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High-Sensitivity Cardiac Troponin: From Patient Phenotypes to Clinical Events in Patients With Heart Failure With Preserved Ejection Fraction

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Previous studies have established the prognostic value of elevated troponin levels in patients with heart failure (HF), even in the absence of chest pain or myocardial infarction.[1–4] Furthermore, contemporary high-sensitivity cardiac troponin I (hs-TnI) assays are able to detect low levels in otherwise healthy individuals without known cardiovascular disease, but with future risk for development of HF, cardiovascular disease, or death.[5] This introduced the role for detection of ongoing maladaptive myocardial changes before full features of the phenotype become manifest, and the diagnosis of subclinical disease. This is supported by findings that there is a strong association between elevated high-sensitivity cardiac troponin (hs-cTn) levels and left ventricular hypertrophy,[6] and future development of HF almost a decade later.[7,8]

Thus, the diagnostic and prognostic role of hs-cTn in HF straddles a wide spectrum,[1–4] and can be incorporated for better characterization of stages of HF that ranges from an asymptomatic individual without macroscopic cardiac structural changes, but with future risk of HF (Stage A); an asymptomatic individual with cardiac hypertrophy or other myocardial structural changes, and with future risk of HF (Stage B); to symptomatic (Stage C) and advanced heart failure (Stage D) (Figure 1). In all these stages, elevated hs-cTn levels have been associated with increased risk of mortality.[1–4]

Though most studies of hs-cTn in HF have been performed in patients with reduced ejection fraction, a few have addressed its prognostic role in patients with HF with preserved ejection fraction (HFpEF).[2,9–12] These demonstrated a similar association of higher troponin levels and risk of future HF rehospitalization or death among symptomatic patients with HFpEF.[2,9–11]

In this issue of the *Journal of the American Heart Association (JAHA)*, using the pooled data from *DOSE* (Diuretic Strategies in Patients with Acute Decompensated Heart Failure),[13] *CARRESS-HF,* (Cardiorenal Rescue Study in Acute Decompensated Heart Failure)[14] and *RELAX* (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction)[15] trials, Fudim and colleagues[16] demonstrate that hs-TnI levels were elevated among 86% of the hospitalized, and among 53% of the ambulatory patients with HFpEF. The pooled data provide us an opportunity to recognize a potential longitudinal pattern of hs-TnI elaboration in these specific populations of HFpEF[16] (Figure 2A), and a better understanding of its role in different disease stages (Figure 1) or phenotypes, ranging from stable ambulatory to hospitalized HF (Figure 2B). In ambulatory, stable NYHA (New York Heart Association) II/III HFpEF patients, hs-TnI levels appeared to be chronically elevated, slightly above the 99% upper reference limit, but not

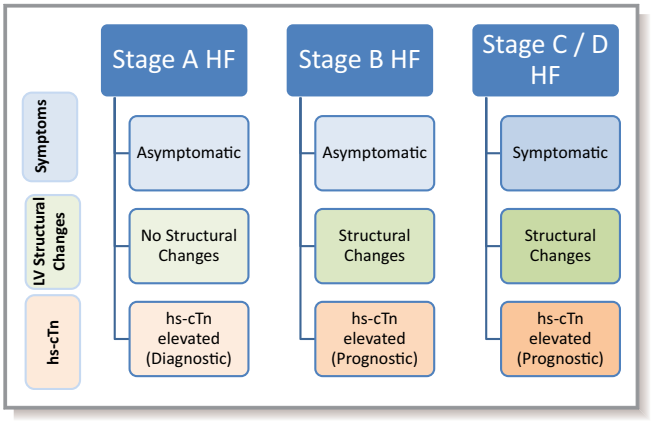

Figure 1. Potential new algorithm for stages of HF with incorporation of elevated high-sensitivity biomarkers such as cardiac troponin (hs-cTn) levels to symptoms and cardiac structural changes. Incremental role of hs-cTn as being diagnostic or prognostic is noted in parentheses. HF indicates heart failure; hs-cTn, high-sensitivity cardiac troponin I; LV, left ventricular.

