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Original article

High-sensitivity troponins for outcome prediction in the general population: a systematic review and meta-analysis

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ABSTRACT

Background: High-sensitivity (hs) assays allow to measure cardiac troponin T and I (cTnT/I) even in healthy individuals. The higher hs-cTn values, the higher the ongoing cardiomyocyte damage, and then reasonably the risk of developing symptomatic cardiac disease.
Methods: We retrieved all studies evaluating the prognostic value of hs-cTnT or I in the general population. We calculated pooled hazard ratio (HR) values for all-cause and cardiovascular death, cardiovascular events and heart failure (HF) hospitalization.
Results: We included 24 studies for a total of 203,202 subjects; 11 studies assessed hs-cTnT and 14 hs-cTnI. One standard deviation (SD) increase in baseline hs-cTn was associated with a 23% higher risk of all-cause death (HR 1.226, 95% CI 1.083-1.388, p<0.001, I^2=88.5%); all these studies measured hs-cTnI. In an exploratory analysis on 3 studies with 25,760 subjects, hs-cTn predicted cardiovascular death (HR 1.822, 95% CI 1.241-2.674, p=0.002, I^2=87.2%). After synthesizing 9 studies with 58,565 subjects, hs-cTn predicted cardiovascular events (HR 1.328, 95% CI 1.167-1.513, p<0.001, I^2=93.8%). Both hs-cTnT (HR 1.627, 95% CI 1.145-2.311, p<0.001) and hs-cTnI (HR 1.260, 95% CI 1.115-1.423, p<0.001; p for interaction <0.001). Furthermore, in 10 studies with 61,467 subjects, hs-cTn predicted HF hospitalization (HR 1.493, 95% CI 1.368-1.630, p<0.001, I^2=76.6%). Both hs-cTnT (HR 1.566, 95% CI 1.303-1.883, p<0.001) and hs-cTnI (HR 1.467, 95% CI 1.321-1.628, p<0.001) were associated with HF hospitalization (p for interaction <0.001).
Conclusions: hs-cTn values hold strong prognostic value in subjects from the general population, predicting the risk of all-cause and cardiovascular mortality, cardiovascular events, and HF hospitalization.

Background

Cardiac troponin T (cTnT) and I (cTnI) are both sensitive and specific indicators of myocardial injury most commonly used to diagnose acute coronary syndrome[1]. From 2005 onwards, new generations of immunoassay methods with progressively better analytical performance allowed the accurate detection of cTnT and cTnI not only in patients with cardiac or extra-cardiac diseases, but even in apparently healthy subjects[2-5]. Detectable low troponin concentrations may reflect an ongoing cardiomyocyte damage, and correlate with the prevalence of cardiovascular risk factors, metabolic disorders, and cardiac hypertrophy or dysfunction[6,7]. Measuring circulating troponin through a high-sensitivity (hs) assay might then predict the progression of cardiac damage to symptomatic HF, as well as other clinical manifestations such as adverse cardiovascular events and mortality. Several studies evaluated this point, and were globally evaluated in two meta-analyses whose study search was performed back in 2016[8,9]. As many studies have been published in the last years (see Table 1), we deemed it useful to reappraise the prognostic value of hs-cTn in the general population.

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Table 1
Characteristics of selected studies.

