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CLINICAL RESEARCH

High-Sensitivity Cardiac Troponin and New-Onset Heart Failure

A Systematic Review and Meta-Analysis of 67,063 Patients With 4,165 Incident Heart Failure Events

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CME/MOC Objective for This Article: Upon completion of this activity, the learner should be able to: 1) discuss prospective evidence regarding the association of high-sensitivity cardiac troponin and subsequent incidence of heart failure; 2) compare association of high-sensitivity troponin T with incident heart failure both with and without other known prognostic factors including natriuretic peptides; and 3) identify possible strengths and limitations of high-sensitivity troponin T as a prognostic marker for incident heart failure

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ABSTRACT

OBJECTIVES The aim of this study was to systematically collate and appraise the available evidence regarding the association between high-sensitivity cardiac troponin (hs-cTn) and incident heart failure (HF) and the added value of hs-cTn in HF prediction.

BACKGROUND Identification of subjects at high risk for HF and early risk factor modification with medications such as angiotensin-converting enzyme inhibitors may delay the onset of HF. Hs-cTn has been suggested as a prognostic marker for the incidence of first-ever HF in asymptomatic subjects.

METHODS PubMed, Embase, and Web of Science were systematically searched for prospective cohort studies published before January 2017 that reported associations between hs-cTn and incident HF in subjects without baseline HF. Study-specific multivariate-adjusted hazard ratios (HRs) were pooled using random-effects meta-analysis.

RESULTS Data were collated from 16 studies with a total of 67,063 subjects and 4,165 incident HF events. The average age was 57 years, and 47% were women. Study quality was high (Newcastle-Ottawa score 8.2 of 9). In a comparison of participants in the top third with those in the bottom third of baseline values of hs-cTn, the pooled multivariate-adjusted HR for incident HF was 2.09 (95% confidence interval [CI]: 1.76 to 2.48; $p < 0.001$). Between-study heterogeneity was high, with an I^2 value of 80%. HRs were similar in men and women (2.29 [95% CI: 1.64 to 3.21] vs. 2.18 [95% CI: 1.68 to 2.81]) and for hs-cTnI and hs-cTnT (2.09 [95% CI: 1.53 to 2.85] vs. 2.11 [95% CI: 1.69 to 2.63]) and across other study-level characteristics. Further adjustment for B-type natriuretic peptide yielded a similar HR of 2.08 (95% CI: 1.64 to 2.65). Assay of hs-cTn in addition to conventional risk factors provided improvements in the C index of 1% to 3%.

CONCLUSIONS Available prospective studies indicate a strong association of hs-cTn with the risk of first-ever HF and significant improvements in HF prediction. (J Am Coll Cardiol HF 2018;6:187–97) © 2018 by the American College of Cardiology Foundation.

Cardiac troponins are structural proteins in the contractile apparatus of the myocyte. Upon myocardial damage, they are released into the circulation (1), and they are therefore central in the diagnosis of myocardial infarction (2). Measurement of cardiac troponin with early assays was considered as a dichotomous test, classifying patients as being positive or negative for myocardial infarction. The advent of high-sensitivity cardiac troponin (hs-cTn) assays in recent years has changed this paradigm. High-sensitivity assays have allowed cardiac troponin to be considered as a quantitative measure of cardiac myocyte injury in the setting of myocardial infarction and can measure cardiac

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troponin at low concentrations in subjects without myocardial infarction, in whom it can be regarded as a marker for myocardial stress (2,3).

We previously demonstrated in a meta-analysis of 29 studies that cardiac troponin concentration in subjects without manifest cardiovascular disease (CVD) is associated with long-term risk for developing coronary heart disease or stroke (4). In addition to these 2 outcomes, hs-cTn may also be a prognostic marker for the development of heart failure (HF). Identification of better prognostic markers for incident HF is important because HF is associated with poor survival, reduced quality of life, and significant health care costs (5). Furthermore, as reported by a recent U.K.-based study, HF has become the most common initial presentation of CVD (6). Still, prediction models aiming to identify subjects at high risk for HF are currently not included in CVD prevention guidelines (7,8) and are not established in clinical practice (9). The potential of cardiac biomarkers in HF prediction is exemplified by a meta-analysis showing that natriuretic peptides improve risk discrimination and classification in general population studies (10). Risk scores for HF could help target preventive medication, such as statins (11), intensive blood pressure control (12), and angiotensin-converting enzyme inhibitors (13).

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The aim of this study was to systematically collate and appraise the available evidence regarding the association between hs-cTn and incident HF and the added value of hs-cTn in HF prediction.

METHODS

This systematic review is reported in accordance with the Meta-Analysis of Observational Studies in Epidemiology guidelines (14), and the protocol was registered prospectively with PROSPERO (CRD42017054828).

