In the past decade, there has been a veritable explosion of studies examining cardiac biomarkers in heart failure (HF). Among the many reasons for this fact is that measurements of such biomarkers as natriuretic peptides (the current gold standard biomarker for HF diagnosis, prognosis, and management decision-making) are easy and safe to obtain, and they can potentially reveal important information about the patient at the biological level. Another class of cardiac biomarkers, the cardiac troponins, also provides important information about the prognosis of patients with HF. Studies have shown that cardiac troponins are typically measurable and sometimes frankly increased in HF patients, with values being closely linked with the severity of illness. Patients with more severe HF usually show higher cardiac troponin concentrations, intriguingly often independently of a diagnosis of coronary artery disease. Interestingly, cardiac troponins have been shown to be independently prognostic in both acute HF and chronic HF, even after adjusting for natriuretic peptide concentrations.

With a new generation of high-sensitivity cardiac troponin assays now or soon to be available, it is possible to detect minute amounts of circulating cardiac troponins with high precision. A substantial percentage of the patients with HF have measurable cardiac troponin values in high-sensitivity assays, often above the 99th percentile for a normal healthy population. For example, in a prior study, Latini and colleagues used a high-sensitivity cardiac troponin T (hs-cTnT) assay to measure cTnT among patients in the Valsartan Heart Failure Trial (Val-HeFT) and reported the biomarker to be measurable in 92% of the study participants and—importantly for prognosis—before and after an adjustment for natriuretic peptide concentrations. This finding is of importance for both monitoring and managing HF, because high-sensitivity cardiac troponin measurements could theoretically be leveraged for monitoring chronic HF stability. If therapies specifically tailored for ameliorating the prognostic blemish associated with an increased high-sensitivity cardiac troponin result could be identified, the concept of “guiding” HF therapy with high-sensitivity assays might be explored, much as it has been recently for natriuretic peptides.

It is in this context that Masson and colleagues proceeded with a large analysis of serial hs-cTnT measurements in 2 large, independent randomized controlled HF trials: the Val-HeFT and the Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca-Heart Failure (GISSI-HF) study. Both trials were randomized controlled trials of patients with stable HF due to left ventricular dysfunction. From these 2 trials together, results for serial samples from 5284 patients with chronic HF were available for analysis at baseline and at 3 months (GISSI-HF) or 4 months (Val-HeFT). All-cause mortality, mortality due to worsening HF, and admission to a hospital for a cardiovascular reason or HF were assessed along with the ability of changes in hs-cTnT over time to predict clinical outcomes in various models.

The authors examined changes in hs-cTnT in 3 different ways: absolute change in terms of the natural logarithm of the hs-cTnT concentration, trends in hs-cTnT concentration over time, and change in categories based on 99th-percentile hs-cTnT cutpoints. In all of the analyses, a systematic method for statistical covariate adjustment was followed. The method started with a baseline hs-cTnT value, followed by adding significant conventional risk factors and then adding established cardiac biomarkers to the model. In the study, increases in hs-cTnT over time were associated with several factors, including age, worsening of renal function, and baseline values for and increases in the N-terminal B-type natriuretic peptide (NT-proBNP) concentration. Interestingly, one of the most powerful predictors of a change in hs-cTnT concentration in both studies was incident diabetes mellitus.

In the fully adjusted models, increasing absolute changes in hs-cTnT concentration had hazard ratios of 1.40–2.99 (all P values <0.0001) for the various adverse outcomes examined. Notably, patients with decreasing trends for hs-cTnT (relative percentage

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1 Cardiology Division, Massachusetts General Hospital, Boston, MA.
2 Nonstandard abbreviations: HF, heart failure; Val-HeFT, Valsartan Heart Failure Trial; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca-Heart Failure; hs-cTnT, high-sensitivity cardiac troponin T (assay); NT-proBNP, N-terminal B-type natriuretic peptide.

