High-sensitivity troponin T, NT-proBNP and glomerular filtration rate: A multimarker strategy for risk stratification in chronic heart failure

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ABSTRACT

Background: In a recent individual patient data meta-analysis, high-sensitivity troponin T (hs-TnT) emerged as robust predictor of prognosis in stable chronic heart failure (HF). In the same population, we compared the relative predictive performances of hs-TnT, N-terminal fraction of pro-B-type natriuretic peptide (NT-proBNP), hs-C-reactive protein (hs-CRP), and estimated glomerular filtration rate (eGFR) for prognosis.
Methods and results: 9289 patients (66 ± 12 years, 77% men, 85% LVEF <40%, 60% ischemic HF) were evaluated over a 2.4-year median follow-up. Median eGFR was 58 mL/min/1.73 m^2 (interquartile interval 46–70; n = 9220), hs-TnT 16 ng/L (8–20; n = 9289), NT-proBNP 1067 ng/L (433–2470; n = 8845), and hs-CRP 3.3 mg/L (1.4–7.8; n = 7083). In a model including all 3 biomarkers, only hs-TnT and NT-proBNP were independent predictors of all-cause and cardiovascular mortality and cardiovascular hospitalization. hs-TnT was a stronger predictor than NT-proBNP: for example, the risk for all-cause death increased by 54% per doubling of hs-TnT vs. 24% per doubling of NT-proBNP. eGFR showed independent prognostic value from both hs-TnT and NT-proBNP. The best hs-TnT and NT-proBNP cut-offs for the prediction of all-cause death increased progressively with declining renal function (eGFR ≥ 90: hs-TnT 13 ng/L and NT-proBNP 825 ng/L; eGFR < 30: hs-TnT 40 ng/L and NT-proBNP 4608 ng/L). Patient categorization according to these cut-offs effectively stratified patient prognosis across all eGFR classes.
Conclusions: hs-TnT conveys independent prognostic information from NT-proBNP, while hs-CRP does not.

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Concomitant assessment of eGFR may further refine risk stratification. Patient classification according to hs-TnT and NT-proBNP cut-offs specific for the eGFR classes holds prognostic significance.

1. Introduction

Heart failure (HF) is a highly prevalent disease condition, and a leading cause of morbidity and mortality worldwide [1]. Accurate risk prediction allows to tailor HF treatment and follow-up strategy in the individual patient, possibly resulting in better quality of life and long-term prognosis [2]. Many predictors of death and/or HF-related hospitalization have been identified, although their applicability in common clinical practice is often limited, and precise risk stratification in HF remains challenging [2].

Cardiac biomarkers are gaining increasing recognition as tools for risk prediction in HF [3]. In particular, the American Heart Association/American College of Cardiology Foundation has issued a class I, level of evidence A recommendation for the assessment of B-type natriuretic peptide (BNP) or the N-terminal fraction of pro-BNP (NT-proBNP) for prognostic stratification in chronic HF [4]. Furthermore, troponin elevation is a frequent finding in chronic HF, and has been established in several studies as a predictor of adverse outcome [5]. In a recent meta-analysis that included individual patient data (IPD) from 9289 individuals derived out of 11 cohorts, we confirmed strong prognostic value of high-sensitivity troponin T (hs-TnT) for all-cause death, cardiovascular death, and cardiovascular hospitalization, additive to established risk markers (sex, age, ischemic vs. non-ischemic etiology, left ventricular ejection fraction - LVEF, estimated glomerular filtration rate - eGFR, and also NT-proBNP) [6].

The mechanisms leading to the production and release of natriuretic peptides in HF include hemodynamic overload and neurohormonal activation, while troponin elevation is driven by ongoing cardiomyocyte injury and necrosis [7]. Furthermore, chronic kidney disease is a common comorbidity in chronic HF, with an established prognostic value in HF [11,12], and its presence is easily detectable by the estimated glomerular filtration rate (eGFR). Renal dysfunction may reduce peptide clearing in patients with HF, contributing to an elevation both of natriuretic peptides and troponin T. This may be an additional reason to investigate the independence of eGFR regarding prediction of outcome, as in clinical practice these markers are almost always measured together. Additionally, other biomarkers could contribute to refine risk stratification: in particular, subclinical myocardial inflammation is frequently observed in HF; in this regard concentrations of hs-C-reactive protein (hs-CRP) may be prognostic in chronic HF [8–10].

