

# Troponin Elevation in Heart Failure

## Prevalence, Mechanisms, and Clinical Implications

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Circulating biomarkers have become increasingly important in diagnosing and risk stratifying patients with heart failure (HF). While the natriuretic peptides have received much focus, there is increasing interest in the role of circulating cardiac troponin (cTn) in detecting myocardial injury (often subclinical) in those with HF. Accumulating evidence suggests that patients with chronic and acute HF may have measurable levels of circulating cTn, whose detection and magnitude may have prognostic implications. Furthermore, as new, more sensitive cTn assays are being developed, larger numbers of HF patients are found to have detectable cTn with a persistent relationship between magnitude and outcome. This knowledge improves our ability to understand the mechanism of worsening HF, improve risk stratification, and detect potential injury related to new therapeutics in HF. As investigators begin to understand the relationship of detectable cTn to HF outcomes, as well as temporal changes in its magnitude, and its relationship to other circulating biomarkers, more insight may be gained into the progressive nature of cardiac dysfunction and the transition from chronic compensated to acute decompensated HF. Ultimately, this information might allow physicians to guide therapy, choose appropriate therapeutics, and improve HF outcomes. (J Am Coll Cardiol 2010;56:1071-8) © 2010 by the American College of Cardiology Foundation

Heart failure (HF) is a growing public health problem with significant morbidity, mortality, and cost to the health care system (1). Circulating biomarkers, most notably the natriuretic peptides, have emerged as central to the diagnosis and

risk stratification of patients with HF (2-4). In addition to being useful clinical tools, biomarkers may provide insights into underlying pathophysiology, suggesting new directions for fundamental research or the development of new therapies. Measurement of circulating cardiac troponins (cTn) plays a fundamental role in the diagnosis and management of the acute coronary syndromes (ACS) (5-7). In addition to their role in ischemic heart disease, accumulating data provide support for the importance of cTn measurement in both acute and chronic HF (8-21). These observations have broad implications for prognosis, selection of therapies, development of new treatments, and understanding underlying mechanisms (22). For purposes of this review, we examined the available data on cTn in HF and the implications of these data on our understanding of this condition. In our review, we will suggest knowledge gaps in our current perception of the role of cTn in HF. For example, what are the mechanisms of cTn release in HF? Does myocardial injury play a role in disease progression or decompensation? Can monitoring of cTn help guide therapy? Can this biomarker be used as an efficacy or safety end point in clinical trials?

### Biology of cTn

Troponins are proteins involved in the regulation of cardiac and skeletal muscle contraction. The troponin complex

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**Abbreviations and Acronyms**

- ACS** = acute coronary syndrome
- BNP** = B-type natriuretic peptide
- CHF** = chronic heart failure
- cTn** = cardiac troponin
- HF** = heart failure
- H-FABP** = heart-type fatty acid binding protein
- HR** = heart rate
- hsTnT** = high-sensitivity troponin T
- MI** = myocardial infarction
- NT-proBNP** = N-terminal pro-B-type natriuretic peptide

modulates calcium-mediated actin and myosin interaction in striated muscle. The skeletal and cardiac isoforms of these proteins are coded for by separate genes and differ in structure. The cardiac troponin complex is made of troponin I (inhibitory), troponin C (calcium binding), and troponin T (tropomyosin binding) proteins. Troponin T (TnT) is a 37 kD protein, tightly bound to the cardiac myofibrillar troponin-tropomyosin complex. Troponin I (TnI) is a 24 kD protein, which decreases troponin C affinity for calcium, thus inhibiting troponin-tropomyosin interactions. Cardiac troponin I (cTnI), in particular, is not expressed by injured or regenerating skeletal muscle and is, therefore, exquisitely specific for myocardial injury (23,24).