SEARCH FOR PUBLISHED STUDIES. Electronic searches of PubMed, Embase, and Web of Science were performed on January 3, 2017 (the search strategy is detailed in Online Table 1), with no filters or language restrictions applied. This was supplemented by review of relevant conference proceedings (i.e., American Heart Association Scientific Sessions, American College of Cardiology Sessions, and European Society of Cardiology Annual Congress from 2014 to 2016) and of the reference lists of identified studies. The searches were conducted by 2 independent investigators (J.D.W.E. and S.D.), and any discrepancies were resolved, by consensus, with a third investigator (S.J.P.).

STUDY ELIGIBILITY CRITERIA. To be eligible for inclusion, studies were required to: 1) have a prospective study design, including studies nested in randomized controlled trials; 2) have enrolled subjects without HF at baseline; 3) have measured hs-cTn; and 4) have recorded incident HF events over at least 1 year. Studies were excluded if they involved patients in the early phase after acute myocardial infarction, those undergoing cardiotoxic chemotherapy, or those with established myocardial or multisystem disease (e.g., sarcoidosis, amyloidosis).

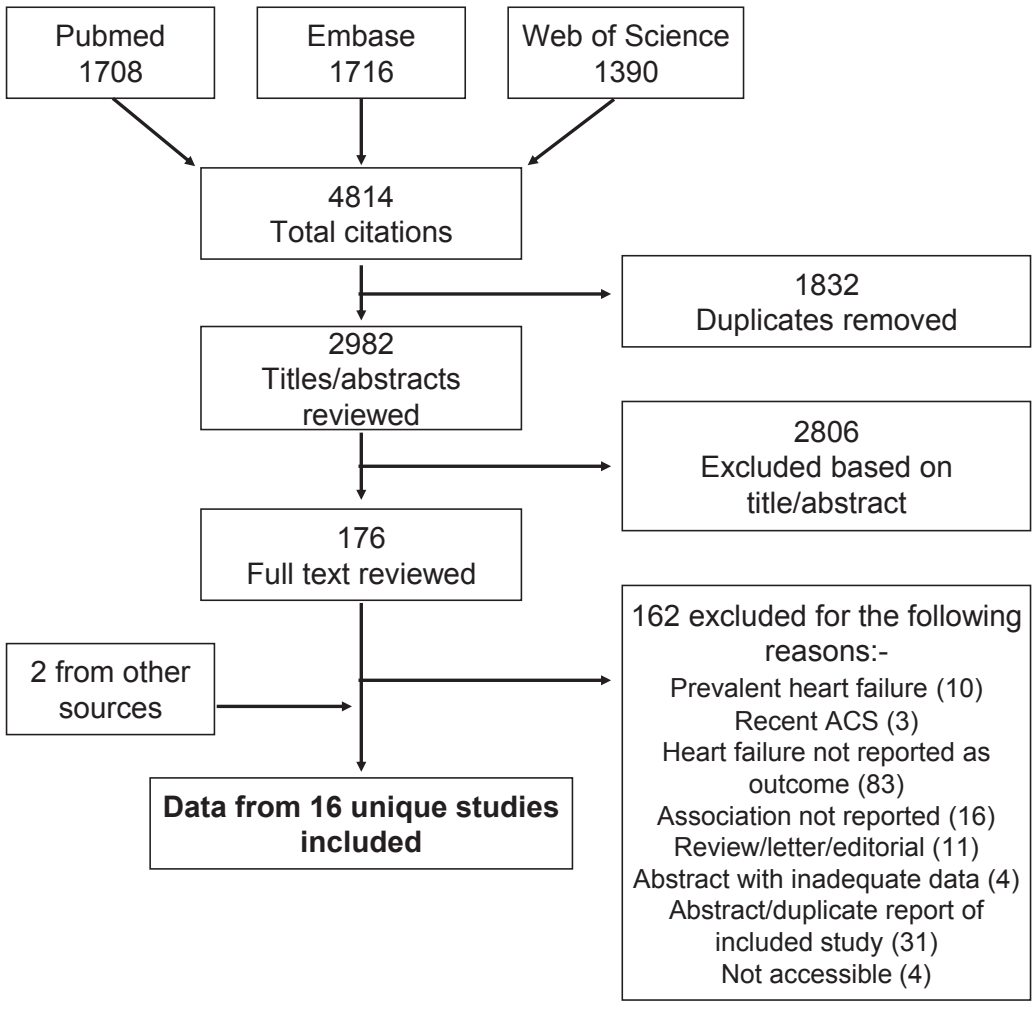
DATA EXTRACTION. Using a pre-specified data collection sheet, data were collated on population type (general vs. high-risk populations); mean age; sex; ethnicity; baseline history of hypertension, diabetes, or CVD; hs-cTn assay type and manufacturer; number of participants; duration of follow-up; and number of incident HF events. Furthermore, we assessed the quality of included studies using the Newcastle-Ottawa tool for cohort studies (15), which considers participant selection, exposure measurement, ascertainment of outcomes, covariate adjustment, and adequacy of follow-up. We also recorded which methods studies used to record incident HF events and how they defined them (fatal, nonfatal, or both). Hazard ratios (HRs) for the association between hs-cTn and incident HF were extracted with the following levels of covariate adjustment, when available: 1) unadjusted or adjusted only for age and sex; 2) adjusted for demographic factors, conventional CVD risk factors, and/or biomarkers other than natriuretic peptides; and 3) adjusted for demographic factors, conventional CVD risk factors, non-natriuretic peptide biomarkers, and natriuretic peptide levels. When reported, C indexes as a measure of risk discrimination were extracted for predictive models with and without hs-cTn assessment.