We thus felt it worthwhile to compare the prognostic performances of NT-proBNP, hs-TnT, hs-CRP, and eGFR, and to evaluate a multi-biomarker strategy for risk stratification in chronic HF in the largest IPD database currently available.

2. Methods

2.1. Search study, study selection

The design and main results of our IPD meta-analysis on hs-TnT in CHF have been reported in detail [6]. Briefly, in April 2017, two authors (AA and GV) independently searched 4 databases (Medline, EMBASE, Cochrane Library, and Scopus), using the following search terms: "troponin" AND "heart failure" OR "cardiac failure" OR "cardiac dysfunction" OR "cardiac insufficiency" OR "left ventricular dysfunction". The inclusion criteria were: English language; patients aged ≥18 years and diagnosed with HF; reported enrolment of outpatients or patients undergoing elective admission; reported use of a hs-TnT and/or I assay; information on patient prognosis; authors' availability to provide IPD data. These last corresponded to as many as possible of the following variables: age, sex, ethnic group, body-mass index, comorbidities (hypertension, atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease), plasma hemoglobin, HF etiology (ischemic vs. non-ischemic), LVEF, hs-TnT and/or I, NPs, serum creatinine, hs-CRP, follow-up duration, and outcome measures (all-cause death, cardiovascular death, and hospitalization for cardiovascular cause) [6].

Ten studies met all these requirements, reporting data on 11 cohorts, with a total patient number of 9289 [13–22]. Since hs-TnI values were available for a small minority of patients [8], only hs-TnT was considered. Five other studies, including a total patient number of 1312, could not be included because of lack of IPD [10,23–26].

2.2. Statistical analysis

For the present analysis, the IBM SPSS Statistics (version 22, 2013) and R statistical software (http://www.r-project.org/, version 3.4.0) were used. Normal distribution was assessed through the Kolmogorov-Smirnov test; variables with normal distribution were presented as mean ± standard deviation, while those with non-normal distribution as median and interquartile interval. Mean differences among groups were evaluated through the unpaired Student t-test for both normally and non-normally distributed variables. Pearson's product moment correlation coefficient (r) was calculated as a measure of linear association between normally distributed variables.

For all the following analyses, NT-proBNP, hs-TnT, hs-CRP, and eGFR were $\log_2$-transformed to account for non-normal distribution. Pearson's product moment correlation coefficient quantified the strength of correlation between normally distributed variables. Categorical variables were compared by the Chi-square test with Yates correction. The log-rank test (Mantel-Cox) was used to compare survival times on Kaplan-Meier curves. The optimal cut-offs for ROC curves were established by Youden's J statistic. Predictors of outcome were searched through univariate and multivariate Cox regression analyses; the assumptions of linearity and proportionality were verified. The Fine-Gray model was used to account for mutually exclusive endpoints; non-cardiovascular death was considered as competing risk for cardiovascular death, and all-cause death as competing risk for cardiovascular hospitalization [27]. In multivariate analyses, hs-TnT, NT-proBNP, and hs-CRP or eGFR were evaluated. Multicollinearity (i.e. interference among variables included into a multivariable prognostic model) was assessed by calculating the Variance Inflation Factor (VIF). p values < 0.05 were considered significant.

3. Results

3.1. Patient population

The main characteristics of the 9289 patients, divided into their cohorts, are reported in Table 1. Overall, patients were aged 66 ± 12 years, and were more often males (n = 7122, 77%). The majority of patients had HF with reduced ejection fraction (LVEF <40%: n = 7902, 85%; LVEF 40–49%: n = 718, 8%; LVEF ≥50%: n = 479, 5%). All patients had available data on HF etiology; ischemic HF was more common (5543 patients, 60%). GFR, estimated from serum creatinine through the chronic kidney disease epidemiology collaboration (CKD-EPI) equation [28], was available for 9220 patients (99%); its median value was 58 mL/min/1.73 m^2 (interquartile interval 46–70); patients on dialysis were not included in the original studies. 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 (8487 patients, 1725 events, 20%), and data on cardiovascular hospitalization for other 6 (8168 patients, 2375 events, 29%) (Table 1). At 1 year, 888 all-cause deaths (10%), 676 (7%) cardiovascular deaths, and 343 (4%) cardiovascular hospitalizations were recorded; at 5 years, these events were 2423 (26%), 1658 (18%), and 2244 (24%), respectively.

