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Scheitz, J.F.; Lim, J.; Broersen, L.H.A.; Ganeshan, R.; Huo, S.F.; Sperber, P.S.; ... ; Liman, T.G.

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ORIGINAL RESEARCH

High-Sensitivity Cardiac Troponin T and Recurrent Vascular Events After First Ischemic Stroke

Jan F. Scheitz , MD*; Jess Lim*; Leonie H. A. Broersen , PhD; Ramanan Ganeshan, MD; Shufan Huo , MD; Pia S. Sperber , MD; Sophie K. Piper , PhD; Peter U. Heuschmann , MD, MPH; Heinrich J. Audebert, MD; Christian H. Nolte , MD; Bob Siegerink , PhD; Matthias Endres , MD; Thomas G. Liman, MD, MSc

BACKGROUND: Recent evidence suggests cardiac troponin levels to be a marker of increased vascular risk. We aimed to assess whether levels of high-sensitivity cardiac troponin T (hs-cTnT) are associated with recurrent vascular events and death in patients with first-ever, mild to moderate ischemic stroke.

METHODS AND RESULTS: We used data from the PROSCIS-B (Prospective Cohort With Incident Stroke Berlin) study. We computed Cox proportional hazards regression analyses to assess the association between hs-cTnT levels upon study entry (Roche Elecsys, upper reference limit, 14 ng/L) and the primary outcome (composite of recurrent stroke, myocardial infarction, and all-cause death). A total of 562 patients were analyzed (mean age, 67 years [SD 13]; 38.6% women; median National Institutes of Health Stroke Scale=2; hs-cTnT above upper reference limit, 39.2%). During a mean follow-up of 3 years, the primary outcome occurred in 89 patients (15.8%), including 40 (7.1%) recurrent strokes, 4 (0.7%) myocardial infarctions, and 51 (9.1%) events of all-cause death. The primary outcome occurred more often in patients with hs-cTnT above the upper reference limit (27.3% versus 10.2%; adjusted hazard ratio, 2.0; 95% CI, 1.3–3.3), with a dose-response relationship when the highest and lowest hs-cTnT quartiles were compared (15.2 versus 1.8 events per 100 person-years; adjusted hazard ratio, 4.8; 95% CI, 1.9–11.8). This association remained consistent in sensitivity analyses, which included age matching and stratification for sex.

CONCLUSIONS: Hs-cTnT is dose-dependently associated with an increased risk of recurrent vascular events and death within 3 years after first-ever, mild to moderate ischemic stroke. These findings support further studies of the utility of hs-cTnT for individualized risk stratification after stroke.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT01363856.

Key Words: epidemiology ■ ischemic stroke ■ mortality/survival ■ troponin ■ vascular disease

See Editorial By Murthy

The burden of recurrent vascular events and death after stroke is a relevant problem.^{1–3} A recent population-based cohort study revealed that patients with first ischemic stroke have a more than 4-fold increased risk of vascular events and cardiovascular

death within 1 year following the index stroke.⁴ However, individualized risk prediction of recurrent vascular events for stroke patients, including recurrent ischemic stroke, is limited. Cardiac biomarkers, particularly high-sensitivity cardiac troponin (hs-cTn) are increasingly discussed in

Correspondence to: Jan F. Scheitz, MD, Charité–Universitätsmedizin Berlin, Campus Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin, Germany. E-mail: jan.scheitz@charite.de

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*J. Scheitz and J. Lim contributed equally.

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CLINICAL PERSPECTIVE

What Is New?

- In this prospective cohort study of individuals with first-ever ischemic stroke, there was a graded association between higher levels of high-sensitivity cardiac troponin T and the occurrence of vascular events and death during 3 years of follow-up.

What Are the Clinical Implications?

- Evidence of myocardial injury in patients with stroke may be considered a risk marker for future vascular events and death and should prompt further cardiac diagnostic workup.
- Our findings support further study on the potential utility of high-sensitivity cardiac troponin T for long-term vascular risk prediction after stroke.