**Prevalence of Detectable Troponin in HF**

Detectable circulating cTnI is rare in the general population using currently available assays (0.7%) (25). In 1997, Missov et al. (26) were the first investigators to demonstrate increased levels of circulating cTnI in patients with HF outside the context of clinically apparent ischemia, reporting a mean cTnI of 0.74 ng/ml in 35 stable patients with advanced HF, using a high-sensitivity assay. When using a standard cTnI assay with a cut-off of 0.1 ng/ml, only 1 of 35

patients had a clearly positive cTn value. Similar findings have been reported by Latini et al. (15) from the Val-HeFT (Valsartan Heart Failure Trial). Using a standard cardiac troponin T (cTnT) assay (detection limit = 0.01 ng/ml), 10.4% of this population with chronic HF had detectable TnT. Using a high-sensitivity research assay for TnT (detection limit <0.001 ng/ml), 92% of patients had a detectable value (15). As summarized in Table 1, multiple studies have now examined the prevalence of cTn elevation in patients with HF (27). As expected, the prevalence has varied widely as a function of the population type being studied, as well as the characteristics of the utilized assay. In general, elevation of cTn has been more marked in patients with more advanced disease, as well as in patients with decompensated HF (10,11,28). In a recent analysis of the ADHERE (Acute Decompensated Heart Failure National Registry) study, 75% of patients hospitalized with acute HF (n = 67,924) had detectable levels of cTn (cTnI >0.4 ng/ml or cTnT >0.01 μg/l) (19). When a higher threshold for cTn elevation was utilized (cTnI of ≥1.0 ng/ml or cTnT of ≥0.1 μg/l), only 6.2% of acute HF patients had levels above these cut points (19).

**Analytic Considerations in Troponin Measurement**

As with all biomarkers, understanding the role of cTn measurements in HF requires an understanding of the available assays' limitations. Only 1 platform exists for measurement of cTnT in the U.S. (Roche Diagnostics). The cut-off for myocardial infarction (MI) set by the manufacturer is ≥0.1 ng/ml. In contrast, there are multiple assays for cTnI, many with different associated cut-off values and sensitivities. The joint European Society of Cardiology

**Table 1 Incidence of Detectable Troponin in Acute and Chronic HF**

First Author, Year (Ref. #)	n	Troponin	Cut-Off Values	HF Type	HF Etiology	Incidence of Circulating Troponin
Peacock et al., 2008 (19)	67,924	TnI and TnT	TnI or TnT >0.1 μg/l	AHF	Ischemic and nonischemic	6.2%
Gheorghade et al., 2005 (10)	51	TnI and TnT	TnI >0.03 μg/l or TnT >0.01 μg/l	AHF	Ischemic	43.5% (TnT) or 73.9% (TnI)
Del Carlo et al., 2004 (8)	62	TnT	TnT ≥0.01 μg/l	AHF	Ischemic and nonischemic	83.9%
La Vecchia et al., 2000 (14)	34	TnI	TnI >0.3 ng/ml	AHF	Ischemic and nonischemic	29.0%
Metra et al., 2007 (28)	116	TnT	TnT >0.01 ng/ml	AHF	Ischemic and nonischemic	38.0% (at baseline)
Niizeki et al., 2007 (58)	126	TnT	TnT >0.01 ng/ml	AHF	Ischemic and nonischemic	26.0%
Parenti et al., 2008 (18)	99	TnI	TnI >0.05 ng/ml	AHF	Unknown	45.0%
Perna et al., 2005 (21)	184	TnT	TnT >0.1 ng/ml	AHF	Ischemic and nonischemic	31.5%
You et al., 2007 (41)	2,025	TnI	TnI >0.5 μg/l	AHF	Ischemic and nonischemic	34.5%
Logeart et al., 2001 (16)	71	TnI	TnI >0.026 ng/ml	AHF and CHF	Nonischemic	27.0%
Horwich et al., 2003 (11)	238	TnI	TnI ≥0.04 ng/ml	CHF	Ischemic and nonischemic	49.1%
Hudson et al., 2004 (12)	136	TnT	TnT ≥0.02 ng/ml	CHF	Ischemic and nonischemic	24.0%
Latini et al., 2007 (15)	4,053	TnT and hsTnT	TnT ≥0.01 ng/ml or hsTnT ≥0.001 ng/ml	CHF	Ischemic and nonischemic	10.0% (TnT) or 92% (hsTnT)
Miller et al., 2007 (17)	190	TnT	TnT ≥0.01 ng/ml	CHF	Ischemic and nonischemic	53.0%
Missov et al., 1999 (27)	33	TnT	TnT >0.1 ng/ml	CHF	Ischemic and nonischemic	15.0%
Perna et al., 2004 (20)	115	TnT	TnT ≥0.02 ng/ml	CHF	Ischemic and nonischemic	32.0%