3.2. Circulating biomarker concentrations

NT-proBNP concentrations were available for 8845 patients (95%; upper reference value in chronic HF 125 ng/L [2]; median 1067 ng/L, interquartile interval 433–2470 ng/L). All patients had hs-TnT measured (Roche Diagnostics®, Basel, Switzerland; limit of blank 3 ng/L, *limit of detection* 5 ng/L, upper reference value 14 ng/L) [29]. Median value was 16 ng/L, with 8–20 ng/L interquartile interval. Finally, 7083 patients (83%) had hs-CRP data (upper reference value 5 ng/L; median 3.3 mg/L, interquartile interval 1.4–7.8 mg/L).

Table 1

Characteristics of study populations.

Author, year, ref.	Pts, n	Sex, men n (%)	Age (years)	BMI (kg/m²)	Ischemic HF, n (%)	LVEF (%)	NT-proBNP (ng/L)	eGFR (mL/min/1.73 m²)	Hypertension (n, %)	hs-CRP (mg/L)	hs-TnT (ng/L)	ACEi/ARB (%)	BB, (%)	MRA, (%)	All-cause deaths (in 1000 person/years)	CV deaths (in 1000 person/years)	CV hospitalizations (in 1000 person/years)
Alonso, 2016 [13]	803	576 (72)	66 ± 11	n/a	419 (52)	31 (25–40)	1187 (476–2676)	51 (34–69)	304 (38)	3.6 (1.3–8.3)	22.3 (10.7–39.2)	731 (91)	723 (90)	466 (58)	103	55	56
Eggers, 2011 [14]	111	68 (62)	53 ± 13	n/a	22 (20)	32 (24–53)	1198 (618–2475)	63 (49–78)	29 (26)	n/a	6.7 (3.5–17.8)	93 (84)	93 (84)	71 (64)	63	n/a	n/a
Egstrup, 2012 [15]	416	295 (71)	71 ± 11	27 ± 5	258 (62)	30 (25–38)	1008 (419–2385)	64 (51–79)	n/a	n/a	18 (10−32)	275 (66)	183 (44)	n/a	102	n/a	n/a
Gaggin, 2014 [16]	150	127 (84)	65 ± 14	n/a	76 (50)	27 (20–35)	1897 (980–3718)	50 (37–65)	72 (48)	4.2 (1.2–10.1)	17.9 (7.3–37.3)	122 (81)	143 (95)	62 (41)	105	81	n/a
Gravning, 2014 [17]	1245	959 (77)	72 ± 7	n/a	1245 (100)	33 (28–37)	1319 (507–2867)	55 (45–65)	377 (30)	3.6 (1.6–7.6)	13.9 (6.6–25.6)	1133 (91)	959 (77)	461 (37)	119	97	215
Masson, 2012 (Val-HeFT) [18]	4053	3253 (80)	63 ± 11	27 ± 4	2345 (58)	27 (22−33)	902 (378–1990)	58 (48–67)	1698 (42)	3.3 (1.4–7.6)	12.5 (5.9–22.4)	3773 (93)	1463 (36)	215 (5)	101	87	92
Masson, 2012 (GISSI-HF) [18]	1231	991 (81)	67 ± 11	27 ± 4	627 (51)	33 (27–38)	846 (376–1869)	63 (49–77)	554 (45)	2.3 (1.1–5.5)	17.0 (10.3–27.8)	1219 (99)	836 (68)	532 (43)	74	54	233
Nakamura, 2014 [19]	444	282 (64)	67 ± 14	n/a	66 (15)	45 (34–57)	n/a	69 (48–92)	77 (17)	n/a	28 (15–61)	355 (80)	355 (80)	n/a	96	54	n/a
Sanders-van Wijk, 2015 [20]	561	340 (61)	77 ± 8	26 ± 4	297 (53)	32 (25–42)	3822 (1907–6947)	52 (37–66)	144 (26)	7.6 (2.8–18.1)	32.4 (18.6–59.8)	533 (95)	432 (77)	213 (38)	176	133	274
Schroten, 2013 [21]	101	94 (93)	64 ± 10	28 ± 4	73 (72)	35 (29–42)	376 (202–808)	75 (65–85)	35 (35)	n/a	4.4 (3.0–12.4)	101 (100)	97 (97)	29 (29)	43	n/a	26
Tentzeris, 2011 [22]	174	134 (77)	64 ± 12	n/a	67 (38)	32 (27–41)	1655 (671–3515)	71 (54–93)	37 (21)	n/a	18.4 (9.1–26.6)	n/a	n/a	n/a	78	n/a	46