Nonstandard Abbreviations and Acronyms

hs-cTn	high-sensitivity cardiac troponin
hs-cTnT	high-sensitivity cardiac troponin T
NIHSS	National Institutes of Health Stroke Scale
PROSCIS-B	Prospective Cohort With Incident Stroke Berlin
TOAST	Trial of Org 10172 in Acute Stroke Treatment
URL	upper reference limit

providing additional prognostic information.^{5,6} According to a recent meta-analysis, elevated hs-cTn is associated with an increased risk of incident stroke in the general population, but data on this association in populations with prior ischemic stroke are scarce.⁵

Hs-cTn elevation indicates myocardial injury and is frequently detected in patients with acute ischemic stroke, even in the absence of acute coronary syndrome or myocardial infarction (MI).^{7–10} Current evidence suggests hs-cTn to be associated with presence and severity of subclinical structural heart disease, which subsequently increases risk of vascular events and all-cause mortality in patients with stroke, the general population, and to a greater extent atrial fibrillation (AF) populations.^{11–13} The extent to which hs-cTn is linked to future vascular risk in patients with ischemic stroke remains largely unexplored.

Considering these potential prognostic implications, we aimed to determine whether high-sensitivity cardiac troponin T (hs-cTnT) levels are associated with

long-term vascular risk and death in a prospective cohort of patients with acute, first-ever, mild to moderate ischemic stroke.

METHODS

Data Availability

The data and software script that support the findings of this study will be made available upon reasonable request via the principal investigator of PROSCIS-B (Prospective Cohort With Incident Stroke Berlin; thomas.liman@charite.de).

Design and Study Population

We analyzed patients with first-ever ischemic stroke who participated in the PROSCIS-B study. In brief, PROSCIS-B is a prospective, observational, hospital-based cohort study of patients enrolled after first-ever stroke. The design and aims of the study have been described elsewhere.¹⁴ Patients with ischemic stroke, primary hemorrhage, or cerebral venous sinus thrombosis were recruited between January 2010 and June 2013 at 1 of 3 stroke units of the Charité–University Hospital Berlin. Within 7 days of stroke onset, patients received structured interviews, extensive clinical examinations, and blood draws for laboratory analysis. During a 3-year period of follow-up, annual telephone-based interviews assessed patients' vital status, incidence of cardiovascular disease, and functional outcomes as well as stroke-associated comorbidities such as post-stroke cognitive decline or depression. Patients aged ≥ 18 years were included after first-ever stroke as defined by World Health Organization criteria.¹⁵ Exclusion criteria were previous stroke (not including transient ischemic attacks), brain tumors or metastases, and participation in any intervention study. Because of limited recruitment of severely affected stroke patients (National Institutes of Health Stroke Scale [NIHSS] >15 ; $n=6$) only patients with mild to moderate ischemic stroke (ie, NIHSS, 0–15) were included in the current analysis. Additionally, we excluded patients with MI 1 month before or during a hospital stay for the incident stroke event, severe renal insufficiency with estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m² and missing hs-cTnT-measurements from the analyses ($n=17$; Figure 1). A local ethics committee of the Charité–University Hospital Berlin approved the respective study (EA1/218/09), and all subjects gave informed consent.

Patient Characteristics

Baseline characteristics included age; sex; NIHSS at admission; stroke subtypes according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment); baseline hs-cTnT (ng/L); history of hypertension, diabetes mellitus,

