SYSTEMATIC REVIEW

Prognostic Value of High-Sensitivity Troponin T in Chronic Heart Failure
An Individual Patient Data Meta-Analysis

BACKGROUND: Most patients with chronic heart failure have detectable troponin concentrations when evaluated by high-sensitivity assays. The prognostic relevance of this finding has not been clearly established so far. We aimed to assess high-sensitivity troponin assay for risk stratification in chronic heart failure through a meta-analysis approach.

METHODS: Medline, EMBASE, Cochrane Library, and Scopus were searched in April 2017 by 2 independent authors. The terms were "troponin" AND "heart failure" OR "cardiac failure" OR "cardiac dysfunction" OR "cardiac insufficiency" OR "left ventricular dysfunction." Inclusion criteria were English language, clinical stability, use of a high-sensitivity troponin assay, follow-up studies, and availability of individual patient data after request to authors. Data retrieved from articles and provided by authors were used in agreement with the PRISMA statement. The end points were all-cause death, cardiovascular death, and hospitalization for cardiovascular cause.

RESULTS: Ten studies were included, reporting data on 11 cohorts and 9289 patients (age 66±12 years, 77% men, 60% ischemic heart failure, 85% with left ventricular ejection fraction <40%). High-sensitivity troponin T data were available for all patients, whereas only 209 patients also had high-sensitivity troponin I assayed. When added to a prognostic model including established risk markers (sex, age, ischemic versus nonischemic etiology, left ventricular ejection fraction, estimated glomerular filtration rate, and N-terminal fraction of pro-B-type natriuretic peptide), high-sensitivity troponin T remained independently associated with all-cause mortality (hazard ratio, 1.48; 95% confidence interval, 1.41–1.55), cardiovascular mortality (hazard ratio, 1.40; 95% confidence interval, 1.33–1.48), and cardiovascular hospitalization (hazard ratio, 1.42; 95% confidence interval, 1.36–1.49), over a median 2.4-year follow-up (all *P*<0.001). High-sensitivity troponin T significantly improved risk prediction when added to a prognostic model including the variables above. It also displayed an independent prognostic value for all outcomes in almost all population subgroups. The area under the curve–derived 18 ng/L cutoff yielded independent prognostic value for the 3 end points in both men and women, patients with either ischemic or nonischemic etiology, and across categories of renal dysfunction.

CONCLUSIONS: In chronic heart failure, high-sensitivity troponin T is a strong and independent predictor of all-cause and cardiovascular mortality, and of hospitalization for cardiovascular causes, as well. This biomarker then represents an additional tool for prognostic stratification.

Alberto Aimo, MD
et al

Clinical Perspective

What Is New?

- In this individual patient data meta-analysis on high-sensitivity troponins and prognosis in chronic heart failure, data were retrieved from 10 studies, corresponding to 11 cohorts and 9289 patients, all with available high-sensitivity troponin T (hs-TnT) data.
- hs-TnT emerged as a strong independent predictor of outcome in chronic heart failure.
- Over a median 2.4-year follow-up, hs-TnT was independent predictor of all-cause and cardiovascular death, and cardiovascular hospitalization.
- The prognostic significance of hs-cardiac TnT was retained across almost all population subgroups.
- A 18 ng/L hs-TnT concentration independently predicted all 3 end points in both the ischemic and nonischemic subgroups, and across categories of renal dysfunction.

What Are the Clinical Implications?

- These results provide conceptual support to the widespread use of hs-cardiac TnT for prognostic stratification in chronic heart failure.
- The information from hs-cardiac TnT seems incremental to other risk predictors, including natriuretic peptides.
- The striking consistency of results irrespective of patient and disease characteristics has important consequences, implying no need to vary measurement of hs-TnT and interpretation of results depending on patients subgroup (eg, ischemic versus nonischemic etiology, or normal versus impaired renal function).

Cardiac isoforms of troponin T (TnT) and troponin I (TnI) are components of the cardiomyocyte contractile apparatus. These proteins are released into the bloodstream on necrotic cell death, and possibly membrane leakage.[1] In heart failure (HF), troponin release is promoted by several postulated mechanisms, including myocardial ischemia attributable to coronary artery disease or microcirculatory dysfunction, damage elicited by neurohormonal overactivation, inflammatory or infiltrative processes, myocardial apoptosis or autophagy, and increased protein turnover, among others.[2] In patients with stable chronic HF, circulating troponin may be detectable in 10% to 60% of patients with traditional assays, and in nearly 100% of patients, when using the high-sensitivity (hs) assays, with a substantial proportion above the 99th percentile of hs-Tn for healthy populations.[2]

Several studies have reported that higher plasma concentrations of troponin, measured with either traditional or hs assays, are associated with worse prognosis in chronic HF. Based on these findings, the 2013 American College of

Cardiology Foundation/American Heart Association Guidelines recommended troponin assay as an additive tool for risk stratification.[3] In contrast, the 2016 European Society of Cardiology Guidelines have not even mentioned troponins among risk predictors.[4] A possible explanation for these diverging opinions is the current absence of comprehensive analyses on troponins and prognosis in chronic HF, with the exception of a 2012 systematic review considering only cumulative, unadjusted data, and including studies on both traditional and hs assays,[5] whereas the latter are replacing traditional assays in current clinical practice.[6]

Meta-analyses based on individual patient data (IPD) are regarded as the gold standard for meta-analyses and are becoming increasingly common, because they have several advantages over meta-analyses of summary statistics.[7] For example, they allow researchers to define exposures and outcomes consistently across studies, adjusting for the same confounders.[7] To establish the prognostic value of hs-Tn in chronic HF, we therefore established a multinational collaboration aiming to collect and evaluate data from published studies on this topic.

METHODS

Data Sources, Search Strategy, and Eligibility Criteria

The meta-analysis was conducted in agreement with the Preferred Reporting Items for Systematic reviews and
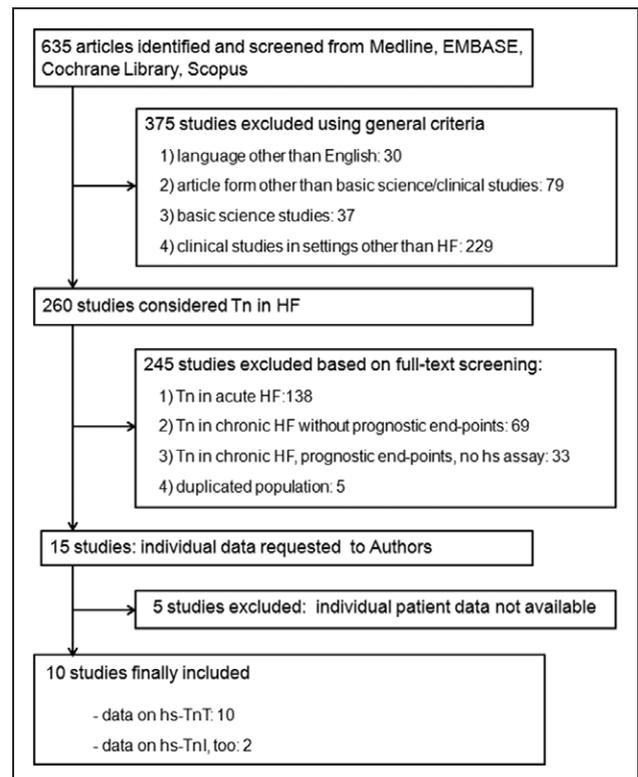

Figure 1. Study selection.
cTnI indicates cardiac troponin I; cTnT, cardiac troponin T; HF, heart failure; hs, high sensitivity; and Tn, troponin.

Table 1. Characteristics of Study Populations

Author, Year	Patients, n	Sex, Men, n (%)	Age, y	BMI, kg/m²	Ischemic HF, n (%)	Hypertension, n (%)	Diabetes Mellitus, n (%)	LVEF,%	NT-proBNP, ng/L	eGFR, mL·min⁻¹·1.73 m⁻²
Alonso et al, 2016[15]	803	576 (72)	66±11	N/A	419 (52)	499 (62)	570 (35)	33±13	1187 (476–2676)	51 (34–69)
Eggers et al, 2011[16]	111	68 (62)	53±13	N/A	22 (20)	29 (26)	18 (16)	39±18	1198 (618–2475)	63 (49–78)
Egstrup et al, 2012[17]	416	295 (71)	71±11	27±5	258 (62)	N/A	79 (19)	31±9	1008 (419–2385)	64 (51–79)
Gaggin et al, 2014[18]	150	127 (84)	65±14	29±6	76 (50)	78 (52)	63 (42)	27±9	1897 (980–3718)	50 (37–65)
Gravning et al, 2013[19]	1245	959 (77)	72±7	N/A	1245 (100)	868 (60)	N/A	32±7	1319 (507–2867)	55 (45–65)
Masson et al, 2012 (Val-HeFT)[20]	4053	3253 (80)	63±11	27±4	2345 (58)	1698 (42)	1049 (26)	27±7	902 (378–1990)	58 (48–67)
Masson et al, 2012 (GISSI-HF)[20]	1231	991 (81)	67±11	27±4	627 (51)	677 (55)	322 (26)	33±10	846 (376–1869)	63 (49–77)
Nakamura et al, 2014[21]	444	282 (64)	67±14	N/A	66 (15)	367 (83)	206 (46)	46±15	N/A	69 (48–92)
Sanders-van Wijk et al, 2015[22]	561	340 (61)	77±8	26±5	297 (53)	417 (74)	204 (36)	35±13	3822 (1907–6947)	52 (37–66)
Schroten et al, 2013[23]	101	94 (93)	64±10	28±4	73 (72)	35 (35)	14 (14)	35±8	376 (202–808)	75 (65–85)
Tentzeris et al, 2011[24]	174	134 (77)	64±12	N/A	67 (38)	130 (75)	61 (35)	34±11	1655(671–3515)	71 (54–93)

(Continued)

Meta-Analyses statement.[8] In April 2017, 2 authors (A.A., G.V.) independently searched 4 databases (Medline, EMBASE, Cochrane Library, and Scopus). The search terms, deliberately generic, were "troponin" AND "heart failure" OR "cardiac failure" OR "cardiac dysfunction" OR "cardiac insufficiency" OR "left ventricular dysfunction."