STATISTICAL ANALYSIS. All statistical analyses were performed using Stata version 13 (StataCorp, College Station, Texas), and a 2-sided p value of <0.05 was deemed to represent statistical significance in the primary analysis; a p value <0.01 indicated significance in meta-regression analyses because of multiple testing. Studies reported HRs in different ways. These included an HR describing those above and below a specific threshold, between top and bottom quartiles or quintiles, and per unit increase or per standard deviation increase in hs-cTn. To allow direct comparison of study-specific HRs, HRs

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
CVD = cardiovascular disease
HF = heart failure
HR = hazard ratio
hs-cTn = high-sensitivity cardiac troponin

FIGURE 1 Search Results and Study Selection Process



ACS = acute coronary syndrome.

were transformed to represent the HR for the top third versus the bottom third of hs-cTn concentration within a given study. This transformation was performed under the assumption that the exposure variable is normally distributed and a log-linear association between exposure and outcome, as previously described (16,17). When estimates were presented both by groups of cardiac troponin as a categorical variable and as a continuous measure, the continuous measure was used, as this is more compatible with the linear assumption used when transforming HRs.

For the primary analysis, the most adjusted study-specific HRs for the association between hs-cTn and incident HF were pooled by random-effects inverse-variance weighted meta-analysis using the method of DerSimonian and Laird (18). This random-effects method was selected a priori because of a degree of anticipated heterogeneity in the populations studied and the design of included studies. Between-study heterogeneity was quantified using the I^2 statistic (19).

Secondary analyses pooled sex-specific HRs using data from studies that reported associations separately in both men and women and compared HRs according to the 3 pre-specified levels of covariate adjustment. Furthermore, meta-regression was used to test whether associations differed according to study-level characteristics. For categorical study-level characteristics, pooled HRs were calculated

TABLE 1 Summary of Included Prospective Cohort Studies and Baseline Characteristics of Participants

First Author (Year) (Ref. #)	Study	Type of Study Population	Mean Age (yrs)	Female (%)	Race (% White)	Hypertension (%)	Diabetes (%)	CVD (%)	Troponin Assay	Follow-Up (yrs)	Participants	HF Events	Outcome Definition	Follow-Up Method
General population														
Brouwers et al. (2014) (24)	PREVEND	General population	49	50	96	14	1	7	hsTnT (Roche)	13*	8,569	374	All	RL‖
deFilippi et al. (2010) (25)	CHS	General population	73	60	NR	60	18	18	hsTnT (Roche)	12*	4,221	1,279	NF	SR, RL‖
Eggers et al. (2016) (26)	PIVUS	General population	70	50	NR	70	11	0	hsTnI (Abbott)	10†	864	67	All	RL
Ford et al. (2016) (36)	WOSCOPS	General population§	55	0	NR	16	1	5	hsTnI (Abbott)	15†	3,318	61	Hosp	RL
Lyngbakken et al. (2016) (27)	HUNT2	General population	47*	56	100	41	2	0	hsTnI (Abbott)	17*	9,114	209	Hosp	RL
McKie et al. (2014) (28)	REP	General population	62	52	NR	28	7	12	hsTnT (Siemens)	11*	1,843	193	All	RL
Neumann et al. (2014) (30)	FINRISK	General population	48	50	100	45	5	0	hsTnI (Singulex)	14†	7,899	505	NR	RL
Saunders et al. (2011) (32)	ARIC	General population	63	59	78	45	15	0	hsTnT (Roche)	10*	9,276	665	Hosp	RL
Seliger et al. (2017) (21)	MESA	General population	62	57	39	42	11	0	hsTnT (Roche)	12*	4,986	177	Hosp	SR‖
Wang et al. (2012) (34)	FHS	General population	59	53	NR	28	12	5	hsTnI (Singulex)	11‡	3,428	149	NF	RL‖
High-risk groups														
Bansal et al. (2014) (23)	CRIC	CKD	58	46	43	NR	46	26	hsTnT (Roche)	6*	3,483	320	Hosp	SR, RL‖
McQueen et al. (2013) (29)	HOPE	High risk§	65	23	NR	42	35	94	hsTnT (Roche)	5‡	2,941	NR	All	Trial‖
Okuyama et al. (2017) (22)	Fujita	Hypertensive	69	29	0	100	43	20	hsTnI (Abbott)	7.2‡	493	44	Hosp	SR, RL
Omland et al. (2009) (31)	PEACE	Stable CVD§	64	19	92	45	16	100	hsTnT (Roche)	5*	3,679	104	Hosp, FHF	Trial
Scirica et al. (2016) (33)	SAVOUR-TIMI 53	Diabetes§	65	33	80	82	100	0	hsTnT (Roche)	2*	2,673	NR	Hosp	Trial
Yiu et al. (2014) (35)	CDATS	Diabetes	64	44	0	70	100	29	hsTnI (Abbott)	5*	276	18	Hosp	SR, RL
Total			57	47	82	40	16	14		11	67,063	4,165		