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; hs-CRP, high-sensitivity C-reactive protein; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FU, follow-up; hs-TnT, high-sensitivity troponin T; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; n/a, not available; NT-proBNP; N-terminal fraction of proB-type natriuretic peptide; pt, patient.

3.3. Biomarkers and prognosis

When performing a comparative assessment of the prognostic performance of hs-TnT and other biomarkers, we found first that hs-TnT displayed higher AUC values than NT-proBNP for all 3 endpoints (all p values < 0.001; Fig. 1).

NT-proBNP, hs-TnT and hs-CRP were univariate predictors of outcome, but only NT-proBNP and hs-TnT remained independent predictors in a model including all 3 biomarkers (Supplemental Table 1). hs-TnT emerged as the strongest predictor of the 3 endpoints: for example, the risk for all-cause death increased by 54% per doubling of hs-TnT vs. 24% per doubling of NT-proBNP (Supplemental Table 1). These findings were replicated across patient subgroups, categorized according to sex, age (≥ or <66 years), etiology (ischemic or non-ischemic), LVEF (<40%, 40–49%, ≥50%), and eGFR (<30, 30–59, 60–89, ≥90 mL/min/1.73 m^2) (Supplemental Table 2).

3.4. hs-TnT, NT-proBNP, renal function, and prognosis

In a model including NT-proBNP and hs-TnT, eGFR was independent predictor of both all-cause (HR 0.72 per standard deviation of log eGFR, 95% CI 0.65–0.81; p < 0.001) and cardiovascular death (HR 0.76, 95% CI 0.67–0.86; p < 0.001), but not of cardiovascular hospitalization (HR 0.97, 95% CI 0.87–1.08; p = 0.59). The variables displayed significant correlations (Supplemental Table 3), but multicollinearity was excluded because of VIF = 1.15 (reference value <10) [30].

The best hs-TnT and NT-proBNP cut-offs for the prediction of the 3 endpoints increased with declining renal function (Table 3). At Kaplan-Meier analysis, patient classification according to these cut-offs proved effective in risk stratification across all eGFR categories. At baseline, the majority of patients had both hs-TnT and NT-proBNP either <cut-off or ≥cut-off; these groups had the longest and the shortest survival, respectively (Fig. 2, Supplemental Figs. 1 and 2), while discordant cases had an intermediate prognosis, with no significant differences between the two combinations (Supplemental Table 4).

4. Discussion

In the largest cohort of patients with chronic HF so far assessed with respect to the prognostic value of biomarkers, concentrations of NT-proBNP, hs-TnT, and hs-CRP were univariate predictors of all-cause death, cardiovascular death, and cardiovascular hospitalization. hs-TnT appeared a stronger predictor of outcome than the other parameters. hs-TnT had also independent prognostic value from NT-proBNP, while hs-CRP did not. Adding hs-TnT to NT-proBNP resulted in better discrimination and reclassification, with a change in risk category for substantial percentages of patients (all-cause death: 28%, cardiovascular death: 24%, and cardiovascular hospitalization: 26%). The combination of hs-CRP, hs-TnT and NT-proBNP did not further improve risk stratification over hs-TnT plus NT-proBNP. On the other hand, eGFR was independent predictor of all-cause and cardiovascular mortality in a model including NT-proBNP and hs-TnT. The best hs-TnT and NT-proBNP cut-offs for the prediction of all-cause death increased with decreasing eGFR, and patient classification according to these cut-offs proved effective in risk stratification across all eGFR categories.