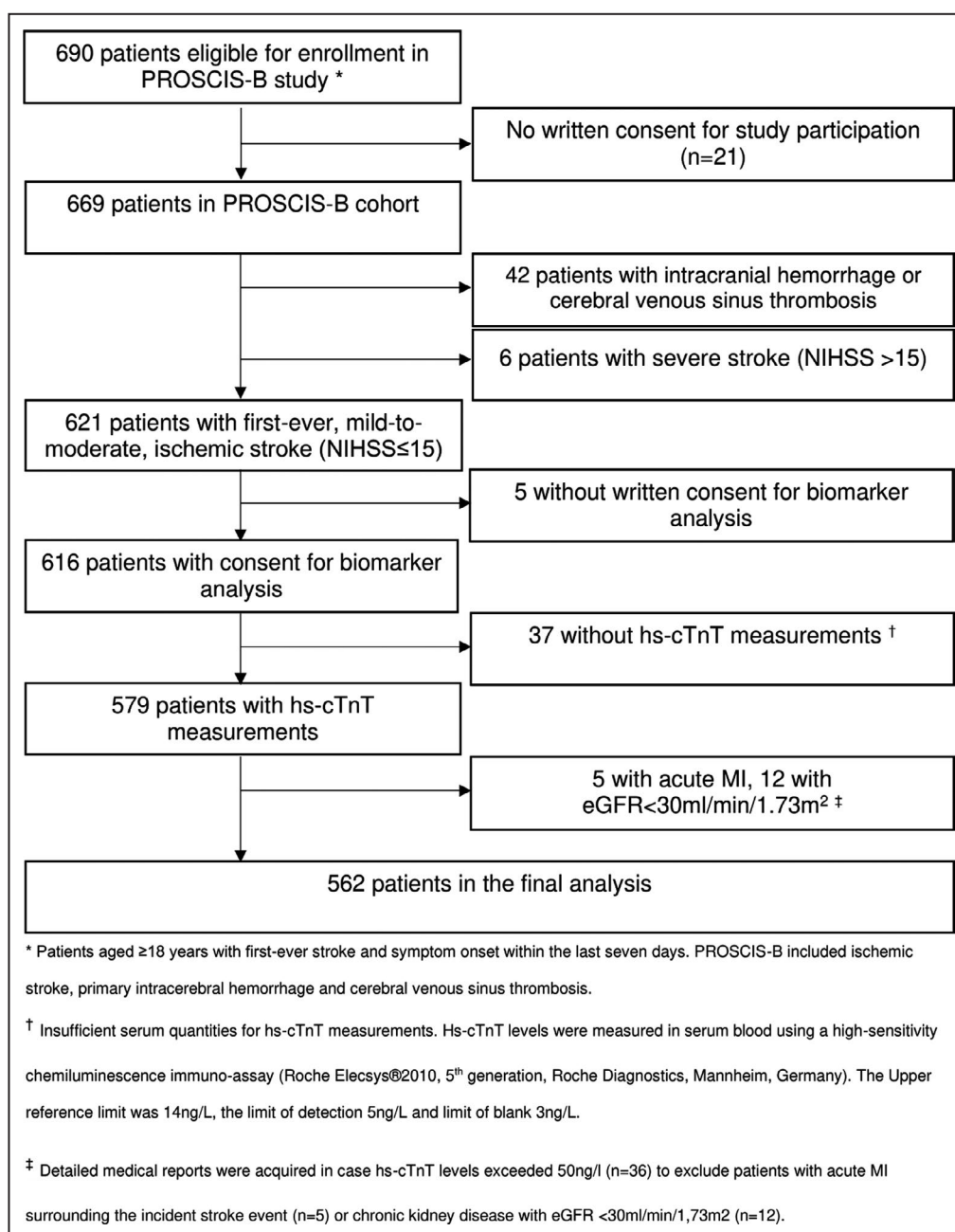


Figure 1. Study recruitment.

eGFR indicates estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; and PROSCIS-B, Prospective Cohort With Incident Stroke Berlin.

AF, or coronary artery disease; kidney function (eGFR, mL/min per 1.73 m²); current smoking; antiplatelet or anticoagulant therapy before stroke; physical activity before stroke; and laboratory values (Table 1).

Biomarker Sampling

Blood samples were obtained at the local stroke unit within 7 days of the initial stroke event by trial physicians. Serum vials were stored at −80°C for future

analyses and shipped on dry ice to the corresponding laboratory. Cardiac troponin T levels were measured using a high-sensitivity electro-chemiluminescence immunoassay (Roche Elecsys 2010, fifth-generation assay, Roche Diagnostics, Mannheim, Germany) with a limit of blank set at 3 ng/L, a limit of detection of 5 ng/L, and an upper reference limit (URL) of 14 ng/L corresponding to the 99th percentile of a healthy reference population. The assay properties have been described elsewhere.¹⁶

