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High-Sensitivity Troponin as a Biomarker in Heart Rhythm Disease

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Abstract

Biomarkers are important prognostic tools in various cardiovascular conditions, including coronary artery disease and heart failure. Although their utility in cardiac electrophysiology (EP) is less established, biomarkers may guide EP clinical practice by identifying patients at risk for developing arrhythmias and their complications, in addition to augmenting therapeutic decisions by targeting appropriate pharmacologic and interventional therapies to patients who may benefit most. In this review, we focus on the prognostic role of high-sensitivity cardiac troponin (hs-cTn) assays—which detect subclinical cardiac myocyte damage—in cardiac arrhythmias and their sequelae. We review the current literature on hs-cTn and its impact on various arrhythmia disease states and also provide suggestions for future research in this field. In conclusion, although the utility of hs-cTn assays remains at an investigational stage in cardiac EP, studies to date have suggested value as a prognostic biomarker in atrial fibrillation and as a screening marker for patients at high risk of sudden cardiac death (both in the general population and among those with hypertrophic cardiomyopathy).

Cardiac arrhythmias remain a significant source of cardiovascular morbidity and mortality with an overall prevalence of 5.3% in the general adult population and a prevalence of up to 40% among patients attending cardiology clinics.¹ Although many demographic and clinical variables have been associated with the future development of cardiac arrhythmias and their sequelae—most notably stroke, heart failure, and sudden cardiac death (SCD)—the prognostic value of these variables is often limited in clinical care.^{2,3} In this context, cardiac biomarkers may add important prognostic information, thereby augmenting and

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personalizing quantitative risk assessment in the prevention and management of arrhythmias.⁴ An emerging electrophysiology (EP) biomarker that has shown substantial promise is high-sensitivity cardiac troponin (hs-cTn). Traditionally, troponin measurements have been used for the diagnosis of myocardial infarction (MI); however, new highly sensitive assays may add important prognostic information regarding cardiovascular risk in various symptomatic and asymptomatic populations.^{5,6} Hs-cTn has several potential advantages over conventional EP biomarkers. For example, hs-cTn assays are extremely specific for cardiac myocyte damage, are measurable in minute concentrations even among asymptomatic persons, and troponin is a widely available, familiar, and intuitive test for most cardiologists and general physicians. This review article explores the evidence supporting the use of hs-cTn as a novel biomarker in heart rhythm disease, organized by major EP disease states and concludes with suggestions for future directions of research.

High-Sensitivity Troponin

Cardiac troponins play a crucial role in the evaluation of acute coronary syndromes, with traditional assays used in clinical practice measuring values below the 99th percentile in <50% of a reference population. More recently, hs-cTn assays have been developed to enhance the early diagnosis of MI and reduce the need for serial testing in symptomatic patients. These hs-cTn assays measure cardiac troponin levels above the limit of detection in 50% of overtly normal subjects, with 10% coefficient of variation at the 99th percentile. Thus, they can typically detect troponin levels 10 or more times lower than the limit of detection of traditional troponin assays (Table 1). The variability and reproducibility of these hs-cTn assays are good and have been reviewed elsewhere.^{7,8}

Atrial Fibrillation

Atrial fibrillation (AF) is by far the most common cardiac arrhythmia, affecting more than 2.2 million adults in the United States.¹ Approximately 25% of subjects aged 40 years and older will develop AF during their lifetime.⁹ Many clinical risk factors for predicting incident AF have been identified and implemented in risk estimation models. One such risk score, devised by the Framingham Heart Study investigators, is based on simple parameters including age, gender, an audible murmur, heart failure, systolic blood pressure, hypertension, body mass index, and PR interval, which together yield a C-statistic of 0.78 (95% confidence interval [CI] 0.76 to 0.80) in the Framingham sample.¹⁰ However, the generalizability of this score to more diverse populations may be limited.

