

A Sensitive Cardiac Troponin T Assay in Stable Coronary Artery Disease

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Cardiac troponins T and I are components of the contractile apparatus of cardiomyocytes and are the preferred biochemical markers of myocardial necrosis in patients with suspected acute coronary syndromes.¹ Among such patients, a strong association between elevated troponin levels and recurrent coronary ischemic events has been firmly established.^{2,3,4}

It has been shown that even very small elevations in troponins are associated with an increased risk of an adverse outcome in patients with acute coronary syndromes.⁵ Moreover, among men clinically free of cardiovascular disease, as well as in patients with recent acute coronary syndromes, levels of cardiac troponin greater than 0.01 µg per liter have been associated with increased mortality.^{6,7} Thus, it seems plausible that cardiac troponin levels below the conventional limits of detection may further discriminate between subjects at high risk and those at low risk for future cardiovascular events.

A highly sensitive assay for cardiac troponin T has recently been developed, permitting measurement of concentrations that are lower by a factor of 10 than those measurable with conventional assays. We hypothesized that with the highly sensitive assay, cardiac troponin T would be detectable in patients who had stable coronary artery disease without heart failure or left ventricular systolic dysfunction and that these levels would be associated with the risk of future cardiovascular events.

Methods

Patients

This substudy involved patients who had been included in the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial. The design, entry criteria, and main results of this trial have been described previously.⁸ In brief, from

November From November 1996 through June 2000, a total of 8290 patients with stable coronary artery disease and preserved left ventricular systolic function were randomly assigned to receive either the angiotensin-converting–enzyme inhibitor trandolapril or placebo. All the participants were free of heart failure at baseline, and none had been hospitalized for unstable angina within the 3 months preceding trial entry. Patients were followed every 6 months until December 2003, for a median of 5.2 years.

Biochemical Analysis

Levels of cardiac troponin T were determined by means of an autoanalyzer (cobas e 411, Roche Diagnostics). The lower limit of detection of the precommercial highly sensitive assay was 0.001 µg per liter.⁹ The value at the 99th percentile in a sample of 1338 apparently healthy blood donors was 0.0133 µg per liter (Roche Diagnostics, data on file). The detection limit of the older Roche troponin T assay (the fourth-generation Elecsys troponin T assay) is 0.01 µg per liter; according to the manufacturer, this corresponds to a value of 0.03 µg per liter with the new assay. N-terminal pro–brain natriuretic peptide (NT-proBNP) concentrations were determined with an electrochemiluminescence immunoassay on a Modular platform (Roche Diagnostics).¹⁰ C-reactive protein (CRP) measurements were performed with the highly sensitive CRP-Latex (II) immunoturbidimetric assay (Denka Seiken) on a Hitachi 911 immunoanalyzer (Roche Diagnostics).¹¹ The glomerular filtration rate was estimated with the use of the four-variable Modification of Diet in Renal Disease (MDRD) equation.¹² All biochemical testing was performed by study personnel who were unaware of the clinical outcomes and treatment assignments in the main study.

Outcomes

The outcomes examined in this analysis included cardiovascular death, fatal and nonfatal heart failure, and fatal and nonfatal acute myocardial infarction. All events were confirmed by a review of medical records. Cardiovascular death and fatal and nonfatal myocardial infarction were prespecified end points of the PEACE trial that underwent blinded review by an outcomes committee. Heart failure was classified by centrally trained local staff and confirmed by staff at the coordinating center through a review of hospital records. For an event to be classified as nonfatal heart failure, hospitalization with a primary cause of heart failure was required. All clinical events were classified before biomarkers were measured.

Results

Baseline Characteristics of the Patients. Baseline troponin T measurements were available from 3679 patients at 187 clinical sites. There were no clinically relevant differences between patients included in the substudy and those not included in it. The mean (\pm SD) age of patients in the substudy was 63.6 \pm 8.2 years, 18.9% were women, and 91.6% were white. All patients had stable coronary artery disease, and 56.3% had a history of myocardial infarction, 45.6% of percutaneous coronary intervention, and 35.8% of coronary-artery bypass grafting.

Distribution and Determinants of Very Low Levels of Troponin T. Concentrations

of troponin T as measured with the highly sensitive assay were at or above the limit of detection (0.001 µg per liter) in 3593 patients (97.7%) and equal to or greater than the 99th percentile value for apparently healthy subjects (0.0133 µg per liter) in 407 patients (11.1%). Troponin T levels were higher in men than in women (median, 0.0063 vs. 0.0046 µg per liter; $P<0.001$).

