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The Role of Troponin for Acute Heart Failure

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Abstract

Purpose of Review To review the mechanisms, clinical interpretation, prognostic role, and future research regarding cardiac troponin (cTn) in the assessment of acute heart failure (AHF) patients presenting to the emergency department (ED).

Recent Findings cTn has become a necessary component of the evaluation of AHF patients in the ED, largely because of its independently predictive value as a prognosticator of poor outcome. High-sensitivity assays (hs-cTn) may add risk stratification value beyond conventional assays, specifically with regard to identifying low-risk AHF patients. Moreover, as the complex mechanisms of cTn release in AHF continue to be elucidated, recent studies suggest that many of the key hemodynamic derangements that define specific AHF syndromes may also be direct culprits in cTn release.

Summary cTn is released in AHF in response to both non-ischemic (e.g., increased afterload, increased preload, inflammatory signaling, altered calcium handling) and ischemic mechanisms. cTn detectable on conventional sensitivity assays predicts poor prognosis when measured in the ED or when noted in historical data such as past ED visits or at the time of discharge from the most recent AHF hospitalization. hs-cTn assays provide detectable values in nearly all AHF patients. Evidence is evolving on using hs-cTn levels below the upper limit of normal to potentially identify low-risk ED patients, and further research is needed. Among the classically cited risk factors for AHF mortality, cTn and natriuretic peptides stand as independent and synergistic prognostic factors even after adjustment for confounders. Many other risk factors, such as ejection fraction, often failed to retain ED prognostic value beyond these two biomarkers.

Keywords Acute heart failure · Emergency department · Risk stratification · Troponin · Cardiac biomarkers · Decompensated heart failure

Introduction

Acute heart failure (AHF) accounts for over 680,000 emergency department (ED) visits annually in the United States (US) and was estimated to cost the US healthcare system $30.7 billion in 2012 [1]. Current guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC) both give Class I recommendations for cardiac troponin (cTn) to be included in the routine ED evaluation for AHF [2–4]. Understanding of the etiology of cTn elevation in AHF and its implications for prognosis and management have evolved greatly over the past 20 years. Here, we review the latest evidence on the use and implications of cTn in AHF, as well as directions for future research.

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Assay and Analytical Considerations

Any discussion of the implications of cTn in AHF must start with some understanding of the assays used as well as their limitations. Troponin represents a broad class of intracellular proteins critical for actin-myosin cross-bridging in both skeletal and cardiac muscle. It was recognized decades ago that cTn is both discretely measurable on blood-based clinical assays and able to be differentiated from skeletal muscle troponin with high specificity [5–8]. The organ-specificity and reliability of clinical assays for cTn led to it becoming the gold-standard diagnostic test for myocyte damage and acute

myocardial infarction (AMI) nearly 20 years ago [8, 9•]. The first reports of cTn elevations among heart failure (HF) patients without acute coronary syndrome (ACS) were published around this same time [10, 11], and for over two decades, there has been an explosion of research into the use of cTn in both acute and chronic heart failure.

cTn assays used clinically can be divided into two groups based on the protein subunit an assay detects. Clinical assays exclusively detect either the T or the I subunit of the troponin complex (cTnT and cTnI, respectively) when released into the bloodstream from cardiomyocytes. In ACS, these two assay types are largely considered equivalent [9•, 12], and both have been used in for research purposes in the setting of AHF. Current guidelines do not distinguish between the two cTn assays for AHF. Nevertheless, differences in the prevalence of positive results and the relative prognostic value of cTnI and cTnT exist for non-ACS conditions. However, few studies have compared troponin subtypes in AHF patients specifically, and no definitive conclusions recommending one over the other can be supported at this time [12].

In recent years, several high-sensitivity cTn assays (hs-cTn) have come in to use in Europe and Canada, though the first such assay was only recently approved by the FDA for use in the US (Roche hs-cTnT) [13]. It has been proposed that 2 criteria be used to define a cTn assay as "high-sensitivity." These include an imprecision $\leq 10\%$ at the 99th percentile, and being able to detect cTn values in $\geq 50\%$ of the healthy population [13–15]. It is worth noting that in studies by Apple et al., the Roche hs-cTnT assay approved by the FDA in 2017 fell short of the second criteria [15, 16]. At least four commercial hs-cTnI assays meet both criteria, and several have become FDA-approved within the past year [15]. Of note, available hs-cTn assays have reported significant sex-specific differences in their 99th percentile values, and include sex-specific reference ranges [15].