Recognizing the potential for biomarkers to improve the clinical prediction of incident AF, investigators have studied the utility of hs-cTn in improving the discrimination and calibration of AF prediction. For example, 2 large prospective cohorts have demonstrated a modest improvement in AF risk prediction using hs-cTn in the general US population. In an analysis of 10,584 participants enrolled in the Atherosclerosis Risk in Communities (ARIC) study,¹¹ Filion et al¹¹ found that the crude incidence rate of AF ranged from 5.5 per 1,000 person-years (95% CI 4.9 to 6.1) among participants with undetectable hs-cTnT levels to 23.6 per 1,000 person-years (95% CI 20.4 to 27.3) among participants with hs-cTnT 14 ng/L ($p < 0.0001$). After adjustment for known clinical risk factors, 1 SD increase in

lognormal (hs-cTnT) was associated with an increased rate of incident AF (hazard ratio [HR] 1.16, 95% CI 1.10 to 1.23).¹¹ However, hs-cTnT did not improve the predictive ability of AF relative to previously identified AF risk factors with no appreciable increase in the C-statistic (0.756 vs 0.758).

A similar large prospective study was undertaken by Hussein et al¹² on 4,262 ambulatory adults without baseline AF participating in the Cardiovascular Health Study. Over a median follow-up of 11.2 years (interquartile range 6.1 to 16.5), 1,363 participants (32.0%) developed incident AF. Higher baseline levels of hs-cTnT were independently associated with incident AF in covariate-adjusted time-dependent analyses that accounted for demographics, traditional risk factors, and incident heart failure cases (HR for third tertile of hs-cTn vs undetectable 1.75, 95% CI 1.48 to 2.08).¹² This association remained statistically significant in analyses further adjusting for C-reactive protein (CRP) and N-terminal prohormone brain natriuretic peptide (NT-pro-BNP) (HR for third tertile vs undetectable 1.38, 95% CI 1.16 to 1.65).¹² Unfortunately, the authors did not report any incremental prognostic results, such as C-statistics or net-reclassification indexes.

As opposed to samples from the general population, hs-cTn may have heightened prognostic power for predicting incident AF in higher risk cohorts, such as patients with cryptogenic ischemic strokes and postoperative patients. In 2015, Sanak et al¹³ undertook a prospective study to detect paroxysmal AF (PAF) using a 3-week Holter in 95 cryptogenic ischemic stroke patients > 50 years. The authors detected PAF by extended Holter in 9.5% of this sample.¹³ Patients with PAF detected during follow-up had elevated baseline serum levels of hs-cTnT, defined as ≥ 14 ng/L, significantly more frequently than patients without detected AF (56% vs 2%, $p = 0.0001$).¹³ A similar trend was seen with NT-pro-BNP (56% vs 3.5%, $p = 0.0001$). Hence, elevated admission hs-cTn in patients with cryptogenic ischemic stroke may identify patients who require prolonged surveillance for PAF. However, this was a small hypothesis-generating study.

Another high-risk cohort of interest is postoperative patients, in whom incident AF is common. Three prospective studies have suggested the value of hs-cTn in this demographic. In the smallest study, Narducci et al¹⁴ measured preoperative and postoperative high-sensitivity CRP (hs-CRP) and hs-TnT among 38 patients with coronary artery disease undergoing cardiopulmonary bypass surgery. Fourteen patients (36%) developed postoperative AF. Although both preoperative hs-CRP and hs-TnT levels did not differ significantly between the persistent sinus rhythm group and the group who developed AF,¹⁴ serum postoperative hs-TnT levels were significantly higher in the postoperative AF group (0.52 [0.32 to 0.86] vs 0.30 [0.23 to 0.42] ng/ml, respectively, $p = 0.016$). Postoperative levels of hs-CRP were similar in both groups (4.02 [3.57 to 4.93] vs 4.54 [3.55 to 5.71] mg/dl, respectively, $p = 0.34$).¹⁴ Based on these findings, the authors hypothesized that ischemia may trigger postoperative AF and that hs-cTn may help in predicting this complication.

