Association between high-sensitivity cardiac troponin and risk of stroke in 96 702 individuals: a meta-analysis

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Association Between High-Sensitivity Cardiac Troponin and Risk of Stroke in 96 702 Individuals

A Meta-Analysis

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Background and Purpose—Our study aim was to estimate risk of incident stroke based on levels of hs-cTn (high-sensitivity cardiac troponin), a specific biomarker indicating myocardial injury, in the general population, patients with atrial fibrillation, and patients with previous stroke.

Methods—Embase, PubMed, and Web of Science were searched until March 14, 2019 to identify relevant articles. Randomized controlled trials and cohort studies assessing the risk of incident stroke based on hs-cTn were eligible. Pooled adjusted hazard ratios including 95% CI were calculated using a random-effects model due to study heterogeneity per population, coding of hs-cTn (categorical/continuous data), per hs-cTn subunit (T or I), for low risk of bias, and for all-cause and ischemic stroke separately.

Results—We included 17 articles with 96 702 participants. In studies conducted in the general population (n=12; 77 780 participants), the pooled adjusted hazard ratio for incident stroke was 1.25 (CI, 1.10–1.40) for high versus low hs-cTn (as defined by included studies) during an average follow-up of 1 to 20 years (median 10). When categorical data were used, this was increased to 1.58 (CI, 1.26–1.90). The results were robust when accounting for stroke classification (all-cause stroke/ischemic stroke), hs-cTn subunit, risk of bias, and coding of hs-cTn. In patients with atrial fibrillation (4 studies; 18 725 participants), the pooled adjusted hazard ratio for incident stroke was 1.95 (CI, 1.29–2.62) for high versus low hs-cTn. Due to lack of data (one study, 197 participants), no meta-analysis could be performed in patients with previous stroke.

Conclusions—This meta-analysis suggests that hs-cTn can be regarded as a risk marker for incident stroke, with different effect size in different subgroups. More research about the association between hs-cTn and incident stroke in high-risk populations is needed, especially in patients with history of ischemic stroke. **(*Stroke*. 2020;51:1085-1093. DOI: 10.1161/STROKEAHA.119.028323.)**

Key Words: atrial fibrillation ■ biomarkers ■ cohort studies ■ stroke ■ troponin

Stroke is a highly prevalent and disabling disease; its global lifetime risk was estimated to be ≈25% in 2016.[1] Several models and tools have been established to estimate the individual risk of stroke and, thereby, guide clinical decision-making. These prediction tools usually include variables like age and medical history, which may not appropriately reflect the individual risk.[2,3]

Adding blood biomarkers to prediction tools is useful to provide an individualized risk estimate and identify high-risk individuals that deserve intensified prevention measures. Especially, cTn (cardiac troponin) is a promising candidate biomarker in low- and high-risk populations.[4–6] Within the last years, hs-cTn (high-sensitivity cTn) assays have been developed that enable detection of minute amounts of circulating cTn. Hs-cTn levels are associated with diagnosis and progression of cardiovascular disease in healthy and diseased cohorts.[5,7]

Compared with a model of classical vascular risk factors, a model including hs-cTn (and other biomarkers) yielded improved reclassification of cardiovascular event risk in patients with stable coronary heart disease.[8,9] Similarly, in atrial fibrillation, hs-cTn was associated with both risk of ischemic but also hemorrhagic stroke. Scores to predict ischemic and hemorrhagic stroke in atrial fibrillation created with biomarkers, especially hs-cTn, replacing classical risk factors had

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better predictive performance than scores including clinical history only.[10,11] Altogether, previous evidence suggests that hs-cTn concentration may be useful to predict risk of incident stroke. Until now, no systematic review or meta-analysis has been performed to summarize the risk of incident stroke based on hs-cTn levels in various populations, especially with focus on different baseline risk of stroke.

Study Aims

The aim of the present study was to evaluate risk of incident stroke based on hs-cTn levels in the general population, patients with atrial fibrillation, and patients with previous stroke.

Methods

Data Availability

All extracted and generated data are available in this manuscript or in the Data Supplement. Our PROSPERO preregistered systematic review and meta-analysis plan can be found at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=126831.

Statistical Analysis

A random-effects logistic regression model was used for all analyses, considering the heterogeneity in study characteristics (eg, coding of hs-cTn, hs-cTn subunits). For comparison, a fixed-effects model was used as a sensitivity analysis in analyses with <5 studies included (presented in the Data Supplement). Outcomes were presented as a pooled relative risk (adjusted hazard ratio) with 95% CI.