Inclusion criteria were as follows:
1. English language
2. Patients aged ≥18 years and diagnosed with HF
3. Reported enrollment of outpatients or patients undergoing elective admission
4. Reported use of a hs assay for TnT and TnI
5. Information on patient prognosis
6. Authors' availability to provide IPD.

Two authors (A.A., G.V.) independently evaluated the studies to be included in the meta-analysis. Disagreement about study inclusion was resolved by discussion with a third author (M.E.).

The following data were extracted from each study: first author's last name, publication year, country where the study was conducted, study period, number of patients enrolled, left ventricular ejection fraction (LVEF) criteria, follow-up duration, outcomes evaluated, and all demographic and clinical baseline data provided. The data were extracted by a reviewer (A.A.), and checked for accuracy by a second reviewer (G.V.).

The authors of each study were then contacted and asked to provide IPD for as many as possible of the following variables: age, sex, ethnic group (black versus others), body mass index, hypertension, atrial fibrillation, diabetes mellitus,

chronic obstructive pulmonary disease, plasma hemoglobin, HF etiology (ischemic versus nonischemic), LVEF, hs-TnT and hs-TnI, natriuretic peptides (NPs: either B-type NP [BNP] or the N-terminal fraction of its precursor [NT-proBNP]), serum creatinine, hs C-reactive protein, follow-up duration, and outcome measures (all-cause death, cardiovascular death, and hospitalization for cardiovascular cause). As specified below, hs-TnI values were available for a small minority of patients. Therefore, only hs-TnT was considered in analysis.

This analysis was not sponsored, and there were no sources of funding.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS Statistics (version 22, 2013) and the R statistical software[9] (version 3.4.0; *metafor*, *pROC*, *predictABEL*, *ResourceSelection*, *riskRegression*, *cmprsk*, and *readxl* packages).

Normal distribution was assessed through the Kolmogorov-Smirnov test; variables with normal distribution were presented as mean±SD, and those with nonnormal distribution as median and interquartile interval. Mean differences among groups were evaluated through the unpaired Student t test or the Mann-Whitney U test, when appropriate. P values of <0.05 were considered significant.

Prognostic Value of hs-TnT

Over the entire patient population, the prognostic value of hs-TnT for 3 end points (all-cause death, cardiovascular death,

Table 1.   Continued

hs-CRP, mg/L	hs-TnT, ng/L	hs-TnI, ng/L	ACEi/ARB, %	BB, %	MRA, %	Follow-Up, months	All-Cause Death, n (%)	Cardiovascular Death, n (%)	Cardiovascular Hospitalization, n (%)
3.6 (1.3–8.3)	22.3 (10.7–39.2)	N/A	731 (91)	723 (90)	466 (58)	68 (33–102)	449 (56)	241 (30)	193 (24)
N/A	6.7 (3.5–17.8)	14.0 (7.8–32.7)	93 (84)	93 (84)	71 (64)	58 (19–107)	27 (25)	N/A	N/A
N/A	18 (10–32)	N/A	275 (66)	183 (44)	N/A	55 (24–93)	211 (51)	N/A	N/A
4.2 (1.2–10.1)	17.9 (7.3–37.3)	10.9 (6.1–23.4)	122 (81)	143 (95)	62 (41)	12 (12–13)	14 (9)	10 (7)	N/A
3.6 (1.6–7.6)	13.9 (6.6–25.6)	N/A	1133 (91)	959 (77)	461 (37)	31 (27–36)	366 (29)	299 (24)	522 (42)
3.3 (1.4–7.6)	12.5 (5.9–22.4)	N/A	3773 (93)	1463 (36)	215 (5)	24 (18–29)	780 (19)	671 (17)	655 (16)
2.3 (1.1–5.5)	17.0 (10.3–27.8)	N/A	1219 (99)	836 (68)	532 (43)	48 (37–56)	330 (27)	243 (20)	692 (56)
N/A	28 (15–61)	N/A	355 (80)	355 (80)	N/A	54 (30–67)	172 (39)	97 (22)	N/A
7.6 (2.8–18.1)	32.4 (18.6–59.8)	N/A	533 (95)	432 (77)	213 (38)	26 (14–38)	217 (39)	164 (29)	281 (50)
N/A	4.4 (3.0–12.4)	N/A	101 (100)	97 (97)	29 (29)	65 (51–74)	22 (22)	N/A	13 (13)
N/A	18.4 (9.1–26.6)	N/A	N/A	N/A	N/A	25 (7–47)	32 (18)	N/A	19 (11)

Individual patient data were available for all variables listed, with the exception of therapy, for which cumulative data were considered. ACEi indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, β-blockers; BMI, body mass index; eGFR, estimated glomerular filtration rate; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca–Heart Failure; hs-CRP, high-sensitivity C-reactive protein; hs-TnI/T, high-sensitivity troponin I/T; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; N/A, not available; NT-proBNP, N-terminal fraction of pro-B-type natriuretic peptide; and Val-HeFT, Valsartan Heart Failure Trial.

and cardiovascular hospitalization) was calculated through a Cox proportional hazards model. Adjusted hazard ratio (HR) values with corresponding 95% confidence intervals (CIs) were computed for standardized $\log_2$(hs-TnT), representing the risk per doubling of hs-TnT. The prognostic model used for adjustment included variables commonly available in the outpatient setting, with potential influence on circulating levels and with prognostic relevance (ie, patient sex and age, ischemic versus nonischemic etiology, LVEF, estimated glomerular filtration rate [eGFR], $\log_2$-transformed NT-proBNP). The Fine-Gray model was used to account for mutually exclusive end points; noncardiovascular death was considered as a competing risk for cardiovascular death, and all-cause death as a competing risk for cardiovascular hospitalization.[10]

As another method for computing global HR, adjusted HR values were calculated for each study by using standardized $\log_2$(hs-TnT), representing the risk per doubling of hs-TnT. HR values were then ln-transformed, and the summary of effect size was computed by using the random-effects model and the generic inverse variance method.

Heterogeneity Analysis, Search for Bias in Included Studies and Across Studies

Heterogeneity across studies was evaluated through unadjusted analysis and random-effects models. The following measures were calculated: I^2 (total heterogeneity/total variability), H^2 (total variability/sampling variability), and H (square root of H^2).[11] Because of the small study number, the Cochran Q test was not used.[11] Meta-regression analysis was performed to search for population characteristics unevenly distributed among studies, thus possibly contributing to different estimates of hs-TnT predictive value.

The risk of bias in included studies was evaluated according to the criteria established by the Cochrane collaboration.[12] Funnel plot analysis integrated by the trim-and-fill method was planned to search for publication bias.

Additional Analyses

Predictors of hs-TnT Levels

Multivariate linear regression analysis was performed to search for predictors of hs-TnT ($\log_2$-transformed). Pearson product moment correlation coefficient (r) was calculated as a measure of linear association between the variable and $\log_2$(hs-TnT). R-squared, expressing explained variation/total variation, was also computed.

Additive Value of hs-TnT in Risk Stratification

The prognostic performance of 2 models was then evaluated. Model 1 included the variables above (patient sex and age, ischemic versus nonischemic etiology, LVEF, eGFR, $\log_2$-transformed NT-proBNP), whereas model 2 also included

log$_2$-transformed hs-Tn. The discriminating power of hs-TnT with regard to the end points was assessed by the DeLong test for 2 correlated receiver operating characteristic curves. The D'Agostino-Nam version of the Hosmer-Lemeshow calibration test was used to calculate χ^2 value as a measure of calibration. The net reclassification improvement (with risk categories set at <10%, 10%–30%, and >30%) and the integrated discrimination improvement were calculated to assess reclassification.[13,14]

Subgroup Analyses and Search for hs-TnT Cutoffs

Optimal hs-TnT cutoffs were searched via receiver operating characteristics curve and Youden J statistic. The analysis was performed in the whole population and in population subsets identified by sex, HF etiology, and eGFR categories; the 3 end points were assessed. Cubic spline interpolation was performed to represent the changes in risk of all-cause death according to hs-Tn values; 5 knots were considered. The hs-TnT value for which HR=1 was chosen as the value corresponding to the inflection point of the curve, ie, the concentration above which the slope of the curve becomes steeper.