First Author, year, ref.	Troponin T/I	Assay	Population setting	Cohort	Patient n	Age (mean/ median) (years)	Men (%)	Diabetes (%)	Hypertension (%)	eGFR (mL/ min/ 1.73 m^2)	Prior HF (%)	Known CV disease (%)	hs-TnT/hs-TnI (mean/ median) (ng/L)
Blankenberg, 2016[26]	I	ARCHITECT i2000SR	10 prospective population-based studies	BiomarCaRE	74,738	52	52	5	42	94	N/A	N/A	N/A
Brouwers, 2014[22]	T	Elecsys Troponin T Gen 5 STAT	HF-free subjects	PREVEND	8,569	49	50	1	14	82	0	7	3
De Lemos, 2010[7]	T	Elecsys Troponin T Gen 5 STAT	Participants aged 30-65 years	Dallas Heart Study	3,546	41	44	12	34	99	4	8	N/A
De Filippi, 2010[23]	T	Elecsys Troponin T Gen 5 STAT	Community-dwelling adults aged ≥65 years without prior HF	Cardiovascular Health Study	4,221	71	40	18	51	N/A	0	N/A	N/A
Eggers, 2013[24]	T	Elecsys Troponin T Gen 5 STAT	Elderly men	Uppsala Longitudinal Study of Adult Men	872	71	100	11	74	75	N/A	40	8
Eggers, 2016[27]	I	ARCHITECT i2000SR	Elderly individuals	Prospective Investigation of the Vasculature in Uppsala Seniors	1,016	70	50	11	72	79	4	15	3
Everett, 2011[21]	T	Elecsys Troponin T Gen 5 STAT	Female health professionals ≥45 years, diabetic	Women's Health Study	512	56	0	100	46	54	0	0	N/A
Everett, 2011[21] (2^{nd} subgroup)	T	Elecsys Troponin T Gen 5 STAT	Female health professionals ≥45 years, non-diabetic	Women's Health Study	564	57	0	0	17	47	0	0	N/A
Everett, 2015[28]	I	ARCHITECT i2000SR	Participants without CV disease	JUPITER	12,956	66	64	0	56	73	0	0	3
Ford, 2016[14]	I	ARCHITECT i2000SR	Men with raised LDLc and no history of MI	West of Scotland Coronary Prevention Study	3,318	55	100	1	16	N/A	N/A	0? (no history of MI)	4
Jia, 2019[17]	I	ARCHITECT i2000SR	Participants aged 54 to 74 years without baseline CV disease	ARIC	8,121	63	43	15	44	87		0	5
Lyngbakken, 2016[29]	I	ARCHITECT i2000SR	Subjects free from known CHD at baseline	HUNT	9,114	47	45	2	41	N/A	0	0	3
McKie, 2014[30]	I	Prototype hs assay on the Dimension Vista® 1500 System	Residents aged ≥45 years, no history of HF	Olmsted County	1,843	62	48	7	28	81	0	N/A	3
McQueen, 2013[13]	T	Elecsys Troponin T Gen 5 STAT	Subjects ≥55 years with vascular disease or diabetes with at least one other cardiovascular risk factor, without HF or systolic dysfunction	HOPE	2,941	66	77	35	42	N/A	0	N/A	6
Neumann, 2014[31]	I	ARCHITECT i2000SR	Population-based cohort without a history of CV events	FINRISK	7,899	48	50	5	45	N/A	0	0	3
Nguyen, 2020[25]	T		Asymptomatic individuals	MESA	5,584	62	48	44	12	78	0	0	7

(*continued on next page*)

Table 1 (*continued*)

First Author, year, ref.	Troponin T/I	Assay	Population setting	Cohort	Patient n	Age (mean/ median) (years)	Men (%)	Diabetes (%)	Hypertension (%)	eGFR (mL/ min/ 1.73 m^2)	Prior HF (%)	Known CV disease (%)	hs-TnT/hs-TnI (mean/ median) (ng/L)
		Elecsys Troponin T Gen 5 STAT											
Pandey, 2018[32]	I	ARCHITECT i2000SR	African Americans without HF	Jackson Heart Study	3,987	53	36	20	54	98	0	0	6
Saunders, 2011[18]	T	Elecsys Troponin T Gen 5 STAT	General population	ARIC	9,698	62	36	12	35	82	N/A	0	N/A
Thorsteinsdottir, 2016[12]	I	ARCHITECT i2000SR	Older community dwellers	AGES-Reykjavik	5764	77	42	12	79	N/A	N/A	0	N/A
Wang, 2012[33]	I	Erenna hsTnI, Singulex	Framingham cohort	Framingham Heart Study	3428	69	47	12	28	N/A	N/A	6	1
Welsh, 2019[19]	T	Elecsys Troponin T Gen 5 STAT	Men aged 40- 59 years from 1 general practice	British Regional Heart Study	3,852	69	100	7	31	N/A	0	18	12
Welsh, 2019[20]	I	ARCHITECT i2000SR	General population	GS:SFHS	19,501	47	42	3	8	72	N/A	N/A	3
Welsh, 2019[20]	T	Elecsys Troponin T Gen 5 STAT	General population	GS:SFHS	19501	47	42	3	8	N/A	N/A	N/A	2
Zeller, 2013[42]	I	ARCHITECT i2000SR	General population	Scottish Heart Health ExtendedCohort	15340	49	50	2	7	N/A	N/A	0? (history of MI and ischaemic or haemorrhagic stroke excluded)	N/A
Zhu, 2017[35]	I	ARCHITECT i2000SR	General population	Busselton Health Study	3,939	52	43	6	20	68	N/A	18	2

AGES-Reykjavik, Age, Gene/Environment Susceptibility–Reykjavik Study; ARIC, Atherosclerosis Risk in Communities Study; BiomarCaRE, Biomarkers for Cardiovascular Risk Assessment in Europe; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GS:SFHS, Generation Scotland Scottish Family Health Study; HF, heart failure; HOPE, Heart Outcomes Prevention Evaluation; hs-TnT/I, high-sensitivity troponin T/I; HUNT, Nord-Trøndelag Health Study; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; LDLc, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; N/A, not available; PREVEND, Prevention of Vascular and Renal End-stage Disease.

