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EDITORIAL COMMENT

High-Sensitivity Troponin in the Triage of Acute Decompensated Heart Failure*

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Hospitalizations for acute decompensated heart failure (ADHF) account for the majority of >$30 billion spent on heart failure (HF) annually in the United States (1). Moreover, the evaluation of these patients adds nearly 1 million emergency department (ED) evaluations annually, and exacerbates ED overcrowding (2). Despite data suggesting that >50% of this population has a low risk of serious complications, >80% are admitted to the hospital (3). Low-risk patients with ADHF may be candidates for outpatient management and follow-up. However, to execute such a strategy, accurate risk stratification is essential. The report by Pang et al. (4) in this issue of *JACC: Heart Failure* addresses whether measurement of high-sensitivity cardiac troponin (hsTn) on ED arrival might identify low-risk patients with ADHF and potentially avoid

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hospitalizations. This approach shares some analogy to the "rule-out myocardial infarction" strategy in patients with chest pain. Given challenges in diagnosis, variability in prognosis, and pressures to reduce hospital admissions, an evidence-based strategy to drive triage and management decisions is appealing.

TROPONIN AND THE IDENTIFICATION OF LOW-RISK PATIENTS WITH ADHF

In prior studies of ADHF, higher concentrations of cardiac troponin measured with earlier-generation assays were strongly associated with poor outcomes. Depending on the assay, the proportion of patients with an elevated cardiac troponin ranges from 6.2% (5) to ~50% (6). In the RELAX-AHF-1 (RELAXin in Acute Heart Failure) trial of patients with ADHF randomized to serelaxin or placebo, the great majority of patients (>90%) had high-sensitivity cardiac troponin T (hsTnT) levels >99th percentile upper reference limit of 14 ng/l (0.014 μg/l), with an increasing gradient of risk of cardiovascular death and rehospitalization for HF with higher concentrations above that threshold (7). The authors' present analysis focuses on 107 patients (9.9% of the cohort) with hsTnT <14 ng/l.

Compared with patients with elevated hsTnT, patients with hsTnT <14 ng/l were healthier, had less ischemic disease, and had better New York Heart Association functional class and left ventricular function. Interestingly, their clinical presentation (e.g., edema, elevated jugular venous pressure, and rales) was similar irrespective of hsTnT values, although patients with low hsTnT had better renal function and lower levels of natriuretic peptide. Moreover, patients with hsTnT <14 ng/l had more rapid symptom resolution, required less diuretic agents, had shorter hospitalizations (7.8 days vs. 10.2 days), had less worsening of HF by 5 days (2.8% vs. 10.3%), and were less likely to be readmitted. Over 6 months of follow-up, only 1 patient with a low hsTnT died, compared with 92 deaths in patients with hsTnT >14 ng/l. The

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rate of cardiovascular death or rehospitalization by 60 days was 6.5% for patients with hsTnT <14 ng/l compared with 13.6% for the remainder.

From a high-level perspective, the findings by Pang et al. (4) raise the possibility that the negative predictive value of an hsTnT value <14 ng/l for death or rehospitalization is sufficiently high for the ~10% of patients with suspected ADHF who have low hsTn values to be discharged for outpatient management or undergo shorter hospitalizations. Their results provide optimism regarding this new application for hsTn in the ED. However, there are several areas of consideration regarding these results that warrant additional probing.

MECHANISTIC CONSIDERATIONS

Multiple prior mechanistic and imaging studies demonstrate a correlation between hsTn and the extent and severity of structural heart disease. The concentration of hsTn also increases with comorbid conditions such as older age, diabetes, and renal dysfunction. Thus, patients with low hsTnT likely had both less severe structural heart disease and fewer comorbidities. In addition, lower levels likely also reflect a less severe clinical syndrome, because ADHF is expected to increase myocardial wall stress and ventricular dilation, which induces subendocardial ischemia (8–10). Moreover, recent work suggests that the most important determinants of elevated hsTn values are microvascular dysfunction and left ventricular end-diastolic pressure (9).

It is also possible that a low hsTn is actually "ruling out" ADHF and that patients identified in this manner in RELAX-AHF either had chronic HF without acute decompensation or did not have HF at all. We speculate that it is unlikely for a patient to have ADHF without any myocardial injury detectable using hsTn. Nevertheless, from the viewpoint of a triage algorithm keyed on low risk, the distinction among the mechanism of disease, diagnosis, and prognosis is not critical; very low-risk patients, regardless of diagnosis, may not require admission.

CLINICAL CONSIDERATIONS

Although patients with hsTnT <14 ng/l in RELAX-AHF were at very low mortality risk, the assertion that outcomes would be the same with discharge from the ED is not directly supported by the study. Such patients were, on average, hospitalized for 8 days, suggesting that they were perceived to need ongoing in-hospital management. Prospective studies randomizing potentially low-risk patients to outpatient versus inpatient management would be required to reach definitive conclusions regarding whether discharge from the ED will achieve equivalent outcomes.

ADDITIONAL AREAS FOR RESEARCH

The hsTn assays open new vistas for clinical research and care in HF (11). There are 3 key aspects (12) relevant to application of hsTn for the early evaluation of ADHF that are left relatively unexplored in the current report: ascertainment of an optimal "cutpoint," the timing of testing, and the value of serial measurements.

The RELAX-AHF investigators applied an hsTnT cutpoint of 14 ng/l. However, in almost all studies of chronic cardiovascular diseases, hsTn assays, with their improved analytical sensitivity, demonstrate a spectrum of risk that begins well below the 99th percentile cutpoint and continues to discriminate risk at higher concentrations. Implementation of the 99th percentile cutpoint, originally conceived for diagnosis of myocardial infarction, for HF is somewhat arbitrary. Unfortunately, the small sample size of the RELAX-AHF cohort with low hsTn precludes further interrogation of prognosis between the limit of detection of the assay and 14 ng/l, or probing specific subsets of HF. Different types of HF (e.g., HF with preserved or reduced ejection fraction, valvular heart disease, and hypertrophic states) may manifest different hsTn patterns. Additional studies in ADHF should evaluate these issues to identify the most appropriate threshold(s) for prognostication.

It is also probable that additional information regarding prognosis and diagnosis may be obtained by evaluating the pattern of serial hsTn values. First, the timing of measurement relative to injury is important. A concentration measured late relative to the injury may be low and may therefore "miss" the maximal prognostic window. The variability of timing between injury and hsTn measurement will likely be even more problematic in more "real world" populations. Second, the presence or absence of dynamic concentrations of hsTn, even below the 99th percentile upper reference limit, is likely to provide additional information. Thus, evaluation for a rapid "delta" in hsTn, analogously to patients with ACS, may also be a better strategy for excluding risk in patients with ADHF (13).

SUMMARY

The report by Pang et al. (4) takes a step toward an exciting new approach integrating hsTn into risk stratification of patients with ADHF. Given the heterogeneity of presentation of these patients, a reliable

algorithm may not be as simple as the one put forward in this study. However, the use of very low concentrations of hsTn to identify low-risk patients appears promising to improve triage of this challenging population.

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