AHF = acute heart failure; CHF = chronic heart failure; HF = heart failure; hsTnT = high-sensitivity troponin T; TnI = troponin I; TnT = troponin T.

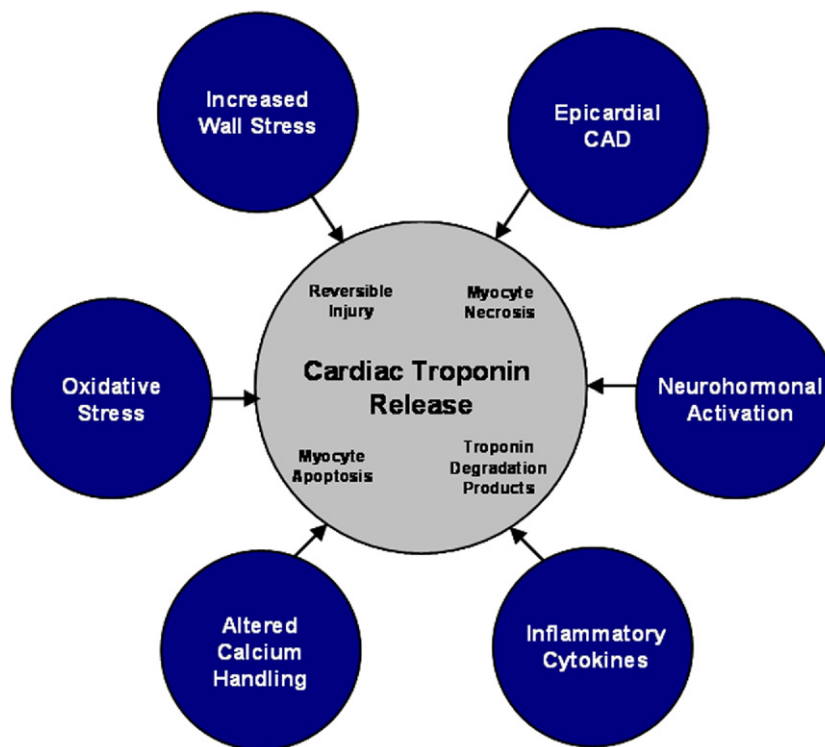
(ESC)/American College of Cardiology (ACC) Committee for the Redefinition of Myocardial Infarction has defined MI as “an increased cTn, exceeding the 99th percentile of the distribution of cTnI in the reference group for that particular assay with an imprecision limit (coefficient of variation) of less than or equal to 10%” (5). However, analysis has shown that precision of commercially available cTn assays are compromised at the 99th percentile reference limit, and that there is large variation in precision between these assays (29). Given the relatively low concentration of circulating cTn detected in acute and chronic HF, limitations of available assays may curb the clinical information that can be derived from these measurements. There are, however, newer high-sensitivity assays that are at least an order of magnitude more sensitive at an imprecision limit of 10% (30,31). The development of such high-sensitivity assays has important implications for the clinical use and interpretation of cTn measurements (32).