In contrast to Narducci's study, a larger prospective trial suggested that preoperative hs-cTn (as opposed to postoperative hs-cTn) is useful in predicting AF. Hernandez-Romero et al¹⁵ assessed preoperative and postoperative hs-cTn and NT-pro-BNP levels in 100 patients

undergoing cardiac surgery (aortic valve and coronary artery bypass surgery), 29% of whom subsequently developed postoperative AF. Higher presurgery hs-cTnT levels were seen in patients who developed AF (area under the curve 0.66, 95% CI 0.54 to 0.78, $p = 0.015$).¹⁵ The best hs-cTnT cutoff level for the development of AF in this study was 11.87 ng/L, with a sensitivity of 76% and a specificity of 54%. In a multivariable model, only higher hs-cTn levels before cardiac surgery (>11.87 ng/L) (odds ratio [OR] 4.27, 95% CI 1.43 to 12.77, $p = 0.009$) and male gender (OR 5.10, 95% CI 1.72 to 15.13, $p = 0.003$) were independently associated with the occurrence of postsurgical AF.¹⁵

A large substudy of the Omega-3 Fatty Acids for Prevention of Postoperative Atrial Fibrillation trial (OPERA), measuring plasma concentrations of NT-pro-BNP and hs-cTnT in 562 patients undergoing cardiac surgery, lends some support to the findings of Hernandez-Romero et al.¹⁶ A total of 173 patients (31%) developed AF. Both NT-pro-BNP and hs-cTnT on the morning of surgery were higher in patients with postoperative AF (376 vs 218 ng/L, $p = 0.004$ and 14.5 vs 11.0 ng/L, $p = 0.002$, respectively).¹⁶ After multivariable adjustment for hypertension, logistic EuroSCORE, valvular surgery, cardioplegia, and durations of pump and cross-clamp time, each unit increase in hs-cTnT, up to 27 ng/L, was associated with higher risk of postoperative AF (HR 1.41, 95% CI 1.08 to 1.85, $p = 0.01$), whereas each unit increase in log NT-pro-BNP for levels was not (HR 1.17, 95% CI 0.99 to 1.38, $p = 0.07$).¹⁶ However, in a second multivariable model with the addition of age, hs-cTnT up to 27 ng/L was no longer significantly associated with postoperative AF.¹⁶

In addition to predicting their onset, biomarkers may also have a role in predicting the sequelae of heart rhythm disorders, for example, AF is a common and treatable risk factor for stroke.¹⁷ However, because patients with AF are a heterogeneous group, the individual risk of stroke varies widely.¹⁸ As a consequence, personalized risk stratification schemes for AF-related stroke emerged in the 1990s^{19,20} (Table 2) and current guidelines recommend a risk-based approach (using the CHADS₂-VASc score) to determine anticoagulation treatment in AF.²³ In an effort to improve the individual precision of these stroke risk scores, hs-cTn has been tested as a prognostic addition. In a subgroup analysis from the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation) study, Hijazi et al²¹ examined the associations between baseline hs-TnT levels and outcomes in 14,897 patients with AF randomized to treatment with apixaban or warfarin using adjusted Cox regression models. Levels of hs-TnT were measurable in 93.5% of the patients. During a median 1.9-year follow-up, the annual rates of stroke or systemic embolism ranged from 0.87% in the lowest hs-TnT quartile to 2.13% in the highest hs-TnT quartile (adjusted HR 1.94, 95% CI 1.35 to 2.78, $p = 0.0010$).²¹ Adding hs-TnT levels to the CHA₂DS₂-VASc score improved the C statistic from 0.620 to 0.635 for stroke ($p = 0.0226$), from 0.592 to 0.711 for cardiac death ($p < 0.0001$), and from 0.591 to 0.629 for major bleeding ($p < 0.0001$).²¹

In a subsequent study by the same group, the authors developed and validated a new biomarker-based risk score known as the “ABC (age, biomarkers, clinical history) stroke risk score,” to improve prognostication of stroke in patients with AF.²² The development cohort was 14,701 patients with AF and biomarkers measured at entry in the ARISTOTLE trial, and the validation cohort was 1,400 participants with AF and biomarkers measured at

entry in the STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY (STABILITY) trial.²² Using the derivation cohort, the authors demonstrated that the most important predictors of stroke were previous stroke or transient ischemic attack, NT-pro-BNP, hs-cTn, and age. Variables such as congestive heart failure, peripheral arterial disease, gender, smoking status, diabetes, hypertension, and previous MI did not add further significant information to the risk score. Thus, the final ABC stroke risk score (ranging from 0 to 30 points) comprised the following variables: age, hs-cTn, NT-pro-BNP, and previous stroke or transient ischemic attack. The ABC stroke score yielded higher c-indices than the widely used CHA2DS2-VASc score in both the derivation cohort (0.68 vs 0.62, $p < 0.001$) and the external validation cohort (0.66 vs 0.58, $p < 0.001$).²² The ABC score may also have utility in predicting bleeding events.²⁴