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as high as the hospitalized patients, and did not change significantly over 6 months. In hospitalized patients with HFpEF, levels were significantly elevated, approximately twice of the 99% upper reference limit, and remained elevated without a significant change during hospitalization, and decreased only modestly by approximately 17% at 60 days, suggesting a sicker population with a higher biomarker expression profile even after hospitalization (Figure 2A and 2B). In addition to potential scenarios depicted in Figure 2, it is also possible that with longer follow-up, these levels might have come down further.

The trial populations in this study were quite different from each other, and possibly from other HFpEF cohorts. Ambulatory HFpEF patients (*RELAX* study) required objective evidence of HF by history of hospitalization, need for diuretics with left atrial enlargement, invasively documented elevation in left ventricular filling pressures, reduced exercise capacity, and elevated natriuretic peptide levels.[15] The majority of patients were overweight or obese and had hypertension, NYHA II/III HF symptoms, reduced peak VO_2 at baseline, and were on Angiotensin-converting-enzyme inhibitor/Angiotensin II receptor blocker (ARB), beta blockers, and diuretics.[15] Only 48% were women, 37% had history HF hospitalization, 43% diabetes mellitus, 39% ischemic heart disease, 45% jugular venous pressure >8 cm, and 60% edema.[15] This phenotype may be different than other HFpEF subtypes with a higher representation of women, diabetes mellitus, chronic kidney disease, and edema; and therefore, the levels and changes over time may differ in other populations with HFpEF. Lack of changes in the hs-TnI levels over time observed in this group implies stability of the patients, but lack of a decline <99% upper reference limit suggest an ongoing myocardial pathology that does not seem to normalize. (Figure 2B).

Within this group, patients with elevated hs-TnI levels above the median (median levels were close to the 99% upper reference limit) appeared to be older, more likely to be male, with higher prevalence of congestion markers (elevated jugular venous pressure, diuretics, higher NT-proBNP levels), and with echocardiographic parameters demonstrating worse diastolic dysfunction, higher filling pressures, and left ventricular hypertrophy compared with lower hs-TnI levels. Interestingly peak VO_2 levels were not different, but they had lower walk distances. Lack of differences in peak VO_2 may be because of differences in sex distribution (more males in higher hs-TnI group, who have higher peak VO_2), small sample size, and homogeneity of the trial population on exercise performance. And also in HFpEF, exercise capacity is strongly associated with factors such as obesity, anemia, and chronotropic incompetence, but not with resting measures of ventricular and vascular structure and function.[17]

As expected, hospitalized HFpEF patients in *DOSE,*[13] *CARRESS-HF*[14] trials were sicker than the ambulatory patients. Though they did not require objective echocardiographic, invasive hemodynamic, or exercise performance criteria or elevated natriuretic peptide levels on entry, patients had to have symptoms or signs of HF by physical exam or