Table 1. Baseline Characteristics of Stroke Patients According to hs-cTnT Levels

	Entire Cohorts (n=562)	hs-cTnT ≤14 ng/L (N=342)	hs-cTnT >14 ng/L (N=220)	Difference (95% CI)
Age, y, mean (SD)	66.7 (13.0)	62.9 (12.7)	72.8 (11.0)	9.8 (7.8 to 11.9)
Male sex, n (%)	345 (61.4)	211 (61.7)	134 (60.9)	0.8 (−7.4 to 9.0)
NIHSS at admission, median (IQR)	2 (1–4)	2 (1–4)	3 (2–5)	
Antiplatelet or anticoagulant therapy, n (%)	186 (33.1)	89 (26.0)	97 (44.1)	18.1 (9.9 to 26.0)
TOAST, n (%)*				
Large-artery atherosclerosis	145 (25.8)	80 (23.4)	65 (29.6)	6.2 (−1.4 to 13.7)
Cardioembolism	132 (23.5)	64 (18.7)	68 (30.9)	12.2 (4.8 to 19.5)
Small-vessel occlusion	90 (16.0)	59 (17.3)	31 (14.1)	−3.2 (−9.3 to 3.0)
Stroke of other determined etiology	17 (3.0)	15 (4.4)	2 (0.9)	−3.5 (−6.0 to −1.0)
Stroke of undetermined etiology	178 (31.7)	124 (36.3)	54 (24.6)	−11.8 (−19.5 to −4.0)
Cardiovascular risk factors				
Hypertension, n (%)	364 (64.8)	201 (58.8)	163 (74.1)	15.4 (7.4 to 23.4)
Diabetes mellitus, n (%)	119 (21.2)	55 (16.1)	64 (29.1)	13.1 (5.8 to 20.4)
Dyslipidemia, n (%)	121 (21.5)	71 (20.8)	50 (22.7)	2.0 (−5.1 to 9.0)
Coronary artery disease, n (%)	88 (15.7)	37 (10.8)	51 (23.2)	12.4 (5.8 to 19.0)
Peripheral artery disease, n (%)	39 (6.9)	19 (5.6)	20 (9.1)	3.5 (−0.9 to 8.1)
Atrial fibrillation, n (%)	115 (20.5)	51 (14.9)	64 (29.1)	14.2 (7.0 to 21.2)
Current smoker, n (%)†	159 (28.3)	113 (33.0)	46 (20.9)	−12.8 (−20.4 to −5.2)
Physical activity before stroke—no or light physical activity, n (%)	376 (67.6)	210 (61.4)	166 (75.5)	14.2 (6.3 to 22.0)
Laboratory values				
hs-cTnT (ng/L), median (IQR)	11.3 (6–19.8)	6.8 (4.5–10.3)	22.1 (17.6–32.7)	
eGFR, mL/min per 1.73 m ² , mean (SD)†	78.3 (19.5)	84.0 (17.3)	69.4 (19.4)	14.6 (11.5 to 17.7)
Total cholesterol, mg/dL, mean (SD)	199.2 (48.0)	201.8 (43.3)	195.1 (54.5)	6.7 (−1.8 to 15.2)
LDL cholesterol, mg/dL, mean (SD)	122.6 (40.9)	126.7 (38.0)	116.0 (44.5)	10.7 (3.6 to 17.8)

eGFR indicates estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*Stroke subtypes according to TOAST. The percentages refer to the respective subgroup, that is, hs-cTnT ≤14 ng/L and hs-cTnT >14 ng/L.

†Data are missing for <2% of patients.

Study Outcomes

Our main outcome of interest was a composite of recurrent stroke (ischemic or hemorrhagic), MI, and all-cause death, which will be referred to as “recurrent vascular events and death.” Another outcome of interest was recurrent ischemic stroke. Annual follow-ups screening for recurrent vascular events and death were conducted via structured telephone interviews using standardized follow-up questionnaires, which have been validated for screening of cardiovascular and cerebrovascular events in prior epidemiologic studies (ie, “Rose Angina Questionnaire” for cardiovascular events and “Stroke Symptom Questionnaire” for cerebrovascular events).^{14,17,18} In case of an event, these were confirmed and verified by obtaining medical records from the corresponding hospital or treating physician (ie, general practitioner). An end-point committee comprising 2 vascular neurologists and clinical epidemiologists validated all recorded events in accordance with World Health Organization criteria.^{14,15,19} We identified unreported outcomes

by screening the medical records of the Charité–University Hospital Berlin. Vital status was verified by the registration office of Berlin in case patients were unreachable. Confirmed events including death of a patient had to occur within the follow-up period to be used for the analysis.