In contrast to other AF stroke scores that can typically increase during follow-up, the ABC stroke score is dynamic, with the potential to increase or decrease in value, thereby allowing the physician to monitor fluctuations in the patient's risk of future events in either direction.²² However, whether such changes should influence clinical care is unknown. Indeed, patients may potentially have their anticoagulant stopped and then recommenced at various time points based on changes in this score, which could place such patients at risk of rebound hypercoagulability.

Besides AF complications, AF recurrence is another problem for electrophysiologists treating AF, particularly after invasive ablative therapy. Compounding this problem, the identification of patients who will develop recurrent AF is a significant challenge. A prospective cohort substudy of GISSI AF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Atrial Fibrillation), which is a trial evaluating the effects of valsartan on AF recurrence, examined the utility of several biomarkers to predict recurrence of AF. This study included 382 patients who either had previous cardioversion or 2 or more episodes of PAF in the preceding 6 months.²⁵ Patients who developed recurrent AF within 12 months (53.1%) had significantly higher baseline concentrations of hs-cTn (mean 8.6 vs 7.6 pg/ml, $p = 0.01$), NT-pro-BNP (mean 197 vs 183 pg/ml, $p < 0.0001$), and mid-regional proatrial natriuretic peptide (mean 167 vs 153 pg/ml, $p = 0.0005$), compared with patients who remained in sinus rhythm.²⁵

However, other reports have contradicted these results. In a double-blind, placebo-controlled study, evaluating 171 patients with AF undergoing cardioversion, Horjen et al²⁶ investigated the prognostic value of hs-cTn in predicting AF recurrence. They found that hs-cTnI was detectable in all subjects, with a median value of 5.3 ng/L (25th percentile 3.7, 75th percentile 7.2).²⁶ Sixty-seven (67%) patients experienced a recurrence of AF in the 6 months of follow-up. However, hs-cTnI level at baseline was not predictive of rhythm outcome 6 months after electrical cardioversion for persistent AF.²⁶ Furthermore, there is no evidence that hs-cTn adds information to other clinical variables in predicting recurrent AF.

Although hs-cTn has been demonstrated to increase following catheter ablation procedures,²⁷ whether it has prognostic utility in predicting AF recurrence or other adverse outcomes in the postablation setting is unknown. Also unknown is whether hs-cTn has any causal

relation to AF or whether it is simply a marker of the underlying substrate, namely atrioopathy and fibrosis, resulting in greater burden of AF and AF recurrence.

Sudden Cardiac Death and Cardiac Arrest

Despite major advances in the treatment of cardiovascular disease and reduction in cardiovascular mortality over the past 30 years, the rate of SCD has declined to a lesser extent.²⁸ With bleak survival rates for out-of-hospital cardiac arrests (OHCA),²⁹ significant reductions in the incidence of SCD will require substantial improvements in primary prevention strategies. Although implantable cardiac-defibrillators (ICD) are routinely implanted in patients with left ventricular systolic dysfunction for primary prevention, most victims of SCD do not have a history of reduced ejection fraction.³⁰ Thus, biomarkers that aid in SCD risk prediction may be extremely valuable.