*Median. †Maximum. ‡Mean. §Nested in RCT. ‖Endpoint adjudication performed.

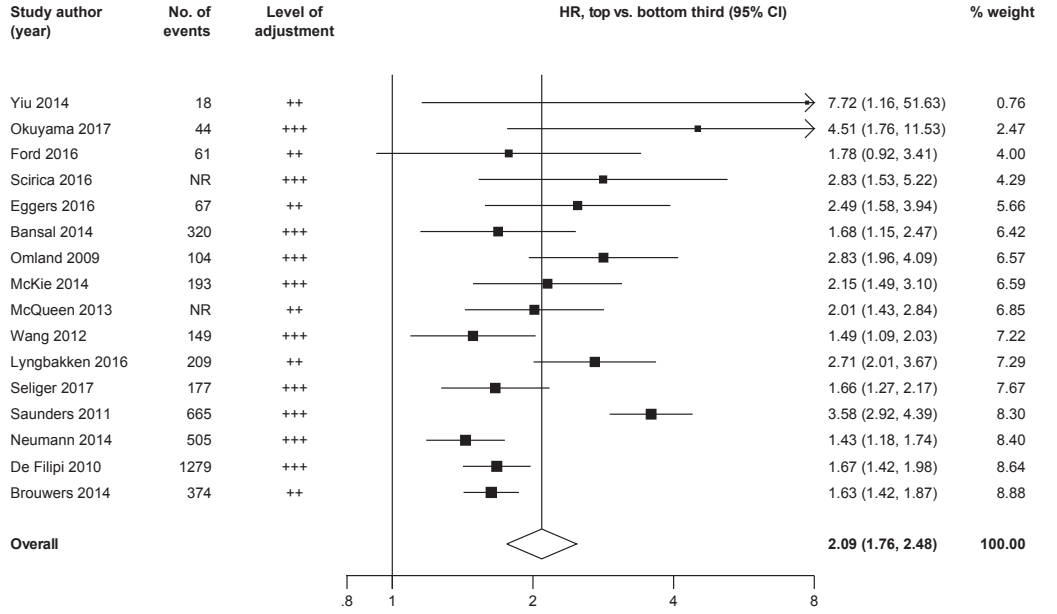
All = fatal and nonfatal heart failure including hospitalization; ARIC = Atherosclerosis Risk in Communities; CDATS = Chinese Diabetic Heart Study; CHS = Cardiovascular Health Study; CKD = chronic kidney disease; CRIC = Chronic Renal Insufficiency Cohort; CVD = cardiovascular disease; FHF = fatal heart failure; FHS = Framingham Heart Study; HOPE = Heart Outcomes Prevention Evaluation; Hosp = hospitalization for heart failure; hsTnI = high-sensitivity troponin I; hsTnT = high-sensitivity troponin T; HUNT2 = Nord-Trondelag Health Study; MESA = Multi-Ethnic Study of Atherosclerosis; NF = nonfatal heart failure; NR = not reported; PEACE = Prevention of Events With Angiotensin Converting Enzyme Inhibition; PIVUS = Prospective Investigation of the Vasculature in Uppsala Seniors; PREVEND = Prevention of Vascular and Renal End-Stage Disease; REP = Rochester Epidemiology Project; RL = record linkage/medical record review; SAVOUR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded With Diabetes Mellitus-Thrombolysis In Myocardial Infarction 53; SR = self-report; Trial = active follow-up within trial; WOSCOPS = West of Scotland Coronary Prevention Study.

within each subgroup. For continuous variables, study-specific estimates of the association between hs-cTn and HF were plotted against the value of the variable of interest, and a regression line was fitted. The presence of publication bias was assessed using funnel plots and Egger's test (20).