Following the previous analyses, a hs-TnT cutoff was selected. It was evaluated at Kaplan-Meier analysis with log-rank test (Mantel-Cox), and its independent prognostic role was evaluated in the entire population and in the subsets identified by sex, HF etiology, and eGFR categories.

RESULTS

Patient Population

Fifteen articles met the inclusion and exclusion criteria.[15–29] Among them, one[20] was a post hoc analysis of 2 trials (Val-HeFT [Valsartan Heart Failure Trial][30] and GISSI-HF [Effects of n-3 PUFA and Rosuvastatin on Mortality-Morbidity of Patients With Symptomatic CHF][31]); 11 patient cohorts were then evaluated. The authors of 10 articles[15–24] sent individual patient data; 5 studies were excluded because the authors could not be contacted,[25–28] or were unable to provide IPD[28,29] (Figure 1). The total patient number from excluded studies was 1312.[25–29] Overall, the present analysis evaluated 9289 patients, all with hs-TnT measured (median, 16 ng/L; interquartile interval, 8–29 ng/L). The assay used in all studies was the only hs-TnT assay available (Roche Diagnostics; lower detection limit of 3 ng/L, 99th percentile value in apparently healthy individuals of 14 ng/L).[32] However, hs-TnI had been assayed (together with hs-TnT) only in 209 patients (2%) from 2 studies (Table 1), using different assays.[16,18] Therefore, we focused on the prognostic performance of hs-TnT.

Patients were aged 66±12 years, with a male prevalence (n=7122, 77%). The majority had HF with reduced ejection fraction (LVEF <40%: n=7902, 85%; LVEF 40–49%: n=718, 8%; LVEF ≥50%: n=479, 5%). Median hs-TnT levels were 15 ng/L (8–28) in the <40% LVEF subgroup versus 18 ng/L (9–38) in pa-

tients with 40% to 49% LVEF, and 22 ng/L (12–43) in those with ≥50% LVEF (P<0.001). All patients had available data on HF etiology; ischemic HF was more common (5543 patients, 60%). All studies but one[21] reported data on NT-proBNP (n=8845, 95%; median value, 1067 ng/L; interquartile interval, 433–2470 ng/L). Median GFR, estimated using the chronic kidney disease epidemiology collaboration equation,[34] was 58 mL·min^{-1}·1.73 m^{-2} (interquartile interval, 46–70). Among patients with therapy data available from published studies (n=9004, 97%), 91% were on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 58% were on β-blockers, and 24% were on mineralocorticoid receptor antagonists. Median follow-up duration was 2.4 years (interquartile interval, 1.6–3.3). Data on all-cause death were available for all cohorts (2620 deaths, 28%), whereas data on cardiovascular death were available for 6 cohorts[15,18–22] (8487 patients, 1725 events, 20%), and data on cardiovascular hospitalization were available for 6 other cohorts[15,19,20,22–24] (8168 patients, 2375 events, 29%) (Table 1).

Independent Prognostic Value of hs-TnT

The prognostic performance of hs-TnT as predictor of all-cause death, cardiovascular death, and cardiovascular hospitalization was evaluated after adjustment for sex, age, ischemic versus nonischemic HF etiology, LVEF, eGFR, and log$_2$-transformed NT-proBNP. Of the entire study population, 8341 patients (90%) had information on all-cause death and all variables needed for adjustment; the corresponding numbers for cardiovascular death and cardiovascular hospitalization were 7685 (83%) and 7803 (84%), respectively. HR values were 1.48 (1.41–1.55) for all-cause death, 1.40 (1.33–1.48) for cardiovascular death, and 1.42 (1.36–1.49) for cardiovascular hospitalization (all P values <0.001).

When repeating the analysis considering study HR values and combining them, very similar results were found after anti ln transformation: HR, 1.43 (95% CI, 1.35–1.52) for all-cause death, HR, 1.39 (95% CI, 1.32–1.48) for cardiovascular death (Figure I in the online-only Data Supplemental), and HR, 1.36 (95% CI, 1.30–1.43) for cardiovascular hospitalization (all P values <0.001).

Among patients with available data for adjusted analysis (n=201), hs-TnI also was independently associated with all-cause death (HR, 2.88; 95% CI, 1.38–6.01; P=0.005).

Heterogeneity Analysis: Search for Bias

HR values were 2.54 (95% CI, 1.65–5.36) for all-cause death, 2.45 (95% CI, 1.45–5.41) for cardiovascular death, and 2.47 (95% CI, 1.52–5.27) for cardiovascular hospital-

Table 2. Performance Metrics of Risk Prediction Models

	Index	Model 1: Sex, Age, HF Etiology, LVEF, eGFR, NT-proBNP	Model 2: Sex, Age, HF Etiology, LVEF, eGFR, NT-proBNP, hs-cTnT
All-cause death			
Discrimination	AUC	0.715 (95% CI, 0.703–0.728)	0.744 (95% CI, 0.732–0.756)
		Reference	$P<0.001$
Calibration	HL	χ^2 10.82, $P=0.212$	χ^2 12.03, $P=0.150$
Reclassification	IDI	Reference	0.031 (95% CI, 0.027–0.035), $P<0.001$
	NRI	Reference	0.336 (95% CI, 0.289–0.383), $P<0.001$
Cardiovascular death			
Discrimination	AUC	0.711 (95% CI, 0.695–0.724)	0.735 (95% CI, 0.721–0.749)
		Reference	$P<0.001$
Calibration	HL	χ^2 4.91, $P=0.767$	χ^2 10.25, $P=0.248$
Reclassification	IDI	Reference	0.022 (95% CI, 0.018–0.026), $P<0.001$
	NRI	Reference	0.288 (95% CI, 0.233–0.343), $P<0.001$
Cardiovascular hospitalization			
Discrimination	AUC	0.664 (95% CI, 0.651–0.677)	0.697 (95% CI, 0.685–0.710)
		Reference	$P<0.001$
Calibration	HL	χ^2 7.54, $P=0.480$	χ^2 16.59, $P=0.634$
Reclassification	IDI	Reference	0.028 (95% CI, 0.024–0.032), $P<0.001$
	NRI	Reference	0.336 (95% CI, 0.287–0.384), $P<0.001$

The whole study population is considered. As specified in the text, 8341 patients (90%) had information on all-cause death and all variables needed for adjustment; the corresponding numbers for cardiovascular death and cardiovascular hospitalization were 7685 (83%) and 7803 (84%), respectively.

Both high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal fraction of pro-B-type natriuretic peptide (NT-proBNP) were $\log_2$ transformed. Discrimination and reclassification analyses evaluated the additive value of hs-cTnT for risk stratification. Continuous NRI is considered. Models with good calibration have P values >0.05 at the HL test.

AUC indicates area under the curve; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HL, Hosmer-Lemeshow; hs-cTnT, high-sensitivity cardiac Troponin T; IDI, integrated discrimination improvement; LVEF, left ventricular ejection fraction; NRI, net reclassification improvement; and NT-proBNP, N-terminal fraction of pro-B-type natriuretic peptide.

ization. I^2 values were 84.45 (95% CI, 63.38–96.52) for all-cause death, 83.39 (95% CI, 52.67–96.59) for cardiovascular death, and 84.60 (95% CI, 62.11–95.97) for cardiovascular hospitalization. These values denoted significant heterogeneity among studies.[11] At meta-regression analysis, all population characteristics listed in Table 1 emerged as significant sources of heterogeneity among studies (all P values <0.001). After careful revision of the included studies, no evidence of bias within studies was detected.[12] Funnel plot analysis (ie, the search for publication bias) was not performed because of the low study number and high degree of heterogeneity.[35]

Predictors of hs-TnT Levels

When entered into a linear regression model, several population characteristics predicted higher $\log_2$(hs-TnT) levels. In decreasing order of strength of association, the predictive variables were: higher $\log_2$(NT-proBNP) (Pearson $r=0.533$), older age ($r=0.439$), lower eGFR ($r=-0.303$), diabetes mellitus ($r=0.210$), hypertension ($r=0.201$), $\log_2$(hs–C-reactive protein) ($r=0.141$), ischemic etiology ($r=0.075$), male sex ($r=0.072$), and lower body mass index ($r=-0.039$). Despite all P values <0.001, many of these variables were very weak predictors of hs-TnT levels, as demonstrated by r values close to 0. The combination of all the variables above yielded a 0.44 R-squared value, ie, it explained only 44% of total hs-TnT variation.