Based on its use in the diagnosis of MI, cTn values are often characterized as “positive” or “negative”—a dichotomy that makes little sense in the context of HF. Increasingly sensitive assays, which have demonstrated that cTn can be detected in most patients with chronic HF (15), will progressively lead to the consideration of cTn as a contin-

uous variable across the spectrum of risk, similar to the current usage of natriuretic peptide measurements.

### Mechanisms of Troponin Release in HF

The mechanisms underlying cTn release in patients with HF remain speculative, and multiple mechanisms are potentially active in any given patient (Fig. 1). A consistently notable finding in published studies is that cTn release occurs in patients with and without obstructive epicardial coronary disease, suggesting that mechanisms other than overt myocardial ischemia are likely to be operative. Multiple potential contributing mechanisms have been proposed, including subendocardial ischemia leading to myocyte necrosis, cardiomyocyte damage from inflammatory cytokines or oxidative stress, hibernating myocardium, or apoptosis (2,16,33-35). In addition, cTn may be released from injured, but viable, myocardium as a result of increased permeability of the plasma membrane and leakage of the cytosolic pool of cTn (20,36). Recent studies demonstrate that viable cardiomyocytes, without necrosis, can release cTn as an intact protein by a stretch-related mechanism mediated by integrins (37). Others have suggested that altered calcium handling, as a result of increased pre-load, results in activation of intracellular proteolytic enzymes that



**Figure 1** Mechanism of Cardiac Troponin Release in Heart Failure

Multiple mechanisms may lead to myocyte necrosis, apoptosis, or reversible injury with increased myocyte membrane permeability, all resulting in cardiac troponin release. CAD = coronary artery disease.

**Table 2** Prognosis and Troponin in HF

First Author, Year (Ref. #)	n	Troponin	Cut-Off Values	HF Type	HF Etiology	Outcome	Adjusted for BNP or NT-proBNP
Peacock et al., 2008 (19)	67,924	TnI and TnT	TnI or TnT >0.1 µg/l	AHF	Ischemic and nonischemic	Increased in-hospital mortality	No
Gheorghiade et al., 2005 (10)	51	TnI and TnT	TnI >0.03 µg/l or TnT >0.01 µg/l	AHF	Ischemic	Baseline and peak TnI or TnT significantly higher in patients with worsening HF or death during index admission	No
Del Carlo et al., 2004 (8)	62	TnT	TnT ≥ 0.01 µg/l	AHF	Ischemic and nonischemic	Increased risk of 1-year death or HF rehospitalization (best ROC at cut-off TnT >0.02)	No
La Vecchia et al., 2000 (14)	34	TnI	TnI >0.3 ng/ml	AHF	Ischemic and nonischemic	3-month mortality HR: 6.86; 95% CI: 1.32-35.4	No
Metra et al., 2007 (28)	116	TnT	TnT >0.01 ng/ml	AHF	Ischemic and nonischemic	Mortality HR: 5.41; 4.40-6.43	Yes
Parenti et al., 2008 (18)	99	TnI	TnI >0.05 ng/ml	AHF	Unknown	RR of death for detectable vs. undetectable 4.65; 95% CI: 1.27-17.11	No
You et al., 2007 (41)	2,025	TnI	TnI >0.5 µg/l	AHF	Ischemic and nonischemic	HR for death 1.49; 95% CI: 1.25-1.77	No
Horwich et al., 2003 (11)	238	TnI	TnI ≥0.04 ng/ml	CHF	Ischemic and nonischemic	Detectable troponin associated with mortality (RR: 2.05; 95% CI: 1.22-3.43)	Yes
Hudson et al., 2004 (12)	136	TnT	TnT ≥0.02 ng/ml	CHF	Ischemic and nonischemic	Elevated troponin associated with increased risk of death or HF hospitalization RR: 2.7; 95% CI: 1.7-4.3; and death RR: 4.2; 95% CI: 1.8-9.5	No
Latini et al., 2007 (15)	4,053	TnT and hsTnT	TnT ≥0.01 ng/ml or hsTnT ≥0.001 ng/ml	CHF	Ischemic and nonischemic	Mortality (cTnT) HR: 2.08; 95% CI: 1.72-2.52 (hsTnT) HR: 1.05; 95% CI: 1.04-1.07 for increments of 0.01 ng/ml	Yes
Miller et al., 2007 (17)	190	TnT	TnT ≥0.03 ng/ml	CHF	Ischemic and nonischemic	Death or cardiac transplantation HR: 4.37; 95% CI: 2.55-7.49	Yes