These results add to our previous report of an incremental prognostic value of hs-TnT, compared to a prognostic model including NT-proBNP (together with patient age, sex, ischemic etiology, LVEF, eGFR) [6]. Interestingly, the same conclusions apply to patients with either ischemic or non-ischemic etiologies, confirming the established notion that the correlates of HF progression are broadly similar after an ischemic or non-ischemic cardiac insult. Similarly, no differences were found across age groups, and there was no interaction with patient sex, although women with HF tend to have lower natriuretic peptides levels, and also lower troponin concentration [31]. Finally, despite the wide heterogeneity in disease mechanisms and clinical presentation, hs-TnT retained an additive prognostic value to NT-proBNP across all categories of systolic dysfunction, namely in the <40% and 40–49% LVEF intervals, as well as among patients with preserved systolic function (LVEF ≥50%), despite the profound differences in pathophysiology among these forms of HF. Finally, circulating hs-TnT and NT-proBNP levels are increased in chronic kidney disease (CKD), because of neurohormonal activation associated with CKD, and contributing to cardiac damage [32], and because of reduced renal clearance [33]. Nonetheless, hs-TnT retains independent prognostic value from NT-proBNP across all eGFR ranges. The best hs-TnT and NT-proBNP cut-offs tend to increase with declining renal function, but patient categorization according to eGFR-specific cut-offs results very effective for risk stratification across all eGFR categories. Indeed, patients with both biomarkers higher than or equal to the respective cut-offs have the worst prognosis, and those with both biomarkers below cut-offs have the better prognosis; furthermore, the condition of only one biomarker ≥cut-off, denoting a moderate severity of ongoing myocardial damage, is associated with an intermediate prognosis.

