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Prognostic Value of Cardiac Troponin I Measured With a Highly Sensitive Assay in Patients With Stable Coronary Artery Disease

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Objectives The aims of this study were to assess the prognostic value of cardiac troponin I levels, measured with a new high-sensitivity assay, in low-risk patients with stable coronary artery disease (CAD) and to contrast its determinants and prognostic merit with that of high-sensitivity cardiac troponin T (hs-TnT).

Background New, highly sensitive cardiac troponin assays permit evaluation of the association between troponin levels and outcomes in patients with stable CAD.

Methods High-sensitivity cardiac troponin I (hs-TnI) levels at baseline were assessed in 3,623 patients with stable CAD and preserved systolic function enrolled in the PEACE (Prevention of Events With Angiotensin-Converting Enzyme Inhibitor Therapy) trial.

Results In total, 98.5% of patients had hs-TnI concentrations higher than the detection level (1.2 pg/ml). hs-TnI correlated moderately with hs-TnT ($r = 0.44$) and N-terminal pro–B-type natriuretic peptide ($r = 0.39$) but only weakly with age ($r = 0.17$) and estimated glomerular filtration rate ($r = -0.11$). During a median follow-up period of 5.2 years, 203 patients died of cardiovascular causes or were hospitalized for heart failure, and 209 patients had nonfatal myocardial infarctions. In analyses adjusting for conventional risk markers, N-terminal pro–B-type natriuretic peptide, and hs-TnT, hs-TnI levels in the fourth compared with the 3 lower quartiles were associated with the incidence of cardiovascular death or heart failure (hazard ratio: 1.88; 95% confidence interval: 1.33 to 2.66; $p < 0.001$). There was a significant, albeit weaker association with nonfatal myocardial infarction (hazard ratio: 1.44; 95% confidence interval: 1.03 to 2.01; $p = 0.031$). In the same models, hs-TnT concentrations were associated with the incidence of cardiovascular death or heart failure but not of myocardial infarction.

Conclusions In patients with stable CAD, hs-TnI concentrations are associated with cardiovascular risk independently of conventional risk markers and hs-TnT. (Prevention of Events With Angiotensin-Converting Enzyme Inhibitor Therapy [PEACE]; NCT00000558) (J Am Coll Cardiol 2013;61:1240–9) © 2013 by the American College of Cardiology Foundation

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In patients with acute chest pain, measurement of cardiac troponin I (cTnI) or cardiac troponin T (cTnT) is routinely used to diagnose acute myocardial infarction (AMI) (1). In the setting of acute coronary syndromes, troponin elevation also provides information concerning the risk for subsequent adverse cardiovascular events, as well as the benefit of therapeutic intervention (2). The introduction of high-sensitivity assays permits the accurate determination of very low levels of circulating cardiac troponins (3). Using a highly sensitive assay for cTnT, we recently demonstrated the presence of detectable levels in a large proportion of patients with stable coronary artery disease (CAD) (4). Moreover, cTnT concentrations were independently associated with the incidence of cardiovascular death and heart failure in these patients.

Although conventional cTnT and cTnI assays have been commonly considered to provide comparable diagnostic information in acute coronary syndromes (5), recent studies comparing the diagnostic value of highly sensitive assays for cTnT and cTnI have revealed interesting differences with potential clinical implications (6). Moreover, acute ischemia may have differential effects on cTnT (7) and cTnI (8) release. Recent data from asymptomatic subjects at high risk for atherosclerotic events suggest that cTnI provides independent information concerning the risk for future AMI (9), whereas in another study, the association between cTnT and the risk for AMI in patients with stable CAD was weak and not significant after adjustment for confounders (4). Taken together, these observations suggest that factors influencing low-level, chronic troponin elevation may differ between cTnT and cTnI. Whether the potential differences in chronic release and degradation patterns have prognostic consequences is unknown. Moreover, whether cTnI provides complementary prognostic information to cTnT in patients with stable CAD has not been evaluated.

Accordingly, the objectives of the present study of a large cohort of patients with stable CAD and preserved left ventricular (LV) ejection fractions were first to assess the determinants and prognostic value of circulating cTnI measured using a prototype high-sensitivity assay and second to contrast the results with those obtained using a high-sensitivity assay for cTnT.

Methods

Study design and patients. This is a biomarker substudy of the PEACE (Prevention of Events With Angiotensin-Converting Enzyme Inhibitor Therapy) trial. The design, entry criteria, and main results of this trial have been described previously (10). In summary, from November 1996 to June 2000, 8,290 patients were randomized to receive either the angiotensin-converting enzyme inhibitor trandolapril or placebo. Entry criteria were age ≥50 years, documented CAD, and LV ejection fraction >40%; qualitatively normal results on left ventriculography; or the absence of LV wall motion abnormalities on echocardiography. None of the patients had been hospitalized with unstable angina during the preceding 3 months. All patients included were deemed to be free of heart failure at the time of randomization. All patients who had baseline ethylenediamine-tetraacetic acid plasma samples available for measurement of high-sensitivity cTnT (hs-TnT) and serum samples available for determination of high-sensitivity cTnI (hs-TnI) (n = 3,623) were included in the present substudy. The institutional review boards of the participating sites reviewed and approved the study, and all participants provided written informed consent.

Abbreviations and Acronyms

AMI = acute myocardial infarction
CAD = coronary artery disease
CI = confidence interval
CRP = C-reactive protein
cTnI = cardiac troponin I
cTnT = cardiac troponin T
GFR = glomerular filtration rate
HR = hazard ratio
hs-TnI = high-sensitivity cardiac troponin I
hs-TnT = high-sensitivity cardiac troponin T
LV = left ventricular
NT-proBNP = N-terminal pro–B-type natriuretic peptide

On the basis of prior data concerning the prognostic value of hs-TnT in patients with stable CAD, the primary outcomes examined in the present analysis were 1) a composite of cardiovascular death and nonfatal heart failure and 2) nonfatal AMI (4). Cardiovascular death and nonfatal AMI were pre-specified endpoints of the PEACE trial. To ascertain these endpoints, medical records were reviewed by a central, blinded morbidity and mortality committee. Heart failure was classified by local staff members and confirmed by the coordinating center through review of medical records and required hospitalization with heart failure as the primary diagnosis. Clinical events were all classified before biomarker measurement.

Blood sampling procedures and biochemical assays. Samples of venous blood were obtained before randomization. The test tube was centrifuged at room temperature, and serum and plasma were aspirated and frozen at −20°C at individual centers. Within 3 months of collection, serum and plasma samples were shipped on dry ice to the central laboratory for storage at −70°C or colder, pending analysis. For hs-TnI and hs-TnT analysis, samples were shipped on dry ice to Akershus University Hospital (Lørenskog, Norway).

hs-TnI in serum was determined using a prototype cTnI assay from Abbott Diagnostics (Lake Forest, Illinois): ARCHITECT STAT High Sensitive Troponin. The level of detection for this assay has been reported to be 1.2 pg/ml (range: 0 to 50,000 pg/ml), with a coefficient of variation of 10% observed at a concentration of 3.0 pg/ml, and the diagnostic cutoff repre-

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