Statistical Analysis

We dichotomized the participants according to hs-cTnT levels into >14 ng/L (elevated above URL) and ≤14 ng/L (below URL; reference group). To assess dose response, patients were additionally categorized into quartiles (quartile 1, quartile 2, quartile 3, and quartile 4) according to hs-cTnT levels using the lowest quartile (quartile 1) as a reference category.

We used unadjusted and adjusted Cox proportional hazard regression analyses to explore the association of hs-cTnT with the respective outcomes by estimating hazard ratios (HRs) and their corresponding 95% CI as measures of relative risk. Potential confounders

at baseline, associated with recurrent vascular events and death and hs-cTnT elevation, were taken into the models as covariables based on literature review before conduction of analyses.^{20,21} The multivariable adjusted model included age (continuous), sex (binary), preexisting self-reported cardiovascular risk factors, hypertension (binary), diabetes mellitus (binary), AF (binary), kidney function (continuous, based on eGFR in mL/min per 1.73 m²), current smoking (binary), antiplatelet or anticoagulant therapy (binary), and coronary artery disease (binary) for the primary outcome. Formal testing of the significance value for the overall test of proportional hazards using SPSS version 27 (IBM, Armonk, NY) was 0.342, indicating that the proportionality assumption was not violated. To further reduce the impact of premorbid coronary artery disease, we performed a sensitivity analysis excluding patients with prior MI. Finally, we performed sensitivity analyses for female and male sex, and performed age-matching (margin, 2 years) between the dichotomized hs-cTnT groups to explore whether the association between hs-cTnT and the primary outcome differs according to sex or after age matching. For recurrent stroke, the multivariable adjusted model included age, sex, hypertension, diabetes mellitus, AF, and eGFR. To estimate the cause-specific hazard for recurrent stroke, death was used as a censoring event instead of a competing risk in the Cox regression analyses, as this is the recommended approach when causal effects of covariates on a certain risk are estimated.²²

We calculated the event rate of the primary and secondary outcome by dividing the number of adverse events by the total observed person time for the entire cohort as well as separately for dichotomous hs-cTnT groups and hs-cTnT quartiles, specifically juxtaposing the highest and lowest hs-cTnT quartiles. Follow-up time was the time from inclusion to the event of interest, or censoring, whichever occurred first. Patients were censored at the time of death. If patients had >1 event, the event-free survival time to the first event was used for the regression analyses. We show the incidence over time using Kaplan–Meier graphs for both recurrent vascular events and death, as well as recurrent stroke according to dichotomous hs-cTnT and hs-cTnT quartiles (Figures 2 and 3, respectively). Our study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.²³ All statistical analyses were performed with IBM SPSS Statistics 27 and STATA version 14.2 (StataCorp, College Station, TX).

RESULTS

Study Population

We included a total of 562 patients with first-ever, mild to moderate ischemic stroke in the final analysis

(mean age, 67 years, SD 13, 38.6% women, median NIHSS=2, interquartile range, 1–4). Hs-cTnT was measured after a median of 4 days following the index stroke event (interquartile range, 3–5) with median hs-cTnT levels of 11.3 ng/L (interquartile range, 6.0–19.8). Overall, 99 (17.6%) patients had hs-cTnT <5 ng/L and 220 (39.2%) patients had elevated hs-cTnT >14 ng/L. The lowest quartile (quartile 1) of hs-cTnT was <6.01 ng/L, quartile 2 was hs-cTnT between ≥6.01 and <11.30 ng/L, quartile 3 was hs-cTnT between ≥11.30 and <19.59 ng/L, and quartile 4 was defined as hs-cTnT ≥19.59 ng/L.

As shown in Table 1, patients with hs-cTnT above URL were older, had a slightly higher baseline NIHSS, more cardiovascular risk factors, and lower eGFR and cardioembolic strokes according to TOAST classification. These findings were more pronounced when patients with highest and lowest hs-cTnT quartile were compared (Table S1). For further information on event distributions of dichotomous hs-cTnT groups and all quartiles, see Tables S2 and S3, respectively.