Degrees of statistical adjustment for included studies were categorized as follows: 0=no adjustment, +=only adjustment for age and sex, or only other adjustments without adjusting for age, sex, and cardiovascular risk factors, ++=adjustment for age, sex, and cardiovascular risk factors smoking, alcohol abuse, hypertension, diabetes mellitus, and atrial fibrillation, +++=same as ++, but with additionally other adjustments (eg, biomarkers, medication). All studies on patients with atrial fibrillation adjusted their analyses for at least all variables of the CHA_2DS_2-VASc score. Due to lack of individual patient-level data, our analyses were not further adjusted for patient characteristics than already provided by the included articles.

All analyses were performed in Stata version 14.2 (Stata Corp, College Station, TX). We performed sensitivity analyses in which studies with at least one high risk of bias item in the CLARITY tool were excluded. The detailed statistical analysis plan can be found in the Data Supplement.

Results

Study Selection

The initial literature search identified 2945 potentially relevant articles. No additional articles were identified by searching through references of included articles. By screening these articles by title and abstract, 2457 articles were excluded. The remaining 488 articles were screened in detail (full text) for exclusion criteria. Reasons for exclusion are summarized in Figure 1. In total, 17 articles were included.

Study Characteristics

We included 12 articles describing the general population,[12–23] 4 describing an atrial fibrillation population,[24–27] and 1 describing a stroke population (Table).[28] Studies were published from 2012 to 2019. Three included studies reported 2 different clinical trials (1 investigating rosuvastatin versus placebo and 2 investigating warfarin versus apixaban), whereas the other 14 studies were observational cohort studies. Eleven studies measured hs-cTnT (high-sensitivity cardiac troponin T) and 6 hs-cTnI (high-sensitivity cardiac troponin I). In total, 96 702 participants were included, of whom 77 780 represented a general population, 18 725 were patients with atrial fibrillation, and 197 were patients with previous stroke. As only one study on patients with previous stroke could be identified, no meta-analysis for this category was performed. For the general population, reported average age varied between 48 and 75 years, and the percentage of males varied between 41% and 100%. For patients with atrial fibrillation, reported average age was 74 to 76 years, and percentage of males was 51% to 64%. The average duration of follow-up was between 1 and 20 years, with all studies on patients with atrial fibrillation <3 years, and a median for the general population of 10 years. Detailed risk of bias assessment can be found in the Data Supplement.

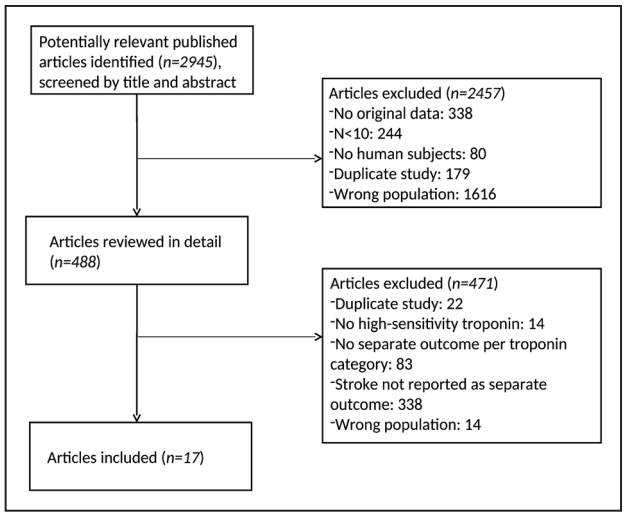

Figure 1. Flow chart of inclusion of articles.

Study Outcomes

Fifteen studies reported hazard ratios for the occurrence of incident stroke, and one study reported an odds ratio (Table). In the general population, there were on average 10.7 cases of incident stroke per 1000 participants at risk per year of follow-up. In the atrial fibrillation population, there were on average 13.2 cases of incident stroke per 1000 patients at risk per year of follow-up.

Meta-Analyses on Risk of Incident Stroke in the General Population

We found an association between hs-cTn and risk of incident stroke in the general population, with a pooled adjusted hazard ratio of 1.25 (95% CI, 1.10–1.40) for high versus low hs-cTn (Figure 2). A lower pooled adjusted hazard ratio was estimated if only continuous data were combined (hazard ratio, 1.15 [95% CI, 1.09–1.20]), than if only categorical data were combined (hazard ratio, 1.58 [95% CI, 1.26–1.90]; Figure 3). Pooled adjusted hazard ratio for risk of all-cause stroke was 1.57 (95% CI, 1.12–2.01), and for risk of ischemic stroke this was 1.23 (95% CI, 1.04–1.42; Figure 4).