Regarding definitions for "abnormal" troponin values in AHF, the recently published fourth universal definition of MI has significant implications [9•]. Similar to past definitions, the cutoff for an abnormal cTn is defined by the 99th percentile of a given assay's distribution in a reference population [9•]. This is true for conventional and hs-cTn assays, whether cTnT or cTnI, regardless of the cause for troponin elevation. However, for the first time, a distinction placing troponin elevations into two classes has been provided: myocardial *infarction* and myocardial *injury*. The former is defined as cTn elevation secondary to ischemia, while the latter is defined as an elevation due to non-ischemic causes of injury (e.g., apoptosis, trauma, and inflammation). Myocardial infarction is further subdivided into 5 types by the etiology of ischemia. While ACS falls strictly within the type 1 designation, cTn elevations in AHF can be due to a number of complex and diverse mechanisms and often fall into the type 2 group when ischemia is the cause of elevation. Because of this etiologic heterogeneity, cTn elevation in AHF can be classified as myocardial injury, infarction (including multiple subtypes), or both.

Ischemic Versus Non-ischemic Pathophysiology Responsible for Troponin Release

Both ischemic and non-ischemic processes have been experimentally observed to cause cTn release in AHF [8, 9•]. The underlying pathophysiology responsible for cTn elevation is highly complex, mechanistically heterogeneous, and differing based on both a patient's underlying cardiac function as well as the decompensating impetus for their current episode of AHF. Figure 1 summarizes the many mechanisms thought to contribute. Understanding the differential ischemic and non-ischemic etiologies of cTn elevation may help clinicians in their risk stratification and management of AHF patients presenting to the ED.

Non-ischemic processes have recently become a larger focus than ischemic processes in the understanding of cTn elevation in HF [9•]. In AHF, such processes often relate to the structural or functional pathology of specific precipitants of AHF itself [9•]. Acute cardiac volume or pressure overload leading to increased wall stress may directly cause non-ischemic cTn release, secondary to a myocardial stretch-related mechanism mediated by integrins [17•, 18, 19]. This effect has been observed to occur even when an increase in preload or afterload is brief and transient [17•]. Most causes of AHF have associated neurohumoral activation leading to increases in circulating cytokines, catecholamine surges, and oxidative stress which may further contribute to troponin release [8]. Additionally, impaired ventricular relaxation and diastolic dysfunction independently predict cTn release in patients with HF with preserved ejection fraction (HFpEF) [20, 21]. Ventricular remodeling and structural changes common in AHF patients, including the formation of scar and hibernating myocardium, also correlate with elevated cTn levels in HF [22–24].

Based on broad familiarity with the pathophysiology of ACS, it might be assumed that cTn becomes detectable in AHF because of infarction and myocyte death. While this is true in some cases of overt ischemia, it has been hypothesized for decades that cTn is also be released into the bloodstream from intact myocardium in HF [25]. This has been borne out in recent experiments, including those evaluating the effects of stretch, volume, and pressure overload [8, 17•, 18]. Currently, it is theorized that certain pathologic stimuli cause release of troponin directly from the cytosol of otherwise intact myocytes, referred to as the "cytosolic pool" [8]. Moreover, when myolysis is responsible for cTn entering the