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change, <15%) had the lowest mortality rates, whereas patients with stable hs-cTnT values (changes between −15% and +15%, roughly the biological variability of the marker) had intermediate event rates. Patients with increasing trends for the hs-cTnT concentration (>15%) had the highest event rates (P values of 0.002–0.0005 for all-cause mortality and P values of 0.0007–0.001 for HF mortality). Lastly, participants who started off with an hs-cTnT below the 99th-percentile cutpoint but ended up above this value at the second hs-cTnT measurement had a higher event rate than patients who remained below the cutpoint.

In a multivariable analysis, adding changes in hs-cTnT concentrations to a model that included conventional risk factors (but not other biomarkers) and the baseline hs-cTnT concentration improved prognostic discrimination for fatal outcomes in reclassification analyses. Once NT-proBNP was added to the model, however, the ability of serial hs-cTnT measurements to improve on the information already provided by the baseline hs-cTnT concentration was modest at best.

This thorough study by Masson and colleagues is an important step forward, but as with many important studies of its kind, it leaves many open questions. Although the statistical analyses were performed elegantly, a major limitation of the study was the fact that only 81% of the patients in the original Val-HeFT analysis and only 18% of those in the GISSI-HF study were included. Nonetheless, the authors dealt well with the heterogeneity of the population by performing statistical analyses separately for the 2 cohorts and building models methodically, with each step being explained and described. Importantly, the application of β-blockers and mineralocorticoid inhibitors in these patients was below current standards; thus, we know little about whether hs-cTnT has prognostic value in optimally managed patients. Furthermore, the mechanistic causes for better outcomes in those with a decreasing hs-cTnT concentration and the reasons for an adverse outcome in those with an increasing value remain unclear. Thus, unless we are certain about what information high-sensitivity cardiac troponin values provide us in the context of HF, treatment strategies for such patients will largely be focused on “doing your best” for patients, carefully assessing their medication programs and lifestyle, and examining patients for obvious signs of clinical instability. Very importantly, the authors were careful to adjust for NT-proBNP as well as for the baseline hs-cTnT concentration. With this approach, serial hs-cTnT measurements did not appear to add substantial prognostic value in the absence of a clear change in hs-cTnT. This finding may have to do with the relatively small number of patients who had significant changes in hs-cTnT concentration: The relative change in hs-cTnT was 0% in the Val-HeFT study and −4% in the GISSI-HF trial. Given the relatively small hs-cTnT changes observed in this study, the overwhelming prognostic importance of the baseline value may have been all that was needed to estimate risk.

The lack of substantial change across hs-cTnT measurements is interesting, given that the proposed mechanisms of troponin increase in HF are numerous and include both ischemic and nonischemic causes. The finding suggests that for most patients with stable HF, the underlying reasons for troponin release are somewhat static (at least over the time period studied in the analysis by Masson and colleagues). Changes in high-sensitivity cardiac troponin values do occur, however—albeit infrequently—and the direction and magnitude of these changes are meaningful. It is tempting to speculate that the value of serial hs-cTnT measurement might be clearer if pharmacologic lowering of the biomarker were possible, as has been demonstrated with natriuretic peptides (4).

According to the evidence to date, a baseline high-sensitivity cardiac troponin measurement adds clinically useful information in chronic HF and is a reasonable addition in the risk stratification of an HF patient. At present, however, the evidence does not yet support serial measurement in this context and will not support it until a better sense is gained about the optimal triggers and time points for measurement, as well as the clinical approach for those with an increased value. Of course, high-sensitivity cardiac troponin measurement as a part of an evaluation for acute coronary syndrome as the precipitant is clearly necessary for a patient with acute HF decompensation.

The future of biomarker testing in HF patients is very bright, and a better grasp of the signal provided by cardiac troponins in this context is crucial. We recently suggested important criteria for the clinical adoption of a biomarker for use in HF patients (6). According to these criteria, high-sensitivity cardiac troponin assays have not yet “hit the mark” for their routine serial use in chronic stable HF, but with more studies like that of Masson and colleagues, it is possible that necrosis markers will stand side by side with natriuretic peptides as part of the routine evaluation of patients with the diagnosis.

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