BNP = B-type natriuretic peptide; CI = confidence interval; cTnT = cardiac troponin T; HR = heart rate; hsTnT = high-sensitivity troponin T; NT-proBNP = N-terminal pro-B-type natriuretic peptide; ROC = receiver-operating characteristic; RR = relative risk; other abbreviations as in Table 1.

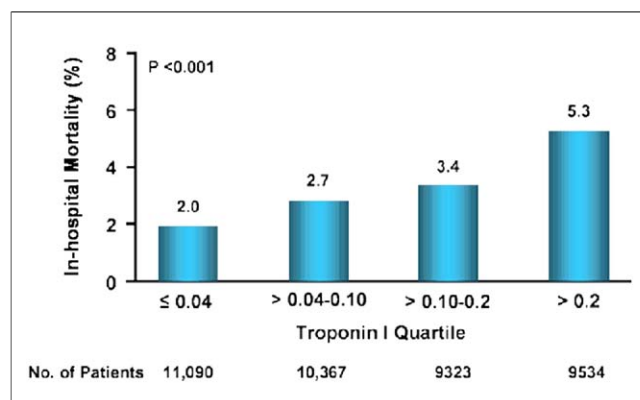
degrade cTn, releasing cTn fragments into the circulation, which may have epitopes with an affinity for the cTnI immunoassays (38). The common denominator of all these processes, be it myocyte necrosis, apoptosis, or cTn degradation or release in otherwise viable cells, would be expected to be worsening cardiac dysfunction and progression of HF. Recent data from a large observational study in Europe have shown an association between low levels of circulating cTn and the future development of HF in completely asymptomatic subjects (39). These data are similar to prior observations with B-type natriuretic peptide (BNP) (40).

**Significance of Troponin Release in HF**

Multiple studies have evaluated the association between elevated circulating cTn and adverse clinical outcomes in various HF populations (Table 2). Despite variations in study design, patient populations, and assay characteristics, there has been a consistent association between cTn elevation and worsened outcomes.

In patients with acute HF, the ADHERE study demonstrated a marked increase in in-hospital mortality (8.0% vs. 2.7%, p < 0.001) for patients with an elevated cTn by any clinical assay at the time of hospitalization (Fig. 2) (19). This relationship was independent of patient demographics, vital signs, physical examination findings, laboratory vari-

ables, and BNP levels. Similarly, You et al. (41) reported data from the EFFECT (Enhanced Feedback for Effective Cardiac Treatment) study showing that elevated cTn (TnI >0.5 ng/ml) was associated with increased mortality even after multivariate adjustment, and demonstrated a dose-response relationship between the magnitude of circulating cTn and outcomes. Although data on the evolution of cTn



**Figure 2** In-Hospital Mortality According to Troponin I Quartile

Inpatient mortality in patients with acute heart failure by troponin I quartile in the ADHERE (Acute Decompensated Heart Failure National Registry) study. Adapted from Peacock et al. (19).

status in the course of acute HF hospitalization are more limited, a few studies have evaluated serial cTn measurements over time. In a small study of 62 patients with acute HF, patients with persistently elevated cTnT ( $\geq 0.02$  ng/ml at baseline and 7 days later) had a worse prognosis than did patients without a persistently elevated cTn (8). Metra *et al.* (28) found that any elevated cTn over the course of acute HF hospitalization conferred substantially increased risk.

