Biomarkers serve 2 potential roles: They provide insight into the pathophysiology of disease, and they aid clinical decision making by clarifying diagnosis, prognosis, or response to therapy. Fulfillment of one role does not ensure fulfillment of the other. For instance, some biomarkers associated with disease progression turn out to provide little incremental clinical value. Thus, studies like the one by Latini and colleagues in this issue of Circulation are valuable because they couple investigation of a biologically interesting association, in this case the link between circulating troponins and heart failure (HF), with a rigorous assessment of clinical utility. The following commentary focuses on 2 questions raised by the study by Latini et al. First, what is the pathophysiological significance of circulating troponins in HF? Second, should we be measuring cardiac troponins in chronic HF patients?

The Significance of Cardiac Troponins in HF

The troponins comprise 3 proteins (troponin T, I, and C) that regulate actin and myosin interactions during muscle contraction. Troponins T and I have distinct isoforms that exist in skeletal and cardiac muscle; newer-generation assays permit the detection of the isoforms unique to cardiac tissue. The release of these proteins into the bloodstream from cardiomyocyte necrosis accounts for their utility as biomarkers of acute coronary syndromes.

In the past decade, it has been recognized that elevated concentrations of cardiac troponins also are detectable in patients with HF in the absence of unstable coronary syndromes. In 1997, Missov and colleagues used a highly sensitive research assay to demonstrate elevated concentrations of troponin I in 35 patients with advanced HF. Subsequent reports extended these observations to troponin T.

For instance, in a Japanese study, troponin T was detectable by a second-generation assay (detection limit, 0.02 ng/mL) in 30 of 58 patients (52%) with chronic HF compared with 4% of healthy control subjects.

Recent studies have indicated that elevated troponin concentrations in patients with HF are associated with more severe disease and a worse prognosis. However, these studies generally are limited by small sample sizes and highly selected populations. These factors make it difficult to determine whether the association between troponin concentrations and outcomes is independent of conventional clinical predictors, which is crucial for establishing the importance of a new biomarker. Statistical power is further limited by the high proportion of patients in these studies with undetectable troponin concentrations.

In this context, the study by Latini and colleagues is an important contribution. Using data on >4000 patients enrolled in the Valsartan Heart Failure Trial (Val-HeFT), the investigators examined the association between baseline troponin T concentrations, all-cause mortality, and hospitalization for HF. The investigators used a new, highly sensitive troponin T (hsTnT) assay that detects concentrations 10-fold lower than the conventional, second-generation assays (cTnT). hsTnT was detectable in 92% of patients in this large cohort of stable HF patients, versus only 10% for cTnT. Not surprisingly, higher concentrations of hsTnT were associated with a greater burden of clinical risk factors for poor outcome, including advanced age, atrial fibrillation, and lower ejection fraction. In a subgroup of 670 patients with clinical stability over 4 months defined by functional class and other predictors, concentrations of hsTnT were remarkably stable.

Latini et al found that baseline hsTnT concentrations predicted mortality and HF hospitalization above and beyond clinical predictors. Indeed, hsTnT was the most significant predictor (χ² statistic, 53.6; P<0.0001) of all-cause mortality in a multivariable model including hsTnT and clinical and echocardiographic variables. The large number of outcomes, centrally validated by an end-point committee, supports the internal validity of the authors’ findings. Confirmation of external validity requires additional studies because randomized trial participants do not necessarily represent typical HF patients. In addition, it is not clear whether potential interactions with the trial medication were tested.

What is the origin of the circulating troponin T, and what is the mechanism linking this biomarker to outcomes in chronic HF? As in prior studies, elevation in troponin T was not strongly related to an ischemic origin of heart failure. Although additional information on creatine kinase or myoglobin would have been confirmatory, an adequate body of evidence supports the notion that circulating troponins in HF do not represent acute ischemia or infarction, at least that...
resulting from epicardial coronary disease.8,12 Similarly, although serum creatinine values were substantially higher in individuals with elevated troponin T, the association between troponin T and clinical outcomes did not appear to be attributable to renal insufficiency.