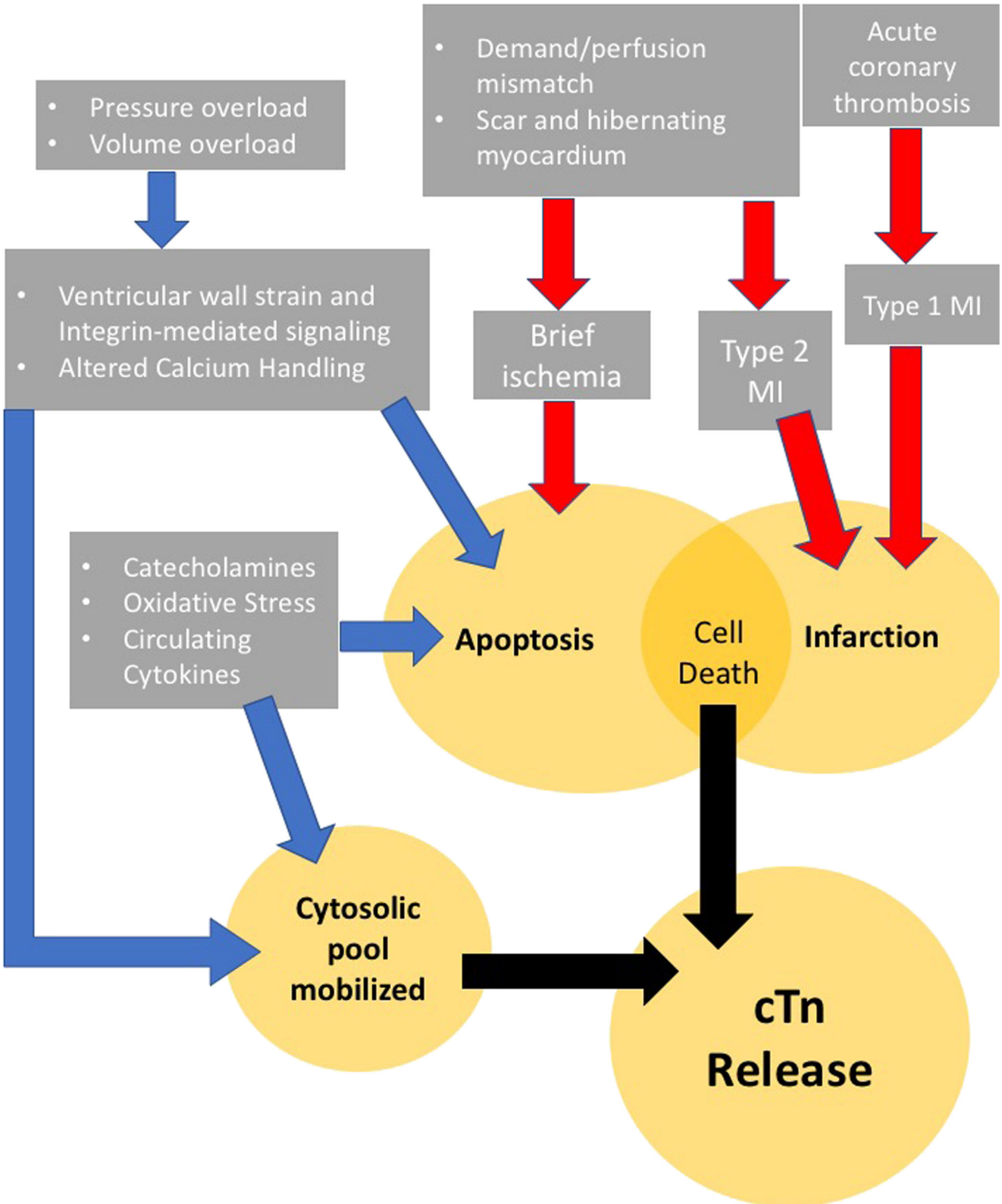

Fig. 1 Current understanding of cTn release in AHF. Multiple potential physiologic stressors converge on 3 different mechanisms for cTn release—apoptosis, infarction, and mobilization of the cytosolic cTn pool. The first two both result in myocyte death, but the last mechanism involves cTn release from viable myocytes. Blue arrow, non-ischemic process; Red arrow, ischemic process

bloodstream in AHF, it is not always due to infarction but often a complex cellular response involving apoptosis of myocytes in response to physiologic stressors or neurohormonal stimulation [17•, 26, 27, 28•]. Stressors can include the influences of myriad inflammatory mediators as well as altered calcium handling leading to the degradation of cTn.

That said, ischemic processes can also exist in AHF and be responsible for cTn elevation. Type 1 MI (i.e., ischemia due to acute coronary thrombosis) may exacerbate underlying myocardial dysfunction or produce it de novo. In these patients, AHF can be a secondary event to acute myocardial infarction (AMI), with the primary cause of cTn elevation being due to a true ACS event. Alternatively, chronic epicardial coronary artery disease (CAD) in a patient with AHF as a primary event may lead to demand-perfusion mismatch and cTn elevation, with resultant designation as type 2 MI [9•]. Even brief myocardial ischemia in AHF can result in significant cTn release, through induction of apoptosis rather than myolysis [28•].

