from published studies. Because each study had limited power to detect differences between men and women, the authors may be reluctant to use limited resources to analyze and publish inconclusive sub-group data. Thus, obtaining data directly from authors is often critical to determine results for sub-populations.

Limitations

Although we observed a difference between men and women in the relationship between troponin and risk of nonfatal myocardial infarction, the cause of this difference could not be determined. The borderline statistical significance indicates that this difference may have occurred by chance.

Future Research

Future studies will be needed to verify and explore possible causes for the finding that troponin results prognosticate nonfatal MI differently in women compared to men. In addition, authors should be encouraged to report outcomes data by sex and ethnic sub-groups or to make these analyses easily available.

References

1. Barish RA, Doherty RJ, Browne BJ. Reengineering the emergency evaluation of chest pain. J Healthc Qual 1997;19(5):6-12.
2. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable Angina/Non-ST elevation MI: A method for prognostication and therapeutic decision making [In Process Citation]. JAMA 2000;284(7):835-42.
3. Heidenreich P, Go A, Melsopo KA, et al. Prediction of risk for patients with unstable angina. Evidence Report No. 31 (prepared by the UCSF-Stanford Evidence-based Practice Center under Contract No. 290-97-0013). AHRQ Publication No. 01-E001. Rockville, MD: Agency for Healthcare Research and Quality. December 2000.
4. Heidenreich PA, Alloggiamento T, Melsop K, et al. The prognostic value of troponin in patients with non-ST elevation acute coronary syndromes: a meta-analysis. J Am Coll Cardiol 2001;38(2):478-85.
5. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36(3):959-69.
6. Safstrom K, Lindahl B, Swahn E. Risk stratification in unstable coronary artery disease--exercise test and troponin T from a gender perspective. FRISC-Study Group. Fragmin during InStability in Coronary artery disease. J Am Coll Cardiol 2000;35(7):1791-800.
7. Lagerqvist B, Safstrom K, Stahle E, et al. Is early invasive treatment of unstable coronary artery disease equally effective for both women and men? FRISC II Study Group Investigators. J Am Coll Cardiol 2001;38(1):41-8.
8. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996;335(18):1342-9.
9. Antman EM, Sacks DB, Rifai N, et al. Time to positivity of a rapid bedside assay for cardiac-specific troponin T predicts prognosis in acute coronary syndromes: a Thrombolysis in Myocardial Infarction (TIMI) 11A substudy. J Am Coll Cardiol 1998;31(2):326-30.
10. Christenson RH, Duh SH, Newby LK, et al. Cardiac troponin T and cardiac troponin I: relative values in short-term risk stratification of patients with acute coronary syndromes. GUSTO-IIa Investigators Clin Chem 1998;44(3):494-501.
11. Hamm CW, Goldmann BU, Heeschen C, et al. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. N Engl J Med 1997;337(23):1648-53.
12. Hamm CW, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. N Engl J Med 1999;340(21):1623-9.

13. Heeschen C, Hamm CW, Goldmann B, et al. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. Lancet 1999;354(9192):1757-62.
14. Lindahl B, Venge P, Wallentin L. Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. The FRISC study group. Circulation 1996;93(9):1651-7.
15. Luscher MS, Thygesen K, Ravkilde J, et al. Applicability of cardiac troponin T and I for early risk stratification in unstable coronary artery disease. TRIM Study Group. Thrombin Inhibition in Myocardial ischemia. Circulation 1997;96(8):2578-85.
16. Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. GUSTO IIA Investigators. N Engl J Med 1996;335(18):1333-41.
17. Stubbs P, Collinson P, Moseley D, et al. Prospective study of the role of cardiac troponin T in patients admitted with unstable angina. BMJ 1996;313(7052):262-4.
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clin Trials 1986;7(3):177-88.
19. Petitti D. Statistical Methods in Meta-Analysis. In: Meta-Analysis, Decision Analysis and Cost-Effectiveness Analysis. New York: Oxford University Press; 1994. p. 90-114.
20. Ravkilde J, Horder M, Gerhardt W, et al. Diagnostic performance and prognostic value of serum troponin T in suspected acute myocardial infarction. Scand J Clin Lab Invest 1993;53(7):677-85.
21. Galvani M, Ottani F, Ferrini D, et al. Prognostic influence of elevated values of cardiac troponin I in patients with unstable angina. Circulation 1997;95(8):2053-9.