In a substudy of the Cardiovascular Health Study, Hussein et al³¹ assessed whether baseline levels of hs-cTnT were associated with SCD risk beyond traditional risk factors in 4,431 ambulatory participants. Over a median follow-up of 13.1 years, 246 participants experienced SCD. Baseline levels of hs-cTnT were significantly associated with SCD (HR for +1 U increase in log[hs-cTnT] of 2.04, 95% CI 1.78 to 2.34).³¹ This finding persisted in analyses accounting for risk factors (HR 1.30, 95% CI 1.05 to 1.62), and after adjustment for incident heart failure and MI (HR 1.26, 95% CI 1.01 to 1.57).³¹

The authors hypothesize that subclinical cardiac myocyte injury, as reflected by detectable levels of circulating hs-cTnT, may provide the anatomical substrate for scar-related electrical re-entry observed with ventricular tachycardia.³¹ In this study, 67% of the patients had baseline detectable levels of hs-cTn (average age 72.8 ± 5.6 years).³¹ Among the 2,039 subjects with hs-cTnT ≤ 5.0 ng/L, only 69 patients had an SCD event.³¹ The negative predictive value of SCD with hs-cTnT ≤ 5.0 ng/L was 96.6%.³¹ The investigators did not establish whether adding hs-cTnT to the current prediction models would help improve SCD prediction, a question that warrants further investigation.

Identifying the cause of OHCA also remains a challenge. Geri et al performed a retrospective analysis to determine whether hs-cTn was useful in diagnosing coronary artery occlusion as the cause of OHCA. All patients with OHCA had a coronary angiogram and hs-cTn levels assessed at intensive care unit admission.³² A culprit coronary occlusion was found in 133 (48.9%) patients.³² In this study, the optimum hs-cTnT cut-point to predict a recent coronary occlusion was 575 ng/L (sensitivity 65.4%, specificity 65.5%).³² In multivariable analysis, current smoking (OR 3.2, 95% CI 1.62 to 6.33), time from collapse to basic life support of <3 minutes (OR 2.11, 95% CI 1.10 to 4.05), initial shockable rhythm (OR 5.29, 95% CI 2.06 to 13.62), ST segment elevation (OR 2.44, 95% CI 1.18 to 5.03), postresuscitation shock onset (OR 2.03, 95% CI 1.01 to 4.07), and hs-cTnT ≥ 575 ng/L (OR 2.22, 95% CI 1.16 to 4.27) were associated with the presence of a recent coronary occlusion.³² Nevertheless, adding hs-cTnT to established clinical risk factors of recent coronary occlusion provided a nonsignificant net reclassification index of just -0.43% . Thus, hs-cTn was not deemed to be a robust diagnostic tool to select candidates for emergent coronary angiogram in OHCA survivors.³² Furthermore, given the likelihood that chest compressions

and defibrillation contribute to increased hs-cTn levels in this setting, the specificity of the marker in predicting coronary occlusion may be limited.

In a substudy of FINNRESUSCI, an observational prospective multicenter study performed by the Finnish Intensive Care Consortium, the prognostic value of hs-cTnT levels was assessed in 155 patients presenting with OHCA who presented with a shockable rhythm.³³ Admission hs-cTnT levels were higher than the 99th percentile of the general population (14 ng/L) in all patients (range 18 to 17,837 ng/L),³³ in 1-year nonsurvivors compared with survivors (median 747 vs 345 ng/L, $p = 0.023$), and in patients with a poor versus favorable neurological outcome (739 vs 334 ng/L, $p = 0.028$).³³ However, hs-cTnT level did not add prognostic information to established risk variables in multivariate analyses and was inferior to Simplified Acute Physiology Score II scores for the prediction of events during follow-up.³³

Although ICDs have been proved to reduce mortality by delivery of appropriate defibrillation, there is compelling evidence that inappropriate shocks from ICDs also cause harm.³⁴ Hs-cTn may have a number of applications in this area. For example, hs-cTn may help in (1) understanding whether and to what extent defibrillation itself is associated with myocardial damage, (2) determining which patients may require ICD after MI by predicting lack of left ventricular ejection fraction recovery,³⁵ (3) predicting survival among patients who already have ICDs implanted, (4) predicting recurrent ICD shocks, and (5) discern appropriate from inappropriate ICD therapies.