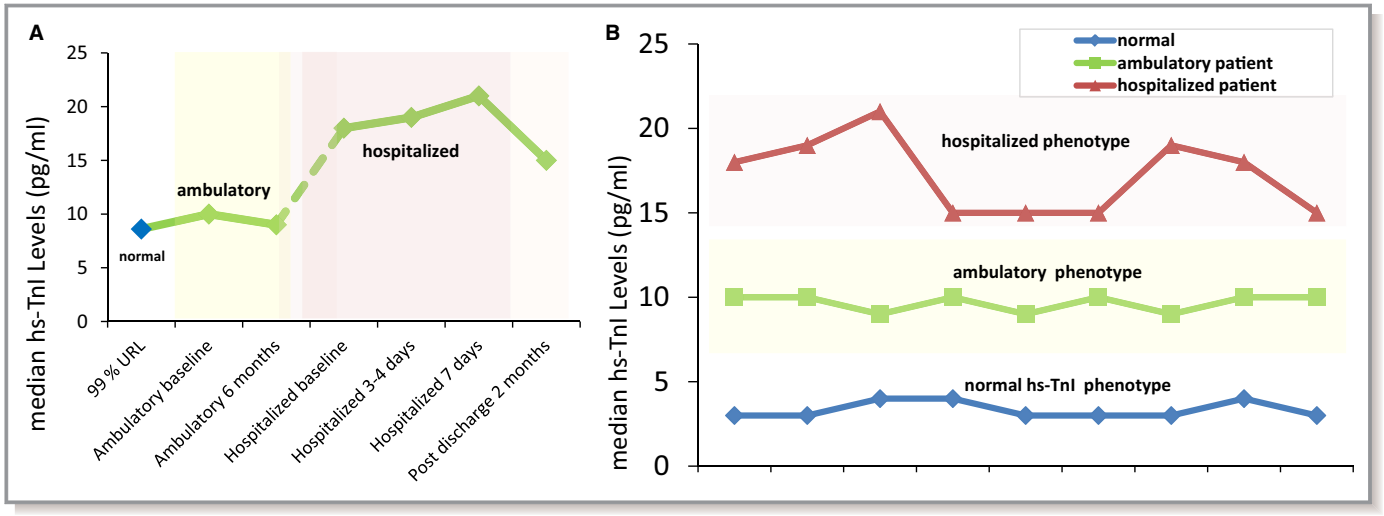

Figure 2. **A**, Characterization of the trajectory of a hypothetical patient with HFpEF, changing from ambulatory state to hospitalization, and subsequently post/discharge. For characterization, hs-TnI median levels reported by Fudim et al were used.[16] **B**, Characterization of hypothetical HFpEF phenotypes, according to trajectories of hs-TnI levels reported by Fudim et al[16]: Normal hs-TnI phenotype: HFpEF patient with hs-TnI levels under the 99th percentile upper reference limit). These patients are likely to be asymptomatic (Stages A or B) or if symptomatic, stable (Stage C, NYHA Class II); Ambulatory phenotype: HFpEF patients with hs-TnI levels just above normal and their levels do not change significantly. They can be symptomatic, but stable (Stage C, NYHA II); Hospitalized phenotype: sicker HFpEF patients with chronically elevated hs-TnI levels, much higher than normal or ambulatory patients with HFpEF, and levels decline slightly after discharge, but do not reach normal or levels of the ambulatory patients.

chest radiography. Almost all the patients were NYHA Class III/IV HF, had elevated jugular venous pressure, edema and/or orthopnea, were on diuretics, had estimated glomerular filtration rate (eGFR)<50 mL/min per 1.73 m^2 and more than two thirds were with history of former hospitalization in the past year. Baseline median NT-proBNP levels (*DOSE* trial approximately 7000 pg/mL, *CARRESS-HF* trial approximately 4000 pg/mL) were markedly higher than the levels in the ambulatory *RELAX* trial patients, (approximately 700 pg/mL) reflecting worse congestion. Among these hospitalized patients, patients with elevated hs-TnI had a lower body mass index, and higher NT-proBNP levels compared with those with lower hs-TnI levels.[16] Despite an aggressive escalated diuretic and decongestion regimen that resulted in significant weight loss in these trials (2.2–4 kg at 72 hours in *DOSE*; 7 L net fluid loss at 96 hours in *CARRESS-HF*) and NT-proBNP reduction (−1541 pg/mL in *DOSE* at 72 hours, −979 pg/mL at 96 hours in *CARRESS-HF*),[13,14] there were no significant reductions in hs-TnI levels during the hospitalization among patients with HFpEF.[16] This may imply that either these patients had chronically elevated troponin levels that did not change significantly with treatment during hospitalization (Figure 2B), or that there might be different subgroups of patients; ie, some whose hs-cTn levels came down; and some, whose levels did not change or even increased, resulting in an overall unchanged net-effect. The different responses in hs-cTn levels, ie, some decreasing, some remaining unchanged or increasing have been reported with treatment in hospitalized HF patients regardless of LVEF.[18,19] Fudim and colleagues also report that in the hospitalized HF-pEF patients, the hs-TnI levels declined slightly 6 months after discharge, by 17%, suggesting a gradual but modest improvement without normalization in hs-TnI levels.