Troponin T and Cardiovascular Events

Cardiovascular Deaths

During follow-up, there were 125 cardiovascular deaths in the biomarker substudy cohort. In the univariate model, the cumulative incidence of cardiovascular deaths was significantly associated with the cardiac troponin T level (hazard ratio per unit increase in the natural logarithm of the value for troponin T, 2.78; 95% confidence interval [CI], 2.24 to 3.45; $P<0.001$). After adjustment for age, sex, smoking status, and high-sensitivity CRP level by using the multivariate model 1, the association remained strong (hazard ratio, 2.39; 95% CI, 1.85 to 3.09; $P<0.001$). The addition of NT-proBNP as a covariate in the multivariate model modestly attenuated the association, but the relation still remained highly significant (hazard ratio, 2.09; 95% CI, 1.60 to 2.74; $P<0.001$). The risk of cardiovascular death associated with increasing quartiles of troponin T was also strong and graded ($P<0.001$ for trend).

Heart Failure

During follow-up there were 104 first hospitalizations for fatal or nonfatal heart failure. In unadjusted analyses, the incidence of heart failure increased with increasing levels of troponin T. After adjustment, the association remained highly significant (hazard ratio, 2.20; 95% CI, 1.66 to 2.90; $P<0.001$). The risk of heart failure associated with increasing quartiles of troponin T levels was also strong and graded in both univariate and multivariate analyses ($P<0.001$ for trend).

Cardiovascular Deaths Not Due to Heart Failure

There were 112 cardiovascular deaths classified as not being due to heart failure during follow-up. In an unadjusted analysis, the cumulative incidence of this end point was significantly associated with troponin T. After adjustment, the association was modestly attenuated but remained highly significant (hazard ratio, 1.95; 95% CI, 1.46 to 2.61; $P<0.001$). The risk of this outcome in association with increasing quartiles of troponin T levels was also strong and graded above the second quartile ($P<0.001$ for trend).

Myocardial Infarction

During follow-up, there were 233 fatal or nonfatal acute myocardial infarctions. In an unadjusted analysis, there was a weak but significant increase in the cumulative incidence of myocardial infarction with increasing troponin T levels. After adjustment, this association was no longer significant (hazard ratio, 1.16; 95% CI, 0.97 to 1.40; $P=0.11$). Likewise, an unadjusted analysis showed a weak association between the risk of myocardial infarction and increasing quartiles of troponin T that was of

borderline significance; after adjustment for potentially confounding variables, this association was no longer significant (P=0.54)

Discussion

This study shows that very low circulating levels of cardiac troponin T are detectable in the great majority of patients who have stable coronary artery disease with preserved left ventricular function, that multiple conventional risk factors are associated with higher troponin T concentrations in this population, and that very low circulating levels of troponin T have a graded relationship with the incidence of cardiovascular death and heart failure in such patients. Conversely, the association between troponin T concentrations and incident myocardial infarction was not significant after adjustment for potential confounding factors. This finding stands in stark contrast to observations in patients with acute coronary syndromes, in whom troponins are considered biomarkers of acute cardiovascular injury due to plaque rupture and intracoronary thrombosis¹⁷ and more accurately predict recurrent myocardial infarction than they do death or heart-failure events.¹⁸

With the use of conventional assays, the prevalence of detectable concentrations of cardiac troponin T in the general population is approximately 0.7%.¹⁹ Detectable troponin T levels in such a population are typically associated with established cardiovascular disease, such as left ventricular hypertrophy or dysfunction, or with high-risk conditions such as kidney disease or diabetes. The mechanisms responsible for the release of very low levels of cardiac troponin T in patients with stable coronary artery disease could include transient, clinically silent ischemic episodes and small-vessel occlusions; inflammatory processes; cardiomyocyte apoptosis²⁰; reduced renal clearance; and increased myocardial strain due to pressure or volume overload. However, the remarkably high prevalence of detectable troponin in this low-risk cohort raises the possibility that some troponin may circulate under normal circumstances in human plasma. Data from population studies will be needed to confirm this hypothesis, and the source of the release of cardiac troponin T will need to be studied in experimental models.

The observations that troponin T was detectable in almost all our patients and that it provided strong prognostic information independently of conventional risk factors and other contemporary biomarkers, such as NT-proBNP and high-sensitivity CRP, suggest that assessment of low-level chronic myocardial injury may represent a new means by which clinicians can stratify risk among patients with stable coronary artery disease and preserved left ventricular function. Unresolved questions that need to be addressed include whether serial testing would enhance the prognostic value of the assay and whether minor changes in very low levels are stronger predictors of events than are absolute values. Moreover, before routine testing is considered, the therapeutic implications will need to be fully explored. Certain negative implications merit consideration as well. As more sensitive assays for troponins are introduced clinically, the specificity of low-level troponin elevation for acute myocardial injury in patients with acute chest pain syndromes may be reduced.

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