Similar data in ambulatory patients with HF have confirmed the prognostic implications of cTn release. In an analysis of data from the Val-HEFT study, Latini *et al.* (15) compared the prognostic implications of elevated cTn using both a standard cTnT assay and a high-sensitivity troponin T (hsTnT) assay. Ninety-two percent of patients had detectable circulating cTn using the high-sensitivity assay, and hsTnT was the most important predictor of mortality among the risk factors analyzed. Increases in deciles of circulating cTn (after the fourth decile) concentration incrementally increased risk for death or mortality (15).

Miller *et al.* (17) examined the value of serial measurements of both cTnT and BNP in chronic HF patients. Fifty-four percent of patients had a detectable cTnT at baseline ( $\geq 0.01$  ng/ml) and 28% of patients had a cTnT  $\geq 0.03$  ng/ml. The study found a highly significant association between risk of death or cardiac transplantation and the presence of circulating cTnT, with the subgroup containing a magnitude of circulating cTnT  $> 0.03$  ng/ml as having the highest risk in multivariate analysis. Additionally, serial measures of biomarkers revealed that changes in cTn levels are also associated with changing levels of risk; declining cTnT was associated with less risk, whereas patients with undetectable cTnT (whose levels were subsequently detectable) moved into a higher risk category. Interestingly, change in BNP over time provided less robust prognostic information in this outpatient population (17). More recently, Miller *et al.* (42) again examined serial cTnT values in ambulatory HF patients. In this analysis, they characterized patients as having no cTnT elevation who had at least 1 cTnT elevation or persistent cTnT elevations. They found that more frequent elevations of cTnT were associated with higher risk of death or cardiac transplantation. Furthermore, they confirmed that a greater magnitude of cTnT ( $\geq 0.03$  ng/ml vs.  $\geq 0.01$  and  $< 0.03$  ng/ml) was associated with worse outcomes (42). These data strengthen the hypothesis that worsening HF is mediated by subclinical myocardial injury. Increased frequency and magnitude of myocardial injury likely result in further deterioration in ventricular function and worse clinical outcomes.

In addition to prognostic information, circulating cTn (when added to other biomarker considerations), may provide insight into the transition from chronic compensated to acute decompensated HF. Investigators have speculated that the transition does not necessarily represent a simple worsening of chronic failure, but rather there is an acute injury to the cardiac renal axis that results in decompensation. Myocardial injury in the setting of acute HF may

either be a cause or an effect of decompensation, but in either case, may predispose patients to subsequent progression of HF. This hypothesis is supported by the strong relationship between hospitalization for HF and subsequent HF events (43,44). In an important recent study, Biolo *et al.* (45) compared BNP, cTn, and markers of ventricular remodeling in patients with acute HF, stable HF, and control subjects. Compared with stable HF and control patients, patients with acute HF had significantly higher levels of circulating cTn, markers of collagen biosynthesis, and markers of extracellular matrix remodeling (45). These data suggest a link between myocardial injury and subsequent ventricular remodeling. After hospital discharge and recompensation, cTn and markers of collagen biosynthesis levels among those admitted for acute HF declined to values similar to those of the chronic HF population.

cTn may not just be a marker of worsening HF, but also a mediator. In some persons, autoantibodies to cTnI develop after MI. Significantly, these autoantibodies may interfere with the detection of circulating cTn by available assays (46). In mouse models, autoantibodies against cTnI result in a severe dilated cardiomyopathy, which is mediated by augmentation of the L-type calcium current and resultant calcium overload, leading to myocyte dysfunction (47). In further murine studies, this has been identified as a CD4 T cell-mediated affect (48). The degree to which these mechanisms contribute to the development and progression of HF in humans is unclear, but may be targets of further investigation and therapeutics.