In a prospective study, Furniss et al³⁶ examined hs-cTn levels and electrocardiogram changes during ICD implantation without defibrillation threshold testing (DFT), ICD implantation with DFT, and DFT as a standalone procedure. There was no significant change in hs-cTnT levels in a group of patients undergoing defibrillation testing alone compared with baseline levels, while hs-cTnT was significantly higher in patients undergoing implantation alone (median increase 96%, $p = 0.005$) and in patients undergoing implantation and testing (median increase 161%, $p = 0.005$). There was a significant correlation between the number of leads implanted and the percent change in hs-cTnT ($r = 0.51$, $p = 0.01$), but no correlation between the number of shocks ($r = 0.26$, $p = 0.25$) or the total delivered energy ($r = 0.24$, $p = 0.30$) and percent change in hs-cTnT levels.³⁶ This suggests that, although device implantation and lead deployment may cause an increase in hs-cTn levels, ICD shocks alone do not appear to cause hs-cTn elevation. In addition, the prognostic implication of elevated hs-cTn in ICD patients has yet to be investigated and warrants future examination.

Patients with hypertrophic cardiomyopathy (HCM) are at particularly high risk for SCD and, consequently, the prognostic utility of hs-cTn has also been investigated in these patients. In 2010, Moreno et al³⁷ measured hs-cTn levels in 95 hemodynamically stable HCM patients. Forty-two percent had increased levels of hs-cTnT. Hs-cTnT levels were more likely to be higher among those with New York Heart Association functional class 3 ($p = 0.020$), outflow obstruction ($p = 0.013$), systolic dysfunction ($p = 0.037$), abnormal blood pressure response to exercise ($p = 0.036$), and presence of ventricular gadolinium enhancement on cardiac magnetic resonance imaging ($p = 0.021$).³⁷ Levels of hs-cTnT also correlated

positively with the maximum left ventricular wall thickness (coefficient $r = 0.47$, $p < 0.001$), left atrial diameter ($r = 0.36$, $p = 0.014$), and outflow gradient ($r = 0.28$, $p = 0.008$).³⁷

Myocardial fibrosis is believed to be the substrate for heart rhythm disorders and SCD in HCM patients. Research by Kawasaki et al³⁸ further demonstrated hs-cTn and BNP to be potential markers of myocardial fibrosis in HCM. Specifically, levels of hs-cTnT and BNP were higher in 23 patients with late gadolinium enhancement compared with 30 patients without fibrosis ($p < 0.01$ for both).³⁸ A hs-cTnT level ≥ 7 ng/L or a BNP level ≥ 70 pg/ml had good diagnostic accuracy for detecting late gadolinium enhancement, with sensitivity of 96% or specificity of 90% with the combination of both.³⁸ Similar correlations were seen in a study by Hasler et al³⁹ of 91 HCM patients, 46 (51%) of whom had elevated hs-cTnT levels (≥ 14 ng/L). Patients with elevated hs-cTnT levels had greater maximum wall thickness (23 ± 7 vs 19 ± 3 mm, $p = 0.001$), more often had myocardial fibrosis detected by cardiovascular magnetic resonance imaging (96% vs 54%, $p < 0.001$), and lower exercise capacity measured in watts (90% predicted vs 76% predicted, $p = 0.002$).³⁹ Although not powered for clinical outcomes, there was also a trend toward higher event-rates in patients with elevated hs-cTnT (15% vs 7%, $p = 0.16$).³⁹

The prognostic implications of hs-cTn levels in HCM was investigated by Kubo et al⁴⁰ on 183 patients, among whom 54% had abnormal hs-cTnT values (>14 ng/L).⁴⁰ During a mean follow-up of 4.1 ± 2.0 years, there was a higher proportion of patients with abnormal hs-cTnT than hs-cTnT levels <14 ng/L that experienced an adverse cardiovascular event (32% vs 7%; HR 5.05, $p < 0.001$).⁴⁰ In this study, the increased cardiovascular events among HCM patients with elevated troponin were because of arrhythmia and heart failure. Abnormal hs-cTnT value remained an independent predictor of poor outcome after multivariate analysis (HR 3.23, $p = 0.012$).⁴⁰ Furthermore, in the elevated hs-cTnT group, overall risk increased with increasing hs-cTnT values (HR 1.89 per 1 SD increase in log hs-cTnT, 95% CI 1.13 to 3.15, $p = 0.015$ [SD 0.59]).⁴⁰