The most likely explanation is that elevated troponins reflect ongoing cardiomyocyte injury in HF. Several processes could contribute. Reversible injury, from myocardial strain or subendocardial ischemia, could lead to transient changes in cell membrane permeability and leakage of cytosolic troponin.13 However, most of the troponin in cells is not free but bound to myofibrils,3 suggesting the presence of more severe injury. Frank myocyte necrosis may contribute to the release of troponins into the bloodstream of patients with HF,14,15 but it is controversial how much necrosis is sustainable over long periods of time in clinically stable patients.16 Apoptosis also has been documented in failing hearts,17,18 although it is not known whether apoptosis leads to troponin release.19 Another interesting possibility is that troponin assays are detecting troponin degradation products that have been released into the bloodstream from proteolysis or turnover of myocardial contractile proteins.19–21 Underlying triggers of either proteolysis or frank necrosis could include mechanical stretch, oxidative stress, neurohormonal activation, or microvascular ischemia.2,14,22 Further experimental studies are necessary to understand the mechanisms of low-level troponin release in chronic HF.

Loss of myocytes has been proposed to play an important role in the progression of both ischemic and nonischemic cardiomyopathy to end-stage HF.23–25 The data of Latini et al7 provide intriguing, albeit indirect, support for this hypothesis by showing that a sensitive biomarker of myocyte damage is elevated before the onset of HF decompensation and mortality. Additional studies should confirm these observations in different cohorts and examine the structural and functional correlates of elevated troponin concentrations in HF.

Recognition that cardiac troponins could represent a new HF biomarker raises interesting parallels between the troponins and the natriuretic peptides. Both biomarker classes share the unique feature of being secreted directly, and almost exclusively, by cardiac tissue. Thus, they serve as a “window” on the myocardium, providing a readout of wall stress and injury that is, in some ways, more sensitive than that obtained from imaging or even invasive hemodynamics. This feature probably contributes to the versatility of both biomarkers in cardiovascular diseases. Indeed, the natriuretic peptides (HF biomarkers) predict prognosis in acute coronary syndromes,26 and the troponins (acute coronary syndrome biomarkers) now appear to predict prognosis in HF.

In addition, the study by Latini et al7 provides a useful reminder that the distinction between “normal” and “elevated” biomarker levels is an artificial one and sometimes a function of the ability of an assay to detect concentrations at the lower end of the range. The vast majority of patients in Val-HeFT had undetectable troponin T concentrations using cTnT, but Latini et al7 nicely show that variation in hsTnT among these patients with “normal” cTnT is strongly associated with outcomes. This observation is reminiscent of the experience with B-type natriuretic peptide (BNP)27 in the ambulatory setting in which concentrations formerly regarded as normal were found to predict future clinical disease.

In summary, the availability of another myocardium-specific biomarker that is detectable in ambulatory individuals with chronic HF should provide a valuable means to learn more about the evolution of HF from its earliest stages to more advanced disease. It would be interesting to know whether low concentrations of troponins also are present in individuals with diastolic HF, in those with left ventricular remodeling without HF, and in those with asymptomatic left ventricular systolic or diastolic dysfunction. Such data could add insight into the preclinical cardiac abnormalities that precede the development HF in the first place.

**Should Troponin T Be Measured in Patients With HF?**

Assessment of prognosis in HF is clinically important, given the need to counsel patients and select appropriate candidates for advanced therapies such as devices and transplantation. Prior small studies have suggested that routine measurement of cardiac troponins could help to identify HF patients in need of escalation of therapy. Nonetheless, only large-scale studies have adequate statistical power to evaluate the value of a new biomarker for assessing prognosis. Thus, it is important to consider the findings of Latini and colleagues7 in view of what they tell us about the clinical utility of troponin measurements in this population.