Methods

Systematic review

This systematic review and meta-analysis was registered on PROSPERO (ID: CRD42021272399) and conducted according to the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement[10] (see **Supplemental material**). The data collected are available upon request.

Articles on hs-cTnT or hs-cTnI for outcome prediction in the general population were searched on the PubMed and Web of Science databases on August 15, with the following keywords: "troponin AND (prognosis OR outcome OR survival OR cardiovascular OR predictive) AND (healthy OR population OR community)". Reference lists of relevant original research papers and review articles were also manually searched. We included studies meeting the following criteria:

1) original research articles,
2) papers in English,
3) assessment of human subjects from the general population or from population subsets at higher risk of cardiovascular disease (such as diabetic or elderly individuals),
4) a baseline evaluation through hs-assays for cTnT and/or cTnI,
5) a prospective follow-up with the evaluation of at least one of the following endpoints: all-cause death, adverse cardiovascular events (regardless of their specific definition), or HF hospitalization.

When multiple studies were conducted on the same populations and did not provide additive information for this analysis, only the largest one was considered. Eligible articles were selected independently by 2 Authors (AA and GP); controversies were solved through discussion with a third Author (AC). The flowchart of study selection is provided in **Supplemental Figure 1**, and the main characteristics of selected studies are reported in **Table 1**.

Meta-analysis

Data extraction and quality assessment

Two authors (AA and GP) independently extracted hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) for the 4 most commonly available endpoints, i.e., all-cause death, cardiovascular death, cardiovascular events (defined as reported in **Supplemental Table 1**), and HF hospitalization. We retained HRs from the most extensively adjusted models (**Supplemental Table 1**). We also retrieved the main characteristics from study populations. We used the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) system to quantify the certainty of evidence on the association between hs-cTn and outcomes in the general population, as previously suggested[11]. Five domains were considered, including risk of bias, consistency of effect, imprecision, indirectness and publication bias[11].

Data synthesis and statistical analysis. We performed a meta-analysis of available individual studies separately for the association between baseline hs-cTn and all-cause death, cardiovascular death, cardiovascular events, and HF hospitalization. We pooled together all studies reporting effect estimates for 1 standard deviation (SD) increase in continuous untransformed or log-transformed hs-cTn values. For 3 studies12-14 we calculated indirectly the effect size by assuming that the estimate corresponding to the comparison of the 4th to the 1st quartile approximated the interquartile range and, thus was equal to 1.35 of the SD of the continuous biomarker. We used the I2-statistic as well as visual checks of Forest plots to infer about heterogeneity among eligible studies and employed random-effects models for all analyses. We opted for the inverse variance method with the Sidik-Jonkman two-step heterogeneity estimator as a more robust approach in case of low number of synthesized studies15. To increase confidence in our results, we also applied the Hartung and Knapp correction to the overall estimate of CIs16. The effect size and CIs of individual studies as well as pooled estimates were visualised with Forest plots. We sought to explore heterogeneity among studies by: a) conducting sensitivity analyses in elderly subjects or stratifying subjects according to the average of mean/median ages across studies (58 years); b) categorizing studies according to the use of hs-cTnT or hs-cTnI assays; c) excluding studies employing hs-cTnI assays other than ARCHITECT i2000SR; d) applying pre-specified random-effects meta-regression to assess the contribution of continuous study moderators (age, prevalence of male sex, diabetes, and estimated glomerular filtration rate [eGFR]) to the overall heterogeneity. Finally, we investigated possible publication bias by funnel plots of precision and by regression tests (i.e., the Egger test and the Begg and Mazumdar test). For cardiovascular death we did not perform meta-regression analyses and publication bias diagnostics due to low number of studies that could be pooled (n=3). Statistical analysis was conducted with Stata v16.0 (StataCorp, College Station, Texas, USA). All tests were 2-tailed, and the level of statistical significance was set at $p<0.05$.

Results

Literature search

Summary of the screening summary and concise results of the literature search are illustrated in the flow-chart of this systematic review (**Supplemental Figure 1**). We initially retrieved 2,042 articles and identified 230 to be evaluated in full-text format. At the final step, 24 studies were included in the quantitative synthesis (**Table 1**).