Additive Value of hs-TnT in Risk Stratification

When added to a prognostic model including the variables above (age, sex, HF etiology, LVEF, eGFR, and NT-proBNP), hs-TnT significantly improved risk prediction (Table 2). For example, area under the curve values for all-cause death increased from 0.715 to 0.744 ($P<0.001$; Table 2 and Figure 2).

hs-TnT and Prognosis: Subgroup Analyses

The availability of IPD allowed us to identify several population subgroups to evaluate the prognostic role of hs-TnT after adjustment for the prespecified model (including age, sex, HF etiology, LVEF, eGFR, and NT-proBNP). Concentrations of hs-TnT independently predicted all-cause death (Figure 3), and cardiovascular death and cardiovascular hospitalization in all subgroups, as well, with the exception of cardiovascular hospitalization in patients with eGFR <30 mL·min^{-1}·1.73 m^{-2} (Figures II and III in the online-only Data Supplement).

Search for hs-TnT Cutoffs

The optimal hs-TnT cutoff for all-cause death, cardiovascular death, and cardiovascular hospitalization was evaluated in the whole population and in several patient subgroups (ie, men versus women, ischemic versus nonischemic HF, and across eGFR categories). In the entire population, the optimal cutoff value for all-cause death was 18 ng/L. When considering other patient subgroups, the optimal cutoff remained at 18 ng/L in both ischemic and nonischemic subgroups, whereas it
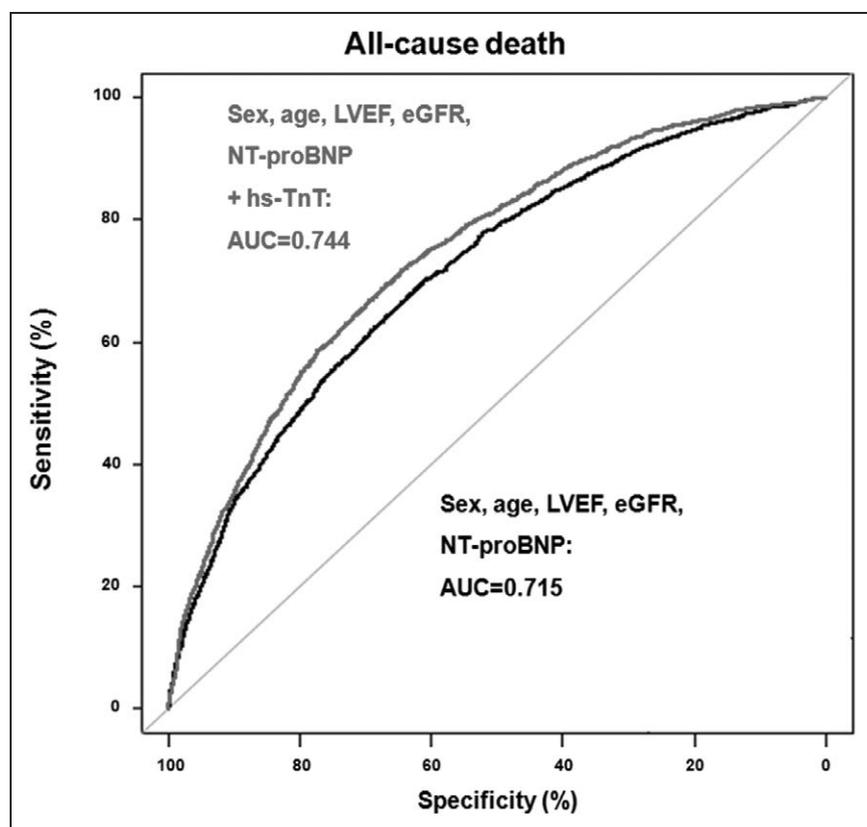
Figure 2. High-sensitivity troponin T (hs-TnT) and refinement in prognostic stratification.
The inclusion of hs-TnT (log$_2$-transformed) significantly (*P*<0.001) improved discrimination when added to a prognostic model including age, sex, left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), and N-terminal fraction of pro-B-type natriuretic peptide (NT-proBNP, log$_2$-transformed). AUC indicates area under the curve.

was slightly higher among men and lower among women. The optimal cutoff values also increased progressively with worse renal function (Table I in the online-only Data Supplement).

The 18 ng/L value was also identified at spline curve analysis as the hs-TnT concentration above which there was a sharp increase in risk of all-cause death (Figure 4). Kaplan-Meier analysis demonstrated that patients with hs-TnT >18 ng/L had significantly shorter time to all-cause death (Figure 5). This cutoff retained independent prognostic value for all 3 end points in the whole population, and in most patient subgroups, as well (Table 3).

DISCUSSION

In a population of 9289 patients from 10 studies and 11 cohorts, hs-TnT emerged as a strong independent predictor of outcome in chronic HF. Over a 29-month median follow-up, hs-TnT predicted all-cause and cardiovascular death, and cardiovascular hospitalization, as well, independent of age, sex, systolic function, renal function, and NT-proBNP. In detail, median HR values were 1.48 for all-cause death, 1.40 for cardiovascular death, and 1.42 for cardiovascular hospitalization (all *P* values <0.001); very similar results were obtained when combining HR values from single studies in Forest plots. The independent prognostic significance of hs-TnT was retained in all population subgroups. A hs-TnT concentration of 18 ng/L was identified as the optimal cutoff

level for the prediction of all-cause death through either receiver operating characteristic or spline analysis. The same threshold resulted as an independent predictor of all 3 end points in men and women, in both ischemic and nonischemic subgroups, and, with a single exception, across all categories of renal dysfunction.

In patients with HF, measurement of circulating biomarkers has emerged as a powerful tool for understanding the mechanism of disease and for patient selection for clinical trials. On a clinical level, biomarker assessment can assist the clinician in diagnosis and risk stratification. The use of BNP and NT-proBNP for such applications is now widespread.[3,4] Our results demonstrate a prognostic role of hs-TnT levels, which is additive to other established risk markers commonly evaluated in the outpatient setting, including NT-proBNP. These results provide a confirmation of the findings previously reported on the Val-HeFT cohort by Latini et al.[36] In our analysis, each doubling of hs-TnT increased the risk of all-cause death by 48%, cardiovascular death by 40%, and cardiovascular hospitalization by 42%, regardless of the other variables. It is also worth considering that, in comparison with other emerging assays with prognostic relevance in chronic HF, such as sST2,[37] the hs-TnT assay has the great advantage of automation and wide availability.[6,38]

The information from measuring hs-TnT seems incremental to other clinical and biohumoral characteristics, as confirmed also by the lack of strong predictors of hs-TnT concentrations. For example, hs-TnT and BNP
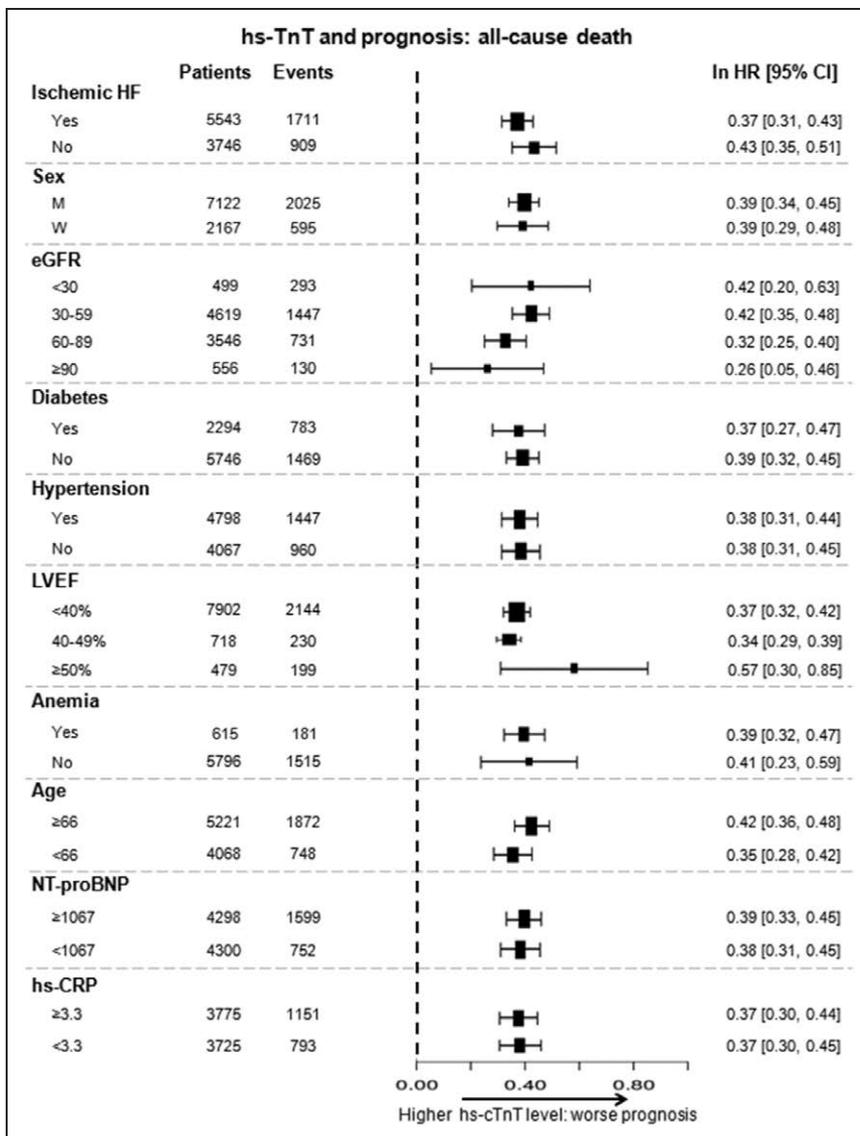
Figure 3. High-sensitivity troponin T (hs-TnT) for the prediction of all-cause death: subgroup analysis. The prognostic value of Hs-TnT ($\log_2$-transformed) is considered in several patient subgroups, after adjustment for age, sex, heart failure (HF) etiology, left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), and $\log_2$-transformed N-terminal fraction of pro-B-type natriuretic peptide (NT-proBNP). As a cut point for age (expressed in years), mean value is considered, whereas median values are reported for NT-proBNP (ng/L), and C-reactive protein (CRP; mg/L). eGFR is expressed as $\text{mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$. All *P* values are <0.001, except for eGFR ≥90 mL/min/1.73 m². CI indicates confidence interval; HR, hazard ratio; and hs-cTNT, high-sensitivity cardiac troponin T.