A recent study confirmed the independent prognostic value of hs-troponin assays (both T and I) compared to NT-proBNP in patients with either LVEF <50% or ≥50%, thus corroborating our conclusions, although in a much smaller population (n = 1096), and with a shorter follow-up duration [34]. Notably, both median levels and AUC-defined hs-TnT cut-offs were higher than those we are reporting, possibly
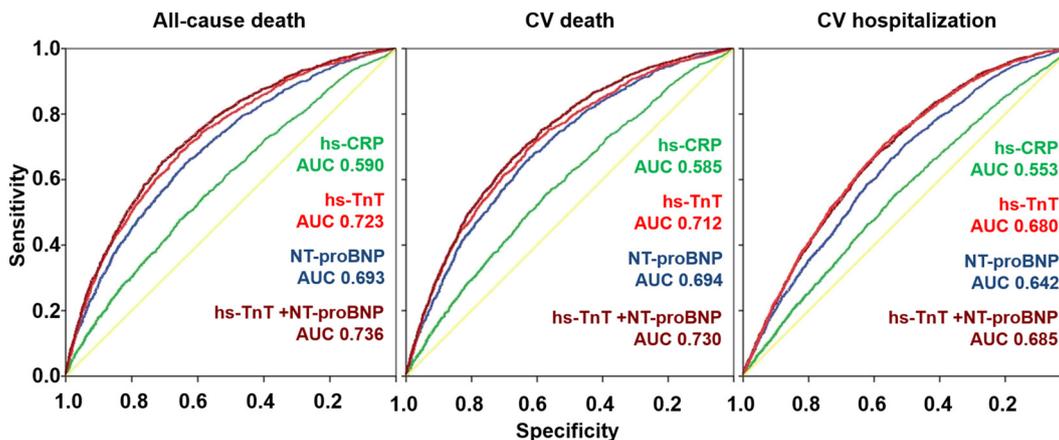
Fig. 1. Biomarkers and prognosis in heart failure. The area under the curve (AUC) values for N-terminal fraction of pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin T (hs-TnT), hs-C-reactive protein (hs-CRP), and the combination of NT-proBNP and hs-TnT are represented. All biomarkers were log$_2$-transformed. As reported in the text, p values for hs-TnT vs. either NT-proBNP or hs-CRP were both <0.001; hs-TnT vs. (hs-TnT + NT-proBNP), p < 0.001 for all-cause and cardiovascular (CV) death, p = 0.005 for cardiovascular hospitalization.
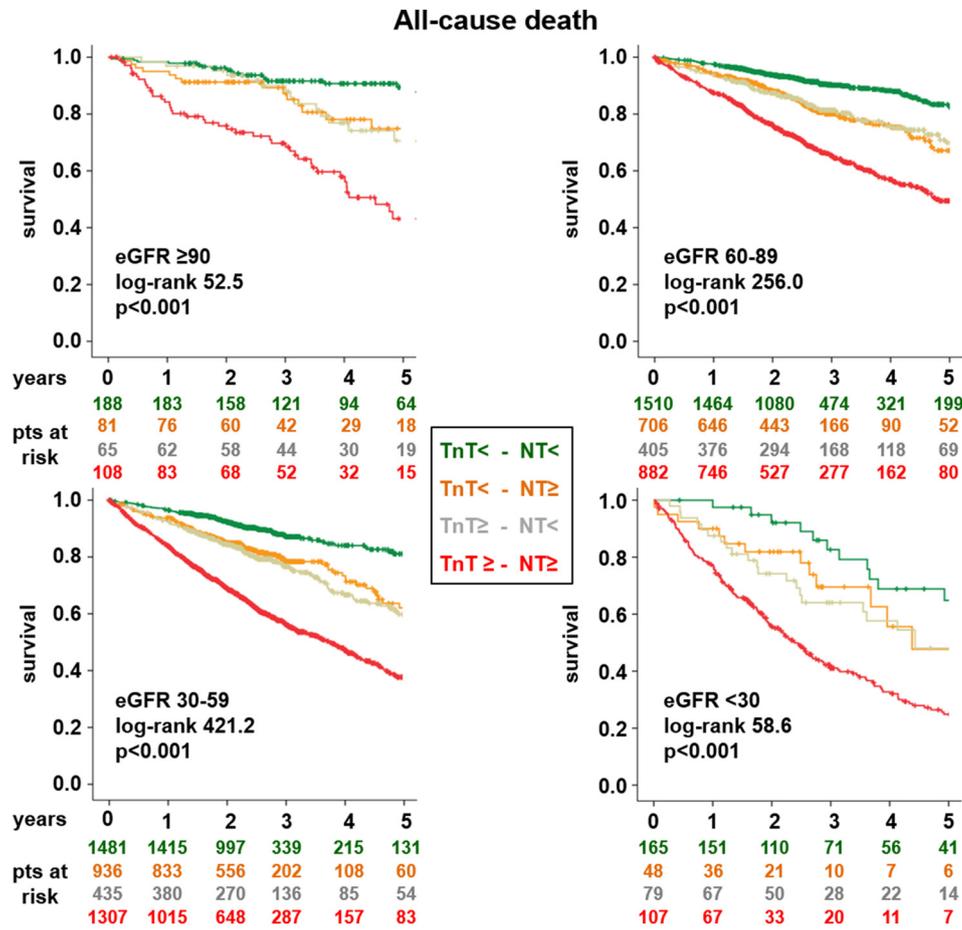
Fig. 2. Biomarker-based categorization for predicting all-cause mortality. For each estimated glomerular filtration rate (eGFR) category, patients were divided into four classes based on eGFR level-specific biomarker cut-offs: 1)high-sensitivity troponin T (hs-TnT) and N-terminal fraction of pro-B-type natriuretic peptide (NT-proBNP) both <cut-offs, 2) hs-TnT ≥cut-off, NT-proBNP <cut-off, 3) hs-TnT <cut-off, NT-proBNP ≥cut-off, 4) hs-TnT and NT-proBNP ≥cut-offs. The cut-offs for each eGFR range and endpoint are specified in Table 2. CV, cardiovascular.

reflecting different inclusion criteria or the specific ethnic group assessed (61% Chinese patients, 27% Malay patients) [34]. On the other hand, the consistency of the main results, i.e. that hs-TnT refines risk stratification when added to NT-proBNP, and that hs-TnT cut-offs close to the upper reference limit are discriminators of prognosis, provide strong conceptual support to the combined assessment of

NT-proBNP and hs-TnT for risk stratification of patients with chronic HF. In particular, the hs-TnT assay is commonly available because of its established role in the diagnosis and management of acute coronary syndromes [35]. The assay has been extensively validated, has limited costs, and is automated, allowing to reduce human workload and sample processing times [29]. Finally, result interpretation is

Table 2
Best biomarker cut-offs for the prediction of all-cause death.