Table. Summary of Included Studies Reporting Risk of (Recurrent) Stroke Based on hs-cTn Levels

Study	Cohort or Center (Period of Inclusion; Treatment for Trials)	Subunit of hs-cTn (Assay)	Median hs-cTn in ng/L (IQR)	Coding of hs-cTn	Number of Participants (Number With Stroke as Outcome)	Adjusted HR/OR for Occurrence of Stroke per Type of Stroke as Outcome (95% CI)	Age in Years (Mean+SD or Median+IQR)	Sex (% Males)	Duration of Follow-Up in Years (Mean+SD or Median+IQR)
General population									
Agarwala et al[12]	ARIC study (1996–1998)	hs-cTnT (Elecsys, Roche Diagnostics)	Not described	Continuous (per unit, log-transformed)	8127 (366)	Ischemic stroke (HR): 1.46 (1.23–1.74)	62.5 (5.6)	41.1	Median 14.9
Eggers et al[13]	ULSAM (1991–1995)	hs-cTnT (Elecsys, Roche Diagnostics)	8.3 (5.8–12.5)	Continuous (per SD, log-transformed)	940 (133)	All stroke (HR): 1.2 (1.0–1.4)	71.0 (0.7)	100	Median 10.0 (range, 0.9–12.4)
Elkind et al[14]	Cardiovascular Health Study (not reported)	hs-cTnT (not reported)	8.2 (5.5–13.2)	Continuous (per doubling) Quintiles (no cutoff reported)	4189 (Not described)	Ischemic stroke (HR): continuous: 1.16 (1.06–1.26); categorical: 1.64 (1.25–2.15)	Not reported	Not reported	Not reported
Everett et al[15]	JUPITER (2003–2006; rosuvastatin vs placebo)	hs-cTnI (ARCHITECT, Abbott Diagnostics)	3.4 (2.6–5.0)	Tertiles (men: 3.0 and 4.6 ng/L; women: 2.6 and 3.9 ng/L)	12 956 (70)	All stroke (HR): 1.84 (0.93–3.64)	Tertile 1: 63 (58–68), tertile 2: 66 (61–71), tertile 3: 68 (63–74)	63.8	Median 2.0 (IQR, 1.5–2.5)
Folsom et al[16]	ARIC study (1996–1998)	hs-cTnT (Elecsys, Roche Diagnostics)	Not described	Five categories (<3, 3–5, 6–8, 9–13, ≥14 ng/L)	10 902 (507)	All stroke (HR): 1.85 (1.31–2.61); ischemic stroke (HR): 2.04 (1.42–2.95)	Quintile 1: 60.7 (5.1), quintile 2: 62.4 (5.5), quintile 3: 63.7 (5.5), quintile 4: 65.1 (5.6), quintile 5: 65.5 (5.6)	43.8	Mean 11.3
Lee et al[17]	Chosun University Hospital, Korea (2011–2012)	hs-cTnT (Elecsys, Roche Diagnostics)	3.0 (3.0–17.0)	Binary (≥14 ng/L)	250 (5)	Ischemic stroke (HR): normal T3: 6.03 (1.40–26.07); low T3: 11.72 (2.83–48.57)	60.2 (16.5)	42.4	Mean 1.3
Neumann et al[18]	FINRISK (1997)	hs-cTnI (ARCHITECT, Abbott Diagnostics)	3.0 (2.6)	Continuous (per SD, log-transformed), 3 categories (<1.9, 1.9–5.1, >5.1 ng/L)	7899 (299)	Ischemic stroke (HR): Continuous: 1.09 (0.96–1.23); Categorical: 0.99 (0.55–1.78)	Median (IQR): 47.8 (21.8)	49.7	14
Nylander et al[19]	PIVUS (2001–2005)	hs-cTnI (ARCHITECT, Abbott Diagnostics)	6 (4–9)	Continuous (per SD)	406 (95)	Ischemic stroke (OR): 0.94 (0.74–1.19)	70	51.7	5
Rydén et al[20]	Karolinska University Hospital, Sweden (2011–2014)	hs-cTnT (Elecsys, Roche Diagnostics)	Not described	Six categories (<5, 5–9, 10–14, 15–29, 30–49, ≥50 ng/L); in subanalysis, 3 categories (<5, 5–14, >14 ng/L)	19 460 (244)	All stroke (HR): 6 categories: 4.32 (1.89–9.91); 3 categories: 1.81 (0.72–4.58)	54 (16)	50.2	Mean 2.1 (SD 1.1)

(*Continued*)