concentrations likely reflect complementary biological information, namely the severity of ongoing myocardial damage and hemodynamic overload, respectively, which are related to yet different from pathophysiological phenomena.[2]

The striking consistency of results irrespective of patient and disease characteristics has important consequences, implying no need to vary the measurement of hs-TnT and interpretation of results depending on patients subgroups. The finding that prognostic relevance of hs-TnT is independent from HF etiology confirms that ischemic heart disease is not a necessary prerequisite for hs-Tn release in HF, and suggests that the severity of ongoing myocardial damage is predictive of prognosis by itself, regardless of the underlying pathogenesis. In addition, the independent prognostic significance of hs-TnT across categories of eGFR is noteworthy, given the potential for abnormal renal function to influence the concentration of this marker.[39] In other words, hs-TnT tended to increase in parallel with declining renal function, reflecting impaired clearance; nonetheless, higher hs-TnT levels remained predictive of worse prognosis within each eGFR range.

With regard to the proposed cutoff for all-cause death, a 18 ng/L value is quite close to the upper reference limit among healthy subjects (ie, 14 ng/L), and optimal cutoffs for other end points were even lower (16 ng/L for cardiovascular death, and 15 ng/L for cardiovascular hospitalization). These findings point to the prognostic relevance of even low-grade, sustained myocardial damage, reflecting active processes, which on the long term may culminate in adverse ventricular remodeling and life-threatening arrhythmias.[40] The same conclusion applies to the general population, as recently reviewed.[41] For simplicity, a single cutoff (18 ng/L) should probably be considered in clinical practice for risk stratification, especially because the same cutoff holds independent prognostic significance in subgroups identified by patient sex, HF etiology, and categories of renal function. It is clear that dedicated studies should establish whether
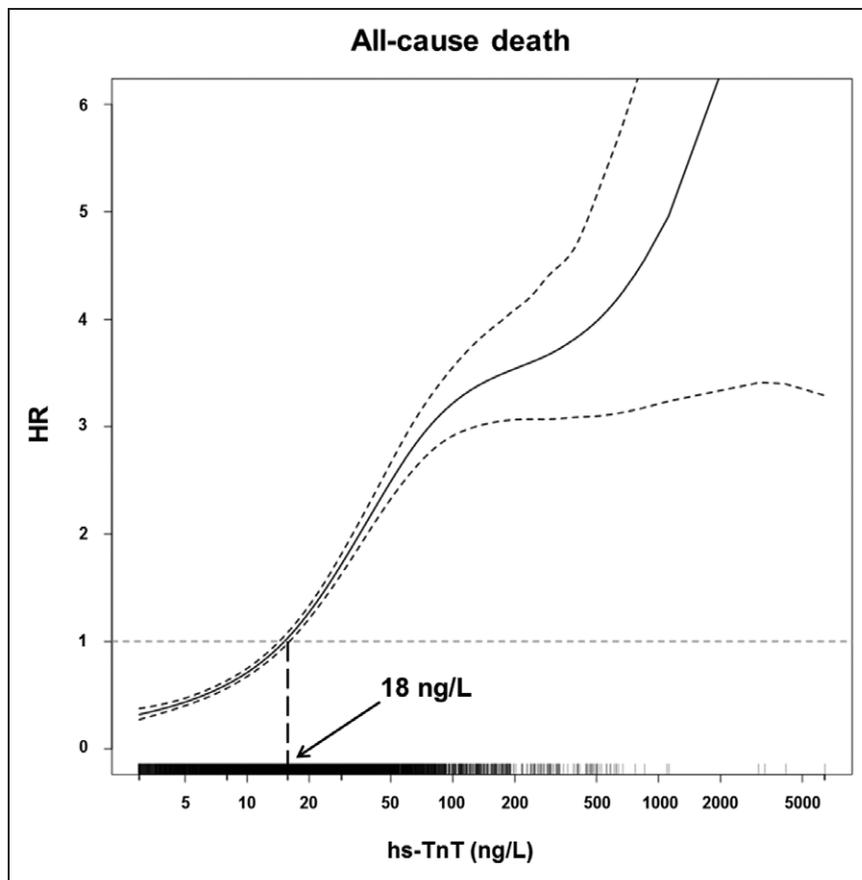
Figure 4. High-sensitivity troponin T (hs-TnT) levels and survival. The spline curve, computed after log-transformation of hs-TnT values, displays the progressive increase in risk of all-cause death with increasing hs-TnT in the whole population. The 18 ng/L cutoff corresponds to the inflection point of the curve, ie, the concentration above which the slope of the curve becomes steeper. On the y axis, hazard ratios relative to the risk above versus below the hs-TnT cutoff are reported. As in all spline curves, hazard ratio (HR) values >1 do not point out a protective role for hs-TnT values higher than the inflection point, and HR <1 to a deleterious effect for lower hs-TnT values.

patient management guided by the same cutoff confers a prognostic benefit and is cost-effective.

The present meta-analysis is the first to assess the prognostic role of hs-TnT through an IPD approach. This was made possible by the active participation of all primary investigators of almost all the individual studies published on the topic, including IPD from large cohorts.[19,20] How-ever, several limitations need to be acknowledged. First, data from 5 studies could not be retrieved.[25–29] It is noteworthy that all excluded studies enrolled relatively small cohorts (patient numbers: 192,[25] 149,[26] 209,[27] 258,[28] and 504[29]) from single centers. Second, the variables included in the prognostic model were selected among those available from the majority of studies. It is noteworthy

Figure 5. High-sensitivity troponin T (hs-TnT) cutoff and survival.
Kaplan-Meier analysis considering the entire study population (**Left**), the ischemic (**Middle**), and nonischemic subgroups (**Right**). FU indicates follow-up; and HF heart failure.

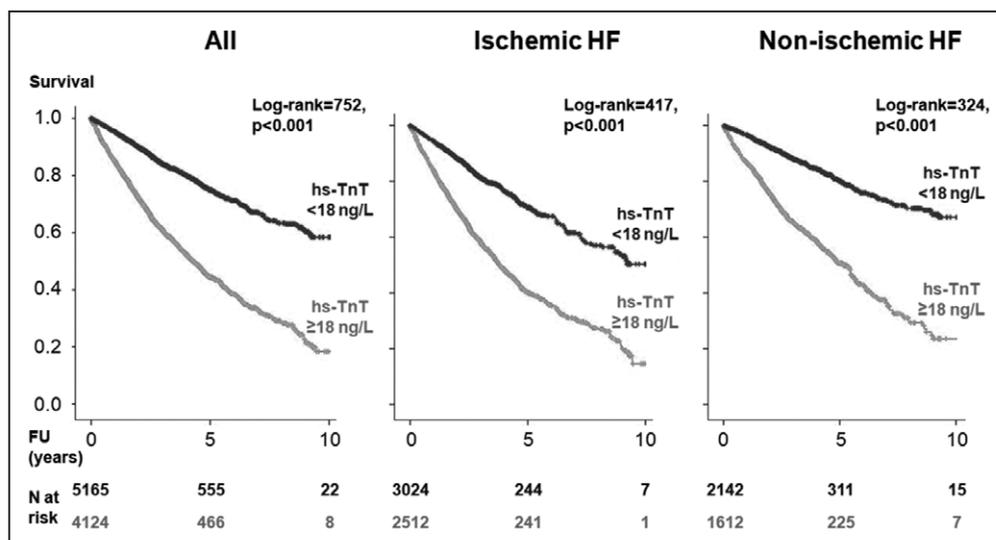**Table 3. Prognostic Value of the High-Sensitivity Troponin T (hs-TnT) Cutoff (18 ng/L)**