RESULTS

SUMMARY OF INCLUDED STUDIES. Electronic searches yielded 2,982 unique citations (Figure 1). Shortly after the date of the electronic searches, full text versions of 2 abstracts identified in the search process were published and included (21,22). Data from 16 unique studies (21–36), reporting data regarding 67,063 participants with 4,165 first HF events, were included in this review. The included studies are summarized in Table 1. Ten studies included a sample of the general population, and 6 comprised high-risk populations with stable CVD, type 2 diabetes, chronic kidney disease, or hypertension. All were prospective cohort studies; 4 were nested within randomized controlled trials. Seven studies were conducted in North America, 5 in Western Europe, 2 in East Asia, and 2 across multiple continents. All studies excluded patients with diagnoses of HF at baseline. Okuyama

FIGURE 2 Forest Plot for Primary Analysis of Maximally Adjusted HRs for the Association Between High-Sensitivity Cardiac Troponin and Incident Heart Failure



Heterogeneity: I^2 = 79.9% (95% confidence interval [CI]: 68.1% to 87.3%). HR = hazard ratio; NR = not reported; ++ = adjusted for demographics and cardiovascular disease (CVD) risk factors; +++ = adjusted for demographics, CVD risk factors, and natriuretic peptides.

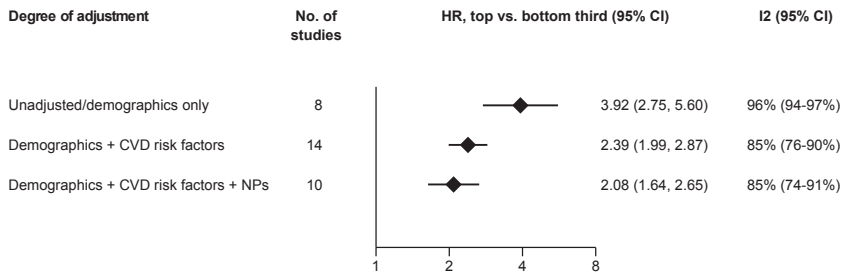
et al. (22) additionally excluded subjects with left ventricular ejection fractions <50%; McQueen et al. (29) and Omland et al. (31) excluded those known to have left ventricular ejection fractions <40%. Eight studies used HF hospitalization alone as the endpoint, 4 used all fatal or nonfatal HF diagnoses and events, and 2 reported all nonfatal HF diagnoses and events. Overall, the quality of the included studies was good. Three studies fulfilled all 9 elements of the Newcastle-Ottawa score, with the other 13 fulfilling 8 of the 9 criteria. The individual elements and overall Newcastle-Ottawa scores are shown in Online Table 5. More detailed descriptions of the study population, method of follow-up, outcome definitions, covariate adjustment, and details of the cardiac troponin assays used are reported in the Online Appendix (Online Tables 2 to 4).

ASSOCIATION OF hs-cTn WITH INCIDENT HF. The pooled HR for incident HF comparing subjects in the top third versus those in the bottom third of hs-cTn concentration was 2.09 (95% confidence interval [CI]: 1.76 to 2.48; p < 0.0001) (**Figure 2**). There was evidence of significant heterogeneity, with an I^2 value of 80% (95% CI: 68% to 87%). The pooled HR was not materially changed upon further adjustment for B-type natriuretic peptide levels on top of CVD risk factors (**Figure 3**).

Sensitivity analysis using meta-regression confirmed that none of the categorical or continuous study-level variables assessed were associated with differences in the HR for the association between hs-cTn and incident HF (**Figure 4,** Online Figure 2). Pooled HRs were 2.29 (95% CI: 1.64 to 3.21) in men, 2.18 (95% CI: 1.68 to 2.81) in women, 2.09 (95% CI: 1.53 to 2.85) with hs-cTnI, and 2.11 (95% CI: 1.69 to 2.63) with hs-cTnT. There was some evidence for publication bias on inspection of the funnel plot, with 2 smaller studies reporting HRs greater than the pooled estimate (Online Figure 3), but the Egger's test was nonsignificant (p = 0.126).