It is often difficult to differentiate ischemia as a primary or secondary process in AHF based on clinical factors alone [3, 29], especially while the patient is still in the initial phase of care. For this reason, in patients with AHF, an elevated cTn alone is not sufficient as an isolated criterion for to establish the diagnosis of ACS or CAD [3, 29]. Current diagnostic criteria for both type 1 and type 2 MI require ischemic ECG changes, confirmatory imaging, or symptoms of ischemia in addition to an acute cTn rise above the 99th percentile [9•]. Furthermore, AHF patients without angiographically identifiable overt CAD may nevertheless have ischemic cTn release due to underlying coronary microvascular dysfunction [21, 30].

Patients presenting to the ED with AHF secondary to an ischemic cause have been shown to benefit from early revascularization during their hospitalization [31–36]. However, specific patient selection indicators remain unclear, and prospective controlled trial data on revascularization for AHF patients is largely lacking [37]. Coronary angiography during AHF hospitalization even without revascularization has the ability to identify CAD and lead to initiation of medical therapy which has proven mortality benefits [37]. Moreover, with the exception of overt cardiogenic shock secondary to AMI (e.g., in the presence of ST-elevation MI), evidence is lacking to suggest that emergent revascularization is needed rather than urgent investigation of potential CAD after admission. For now, clinical judgment applied to individual AHF patients should guide any consideration of the need for and timing of revascularization.

Epidemiology

Estimates of the prevalence of cTn elevation in AHF vary. In the largest study to date from the Acute Decompensated Heart Failure National Registry (ADHERE) [38], among 84,872 patients hospitalized for AHF, 6.2% had a positive cTnI or cTnT using conventional sensitivity assays. Other studies using conventional assays have reported even higher prevalence, ranging from 10 to 30% or more, through studies used different cutoff concentrations and included a variety of patients with divergent baseline characteristics [39–44, 45•]. One recent study of 2025 AHF patients from 109 hospitals in Ontario, Canada, found a 34.5% prevalence of cTnI values above the 99th percentile [46].

Despite their enhanced sensitivity, studies including hs-cTn assays have not found a higher prevalence of cTn > 99th percentile [47]. Nonetheless, while still dependent on individual assay characteristics, hs-cTn above the limit of detection may be present in 80–100% of ED patients with AHF [48, 49].

Prognosis and Risk Stratification

Numerous studies have shown a strong association between cTn and mortality as well as other adverse outcomes in AHF (Table 1) [24, 31, 35, 36, 38, 40–43, 45•, 46, 48, 50–76]. Peacock et al. found an in-hospital mortality rate for AHF patients with elevated cTn of 8% in their analysis of ADHERE data, compared to 2% in AHF patients without an elevated troponin. Many other studies have looked at mortality including some differentiating by short- and long-term follow-up. In a metaanalysis from 2016 that included 26 studies, any cTn above an assay's detectable limit (i.e., including values below the 99th percentile) in AHF was predictive of mortality similarly at short-term (odds ratio [OR] = 2.11), intermediate-term (OR = 2.3), and long-term (OR = 3.69) follow-up [45•]. Other studies have found that cTn signals an increase in AHF mortality regardless of whether HFpEF or HFrEF is present [58]. ED to hospital admission and risk of intensive care unit (ICU) admission for AHF are also significantly higher when cTn is elevated [31].

Importantly, several studies have shown cTn to be an independent predictor of mortality even when adjusting for confounders on multivariate regression [50, 52, 54–56]. In many of these analyses, cTn was one of just a few independently predictive factors remaining after adjustment (Table 2). Interestingly, other AHF prognostic factors such as ejection fraction (EF) did not retain independent prognostic value beyond that associated with cTn [52, 54, 57]. cTn has additive prognostic benefit when used in conjunction with other biomarkers (Table 2), especially natriuretic peptides [52, 63, 67, 74, 80]. Overall, extensive evidence supports that detectable cTn on conventional sensitivity assays in AHF should prompt consideration of more aggressive ED care and admission to a higher level of inpatient care (Table 1).