	All-Cause Death								
	All (n=9289)	Men (n=7122)	Women (n=2167)	Ischemic (n=5543)	Nonischemic (n=3746)	eGFR <30 (n=496)	eGFR 30–59 (n=4535)	eGFR 60–89 (n=3615)	eGFR ≥90 (n=574)
HR	2.28	2.32	2.19	2.18	2.55	1.99	2.26	2.10	1.86
95% CI	2.03–2.57	2.02–2.65	1.70–2.82	1.88–2.53	2.08–3.12	1.04–3.84	1.92–2.66	1.72–2.56	1.06–3.26
	Cardiovascular Death								
	All (n=7553)	M (n=6500)	W (n=1943)	Ischemic (n=5100)	Nonischemic (n=3343)	eGFR <30 (n=452)	eGFR 30–59 (n=4249)	eGFR 60–89 (n=3232)	eGFR ≥90 (n=445)
HR	2.21	2.23	2.08	2.16	2.30	1.41	2.06	2.02	2.62
95% CI	1.92–2.54	1.91–2.61	1.54–2.81	1.83–2.56	1.81–2.94	0.69–2.86	1.71–2.48	1.59–2.56	1.22–5.63
	Cardiovascular Hospitalization								
	All (n=7382)	M (n=6349)	W (n=1819)	Ischemic (n=5073)	Nonischemic (n=3094)	eGFR <30 (n=411)	eGFR 30–59 (n=4120)	eGFR 60–89 (n=3185)	eGFR ≥90 (n=387)
HR	2.33	2.28	2.47	2.27	2.44	1.85	2.08	1.86	1.80
95% CI	2.07–2.63	1.99–2.61	1.92–3.18	1.96–2.63	2.00–2.98	0.95–3.59	1.77–2.46	1.53–2.27	1.02–3.18

Hazard ratio (HR) and 95% confidence interval (CI) values were calculated after adjustment for age, sex, heart failure (HF) etiology, left ventricular ejection fraction, estimated glomerular filtration rate (eGFR), and N-terminal fraction of pro-B-type natriuretic peptide (log$_2$-transformed). eGFR is expressed as mL·min^{-1}·1.73 m^{-2}. All P values were <0.001, with the exception of all-cause death and eGFR <30 mL·min^{-1}·1.73 m^{-2} (P=0.039) or ≥90 mL·min^{-1}·1.73 m^{-2} (P=0.031), cardiovascular death and eGFR <30 mL·min^{-1}·1.73 m^{-2} (P=0.345) or ≥90 mL·min^{-1}·1.73 m^{-2} (P=0.017), cardiovascular hospitalization and eGFR <30 mL·min^{-1}·1.73 m^{-2} (P=0.071) or ≥90 mL·min^{-1}·1.73 m^{-2} (P=0.041).

that these variables are commonly available in the out-patient setting, and all are recognized markers of risk. Third, a high degree of heterogeneity was found among studies, possibly affecting our conclusions; nonetheless, the results from all the largest cohorts were consistent and seemed to provide robust evidence of an independent prognostic value of hs-TnT. Fourth, we focused on the prognostic relevance of point hs-TnT measurement, without considering the impact of serial testing, which may[20] or may not[18] add substantially to risk prediction. Fifth, a malcalibration or low-end shift issue affected the Roche hs-TnT lots used clinically in 2010 to 2012 world-wide, possibly affecting the reliability of the measured TnT concentrations.[42] Unfortunately, it was not possible to establish which patients had been evaluated using the 2010-to-2012 lots. Nevertheless, assay malcalibration was certainly not an issue for original studies published before 2010. This was the case for the Val-HeFT (2001),[30] GISSI-HF (2008),[31] CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) (2007),[43] and TIME-CHF (Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure) (2009),[44] accounting for a total patient number of 7090 (76%). Furthermore, a dedicated analysis of the 2010-to-2012 lots found that deviations nearly exclusively affected hs-TnT levels below the 99th percentile (14 ng/L), with a very limited clinical impact (only 8.5% of patients triaged for myocardial infarction were at risk for misdiagnosis).[42] We can then estimate that the 2010-to-2012 low-end shift had limited impact (if any) on our results. Finally, dedicated studies should establish whether a hs-TnT–guided approach to therapy decision making and follow-up results in improved patient prognosis.

In conclusion, in our IPD meta-analysis, hs-TnT levels emerged as independent predictor of all-cause and cardiovascular mortality, and hospitalization for cardiovascular causes, as well, over a long follow-up period. The prognostic value of hs-TnT was unaffected by HF etiology (ischemic versus nonischemic) or renal function, and a 18 ng/L hs-TnT cut point provided independent prognostic value. These results provide conceptual support to the widespread use of hs-TnT in addition to BNPs for risk stratification in stable chronic HF.

AUTHORS

Alberto Aimo, MD; James L. Januzzi Jr, MD; Giuseppe Vergaro, MD, PhD; Andrea Ripoli, EngD; Roberto Latini, MD; Serge Masson, PhD; Michela Magnoli, BSc; Inder S. Anand, MD, PhD; Jay N. Cohn, MD; Luigi Tavazzi, MD; Gianni Tognoni, MD; Jørgen Gravning, MD, PhD; Thor Ueland, PhD; Ståle H. Nymo, MD; Hans-Peter Brunner-La Rocca, MD; Antoni Bayes Genis, MD, PhD; Josep Lupón, MD; Rudolf A. de Boer, MD; Akiomi Yoshihisa, MD, PhD; Yasuchika Takeishi, MD; Michael Egstrup, MD, PhD; Ida Gustafsson, MD, PhD; Hanna K. Gaggin, MD, MPH; Kai M. Eggers, MD, PhD; Kurt Huber, MD; Ioannis Tentzeris, MD; Wai H.W. Tang, MD; Justin Grodin, BSc; Claudio Passino, MD; Michele Emdin, MD, PhD

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AFFILIATIONS

Scuola Superiore Sant'Anna, Pisa, Italy (A.A., G.V., C.P., M.E.). Massachusetts General Hospital and Harvard Clinical Research Institute, Boston (J.L.J., H.K.G.). Fondazione Toscana G. Monasterio, Pisa, Italy (G.V., A.R., C.P., M.E.). Department of Cardiovascular Research IRCCS - Istituto di Ricerche Farmacologiche - "Mario Negri," Milano, Italy (R.L., S.M., M.M., G.T.). Division of Cardiovascular Medicine, University of Minnesota, Minneapolis (I.S.A., J.N.C.). Department of Cardiology, VA Medical Centre, Minneapolis, MN (I.S.A.). GVM Hospitals of Care and Research, E.S. Health Science Foundation, Cotignola, Italy (L.T.). Department of Cardiology, Oslo University Hospital, Ullevål, Norway (J.G.). Centre for Heart Failure Research, University of Oslo, Norway (J.G.). Research Institute of Internal Medicine, Oslo University Hospital, Rikshospitalet, Norway (T.U., S.H.N.). Faculty of Medicine, University of Oslo, Norway (T.U.). K. G. Jebsen Thrombosis Research and Expertise Centre, University of Tromsø, Norway (T.U.). Department of Cardiology, Maastricht University Medical Centre, The Netherlands (H.-P.G.-L.R.). Hospital Universitari Germans Trias i Pujol, Badalona (Barcelona), Spain (A.B.G., J.L.). University Medical Centre Groningen, The Netherlands (R.A.d.B.). Department of Cardiovascular Medicine, Fukushima Medical University, Japan (A.Y., Y.T.). Department of Cardiology, Copenhagen University Hospital Rigshospitalet, Denmark (M.E., I.G.). Department of Medical Sciences, Cardiology, Uppsala University, Sweden (K.M.E.). Faculty of Internal Medicine, Wilhelminenspital and Sigmund Freud University, Medical School, Vienna, Austria (K.H., I.T.). Heart and Vascular Institute, Cleveland Clinic, OH (W.H.W.T.). Department of Internal Medicine, Division of Cardiology, University of Texas Southwestern Medical Center, Dallas (J.G.).