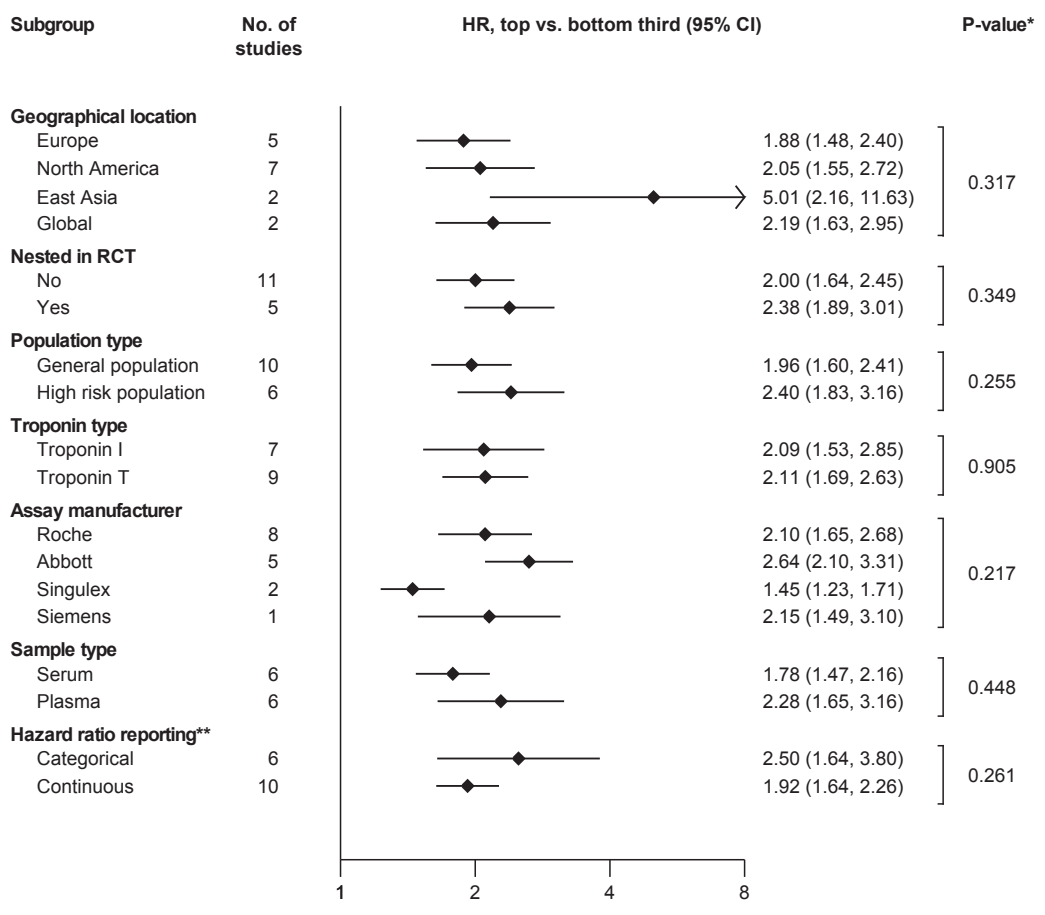
ASSOCIATION OF hs-cTn WITH HF SUBTYPES. Two studies reported associations between hs-cTn and HF with preserved and reduced ejection fraction separately. In the PREVEND (Prevention of Vascular and Renal End-Stage Disease) study, the HR for those with hs-cTnT in the top versus bottom third was greater for HF with reduced ejection fraction (HR: 1.79; 95% CI: 1.55 to 2.07) than for HF with preserved ejection fraction (HR: 1.30; 95% CI: 1.07 to 1.50) (24). In the

FIGURE 3 HRs for Association Between High-Sensitivity Cardiac Troponin and Incident Heart Failure by the Degree of Covariate Adjustment



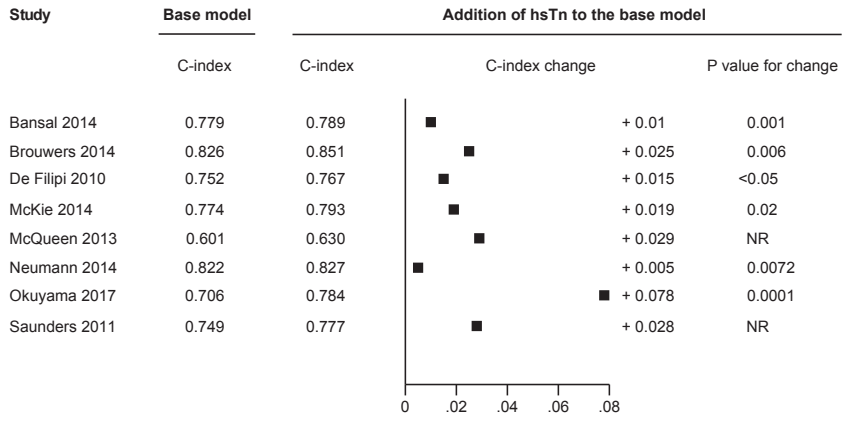
Studies contribute to multiple levels if hazard ratios are reported at each level of adjustment. Comparisons are indirect because not all studies were included in analyses at each level of covariate adjustment. CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; NP = natriuretic peptide (N-terminal pro-B-type natriuretic peptide or B-type natriuretic peptide).