As expected, elevated hs-TnI levels were associated with worse clinical outcomes, reported as the combined end point of emergency room visits, readmissions, and death at 60 days in this study.[16] These findings were similar to other studies which reported elevated hs-cTn levels were associated with increased mortality and readmission rates in patients with acute decompensated HF regardless of LVEF.[3] In some studies, this association was even stronger in patients with HFpEF than HFrEF,[20] suggesting that elevated hs-cTn levels may be a reflection of a sicker phenotype with long-term implications of higher risk in patients with HFpEF.

High-sensitivity biomarkers such as hs-cTn have allowed us to recognize subclinical disease and future risk and will likely shift the paradigm for individualization of therapies in different phenotypes. Whether elevated hs-cTn levels are a reflection of episodic worsening, such as decompensation requiring hospitalizations (Figure 2A), versus fingerprints of characterization of chronic elevations in different phenotypes of patients (Figure 2B), or both, remain unanswered in HFpEF. It is intriguing to imagine the possibility of targeted therapies to prevent HF in patients with elevated hs-cTn levels, but without symptoms of HF or structural changes; or to prevent worsening and adverse clinical outcomes among those who are higher risk with symptomatic HF and elevated hs-cTn levels. It is critical to recognize that a significant proportion of the general adult population has detectable hs-cTn levels associated with future HF risk,[6,8] which expands the definition of Stage A HF and the possibility of preventive strategies to large populations. Furthermore, approximately half of the ambulatory and the majority of the hospitalized HFpEF patients have elevated hs-cTn levels associated with higher risk.[16] This may provide us an opportunity to define a common pathway for targeted therapies in these high-risk patients, for whom currently no definitive therapy exists.

Disclosures

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References

1. Peacock WF, DeMarco T, Fonarow GC, Diercks D, Wynne J, Apple FS, Wu AH. Cardiac troponin and outcome in acute heart failure. *N Engl J Med*. 2008;358:2117–2126.
2. Pandey A, Golwala H, Sheng S, DeVore AD, Hernandez AF, Bhatt DL, Heidenreich PA, Yancy CW, de Lemos JA, Fonarow GC. Factors associated with and prognostic implications of cardiac troponin elevation in decompensated heart failure with preserved ejection fraction: findings from the American Heart Association get with the guidelines-heart failure program. *JAMA Cardiol*. 2017;2:136–145.
3. Yousufuddin M, Abdalrhim AD, Wang Z, Murad MH. Cardiac troponin in patients hospitalized with acute decompensated heart failure: a systematic review and meta-analysis. *J Hosp Med*. 2016;11:446–454.
4. Pang PS, Teerlink JR, Voors AA, Ponikowski P, Greenberg BH, Filippatos G, Felker GM, Davison BA, Cotter G, Kriger J, Prescott MF, Hua TA, Severin T, Metra M. Use of high-sensitivity troponin t to identify patients with acute heart failure at lower risk for adverse outcomes: an exploratory analysis from the RELAX-AHF Trial. *JACC Heart Fail*. 2016;4:591–599.
5. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. *Clin Chem*. 2012;58:1574–1581.
6. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, Hashim I, Berry JD, Das SR, Morrow DA, McGuire DK. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA*. 2010;304:2503–2512.
7. McEvoy JW, Chen Y, Ndumele CE, Solomon SD, Nambi V, Ballantyne CM, Blumenthal RS, Coresh J, Selvin E. Six-year change in high-sensitivity cardiac troponin t and risk of subsequent coronary heart disease, heart failure, and death. *JAMA Cardiol*. 2016;1:519–528.
8. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, Folsom AR, Heiss G, Coresh J, Ballantyne CM. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation*. 2011;123:1367–1376.
9. Sanders-van Wijk S, van Empel V, Davarzani N, Maeder MT, Handschin R, Pfisterer ME, Brunner-La Rocca HP; TIME-CHF investigators. Circulating biomarkers of distinct pathophysiological pathways in heart failure with preserved vs. reduced left ventricular ejection fraction. *Eur J Heart Fail*. 2015;17:1006–1014.
10. Perna ER, Aspromonte N, Cimbaro Canella JP, Di Tano G, Macin SM, Feola M, Coronel ML, Milani L, Parras JI, Milli M, García EH, Valle R. Minor myocardial

damage is a prevalent condition in patients with acute heart failure syndromes and preserved systolic function with long-term prognostic implications: a report from the CIAST-HF (Collaborative Italo-Argentinean Study on cardiac Troponin T in Heart Failure) study. *J Card Fail*. 2012;18:822–830.