FOOTNOTES

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Circulation

Prognostic Value of High-Sensitivity Troponin T in Chronic Heart Failure: An Individual Patient Data Meta-Analysis

Alberto Aimo, James L. Januzzi, Jr, Giuseppe Vergaro, Andrea Ripoli, Roberto Latini, Serge Masson, Michela Magnoli, Inder S. Anand, Jay N. Cohn, Luigi Tavazzi, Gianni Tognoni, Jørgen Gravning, Thor Ueland, Ståle H. Nymo, Hans-Peter Brunner-La Rocca, Antoni Bayes Genis, Josep Lupón, Rudolf A. de Boer, Akiomi Yoshihisa, Yasuchika Takeishi, Michael Egstrup, Ida Gustafsson, Hanna K. Gaggin, Kai M. Eggers, Kurt Huber, Ioannis Tentzeris, Wai H.W. Tang, Justin Grodin, Claudio Passino and Michele Emdin

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Supplemental material

PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6,7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7,8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8,9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12,13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-15

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

Supplemental Table 1. Definition of high-sensitivity troponin T (hs-TnT) cut-offs

	All-cause death								
	All (n=9289)	**M** (n=7122)	**W** (n=2167)	**Ischemic HF** (n=5543)	**Non-ischemic HF** (n=3746)	**eGFR <30 mL/min/ 1.73 m^2** (n=496)	**eGFR 30-59 mL/min/ 1.73 m^2** (n=4535)	**eGFR 60-89 mL/min/ 1.73 m^2** (n=3615)	**eGFR ≥90 mL/min/ 1.73 m^2** (n=574)
AUC	0.723	0.720	0.735	0.719	0.730	0.660	0.708	0.699	0.683
Optimal cut-off (ng/L)	18	23	17	18	18	40	22	15	13
Sensitivity (%)	70	59	60	69	70	59	62	61	66
Specificity (%)	64	74	69	64	65	65	68	68	64
	CV death								
	All (n=8443)	**M** (n=6500)	**W** (n=1943)	**Ischemic HF** (n=5100)	**Non-ischemic HF** (n=3343)	**eGFR <30 mL/min/ 1.73 m^2** (n=452)	**eGFR 30-59 mL/min/ 1.73 m^2** (n=4249)	**eGFR 60-89 mL/min/ 1.73 m^2** (n=3232)	**eGFR ≥90 mL/min/ 1.73 m^2** (n=445)
AUC	0.711	0.708	0.724	0.708	0.718	0.605	0.699	0.681	0.707
Optimal cut-off (ng/L)	16	22	17	17	17	41	22	15	13
Sensitivity (%)	73	60	67	71	74	60	63	61	72
Specificity (%)	59	71	65	60	59	58	66	66	61

	CV hospitalization								
	All **(n=8168)**	**M** **(n=6349)**	**W** **(n=1819)**	**Ischemic** **HF** **(n=5073)**	**Non-** **ischemic** **HF** **(n=3095)**	**eGFR** **<30 mL/min/** **1.73 m^2** **(n=411)**	**eGFR** **30-59 mL/min/** **1.73 m^2** **(n=4120)**	**eGFR** **60-89 mL/min/** **1.73 m^2** **(n=3185)**	**eGFR** **≥90 mL/min/** **1.73 m^2** **(n=387)**
AUC	0.678	0.674	0.696	0.670	0.690	0.572	0.670	0.671	0.660
Optimal cut-off (ng/L)	15	22	16	13	15	38	22	15	11
Sensitivity (%)	71	53	60	75	72	54	58	55	55
Specificity (%)	57	71	69	51	58	55	67	70	63

Unadjusted analyses considering $\log_2$(hs-TnT) values were performed. AUC, area under the curve; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; M, men; W, women.

hs-TnT and prognosis

All-cause death

Alonso 2016		0.44 [0.29, 0.59]
Eggers 2011		0.96 [-0.40, 2.32]
Egstrup 2012		0.40 [0.16, 0.64]
Gravning 2013		0.38 [0.24, 0.52]
Masson 2012 (Val-HeFT)		0.33 [0.26, 0.40]
Masson 2012 (GISSI-HF)		0.49 [0.32, 0.65]
Sanders-van Wjik 2015		0.24 [0.09, 0.39]
Schroten 2013		0.57 [0.02, 1.12]
Tentzeris 2011		-0.36 [-1.11, 0.38]
Total		0.36 [0.30, 0.42]
n=8695		p<0.001

-2.00   0.00 1.00 2.00 3.00

RE model;
ln-transformed HR values

Higher hs-cTnT level: worse prognosis

CV death

Alonso 2016		0.28 [0.13, 0.43]
Gravning 2013		0.31 [0.16, 0.47]
Masson 2012 (Val-HeFT)		0.35 [0.27, 0.42]
Masson 2012 (GISSI-HF)		0.48 [0.29, 0.67]
Sanders-van Wjik 2015		0.24 [0.08, 0.39]
Total		0.33 [0.28, 0.39]
n=7893		p<0.001

0.00   0.20   0.40   0.60   0.80

RE model;
ln-transformed HR values

Higher hs-cTnT level: worse prognosis

Supplemental Figure 1. High-sensitivity troponin T (hs-TnT) for the prediction of all-cause and cardiovascular (CV) death

Forest plot analysis exploring the prognostic value of hs-TnT ($\log_2$-transformed) after adjustment for age, sex, heart failure etiology, left ventricular ejection fraction, estimated glomerular filtration rate, and $\log_2$-transformed N-terminal fraction of pro-B-type natriuretic peptide. Hazard ratio (HR)

values are ln-transformed. The HR could not be calculated for the Gaggin study[1], because patients experiencing all-cause death (n=14) did not have data available for all variables considered in the adjustment process. RE, random-effects model.

hs-TnT and prognosis: CV death

	Patients	Events		In HR [95% CI]
Ischaemic HF				
Yes	5100	1166		0.31 [0.25, 0.37]
No	3343	559		0.39 [0.30, 0.48]
Sex				
M	6500	1362		0.34 [0.28, 0.40]
W	1943	363		0.32 [0.21, 0.42]
eGFR				
<30	455	187		0.27 [0.07, 0.47]
30-59	4333	1019		0.37 [0.30, 0.44]
60-89	3163	451		0.29 [0.21, 0.38]
≥90	427	56		0.31 [0.05, 0.58]
Diabetes				
Yes	2101	525		0.35 [0.25, 0.46]
No	5097	901		0.33 [0.26, 0.40]
Hypertension				
Yes	4570	1006		0.35 [0.27, 0.42]
No	3873	719		0.33 [0.26, 0.41]
LVEF				
<40%	7400	1498		0.33 [0.28, 0.39]
40-49%	551	105		0.24 [0.03, 0.46]
≥50%	456	112		0.46 [0.17, 0.75]
Anemia				
Yes	614	138		0.37 [0.30, 0.43]
No	5753	1123		0.29 [0.11, 0.47]
Age				
≥66	4756	1190		0.36 [0.29, 0.43]
<66	3698	535		0.31 [0.23, 0.39]
NT-proBNP				
≥1067	3840	1064		0.35 [0.28, 0.42]
<1067	3938	493		0.33 [0.25, 0.41]
hs-CRP				
≥3.3	3753	873		0.31 [0.24, 0.38]
<3.3	3706	593		0.36 [0.28, 0.45]

0.00   0.40   0.80

Higher hs-cTnT level: worse prognosis
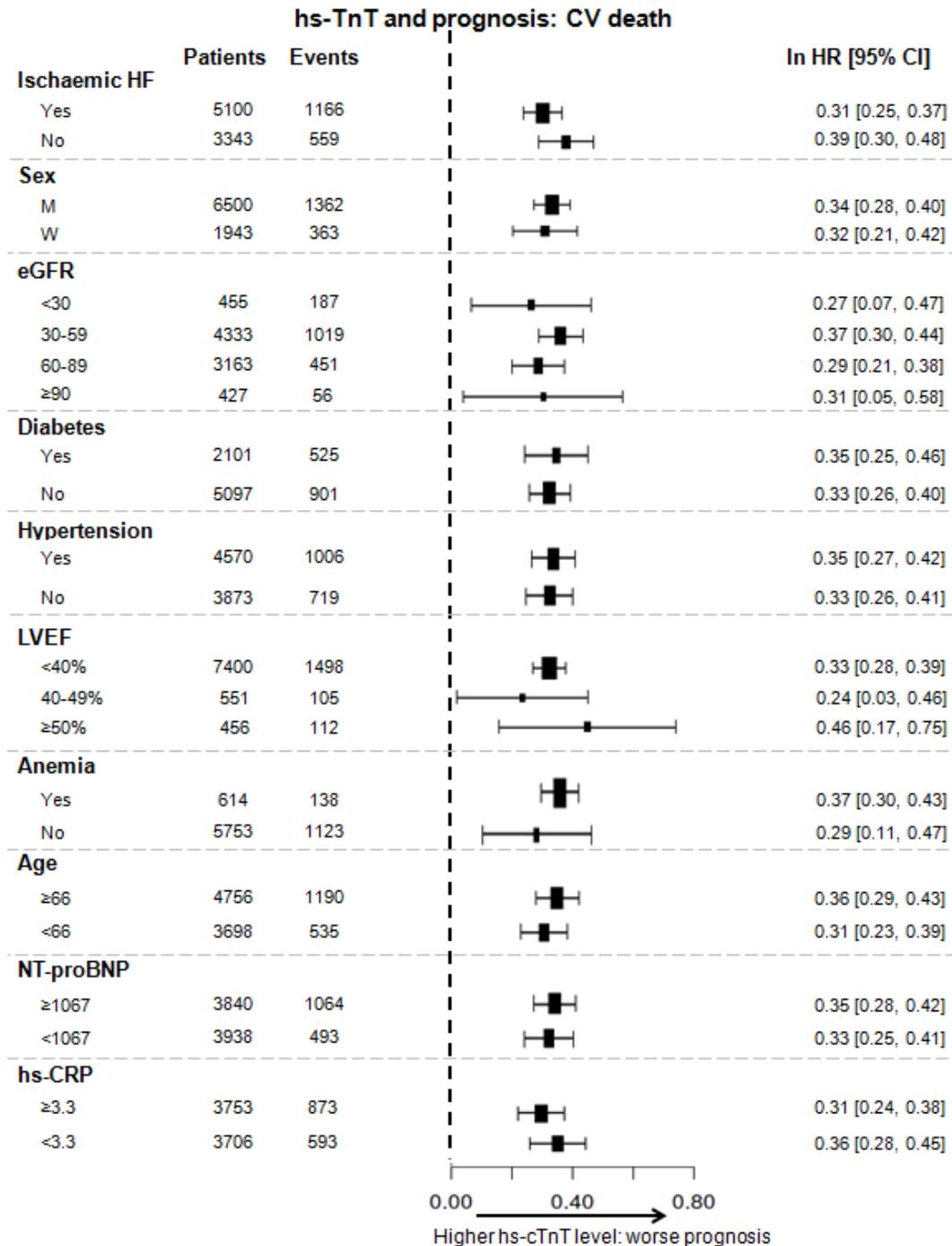
Supplemental Figure 2. High-sensitivity troponin T (hs-TnT) for the prediction of cardiovascular (CV) death: subgroup analysis