Table. Continued

Study	Cohort or Center (Period of Inclusion; Treatment for Trials)	Subunit of hs-cTn (Assay)	Median hs-cTn in ng/L (IQR)	Coding of hs-cTn	Number of Participants (Number With Stroke as Outcome)	Adjusted HR/OR for Occurrence of Stroke per Type of Stroke as Outcome (95% CI)	Age in Years (Mean+SD or Median+IQR)	Sex (% Males)	Duration of Follow-Up in Years (Mean+SD or Median+IQR)
Xiao et al[21]	Chinese PLA General Hospital, China (2007–2009)	hs-cTnT (Elecsys, Roche Diagnostics)	6.21	Continuous (per unit, log-transformed), 4 categories (<3, 3–6.21, 6.22–<14, ≥14 ng/L)	1499 (61)	All stroke (HR): continuous: 1.06 (0.87–1.32); categorical: 1.27 (0.69–2.62)	61.4 (11.4)	58.0	Median 4.8 (IQR, 4.5–5.2)
Zeller et al[22]	SHHEC (1984–1995)	hs-cTnI (ARCHITECT, Abbott Diagnostics)	Not described	Continuous (per SD, cubic-root transformed)	15 340 (797)	Ischemic stroke (HR): 1.13 (1.05–1.21)	48.9 (9.3)	49.5	20
Zhu et al[23]	Busselton health study (1994–1995)	hs-cTnI (ARCHITECT, Abbott Diagnostics)	Not described	Continuous (per doubling, log-transformed), 5 categories (≤1.2, 1.3–2.4, 2.5–3.9, 4.0–5.9, ≥6.0 ng/L)	3939 (349)	All stroke (HR): continuous: 1.14 (1.03–1.25); categorical: 2.13 (1.32–3.44)	Male: 52.5 (15.2); female: 52.4 (15.6)	42.9	20
Atrial fibrillation population									
Hijazi et al[24]—hs-cTnI	ARISTOTLE (2006–2011; warfarin vs apixaban)	hs-cTnI (ARCHITECT, Abbott Diagnostics)	5.4 (3.3–10.1)	Quartiles (≤3.3, >3.3–5.4, >5.4–10.1, >10.1 ng/L)	14 821 (378)	Ischemic stroke (HR): 1.73 (1.18–2.54); hemorrhagic stroke (HR): 2.42 (1.18–4.96)	Quartile 1: 66 (59–73), quartile 2: 70 (63–76), quartile 3: 72 (65–77), quartile 4: 71 (64–77)	64.3	Median 1.9
Hijazi et al[25]—hs-cTnT	ARISTOTLE (2006–2011; warfarin vs apixaban)	hs-cTnT (Elecsys, Roche Diagnostics)	11.0 (7.5–16.7)	Quartiles (≤7.5, >7.5–11.0, >11.0–16.7, >16.7 ng/L)	14 897 (380)	Ischemic stroke (HR): 1.78 (1.16–2.73) Hemorrhagic stroke (HR): 2.62 (1.28–5.36)	Quartile 1: 64 (58–70), quartile 2: 70 (63–75), quartile 3: 72 (66–77), quartile 4: 74 (67–79)	64.4	Median 1.9
Roldán et al[26]	University of Murcia, Spain (not reported)	hs-cTnT (Elecsys, Roche Diagnostics)	8.86 (4.24–15.21)	Binary (≥8.04 ng/L)	930 (37)	Ischemic stroke (HR): 2.44 (1.13–5.26)	76 (70–81)	50.5	Median 2.6 (IQR, 2.1–3.0)
Vafaie et al[27]	University of Heidelberg, Germany (2009–2013)	hs-cTnT (Elecsys, Roche Diagnostics)	17.0 (9.0–37.0)	Binary (>14 ng/L)	2898 (60)	Ischemic stroke (HR): 2.35 (1.26–4.36)	74 (66–81)	58.8	Median 1.9 (IQR, 0.8–2.9)
Stroke population									
Stahrenberg et al[28]	Find-AF (2009–2010)	hs-cTnT (Elecsys, Roche Diagnostics)	6.15 (3.00–13.9)	Binary (≥6.15 ng/L, log-transformed)	197 (12)	All recurrent stroke: no HR/OR reported; calculated OR: 3.17 (0.83–12.07)	67 (13)	58.9	Median 1.0 (IQR, 1.0–1.0)

ARIC indicates Atherosclerosis Risk in Communities; HR, hazard ratio; hs-cTn, high sensitivity cardiac troponin; hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; OR, odds ratio; PLA, People's Liberation Army; and ULSAM, Uppsala Longitudinal Study of Adult Men.