Study characteristics

The 24 studies were carried out on 23 cohorts, with 2 studies evaluating the prognostic value of hs-cTnT and hs-cTnI in the Atherosclerosis Risk in Communities Study (ARIC)[17,18]. Furthermore, both hs-cTnT and hs-cTnI were evaluated in the Generation Scotland Scottish Family Health Study (GS:SFHS)[19,20], and an analysis on the Women's Health Study considered separately diabetic and non-diabetic women[21]. When removing the smallest ARIC study[17] and one of the 2 GS:SFHS cohorts[19,20], the total number of subjects was 203,202. Eleven studies assessed hs-cTnT[7,13,18,19,21-25], all of them using the Elecsys Troponin T Gen 5 STAT assay. Fourteen studies evaluated hs-cTnI[12,14,17,20,26-35], measured in all studies through the Architect i2000SR assay except for 2 studies employing the Erenna Singulex assay[33] or a prototype assay[30]. Four studies evaluated only elderly individuals[12,23,24,27], 3 studies only male individuals[14,19,24], and 1 only female subjects[21]. In this last study, the prognostic value of hs-cTnT was evaluated separately in women with or without diabetes[21]. The prevalence of known cardiovascular disease ranged from 0% in 9 studies[12,17,18,21,25,28,29,31,32] to 40% in a single study[24]. The mean of available hs-cTnT values was 6 ng/L, and the mean of hs-cTnI was 3 ng/L. Other variables are reported in **Table 1**. Thirteen studies reported data on all-cause death[7,12,17-20,24,26-28,31,33,35], 8 on cardiovascular death[13,14,18,19,23,26,28,35], 16 on cardiovascular events[12,14,17,19-21,24-29,31,33-35], and 13 on HF hospitalization[17-20,22,23,25,29,31-33,35]; the prognostic value of hs-cTnT or I was most commonly reported as increase in risk for each standard deviation (SD) of log-transformed biomarker value[19,20,24,25,27,29-33] (**Supplemental Table 1**). Numerical values of 1 SD across the different studies are reported in **Supplemental Table 2.**

Association of high sensitivity troponin with outcomes

All-cause death

Based on published data, a pooled assessment of the relationship

between hs-cTn and the incidence of all-cause death could be examined in 7 studies with 42,769 subjects. We found that 1-SD increase in baseline hs-cTn was associated with 23% higher risk of all-cause death (pooled HR: 1.226, 95% CI 1.083-1.388, p<0.001) (Fig. 1). Substantial heterogeneity was observed (I^2=88.5%).

All studies measured hs-cTnI. After excluding the studies employing assays other than the ARCHITECT i2000SR[30,33], the HR was 1.280 (95% Ci 1.091-1.501, p=0.002, n=5 studies, I^2=90.2%).

Cardiovascular death

In an exploratory analysis on 3 studies with 25,760 subjects, hs-cTn significantly predicted cardiovascular death across the follow-up period (pooled HR per 1-SD increase: 1.822, 95% CI 1.241-2.674, p=0.002, I^2=87.2%) (Fig. 2).

Because of the small number of studies (n=3), no subgroup analysis was conducted according to assay type. We just excluded the studies employing assays other than the ARCHITECT: HR=1.552, 95% Ci 1.391-1.731, p<0.001, n=2 studies, I^2=0 %.

Cardiovascular events

After synthesizing 9 studies with 58,565 subjects, hs-cTn was associated with the occurrence of cardiovascular events (pooled HR per 1-SD increase: 1.328, 95% CI 1.167-1.513, p<0.001, I^2=93.8%) (Fig. 3). When the analysis was stratified by troponin subtype, both hs-cTnT (pooled HR per 1-SD increase: 1.627, 95% CI 1.145-2.311, p<0.001, n=2 studies) and hs-cTnI (pooled HR per 1-SD increase: 1.260, 95% CI 1.115-1.423, p<0.001, n=7 studies) predicted the incidence of cardiovascular events, with a greater magnitude for hs-cTnT (p for interaction <0.001) (**Supplemental Figure 2**). After excluding the 2 studies not employing the ARCHITECT i2000SR assays, the HR for hs-cTnI was 1.285 (95% CI 1.118-1.477, p<0.001, n=6 studies, I^2=91.8 %; p for interaction <0.001).

Heart failure hospitalization

In 10 studies with 61,467 subjects, hs-cTn predicted HF hospitalization (pooled HR per 1-SD increase: 1.493, 95% CI 1.368-1.630, p<0.001, I^2=76.6%) (Fig. 4).

Both hs-cTnT (pooled HR per 1-SD increase: 1.566, 95% CI 1.303-1.883, p<0.001, n=3 studies) and hs-cTnI (pooled HR per 1-SD increase: 1.467, 95% CI 1.321-1.628, p<0.001, n=7 studies) were associated with the occurrence of HF, although hs-cTnT demonstrated a higher effect size (p for interaction <0.001). After excluding the 2 studies not using the ARCHITECT i2000SR assay, the HR for hs-cTnI was 1.489 (95% Ci 1.418-1.565, p<0.001, n=5 studies, I^2=0%; p for interaction=0.471).