Future Directions

Demographic changes and improvements in surveillance (including the use of mobile health technologies) are leading to an ever increasing burden of cardiac arrhythmias.^{41,42} As a result, the effort to prevent and treat cardiac arrhythmias and their sequelae is becoming increasingly challenging. In this context, biomarkers may provide useful screening and prognostic information for EP providers. We believe that hs-cTn can offer distinct advantages over other biomarkers of rhythm disease in that it is specific for cardiac myocyte injury, measureable in minute concentrations, and is a familiar assay for physicians. Currently, there are several contemporary high-sensitivity assays available for clinical use in Europe, varying in limits of detection and coefficient of variance (Table 1); however, these assays are not yet clinically available in the United States (hs-cTnT just recently obtained food and drug administration approval for chest pain evaluation, hs-cTnI assays remain investigational in the US).

Research to date suggests a number of promising hypothetical EP applications of hs-cTn assays: (1) hs-cTn has modest utility in predicting new-onset AF and AF sequelae in the

general population,¹¹ and may especially improve prediction of AF in high-risk populations, potentially guiding early treatment and prevention strategies and anticoagulant allocation^{14–16}; and (2) hs-cTn assays could augment the screening of patients at-risk for SCD (e.g., persons with family history of SCD or those with HCM).

These hypothetical applications require further investigation and future large, well-powered studies demonstrating meaningful improvement in clinical outcomes are required. The latter is particularly important as the goal of measuring a biomarker should not only be to assess risk but also to determine whether the biomarker can alter the pretest risk threshold in a cost-effective way that can result in an efficacious change in clinical management.⁴³

Furthermore, the value of these high-sensitivity troponin assays has yet to be studied in numerous important arrhythmias not discussed in this review, including supraventricular tachycardias and nonsustained ventricular tachycardias. Finally, the prevalence of measurable or elevated hs-cTn in patients with arrhythmogenic right ventricular dysplasia and other inherited cardiac arrhythmia syndromes has yet to be studied. Ultimately, like most novel biomarkers, it is important to distinguish causality from association. Rigorous investigation of hs-cTn in arrhythmic syndromes is needed to demonstrate a consistent, clinically meaningful incremental predictive value in risk prediction and reclassification beyond conventional factors and distinguish itself from simply being a marker of the underlying diseased substrate.

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Table 1

High-sensitivity cardiac troponin assays

ASSAY	Limit of detection (ng/L)	99% percentile in reference sample (ng/L)	10% coefficient of variance (ng/L)
Siemens Centaur	6.0	40	30
Mitsubishi Pathfast	8.0	29	14
Radiometer AQT90	9.5	23	39
Hs-cTn-T Roche Elecsys	5.0	14	13
Abbot ARCHITECT	1.1–1.9	16	3
Beckman ACCESS	2 to 3	8.6	8.6
Nanosphere	0.2	2.8	0.5
Singulex Erenna	0.09	10.1	0.88
Siemens Vista	0.5	9	3

Hs-cTn = high-sensitivity cardiac troponin; ng/L = nanograms/liter.

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Table 2

Stroke risk scores in atrial fibrillation

Risk Score	Components										C Statistic	Reference	
	CHF	HTN	Age	Gender	Diabetes	Stroke/TIA	Renal disease	Vascular disease	Hs-cTn	NT-proBNP			
CHA ₂ DS ₂ -VASc	+	+	+	+	+	+	+	+	0	0	0	0.62–0.888	19,22
CHADS ₂	+	+	+	0	+	+	0	0	0	0	0	0.673–0.812	19,20
ATRIA	+	+	+	+	+	+	+	0	0	0	0	0.70	20
ABC (age, biomarkers, clinical history)	0	0	+	0	0	+	0	0	+	+	+	0.68	22

CHF = congestive heart failure; Hs-cTn = high-sensitivity troponin; HTN = hypertension; NT-proBNP = N-terminal pro-b-type natriuretic peptide; TIA = transient ischemic attack.