### Troponin Measurements in Clinical Research

Despite advances in treatment, HF follows a progressive course in the majority of patients, and there remains a substantial need to develop new therapies for this syndrome. Most recent drug development programs in both acute and chronic HF have failed to conclusively demonstrate efficacy and safety (49,50). In acute HF in particular, the development of new treatments has been hampered by unintended consequences of therapies (e.g., inotropic agents improve hemodynamics but also may cause arrhythmias or myocardial ischemia). Patients with underlying ischemic heart disease and HF may be particularly at risk for such effects. In a subgroup analysis of the OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) study, there was a notable differential effect of milrinone on the basis of HF etiology, with substantial harm to patients with underlying ischemic heart disease (51). Adding to these observations, Gheorghiu *et al.* (10) observed that among a cohort of patients with ischemic heart disease admitted to the hospital for acute HF without evidence of ACS, 41.7% of those with negative cTnI at baseline had detectable cTnI with serial measurements. The release of cTnI in these patients reflects a post-admission event that may be related to the disease process, administered therapies, or a combination of factors

(10). In the ADHERE study, cTn-elevated patients had markedly higher in-hospital mortality when treated with intravenous inotropic therapy as compared with intravenous vasodilator therapy, with an adjusted odds ratio of 4.44 (95% confidence interval: 2.90 to 6.81;  $p < 0.001$ ) (19). Although currently speculative, assessments of myocardial injury using sensitive biomarkers such as cTn may play an important role in the development of new therapies, by identifying signals of myocyte damage earlier in the development process (52). Finally, avoidance of myocardial injury may be a goal of therapy in the development of new HF drugs, which could be incorporated into clinical trial end points (10). For example, in a recent phase II study of a novel inotropic and lusitropic compound called istaroxime, Gheorghide et al. (53) used cTnI as a secondary safety end point to look for evidence of treatment-induced myocardial necrosis.

### Unanswered Questions and Future Directions

While the data summarized in the preceding text clearly suggest the potential value of cTnI in HF risk stratification, the clinical use of cTnI remains ill defined. Measurement of cTnI in patients hospitalized for acute HF seems warranted, given the desire to identify patients at high risk for adverse outcomes, as well as to identify patients in whom ischemia appears to be a trigger of decompensation. The most recent update of the ACC/AHA HF guidelines recommend that cTn testing be performed in patients hospitalized with HF (Class I, Level of Evidence: C). In ambulatory patients, evidence of ongoing cardiac injury suggests the risk of HF progression, particularly in patients with previously undetectable cTn.

Among patients presenting with HF and an elevated cTn, this cTn elevation may represent either myocardial injury in the setting of acute decompensated HF or frank ACS (type 2 vs. type 1 MI based on the universal definition of MI) (5). This represents a common conundrum for clinicians, as ACS complicated by HF mandates different management than acute decompensated HF alone. This clinical problem is particularly difficult in the setting of

underlying ischemic heart disease, the most common etiology of HF in the U.S. (54). Although some characteristics of the clinical presentation may provide important clues (Table 3) (55), a definitive answer may require angiography in some patients. More reliable distinction between acute decompensated HF and ACS with biomarkers is an important area for further research.

A variety of important clinical questions remain unanswered about the role of cTn in HF. In general, studies evaluating serial measurements have been much less common than studies focused on baseline values. In acute HF, the time course of the myocardial injury relative to presentation remains unclear—is myocardial injury the cause of decompensation, the result of hemodynamic changes leading to decompensation, or the result of therapies for acute HF? Additionally, most of the studies to date have focused on patients with HF due to systolic dysfunction, so few data exist on the role of cTn measurement in epidemiologically important groups such as patients with HF and preserved ejection fraction. Cardiac troponin measurements may have important implications in other clinical scenarios, such as in the monitoring of potential cardiotoxicity from chemotherapeutic regimens in patients with cancer.