We performed separate analyses per subunit of hs-cTn (T or I, see the Data Supplement). In summary, for hs-cTnT overall, the pooled adjusted hazard ratio was 1.48 (95% CI, 1.13–1.83), whereas it was 1.13 (95% CI, 1.01–1.26) for hs-cTnI. Pooled adjusted hazard ratio for risk of all-cause stroke was 1.45 (95% CI, 0.95–1.94) for hs-cTnT,

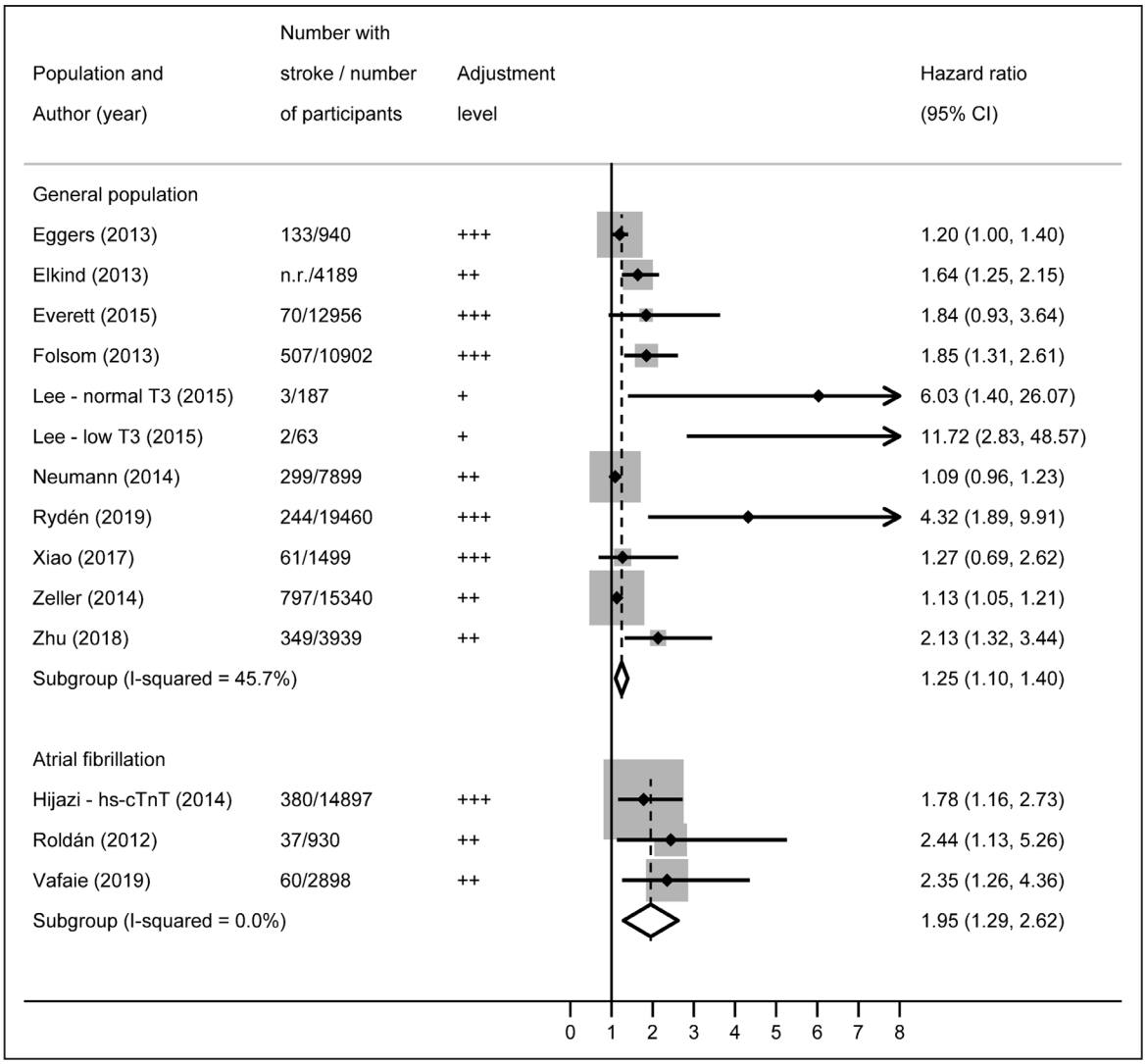

Figure 2. Meta-analysis of risk of incident stroke based on hs-cTn (high-sensitivity cardiac troponin) per population.

and 2.02 (95% CI, 1.19–2.85) for hs-cTnI. Pooled adjusted hazard ratio for risk of ischemic stroke was 1.75 (95% CI, 1.36–2.14) for hs-cTnT, and 1.12 (95% CI, 1.05–1.19) for hs-cTnI.

When considering studies using the 99th percentile upper reference limit for hs-cTnT (ie, 14 ng/L) only, the pooled adjusted hazard ratio was 1.69 (95% CI, 1.17–2.21) (Data Supplement). Pooled adjusted hazard ratio for risk of all-cause stroke was 1.68 (95% CI, 1.16–2.20), and for risk of ischemic stroke this was only 2.07 (95% CI, 1.30–2.83).