The prognostic value of hs-TnT ($\log_2$-transformed) is considered in several patient subgroups, after adjustment for age, sex, heart failure (HF) etiology, left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), and $\log_2$-transformed N-terminal fraction of pro-B-type

natriuretic peptide (NT-proBNP). As a cut-point for age (expressed in years), mean value is considered, while median values are reported for NT-proBNP (ng/L), and C-reactive protein (CRP; mg/L). eGFR is expressed as ml/min/1.73 m^2. All p values are <0.001 except for eGFR <30 mL/min/1.73 m^2 (p=0.009) or ≥90 mL/min/1.73 m^2 (p=0.024), LVEF 40-49% (p=0.048), LVEF ≥50% (p=0.003), and absence of anemia (p=0.002).

hs-TnT and prognosis: CV hospitalization

	Patients	Events		ln HR [95% CI]
Ischaemic HF				
Yes	5073	1621		0.32 [0.27, 0.38]
No	3094	754		0.40 [0.32, 0.47]
Sex				
M	6349	1813		0.34 [0.29, 0.40]
W	1819	562		0.37 [0.28, 0.46]
eGFR				
<30	414	200		0.16 [-0.03, 0.35]
30-59	4204	1298		0.37 [0.31, 0.44]
60-89	3118	755		0.34 [0.26, 0.41]
≥90	367	100		0.27 [0.08, 0.46]
Diabetes				
Yes	1928	662		0.35 [0.26, 0.45]
No	4992	1190		0.39 [0.32, 0.45]
Hypertension				
Yes	4324	1434		0.31 [0.25, 0.37]
No	3837	940		0.39 [0.32, 0.45]
LVEF				
<40%	7293	2051		0.34 [0.29, 0.39]
40-49%	510	185		0.37 [0.19, 0.56]
≥50%	282	131		0.40 [0.14, 0.66]
Anemia				
Yes	615	227		0.40 [0.34, 0.45]
No	5796	1487		0.43 [0.27, 0.60]
Age				
≥66	4577	1602		0.34 [0.28, 0.40]
<66	3591	773		0.36 [0.30, 0.43]
NT-proBNP				
≥1067	3888	1361		0.32 [0.25, 0.38]
<1067	4056	916		0.42 [0.35, 0.48]
hs-CRP				
≥3.3	3713	1214		0.34 [0.27, 0.40]
<3.3	3675	942		0.38 [0.31, 0.45]

-0.20   0.20 0.40 0.60 0.80

Higher hs-TnT level: worse prognosis

Supplemental Figure 3. High-sensitivity troponin T (hs-TnT) for the prediction of cardiovascular (CV) hospitalization: subgroup analysis

The prognostic value of hs-TnT (log$_2$-transformed) is considered in several patient subgroups, after adjustment for age, sex, heart failure (HF) etiology, left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), and log$_2$-transformed N-terminal fraction of pro-B-type
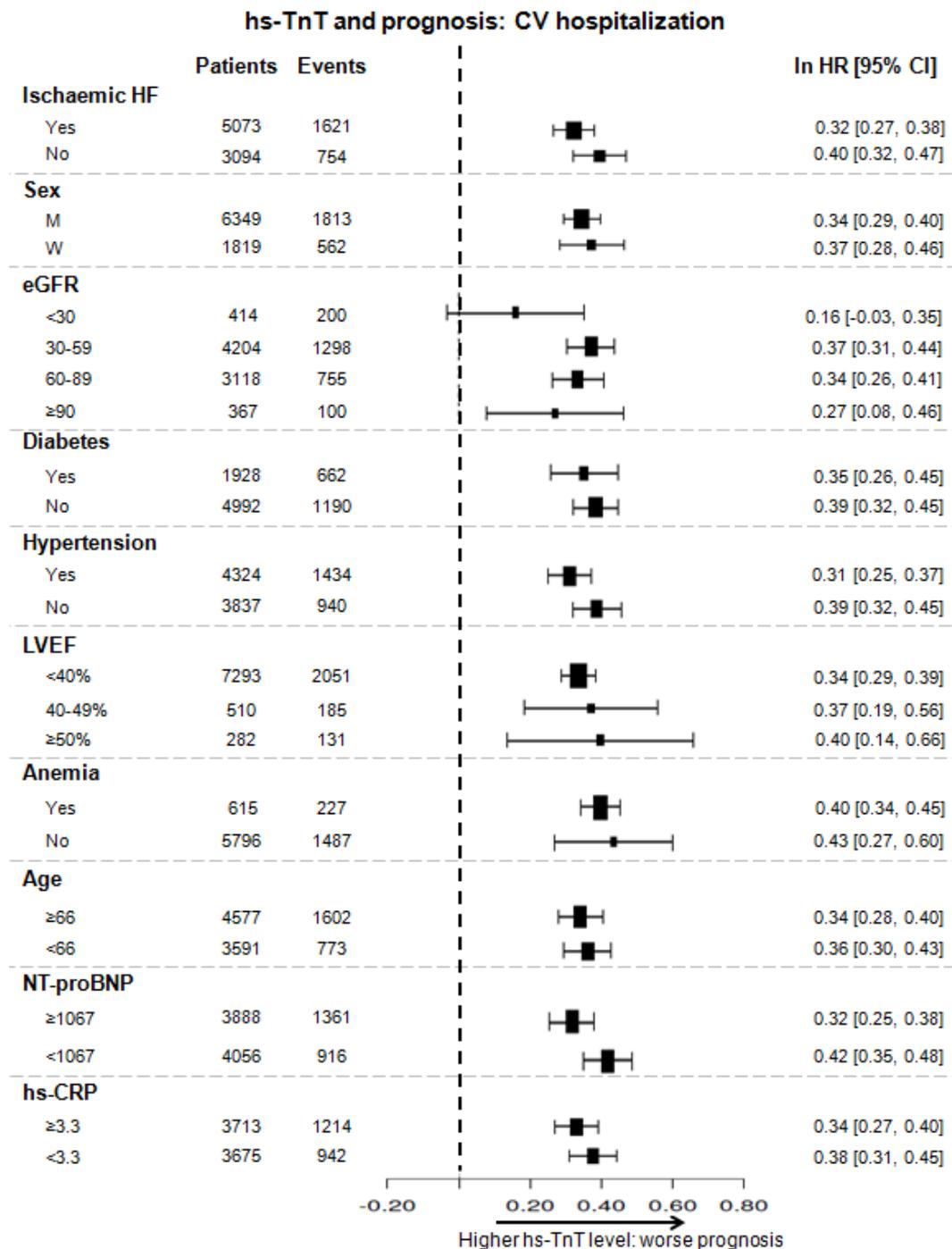
natriuretic peptide (NT-proBNP). As a cut-point for age (expressed in years), mean value is considered, while median values are reported for NT-proBNP (ng/L), and C-reactive protein (CRP; mg/L). eGFR is expressed as ml/min/1.73 m^2. All p values are <0.001 except for eGFR <30 mL/min/1.73 m^2 (p=0.110) or ≥90 mL/min/1.73 m^2 (p=0.007), and LVEF ≥50% (p=0.003).

Supplemental material references

1. Gaggin HK, Szymonifka J, Bhardwaj A, Belcher A, De Berardinis B, Motiwala S, Wang TJ, Januzzi JL Jr. Head-to-head comparison of serial soluble ST2, growth differentiation factor-15, and highly-sensitive troponin T measurements in patients with chronic heart failure. *J Am Coll Cardiol HF*. 2014;2:65-72.

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