When a baseline cTn value is known, it can add prognostic value to the risk stratification of patients arriving to the ED in AHF. Any chronic elevation of cTn (especially > 0.04 ng/ml for cTnT) or persistently elevated cTn at the time of discharge

Table 1 Conventional sensitivity cTn predicts mortality in AHF

Study	*n*	Predictor (cutoff)	Outcome (follow-up)	Effect size (95% CI)	Comments
La Vecchia 2000 [40]	34	Any detectable cTnI	Mortality (3 months)	HR = 6.86 (1.32–35.4)	Prevalence of detectable cTnI = 29%
Perna 2004 [24]	159	Abnormal cTnT (> 99th percentile)	Mortality or refractory HF (in-hospital)	OR = 6.8 (1.5–31.2)	Rates of primary outcome 20.7% vs. 3.7% (cTnT+ vs. cTnT−)
Perna 2005 [50]	184	Abnormal cTnT (> 99th percentile)	Mortality (mean 9 months)	HR = 1.74, (1.05–2.9)	After multivariate adjustment cTnT and retained independent prognostic value
Demir 2007 [51]	55	cTnT > 99th percentile	Mortality (3 years)	73% vs. 39% $p = 0.05$	Prevalence of detectable cTnT = 20%
Metra 2007 [52]	107	Any detectable cTnT	Mortality (median 184 days)	HR = 5.41 (4.40–6.43)	After multivariate adjustment cTnT and pro-BNP retained independent prognostic value but EF did not
You 2007 [46]	2025	cTnI > 99th percentile	Mortality (1 year)	HR = 1.49 (1.25–1.77)	34.5% prevalence of abnormal cTnI across 103 Ontario hospitals. HR adjusted for multiple confounders
Parenti 2008 [53]	99	Any detectable cTnI	Mortality (median 12 months)	RR = 4.65 (1.27–17.11)	Entire cohort was AHF patients discharged from ED
Peacock 2008 [38]	67,924	cTnI or cTnT > 99th percentile	Mortality (in-hospital)	OR = 2.55 (2.24–2.89)	Mortality increased incrementally by each quartile of increasing cTn level. Overall prevalence of abnormal cTn = 6.2%
Del Carlo 2009 [54]	70	Abnormal cTnT > 99th percentile	Mortality (1 year)	HR = 3.95 (1.64–9.49)	After multivariate adjustment cTnT retained independent prognostic value but EF did not
O'Connor 2011 [55]	288	cTnT > 0.03 ng/ml	Mortality or rehospitalization (60 days)	HR = 1.84 (1.04–3.26)	After multivariate adjustment cTnT retained independent prognostic value. Cutoff of 0.03 ng/ml was below 99th percentile but above limit of detection (0.01 ng/mL) of the assay
Parissis 2011 [56]	837	cTnT > 0.01 ng/ml	Mortality (in-hospital)	HR = 3.37 (1.18–9.55)	Cohort of patients with preserved ejection fraction. After multivariate adjustment cTnT retained independent prognostic value.
Perna 2012 [57]	500	cTnT 0.02 ng/ml	Mortality or rehospitalization (6 months)	HR = 1.82 (1.28–2.58)	After multivariate adjustment cTnT and natriuretic peptides retained independent prognostic value but EF did not
Braga 2013 [31]	13,656	cTnT > URL	Mortality (30 days)	HR = 9.17 (8.31–10.12)	ED Admission (88% vs. 70.3% $p < 0.001$) and ICU admission (36.5% vs. 15.6% $p < 0.001$) higher when cTnT > 99th percentile
Pandey 2017 [58]	34,233	cTnT or cTnI > URL	Mortality (in-hospital)	HR = 2.19 (1.88–2.56)	Multicenter HFpEF AHF population. 30-day mortality and readmission also independently predicted by cTnT+
Thawabi 2017 [59]	363	cTnI > 99th Percentile	Mortality (30 days)	HR = 8.48 (1.02–76.34)	HFpEF cohort. Nearly half had cTnI > 99th percentile. After multivariate adjustment cTnT and natriuretic peptides retained independent prognostic value