The first item to consider is the strength of the association between cardiac troponin and outcomes. Relative risks (or hazards ratios) provide a basic measure of the strength of associations in longitudinal studies. In the study by Latini et al7 there was an approximate doubling in the adjusted risk of mortality for those with troponin concentrations ≥0.01 ng/mL compared with those with a level <0.01 ng/mL, consistent with a sizable effect. Adjustment for clinical characteristics is critical because troponin concentrations track with many easily obtainable clinical risk factors. It is reasonable to ask whether the investigators adequately accounted for all potential confounders because the article does not mention several variables that are part of validated HF risk scores28,29 such as serum sodium and hematocrit. On the other hand, unless troponin concentrations are strongly correlated with these analytes, further attenuation in hazards ratios should be modest.

Next, how well do troponin concentrations identify individuals who will experience an adverse outcome? An important feature of a test is known as “discrimination.” In the context of a survival analysis, as in the study by Latini et al7 discrimination refers to the ability of a test to identify the member of a randomly selected pair who will reach an end point first. The standard measure of discrimination is the c statistic, which is a generalization of the area under the receiver-operating characteristic curve for diagnostic or screening tests. Values for the c statistic range from 0.5 (uninformative test) to 1.0 (perfect discrimination). In the Val-HeFT cohort, the addition of hsTnT to risk models for mortality increased the c statistic from 0.685 (clinical risk factors alone) to 0.697 (risk factors plus hsTnT). When BNP measurements were included, addition of hsTnT raised the c
statistic from 0.702 (risk factors and BNP) to 0.711 (risk factors, BNP, and hsTnT).

These small differences in c statistic are statistically significant, which may reflect the large sample size, but are they clinically important? Interpreting changes in c statistic can be difficult, in part because the c statistic is constrained to a narrow range between the value achieved by clinical risk factors (generally 0.7 to 0.8) and 1.0, the latter being impossible to achieve. Thus, small absolute increments are common, even with strong risk factors. In addition, the meaning of a given change in the c statistic is difficult to articulate in clinical terms. To the closest approximation, a 0.01 increment in the c statistic corresponds to 1 additional pair of 100 in which the higher-risk member is correctly identified. Most would regard such an increment in c statistic as indicating, at best, a modest improvement in discrimination.

Lastly, do troponin measurements improve the accuracy of predicted probabilities of adverse events? Calibration refers to the correspondence between predicted probabilities and actual event rates. The Hosmer-Lemeshow statistic frequently is used to assess calibration. Well-calibrated models, in which only small differences are present between predicted and actual risks, have Hosmer-Lemeshow statistics that are small in absolute value and have nonsignificant probability values. For the mortality end point in Val-HeFT, the Hosmer-Lemeshow probability values exceeded 0.50 for all models with clinical risk factors with or without biomarkers. Thus, the addition of hsTnT did not result in a meaningful change in calibration, in part because the clinical risk factor model was already well calibrated. Indeed, for unclear reasons, the Hosmer-Lemeshow probability values for models containing hsTnT were lower (in the direction of worse calibration) than for models with clinical risk factors alone.

In conclusion, although the data from Latini et al support a strong association between troponin T and clinical outcomes in chronic HF, hsTnT added only modestly to risk discrimination and did not improve calibration of risk models. These findings suggest that routine assessment of troponin concentrations in chronic HF patients is not warranted and highlight the importance of considering discrimination and calibration in tandem with measures of association. It remains possible that troponin measurements have greater prognostic value in specific subgroups, such as those with more advanced HF or lower ejection fraction. Large datasets such as Val-HeFT could provide an opportunity for hypothesis-generating analyses to examine such questions. Furthermore, a biomarker associated with high relative risks such as hsTnT could be useful for clinicians who are “on the fence” about adding a new therapy or intervention because the additional prognostic information could shift the risk–benefit assessment. Global measures of discrimination or calibration do not address such situations.

Ultimately, prospective clinical trials are necessary to establish the utility of a new biomarker in specific clinical settings. Even excellent performance in observational studies is not sufficient for recommending that therapy be targeted to changes in biomarker levels. The biomarkers most powerfully related to prognosis in HF are the natriuretic peptides, but early trials of BNP-guided therapy in HF have yielded mixed results. Whether a combination of biomarkers, including BNP and perhaps hsTnT, could be used for guiding management remains an unanswered question.

Disclosures

None.

References


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Significance of Circulating Troponins in Heart Failure: If These Walls Could Talk
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