	eGFR ≥ 90 n = 584	eGFR 60–89 n = 3738	eGFR 30–59 n = 4439	eGFR < 30 n = 461	eGFR ≥ 90 n = 461	eGFR 60–89 n = 3517	eGFR 30–59 n = 4161	eGFR < 30 n = 399
	hs-TnT				NT-proBNP			
All-cause death								
AUC	0.683	0.699	0.708	0.660	0.655	0.672	0.669	0.602
Best cut-off (ng/L)	13	15	22	40	825	858	1247	4608
Sensitivity	66	61	62	59	62	65	71	46
Specificity	64	68	68	65	65	60	54	71
Cardiovascular death								
AUC	0.707	0.681	0.699	0.605	0.628	0.666	0.679	0.595
Best cut-off (ng/L)	13	15	22	41	829	858	1375	1416
Sensitivity	72	61	63	60	56	66	71	85
Specificity	61	66	66	58	62	59	55	32
Cardiovascular hospitalization								
AUC	0.660	0.671	0.670	0.572	0.637	0.630	0.636	0.569
Best cut-off (ng/L)	11	15	22	38	647	863	1296	2462
Sensitivity	55	55	58	54	68	59	67	64
Specificity	63	70	67	55	55	61	54	49

Estimated glomerular filtration rate (eGFR) is expressed as mL/min/1.73 m². For each eGFR class, the number refers to patients with available biomarker data. AUC, area under the curve; hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal fraction of pro-B-type natriuretic peptide.

straightforward, especially since the 18 ng/L cut-off holds independent prognostic significance in the whole population, as well as in categories identified by patient sex, HF etiology, and eGFR classes (as demonstrated in our previous meta-analysis) [6]. Overall, the hs-TnT assay seems to meet the prerequisites for widespread use as a tool for risk stratification of stable chronic HF patients [36], although dedicated analyses should explore the balance between increased costs and prognostic benefit from combined NT-proBNP and hs-TnT evaluation.

In the search for a multi-marker strategy for chronic HF, many circulating molecules have been evaluated in addition to natriuretic peptides and troponins. Among them there are soluble suppression of tumorigenesis-2 (sST2) [9,37], galectin-3 [10], growth-derived factor-15 (GDF-15) [10], and hs-CRP. In particular, in the Val-HeFT cohort (included in our population), a relationship between hs-CRP quartiles and mortality was observed, the prognostic power of hs-CRP being independent of HF etiology and BNP [38]. In a small study on advanced chronic HF, not included in the meta-analysis because of no available individual patient data, hs-CRP was predictive over both NT-proBNP and hs-TnT [10]. In the present analysis, the majority of studies reporting data on hs-TnT considered also NT-proBNP and hs-CRP. This biomarker of inflammation was not an independent predictor of outcome or improved prognostic performance over hs-TnT plus NT-proBNP, possibly because of the link between myocardial necrosis and inflammation, reflecting in overlapping prognostic information. The same conclusion applied to several patient categories.

Although large and well-powered, the present study has important limitations. First, it does not include papers published after April 2017 [34]. Second, only NT-proBNP was evaluated, although the assessment of BNP would be interesting as well. Third, the impact of comorbidities and drug or device therapies on the prognostic relevance of biomarkers was not specifically explored, and the setting of patients on dialysis was not evaluated. Fourth, repeated biomarker measurements were not considered, albeit potentially useful in order to further refine prognostic stratification. Fifth, a reduction of patient numbers from the second year of follow-up was noted, especially for some subgroups, with a low percentage of patients reaching the fifth year. Sixth, a high degree of heterogeneity in medical therapy was observed; this variability may have influenced the analyzed cardiovascular end-points and biomarkers values that are notoriously influenced by the neurohormonal system. On the other hand, the assessment of individual patient data likely reduced the impact of such heterogeneity compared to pooled data meta-analyses. Seventh, it would have been of interest to assess the time for blood sampling relative to the latest HF episode, as this would help clarify how "stable" these patients were. Indeed, cardiac biomarkers may be influenced by the clinical stability or recent instability. Unfortunately, this time was not specified in most studies, or was provided only as a broad time range ("CHF hospitalization within the last year") [20]. Finally, as stated above, dedicated studies are required to assess the cost-efficacy balance of a multi-marker assessment in HF outpatients.

In conclusion, hs-TnT conveys prognostic information that is independent from NT-proBNP, while hs-CRP does not. Concomitant assessment of eGFR may further refine risk stratification. The best hs-TnT and NT-proBNP cut-offs for the prediction of all-cause death increased progressively with declining renal function. Patient categorization according to these cut-offs helped predict all-cause and cardiovascular mortality and cardiovascular hospitalization across the whole range of renal function.

Conflict of interest disclosures

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.079.

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