Subgroup analyses

Beyond the hs-cTn assay, we stratified patients based on their age.

For all-cause mortality, studies with a mean/median age <58 years had a HR of 1.169 (95% CI 1.049-1.302, p=0.005, n=3 studies I^2=68.7%), and those ≥58 years a HR of 1.265 (95% CI 1.025-1.561, p=0.028, n=4 studies, I^2=91.3%), with a borderline significant p for interaction (0.049).

In the 2 studies that recruited elderly subjects, hs-cTn was still related to cardiovascular death (pooled HR per 1-SD increase: 2.01, 95% CI 1.129-3.561, p=0.018, I^2=85.9%). In studies with mean/median age <58 years, the HR was 1.552 (95% CI 1.391-1.731, p<0.001, n=2 studies, I^2=0%), while only 1 study had a mean/median age ≥58 years.

As for cardiovascular events, when the analysis was restrained to elderly subjects, the direction and magnitude of the association did not change considerably (pooled HR per 1-SD increase: 1.502, 95% CI 1.183-1.908, P<0.001, I^2=82%, n=3 studies)[13,14,29]. Studies with a mean/median age <58 years had a HR of 1.251 (95% CI 1.181-1.325, p<0.001, n=4 studies, I^2=48.8%), and those ≥58 years a HR of 1.383 (95% CI 1.091-1.753, p=0.007, n=5 studies, I^2=94.3%), with a p for interaction of 0.015.

With respect to the prediction of HF hospitalization, analysis in elderly subjects showed a pooled HR of 1.826 (95% CI 1.392-2.396, p<0.001, I^2=0%, n=2 studies)[13,14]. Studies with a mean/median age <58 years had a HR of 1.489 (95% CI 1.418-1.565, p<0.001, n=5 studies, I^2=0%), and those with a mean/median age ≥58 years a HR of 1.452 (95% CI 1.254-1.680, p<0.001, n=5 studies, I^2=79.1%), with a p for interaction of 0.522.

Meta-regression analyses

We then performed meta-regression analyses to examine the effect of age, prevalence of male sex, diabetes, and eGFR on pooled estimates. We did not identify any variable that affected the magnitude of the association between hs-cTn and the incidence of all-cause death, cardiovascular events or HF development (p >0.1 for all analyses).

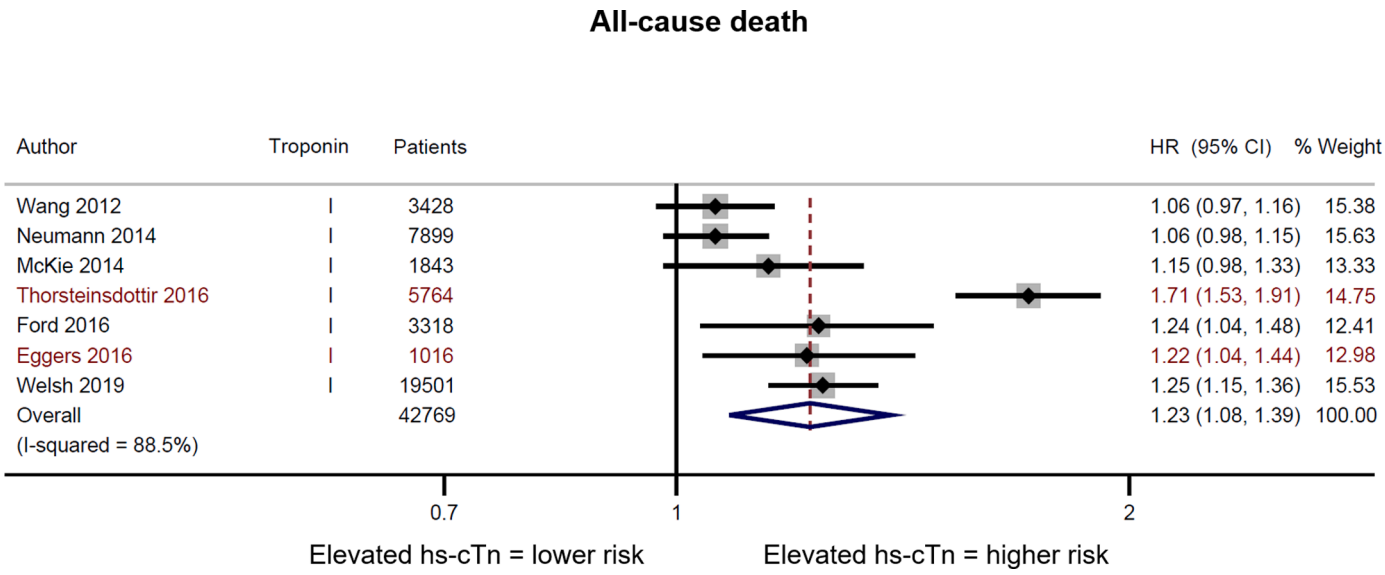

Fig. 1. Pooled estimates for baseline high-sensitivity cardiac troponin (hs-cTn) and the incidence of all-cause death.
Diamonds and their width represent pooled hazard ratios (HRs) and their 95% confidence intervals (CIs), respectively. Pooled estimates are derived from a random-effects model with the Hartung and Knapp correction to address the small number of studies. Studies in red evaluated elderly subjects only.