HR, hazard ratio; *OR*, odds ratio; *RR*, relative risk; *95% CI*, 95% confidence interval; *URL*, upper reference limit of local hospital; *EF*, ejection fraction; *HFpEF*, heart failure with preserved EF

Table 2 Clinical considerations in the interpretation of cTn for risk stratifying ED AHF patients

Clinical finding	Implication
Contemporary sensitivity cTn > 99th percentile/URL	High mortality risk, needs admission and possibly more intensive AHF care
Contemporary sensitivity cTn < 99th percentile/URL but detectable	High mortality risk, likely needs admission
Elevated cTn but normal EF	High 30-day mortality risk even with HFpEF. Also, some studies found cTn is independent predictor without any added additional prognostic value from low EF
Patient has known detectable or elevated cTn at baseline	Any baseline detectable cTn in chronic HF is associated with increased mortality [77]. Persistent elevation at baseline has poor prognostic implications. If the lowest recent cTn is greater than 0.04 ng/ml (trough), this may be more predictive of mortality than a peak value when trending [61] at ED arrival.
Patient had elevated cTn at the end of most recent AHF hospitalization	Predicts readmission and mortality from cardiovascular cause [68, 75]. If hs-cTn value is low or decreasing from previous baseline prognosis may be better, however [75]
Interpreting cTn in the context of other prognostic factors	In multivariate analysis, an elevated cTn was one of only a few independently predictive risk factors for mortality [50, 52, 54–56]. Two factors which consistently have synergistic prognostic value in addition to cTn include natriuretic peptides (BNP and NT-proBNP) and New York Heart Association heart failure classification.
Patient has newly elevated hs-cTn below the limit of detection of a conventional cTn assay	Likely poorer prognosis compared to if hs-cTn is normal, but evidence is mixed on how clinically significant this is [43, 60, 65, 69, 70, 78]. TACIT trial [79] is currently underway to assess whether 0 h and 3 h low hs-cTnT values (i.e., below limit of detection of conventional assays) may be able to detect a subset of AHF patients who are low risk enough for discharge.

from a recent AHF hospitalization increases the risk of mortality [81]. Additionally, when a patient has a chronically elevated cTn, the lowest recent value (i.e., the "trough") may have a stronger association with mortality than the highest recent levels (i.e., the "peaks") [61].

While cTn detectable or elevated on conventional sensitivity assays clearly denote a high-risk group of AHF patients, those with undetectable conventional sensitivity cTn cannot be assumed to be at low risk. Alternatively, hs-cTn may allow identification of an AHF population in the ED that is low risk enough to consider for discharge rather than admission [69, 79]. Since detectable levels of hs-cTn are nearly ubiquitous in AHF patients, if a low-risk hs-cTn threshold can be identified, risk stratification for ED patients could be enhanced [69]. This is potentially a promising feature of Hs-cTn for emergency physicians and is currently undergoing further study at this time [79].

Currently, the evidence to support added risk stratification benefits with hs-cTn is mixed but still evolving. Very low serum concentrations of cTn detectable on hs-cTn assays have been observed in some studies to add prognostic value beyond that seen in conventional assays [48, 70–72]. Pascal-Figal and colleagues noted in a multivariate analysis of 107 AHF patients that every 0.1 ng/mL of hs-cTnT above the detectable limit predicted an incremental increase in mortality (hazard ratio [HR] = 1.16, 95% confidence interval [95% CI] 1.09–1.24). In the same analysis, it was calculated that a hs-cTnT cutoff of 0.023 ng/mL had a 91% negative predictive value for mortality (at a median follow-up of 739 days) [71] More recently, Pang and colleagues found that none of the 1076 patients in a post hoc analysis of the RELAX-AHF trial died from a cardiovascular cause at 180 days [69]. However, in a recent large study of 34 Spanish EDs with 4705 AHF patients, hs-cTn failed to outperform conventional sensitivity assays for prediction of 1-year mortality [43]. Nevertheless, 1-year mortality is likely too long of a follow-up time to be useful for risk-profiling of ED patients with AHF patients. Additionally, practice patterns outside the US may differ substantially, making the applicability to US populations questionable.