FIGURE 4 Meta-Regression by Categorical Study-Level Characteristics



*P value calculated using meta-regression. **Manner in which HRs were reported in original paper. CI = confidence interval; HR = hazard ratio; RCT = randomized controlled trial.

FIGURE 5 Change in C Index With Addition of High-Sensitivity Cardiac Troponin by Study



NR = not reported.

CHS (Cardiovascular Health Study), in those without left ventricular hypertrophy by echocardiography at baseline, the corresponding HRs were 2.70 (95% CI: 1.64 to 4.40) for HF with reduced ejection fraction and 1.85 (95% CI: 1.30 to 2.68) for HF with preserved ejection fraction (37). No studies reported data regarding HF with midrange ejection fraction.

ASSOCIATION OF CHANGES IN hs-cTn AND INCIDENT HF. Two studies reported the association between changes in hs-cTn over time and incident HF. In the CHS, in those with detectable hs-cTnT at baseline, the HR associated with a >50% increase 2 to 3 years later was 1.61 (95% CI: 1.32 to 1.97) after adjusting for conventional CVD risk factors. In the ARIC (Atherosclerosis Risk In Communities) study, the corresponding HR for a >50% change in hs-cTnT at 6 years was 1.64 (95% CI: 1.39 to 1.95) (38). In those with undetectable hs-cTnT (<5 ng/l) at baseline, a detectable value (>5 ng/l) at 6 years was associated with an HR of 1.96 (95% CI: 1.62 to 2.37) (38).

INCREMENTAL DISCRIMINATION WITH ADDITION OF hs-cTn. Eight studies reported improvements in the C index upon assessment of hs-cTn in addition to assessment of conventional CVD risk factors. Reported findings generally demonstrated improvements in risk discrimination, with C index changes in the region of 0.01 to 0.03 with the additional assessment of hs-cTn (**Figure 5**). Because some studies did not report confidence intervals for C indexes and their changes, it was not possible to conduct a quantitative meta-analysis of the C index data.

DISCUSSION

This systematic review and meta-analysis involving data from 16 prospective studies demonstrates a strong association between hs-cTn and the development of incident HF. The data suggest that subjects with hs-cTn values in the top third of the population have a >2-fold increased risk for developing HF compared with those in the bottom third. This association was independent of conventional cardiovascular risk factors and natriuretic peptide levels and consistent in the general population and high-risk groups and in men and women. Assessment of hs-cTn in addition to conventional CVD risk factors improved risk discrimination quantified with the C index, with study-specific estimates between 0.01 and 0.03. These data suggest that measurement of hs-cTn may enhance the ability to identify subjects at greater risk for developing HF.

Hs-cTn troponin may be useful as a means of targeting echocardiographic screening for HF in high-risk subjects to identify asymptomatic left ventricular dysfunction and allow early treatment (13), as has been studied for natriuretic peptides (39), although such an approach would require further evaluation.

Hs-cTn assays have been used in clinical practice in the diagnosis of myocardial infarction for some time and have recently been approved by the U.S. Food and Drug Administration for use in the United States (40). Elevated circulating cardiac troponin has been associated with worse clinical outcome in patients with acute decompensated HF (41) and chronic stable HF (42). The mechanisms triggering the release

of circulating cardiac troponin in people without clinically manifest myocardial ischemia are unclear. It is speculated that contributing factors include underlying coronary artery disease, subendocardial ischemia, increased wall stress, and left ventricular hypertrophy (25). Another possible mechanism is the cardiac stress characterized by activation of the renin-angiotensin and adrenergic systems, which has been studied in detail in patients with HF (43).

The studies contributing to our meta-analysis excluded patients with symptomatic HF or previous diagnoses of HF at baseline. However, some of them enrolled subjects with subclinical myocardial dysfunction at baseline, who tend to have higher levels of hs-cTn. Among participants with hs-cTnT (>8.8 ng/l) in MESA (Multi-Ethnic Study of Atherosclerosis), 8.4% of men and 4.3% of women had left ventricular ejection fractions <50%, and 18.2% of men and 27.7% of women had left ventricular hypertrophy assessed with cardiac magnetic resonance imaging (21). In the PEACE (Prevention of Events With Angiotensin Converting Enzyme Inhibition) study involving patients with stable coronary heart disease, the prevalence of left ventricular ejection fraction between 40% and 50% was 14.4% in the whole cohort, increasing from 11.4% to 18.4% in the lowest to the highest quartile of hs-cTnT (31). It should be noted, however, that the association of hs-cTn and incident HF was observed even after the exclusion of patients with left ventricular hypertrophy in the CHS (37).