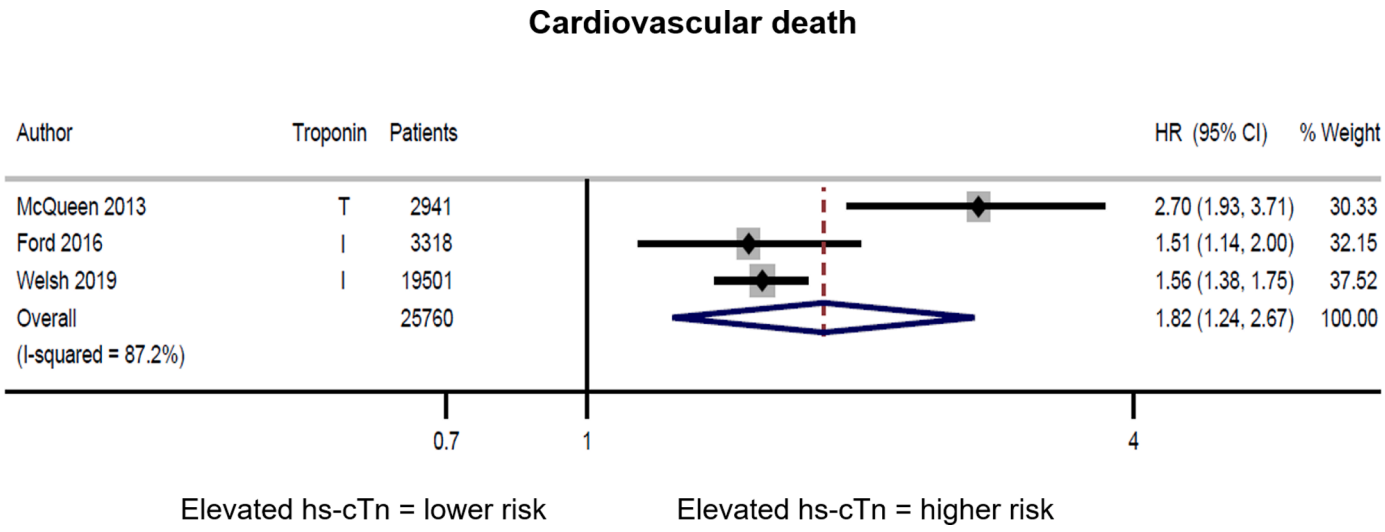

Fig. 2. Pooled estimates for baseline high-sensitivity cardiac troponin (hs-cTn) and the incidence of cardiovascular death. See legend to Fig. 1 for further details.