An additional area for further research is to better understand the incremental prognostic value of cTn when added to models containing BNP. The fact that cTn has prognostic significance independent of BNP has been well established (11,15,56). In a study of the ADHERE study, for every level of admission BNP, a positive value of troponin was associated with a 2- to 3-fold increased rate of inpatient mortality (56). The ADHERE study modeled outcomes among HF patients using clinical variables; BNP and high-sensitivity cTn revealed improved discrimination by adding cTn to a model containing clinical variables and BNP, but the increase in discrimination was modest (change in *c*-index from 0.702 to 0.711) (15,57). More research is needed in large, real-world populations to better understand the incremental improvement in discrimination and risk reclassification by adding cTn to prognostic models.

Finally, other novel markers of cardiac injury may prove superior or complementary to cTn assessments. Heart-type fatty acid binding protein (H-FABP) is a small cytosolic protein that may be a more sensitive and reliable indicator of low-level myocardial damage in HF, especially when used together with circulating cTn (58,59). Since H-FABP is cytosolic, reversible myocyte injury resulting in increased membrane permeability would cause its release, whereas cTn is a myofibrillar protein with less in the cytosolic pool. Thus, more extensive myocyte injury must occur before significant amounts of cTn are released. Additionally, cTn and H-FABP rates of clearance from the bloodstream are quite different: H-FABP is cleared within 24 h, whereas cTn is detectable for days after its release. Hence, a patient with an elevated cTn and normal H-FABP possibly experienced cardiac injury at some point in the recent past, but is unlikely to be acutely experiencing injury.

**Table 3** Signs and Symptoms Differentiating AMI From AHF in the Setting of Positive Troponin

	AMI (Type I NSTEMI)	AHF
Chest pain	Usually	Occasionally
Shortness of breath	Sometimes	Usually
Detectable troponin	Always	Sometimes
Troponin level >1.0 ng/ml	Usually	Occasionally
CK-MB elevation	Usually	Rarely
Troponin pattern	Rise and fall	Persistent low level elevation or gradual decline
BNP >100 pg/ml	Sometimes	Almost always
BNP >400 pg/ml	Rarely	Usually

AMI = acute myocardial infarction; CK-MB = creatine kinase-myocardial band; NSTEMI = non-ST-segment elevation myocardial infarction; other abbreviations as in Tables 1 and 2.

## Recommendations

We recommend an initial determination of cTn for patients presenting to the hospital with acute HF. Troponin assessment can be used for immediate risk stratification and may also suggest ACS as the underlying etiology, depending on other presenting features. In patients with initially elevated cTn levels, a repeat cTn measurement within 6 to 12 h in patients can help determine whether or not the kinetics of cTn change are more consistent with either ACS or acute decompensated HF. In ambulatory patients with HF, cTn measurement is a reasonable prognostic indicator. Persistently elevated cTn values in chronic HF patients should lead to consideration of more intensive medical therapy, as well as an evaluation for ischemic heart disease (if not already performed).

## Conclusions

Cardiac troponin represents markers of myocardial injury that are detected in a significant portion of patients with acute and chronic HF. The incidence of detection depends on the sensitivity of the assay used. At all concentrations, the presence of circulating, detectable, cTn appear to have important prognostic significance. Cardiac troponin levels are associated with an increased risk of morbidity and mortality in both acute and chronic HF, providing incremental prognostic information to standard clinical assessment and other laboratory variables. As the sensitivity of assays improves, cTn will increasingly be seen as a continuous (rather than dichotomous) variable. Preliminary studies suggest cTn may help assess response to HF therapy and identify patients for whom more intensive monitoring and management may be needed. The mechanisms of cardiac injury in acute and chronic HF resulting in cTn release needs to be clearly elucidated. Many unanswered questions point toward the need to accumulate more prospective, high-quality data on the mechanisms, timing, and clinical implications of cTn release in HF.

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