In our sensitivity analyses excluding high risk of bias studies, we found slightly higher pooled adjusted hazard ratios than in the main analyses (Data Supplement), for example, 1.57 (95% CI, 1.07–2.07) compared with 1.25 (95% CI, 1.10–1.40) for risk of incident stroke in the general population. For analyses with <5 studies, we also performed sensitivity analyses using fixed-effects meta-analyses (Data Supplement), with results similar to the main analysis.

Meta-Analyses on Risk of Incident Stroke in Patients With Atrial Fibrillation

Pooled adjusted hazard ratio for risk of incident stroke in patients with atrial fibrillation (4 studies) was 1.95 (95% CI, 1.29–2.62) for high versus low hs-cTn (Figure 2). An insufficient number of studies was included to perform any additional meta-analyses.

Discussion

This systematic review and meta-analysis supports the hypothesis that higher hs-cTn levels may indicate a modestly increased risk of incident stroke. This association was observed in populations with different baseline stroke risk, with some suggestion of stronger effects in higher risk populations. Overall, we found an increased risk of incident stroke in participants with higher hs-cTn levels, with pooled hazard ratios of ≈1.13 to 2.07 for the general population and ≈1.95 for patients with atrial fibrillation. This association remained consistent after considering different aspects such as coding of hs-cTn (continuous/categorical), type of stroke (all-cause/ischemic only), potential bias, and hs-cTn subunit (I or T).