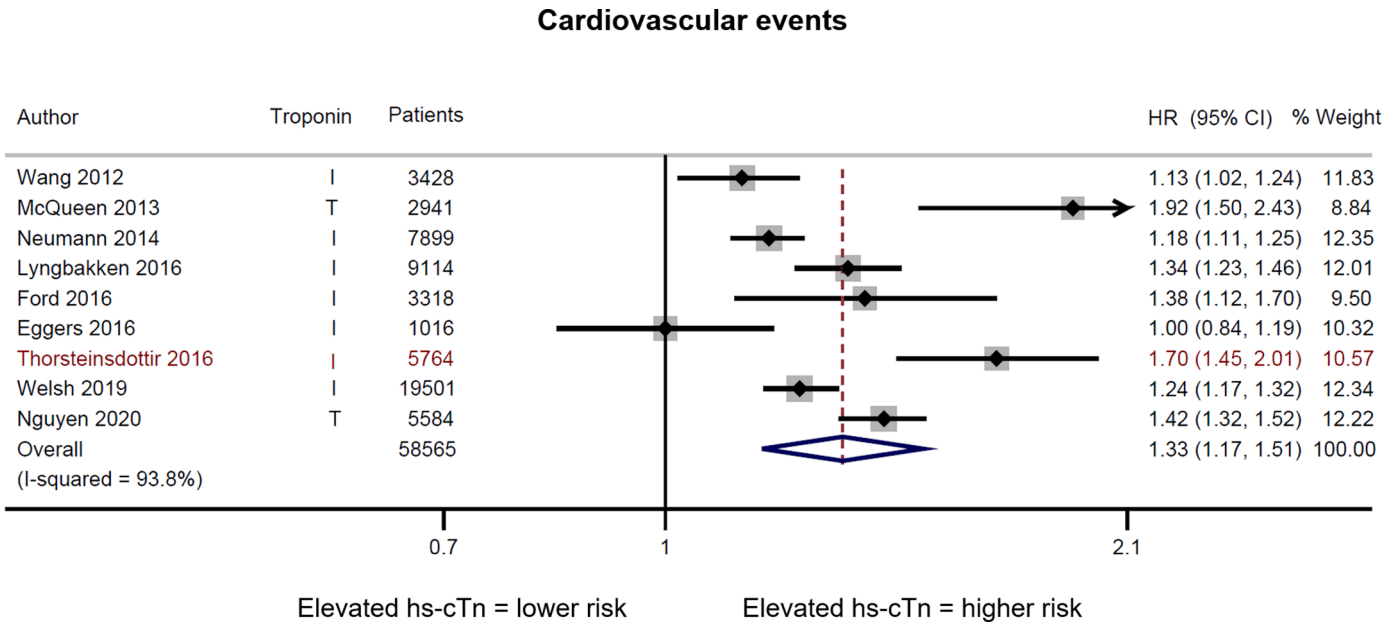

Fig. 3. Pooled estimates for baseline high-sensitivity cardiac troponin (hs-cTn) and the incidence of cardiovascular events. See legend to Fig. 1 for further details. Studies in red evaluated elderly subjects only.

Publication bias and grading of evidence

Funnel plots for the association between hs-cTn and all-cause mortality or cardiovascular events were rather symmetrical; the funnel plot for HF hospitalization was rather asymmetrical at its right bottom, implying either potential publication bias or absence of negative studies. However, statistical tests for small-study effect did not raise any concern with respect to publication bias ($p > 0.1$ with either Egger's or Begg and Mazumdar test for all 3 outcomes). According to the GRADE system, a moderate level of certainty was found for the association between hs-cTn and the risk of outcomes (**Supplemental Table 3**).

Discussion

The scope of this study was to estimate the prognostic value of hs-troponin values in the general population, and mostly within normal limits. This meta-analysis provides a robust confirmation that both hs-cTnI and hs-cTnT are reliable predictors of cardiovascular risk in the general population. In particular, a pooled analysis of all studies showed that the risk of all-cause death, cardiovascular death, cardiovascular events and HF hospitalization increases on average by 23%, 82%, 33% and 49%, respectively, for each SD increase in biomarker levels. However, considering that not all studies evaluated the 4 outcomes, the prognostic values of hs-cTnT and hs-cTnI could be separately compared only for 2 endpoints, namely cardiovascular events and HF hospitalization. Both biomarkers emerged as strong predictors. Interestingly, hs-cTnT emerged as more predictive than hs-cTnI for the prediction of cardiovascular events, while hs-cTnT and hs-cTnI were similarly predictive of HF hospitalization. Due to the large heterogeneity in study design and follow-up duration, further evidence is needed to confirm that there are significant differences between the relative prognostic value of hs-cTnI vs. hs-cTnT. hs-cTnT and hs-cTnI are cardiac-specific biomarkers with a very low index of individuality, which is defined as the ratio of the within-subject variation to the between-subject variation, i.e., the variation between the biological set-points. hs-cTnT and