Future Research

Given the current conflicting and limited evidence regarding the use of a low hs-cTn to predict safety for ED discharge, a multicenter prospective study to better evaluate in the US is currently underway [79]. The "hs-cTnT Rules Out Cardiac Insufficiency Trial" (TACIT) will evaluate serial hs-cTnT levels at 0 and 3 h post-arrival in the ED. If able to show an increased rate of safe ED discharge, this could be extremely impactful in the US, where 88% of AHF patients are admitted to the hospital despite estimates that only about 50% likely need to be [69, 79, 81, 82].

There is strong evidence for additive prognostic power when combining cTn with natriuretic peptides, and additional research should explore whether other less-studied risk stratification techniques can add predictive power to these biomarkers. Many studies included cTn and natriuretic peptides in multivariate analyses for prognosis and found several classic risk factors such as EF or serum chemistry data such as renal function or sodium concentration to have limited additional value. However, newer techniques such as point of care ultrasound (POCUS) have not been well studied in conjunction with these biomarkers. Lung ultrasound or advanced POCUS echocardiography techniques such as speckle tracking (strain) imaging [83] have shown promise and may add information beyond a biomarker-based approach.

While much has been learned about the physiology of cTn release in AHF, many questions remain. In particular, studies directly implicating common hemodynamic disturbances such as increased afterload, preload, and ventricular stretch as a causal mechanism need to be replicated and evaluated more closely within the context of the most acute stages of AHF. Further, such studies could potentially forge links between certain hemodynamic derangements and targets for treatment. For example, one group of investigators has already demonstrated hs-cTn to have a potential role in assessing diuretic response [66]. Similarly, while elevated cTn values clearly portend a poor prognosis, future studies should evaluate if cTn elevations with or without other risk factors can indicate the need for specific higher-level AHF interventions (e.g., positive pressure ventilation, high-dose IV vasodilators, ICU admission), and if resultant changes in cTn concentrations correspond to better (or worse) outcomes.

As new cTn assays continue to emerge, so must evaluation of their relative importance in guiding patient care. For instance, new assays using single-molecule counting methods have recently been developed. Described as "ultrasensitive" (i.e., with limits of detection 10–100 times lower than most current hs-cTn assays), how these assays will impact AHF management need to be investigated [84]. Additionally, while we know of no current evidence clearly demonstrating a clinically significant difference between cTnT versus cTnI, such a difference has been demonstrated for other non-ACS conditions in which cTn is used as a prognostic factor [12, 85]—a rigorous comparison study specifically in AHF patients would be helpful.

Conclusions

cTn is a useful component of a biomarker-based ED evaluation strategy for AHF. Unlike the natriuretic peptides, cTn cannot currently be recommended for diagnosis or rule out of risk, though recent studies suggest a potential such role in the future and are currently being studied in a large US multicenter trial (TACIT). However, there is extensive evidence for the prognostic value of cTn in defining high-risk AHF patients who require admission and likely a higher level of care. This is especially true for any AHF patient with a contemporary or hs-cTn value greater than the 99th percentile for a given assay, and likely true for any detectable troponin on a contemporary assay. Levels below the 99th percentile but above the limit of detection on hs-cTn assays also may portend increased risk of adverse outcome, but the clinical utility of such values has not yet been fully defined. Of note, historical cTn elevations (e.g., at discharge, or chronically over several past measurements) predict a high-risk phenotype specifically related to the magnitude of the trough cTn, and should be taken into account when evaluating risk among AHF patients. Finally, it should be recognized that cTn elevation in AHF may be ischemic, non-ischemic, or both. Emergency physicians should be aware that outcomes are significantly improved with revascularization when an ischemic cause is present, and every effort should be made to delineate the specific cause of AHF in the ED, when possible. Better understanding of the ischemic and non-ischemic mechanisms of cTn release will undoubtedly help clinicians guide their management to target specific hemodynamic and physiologic derangements in their AHF patients.

Compliance with Ethical Standards

Conflict of Interest Nicholas Harrison and Mark Favot each declare no potential conflicts of interest. Phillip Levy reports grants from Roche Diagnostics, Beckman Coulter, and Arterez, LLC. And personal fees from Siemens, Roche Diagnostics, Ortho Diagnostics, and Arterez, LLC.

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