Natriuretic peptides are the best-studied biomarkers in HF and strong predictors of prognosis in patients with established HF (44). A recent individual participant data meta-analysis of the association between natriuretic peptide levels and incident HF in the general population reported a risk ratio for subjects in the top third versus the bottom third of 3.45 (95% CI: 2.66 to 4.46) (10). The magnitude of this association for natriuretic peptide is greater than that observed in our meta-analysis for hs-cTn, but those studies did not adjust for hs-cTn. Although subjects with hs-cTn tend to have higher natriuretic peptide levels (21,25,31), the magnitude of the Spearman correlation coefficient was modest at 0.36 in the CHS (25). In studies that adjusted for natriuretic peptide in our analysis, the pooled HR was 2.08 (95% CI: 1.64 to 2.65), only a slight attenuation of the association without adjustment for natriuretic peptides of 2.39 (95% CI: 1.99 to 2.87). This suggests that hs-cTn has a strong association with incident HF independent of natriuretic peptide levels. A meta-analysis of 29 published studies examining the association between hs-cTn and coronary heart disease and stroke reported risk ratios for the top versus the bottom third of 1.59 (95% CI: 1.38 to 1.83) for coronary heart disease and 1.35 (95% CI: 1.23 to 1.48) for stroke (4). Thus, the association between hs-cTn and HF is stronger than that for either coronary heart disease or stroke, a similar trend to that observed for N-terminal pro-B-type natriuretic peptide (10). With regard to improvement in risk discrimination, the C index change with additional assessment of hs-cTn was lower than that previously observed for natriuretic peptides (0.01 to 0.03 vs. 0.038) (10).

It must be noted that the studies included in our meta-analysis relied on a single measurement of hs-cTn, whereas repeat measurements are likely to be more informative. In the CHS, in subjects with elevated baseline hs-cTn, those with further increases at follow-up had higher HF risk compared with those with no change or decreases in hs-cTn (25). This observation is in line with similar data from the ARIC study (38), suggesting that serial measurements of biomarkers may provide additional information over a single measurement. After developing a biomarker score on the basis of concentrations of 5 biomarkers, including hs-cTn, investigators from the Framingham Heart Study observed a >6-fold increase in the risk for HF in those with scores in the top quintile versus the bottom quintile (34). This score also improved discrimination and reclassification in terms of HF risk. Serial testing of biomarkers including hs-cTn and the use of multiple biomarkers simultaneously appear to hold promise, but these approaches are inevitably more resource intensive and costly.

STUDY STRENGTHS AND LIMITATIONS. For this systematic review we pooled data from 16 studies reporting data from 67,063 participants with 4,165 HF events, providing significant statistical power. This study adds to the existing research in this field by providing an overview of all the available evidence regarding the association between hs-cTn and HF, with particular strengths including the thorough and comprehensive search strategy, the transformation of study-specific HRs to a common scale to allow comparison, and the high methodological quality of the included studies.

However, there were a number of limitations that merit discussion. Significant heterogeneity was observed in our analyses. No single factor was clearly demonstrated to account for a large proportion of this heterogeneity in meta-regression analyses, and it is likely to be multifactorial. The assumption of a normally distributed exposure variable and a linear association with the outcome of interest may have been violated in some studies in which subjects were categorized on the basis of

hs-cTn levels. A nonlinear relationship could lead to an inflated HR after transformation, but there was no significant interaction between estimates from studies that modeled hs-cTn as a continuous or categorical variable. Finally, incomplete reporting of confidence intervals for C index values prevented quantitative synthesis of these data, and this element is descriptive only.

Given the potential for both clinical and methodological sources of heterogeneity in the included studies, collating patient-level data from all of these studies would be valuable. This would allow standardization of outcome definitions and covariate adjustment. It would also allow analysis of associations and assessment for effect modification in important subgroups and standardized assessment of the effect of adding hs-cTn to HF risk prediction models in terms of discrimination and calibration.

CONCLUSIONS

Serum hs-cTn is associated with the risk for incident HF. The association applied equally to the general and high-risk populations and was independent of conventional CVD risk factors and natriuretic peptide levels. Preliminary data showing discrimination improvements in HF risk with hs-cTn assessment suggest that it may be a promising biomarker for measurement as part of primary prevention of HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Subjects with higher levels of circulating cardiac troponin are at higher risk for developing new-onset HF, after accounting for conventional risk factors and natriuretic peptide levels. Measurement of hs-cTn improves the discrimination of HF risk. Hs-cTn may be useful in identifying subjects at high risk for HF to target preventive interventions.

TRANSLATIONAL OUTLOOK: An individual-participant-data meta-analysis would help clarify the added value of hs-cTn in the prediction of new-onset HF, beyond conventional risk factors.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.

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