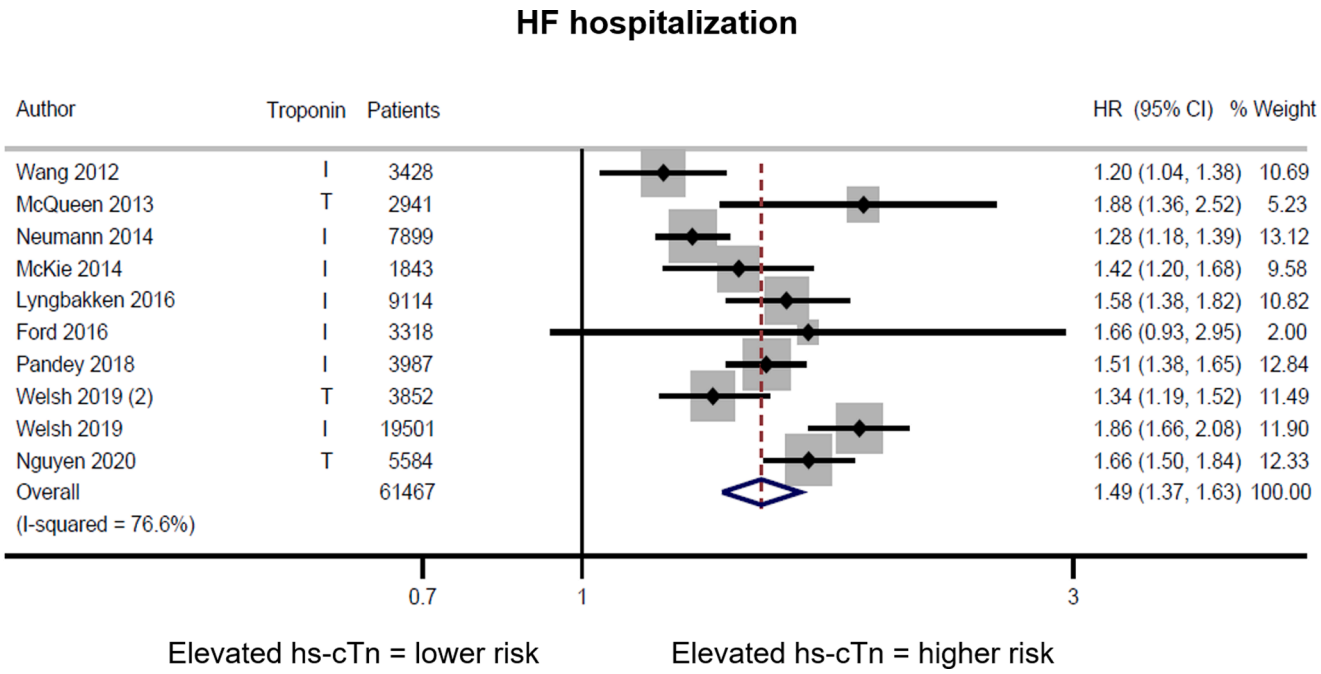

Fig. 4. Pooled estimates for baseline high-sensitivity cardiac troponin (hs-cTn) and the incidence of heart failure (HF) hospitalization.
See legend to Fig. 1 for further details.

hs-cTnI have an index of individuality of about 0.3 because of a low intra-individual variability (8-10%) and an inter-individual variability of 40-50%[3,5,36,37]. By contrast, the other cardiac-specific biomarkers B-type natriuretic peptide (BNP) and N-terminal pro-BNP have both intra- and inter-individual variabilities about 40-60%, and then a much higher index of individuality. In other words, slightly different hs-Tn values across serial measurements are more likely to reflect changes in the severity of cardiac damage than slightly different BNP or NT-proBNP levels. A low index of individuality (<0.6) actually plays an important clinical role, especially when biomarker cut-offs are taken into account for clinical decision, as in the case of hs-cTn cut-offs for the diagnosis of myocardial infarction[3,36-38]. We may add that hs-cTnT and hs-TnI assays may detect even very low circulating levels of troponins, which is particularly important when evaluating subjects from the general population[39-41].

Another important point is the influence of age on the prognostic value of hs-cTn. Considering that the mean/median ages of studied populations vary greatly among the 24 selected studies, from 41 to 71 years, we divided the studies in two age groups according to the average of mean/median ages in all studies (58 years). In agreement with epidemiological data (34), studies with a mean/median age ≥58 years showed a greater risk of all-cause death than those with a mean/median age <58 years, with an increase in risk by 27% for each SD increase in log-transformed hs-cTn vs. a 17% increase. A greater difference was also found for cardiovascular events (38% for age ≥58 years vs. 25% for age <58 years). Conversely, no significant difference emerged for HF hospitalization between the two age groups.

Overall, this meta-analysis confirms the finding from individual studies that hs-Tn levels hold strong prognostic significance, and that this applies to several endpoints, from all-cause death to HF hospitalization. Clinical studies should then evaluate the cost-effectiveness of a hs-cTn-based screening strategy in the general population, or in specific subsets such as elderly individuals, to identify subjects at higher risk of cardiovascular events.

An intrinsic limitation of meta-analyses of aggregated data is the pooled assessment of studies that had heterogeneous designs and assessed different endpoints. Furthermore, several studies expressed the relationship between hs-cTn and outcomes in terms of difference between categories, such as the lowest vs. highest hs-cTn quartiles. Individual subject meta-analyses would be useful to quantify more precisely the prognostic value of hs-cTn (either single or repeated values, or values higher than 99th percentile upper reference limit), to search for prognostic cut-offs and the influence of factors such as age, sex, chronic kidney disease or other comorbidities.

In conclusion, hs-cTn values hold strong prognostic value in subjects from the general population, predicting the risk of all-cause and cardiovascular mortality, cardiovascular events, and HF hospitalization. Screening programs of cardiovascular risk stratification and prevention strategies incorporating hs-cTn require further investigation to define the optimal target populations, timing of measurement, and preventive interventions.

Conflicts of interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.01.012.

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