11. Felker GM, Mentz RJ, Teerlink JR, Voors AA, Pang PS, Ponikowski P, Greenberg BH, Filippatos G, Davison BA, Cotter G, Prescott MF, Hua TA, Lopez-Pintado S, Severin T, Metra M. Serial high sensitivity cardiac troponin T measurement in acute heart failure: insights from the RELAX-AHF study. *Eur J Heart Fail*. 2015;17:1262–1270.
12. Jhund PS, Claggett BL, Voors AA, Zile MR, Packer M, Pieske BM, Kraigher-Krainer E, Shah AM, Prescott MF, Shi V, Lefkowitz M, McMurray JJ, Solomon SD; PARAMOUNT Investigators. Elevation in high-sensitivity troponin T in heart failure and preserved ejection fraction and influence of treatment with the angiotensin receptor neprilysin inhibitor LCZ696. *Circ Heart Fail*. 2014;7:953–959.
13. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364:797–805.
14. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012;367:2296–2304.
15. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, Deswal A, Stevenson LW, Givertz MM, Ofili EO, O'Connor CM, Felker GM, Goldsmith SR, Bart BA, McNulty SE, Ibarra JC, Lin G, Oh JK, Patel MR, Kim RJ, Tracy RP, Velazquez EJ, Anstrom KJ, Hernandez AF, Mascette AM, Braunwald E; RELAX Trial. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2013;309:1268–1277.
16. Fudim M, Ambrosy AP, Sun JL, Anstrom KJ, Bart BA, Butler J, Abouezzedine O, Greene SJ, Mentz RJ, Redfield MM, Reddy Y, Vaduganathan M, Braunwald E, Hernandez AF, Borlaug BA, Felker GM. High sensitivity troponin I in hospitalized and ambulatory patients with heart failure with preserved ejection fraction: insights from the Heart Failure Clinical Research Network. *J Am Heart Assoc*. 2018;7:e010364. DOI: 10.1161/JAHA.118.010364.
17. Mohammed SF, Borlaug BA, McNulty S, Lewis GD, Lin G, Zakeri R, Semigran MJ, LeWinter M, Hernandez AF, Braunwald E, Redfield MM. Resting ventricular-vascular function and exercise capacity in heart failure with preserved ejection fraction: a RELAX trial ancillary study. *Circ Heart Fail*. 2014;7:580–589.
18. Takashio S, Nagai T, Sugano Y, Honda S, Okada A, Asaumi Y, Aiba T, Noguchi T, Kusano KF, Ogawa H, Yasuda S, Anzai T; NaDEF Investigators. Persistent increase in cardiac troponin T at hospital discharge predicts repeat hospitalization in patients with acute decompensated heart failure. *PLoS One*. 2017;12:e0173336-.
19. Ferreira JP, Santos M, Almeida S, Marques I, Bettencourt P, Carvalho H. High-sensitivity troponin T: a biomarker for diuretic response in decompensated heart failure patients. *Cardiol Res Pract*. 2014;2014:269604-.
20. Gohar A, Chong JPC, Liew OW, den Ruijter H, de Kleijn DPV, Sim D, Yeo DPS, Ong HY, Jaufeerally F, Leong GKT, Ling LH, Lam CSP, Richards AM. The prognostic value of highly sensitive cardiac troponin assays for adverse events in men and women with stable heart failure and a preserved vs. reduced ejection fraction. *Eur J Heart Fail*. 2017;19:1638–1647.

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