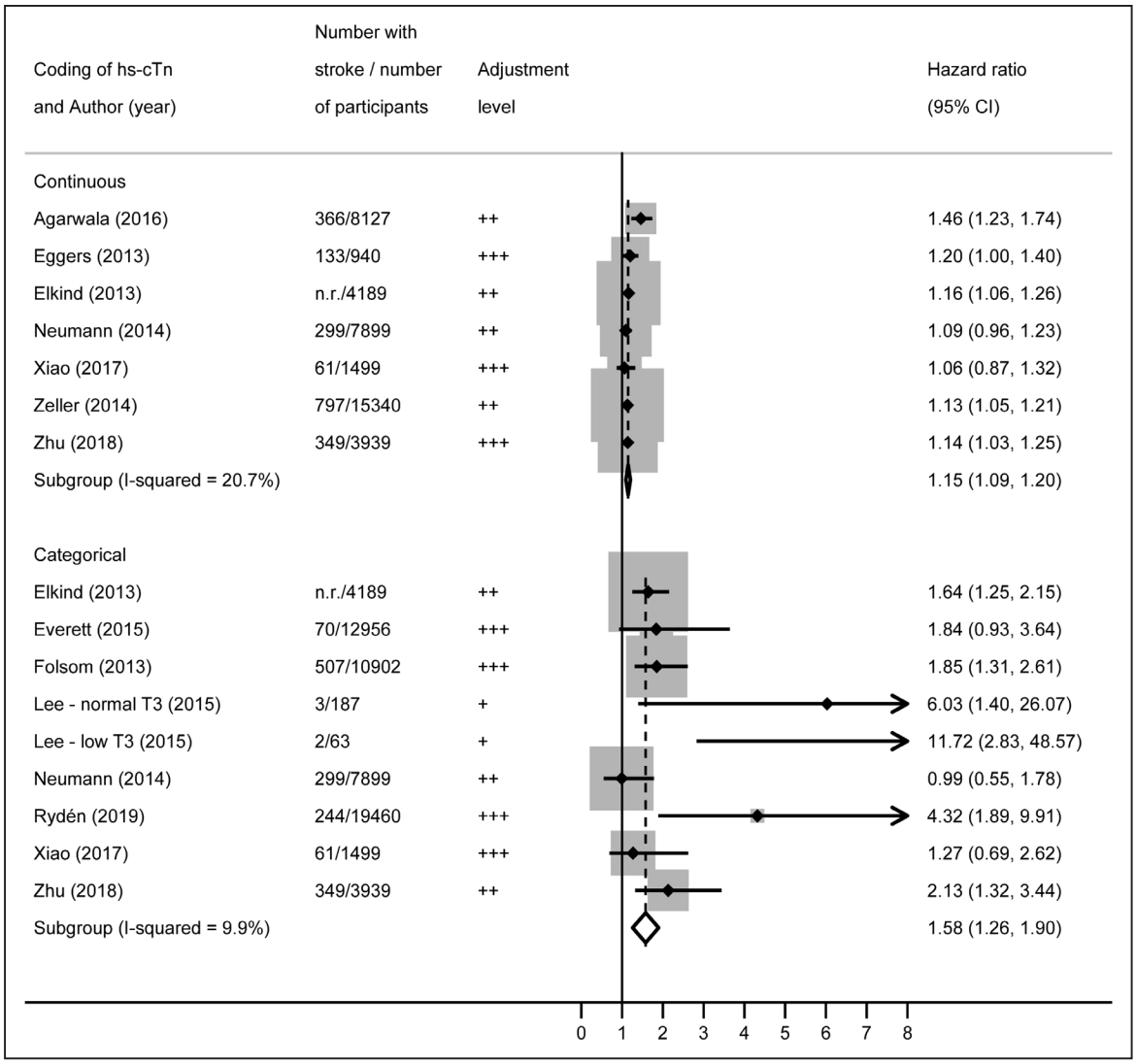

Figure 3. Meta-analysis of risk of incident stroke based on hs-cTn (high-sensitivity cardiac troponin) by coding of hs-cTn in the general population.

When comparing our work with previous publications, our results on the increased risk of incident stroke in the general population for higher hs-cTn levels are consistent with the only previously published meta-analysis about hs-cTn and risk of cardiovascular events in primary prevention settings. This meta-analysis found a relative risk of 1.35 (95% CI, 1.23–1.48) for incident stroke in the general population when comparing the top versus bottom hs-cTn third.[29]

There has been a discussion as to whether different subunits of hs-cTn have different predictive performance regarding cardiovascular events and mortality. Both subunits (T and I) of hs-cTn may have complementary predictive capability, with different associations with cardiovascular disease outcomes, and noncardiovascular death.[30] Further research is needed to clarify potential differences in association with incident stroke between hs-cTnT and hs-cTnI.

Although the pathophysiological mechanisms underlying the relationship between hs-cTn and stroke are not yet fully understood, there are at least 3 potential mechanisms that need to be considered.[31,32] First, heart disease may cause brain ischemia, which occurs for instance when atrial fibrillation leads to ischemic stroke via embolism.[31] Hs-cTn levels strongly correlate with individual state of structural heart disease.[7] Second, any kind of preexisting brain damage, such as previous stroke, white matter lesions, or silent stroke, may lead to heart disease. For instance, it has been shown that impaired autonomic cardiac function after stroke is associated with myocardial damage (the so-called stroke-heart syndrome).[33] Autonomic dysfunction may also promote progression of heart failure and development of future embolic events.[34] Third, common vascular risk factors may simultaneously lead to damage of heart and brain, for example, through small vessel disease in both organs.[35,36] In this model, both myocardial injury (elevated hs-cTn) and brain injury would be considered symptoms of end organ damage due to an underlying systemic disease.

In accordance with these pathophysiological mechanisms, and despite heterogeneity, there was a clear increase in risk ratio for incident stroke based on hs-cTn for both the general population, and patients with atrial fibrillation. Furthermore, the increase in the risk of incident stroke compared with the reference category of hs-cTn in the same population was

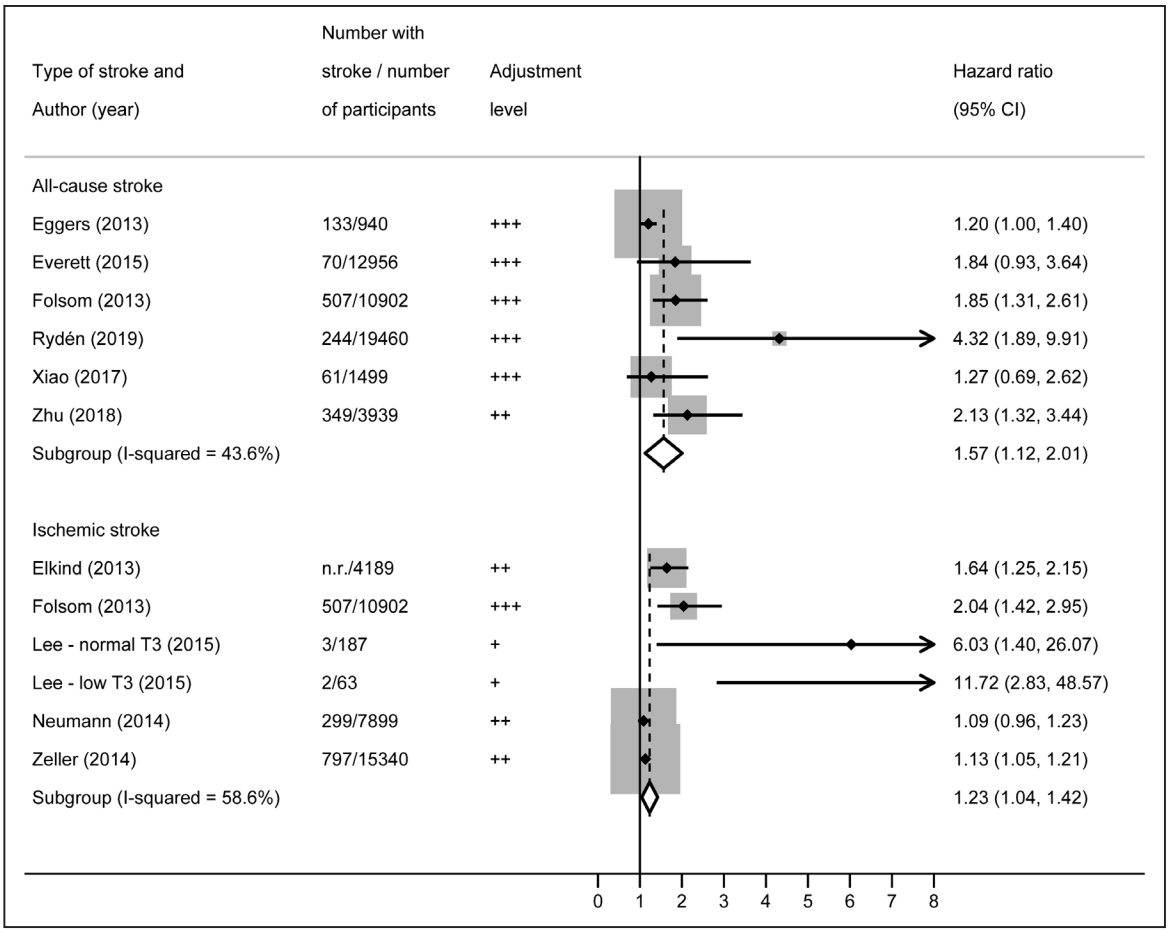

Figure 4. Meta-analysis of risk of all-cause and ischemic stroke based on hs-cTn (high-sensitivity cardiac troponin) in the general population.

even more pronounced in the high-risk population for stroke of patients with atrial fibrillation,[31,37] suggesting a biological interaction between hs-cTn and other risk factors for stroke. Another explanation would be that in patients with prevalent atrial fibrillation (potentially) subclinical ischemic heart disease or heart failure might be an important contributor for a higher abundance of high hs-cTn levels.

Strengths of this study include our analyses for different populations (ie, the general population and patients with atrial fibrillation), and the separate analyses for all-cause stroke and ischemic stroke. However, the following study limitations need to be taken into account when interpreting our study results. There was a large amount of heterogeneity in the included studies, regarding population, subunit of hs-cTn measured (T and I), and coding of hs-cTn used for calculating the risk of (recurrent) stroke based on hs-cTn. Nonetheless, several subgroup analyses could be performed, especially for the studies including a general population. A further study limitation is potential bias in the included studies. Therefore, we performed sensitivity analyses excluding all studies with high risk of bias (at least one high risk of bias CLARITY tool item). This resulted in even slightly higher hazard ratios compared with the main analyses. This means that the hazard ratios in our main analyses should be estimated potentially slightly higher than presented in our results section due to bias. In our study, the chance of too high risk estimates through publication bias is low, as only one small study was included in our meta-analysis,[17] and generally, publication bias occurs when small studies with negative results remain unpublished.

As there were few studies included describing patients with atrial fibrillation, and only one study describing patients with previous stroke, more research is needed on the association between hs-cTn and risk of incident stroke in these populations, to conclusively determine whether preventive measures for incident stroke are warranted based on hs-cTn levels. As the single study on patients with previous stroke resulted in a high odds ratio with wide 95% CI for incident stroke (3.17 [95% CI, 0.83–12.07]), it is especially important to further investigate the potential association between hs-cTn and incident stroke in this population. Because this population already has a high baseline risk of incident stroke, it is clinically relevant to have more information on potential further risk factors for recurrent stroke. For example, initiation of moderate physical activity reduced increase in hs-cTnT, thereby potentially modifying subclinical heart disease.[38] There is also evidence that the absolute and relative benefit of intensified statin treatment on cardiovascular risk was markedly higher in individuals within the highest hs-cTn quartile compared with those within the lowest quartile.[39]

In conclusion, our findings add to the growing literature suggesting that hs-cTn may aid individualized stratification of

future cardiovascular risk. Our results suggest hs-cTn may be regarded as a risk marker for incident stroke in the general population and individuals with atrial fibrillation. Limited evidence exists whether this also holds true in high-risk populations with previous stroke. Further research is needed to investigate whether intensified stroke prevention measures are warranted in case of high hs-cTn levels and to determine the added value of hs-cTn levels in stroke prediction models.

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