Hs-cTnT and Occurrence of Recurrent Vascular Events

During the 3-year follow-up period (median, 1094 days, interquartile range, 737–1162) the primary outcome measure (recurrent stroke, MI, and all-cause death) occurred in 89 patients (15.8%) including 40 recurrent strokes (7.1%), 4 myocardial infarctions (0.7%), and 51 all-cause deaths (9.1%). All recurrent strokes were ischemic. In total, only 6 patients had 2 events during the observation period (MI and all-cause death in 2 patients, recurrent stroke and all-cause death in 4 patients). The cohort contributed a total person-time of 1397 person-years, which equates to an event rate for the combined outcome of 6.8 events per 100 person-years. No patient in the cohort had ≥3 events during follow-up.

Patients with hs-cTnT above the URL had a higher recurrent vascular event rate compared with those below the URL (11.8 events versus 4.0 events per 100 person-years, respectively; multivariable adjusted HR, 2.03; 95% CI, 1.25–3.29). Recurrent vascular events and death were more frequent in patients with stroke of the highest hs-cTnT quartile with a graded relationship across all quartiles (quartile 4 versus quartile 1—15.2 events versus 1.8 events per 100 person-years; multivariable adjusted HR, 4.73; 95% CI, 1.92–11.65; see Table 2). Figure 2 shows unadjusted Kaplan–Meier curves depicting hazard for recurrent vascular events and death since the index stroke event for dichotomous hs-cTnT and hs-cTnT quartiles, respectively. In a sensitivity analysis excluding patients with prior MI, hs-cTnT above the URL remained associated with recurrent vascular events

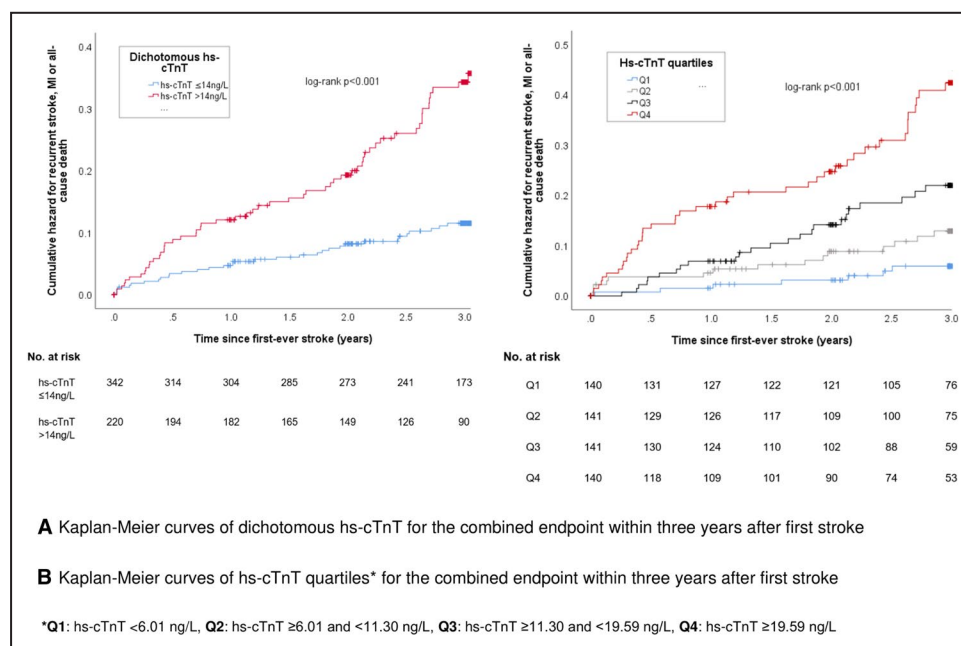


Figure 2. Kaplan-Meier curves of the combined end point within 3 years after first stroke according to hs-cTnT.

A, Kaplan-Meier curves of dichotomous hs-cTnT for the combined end point within 3 years after first stroke. **B**, Kaplan-Meier curves of hs-cTnT quartiles* for the combined end point within 3 years after first stroke. hs-cTnT indicates high-sensitivity cardiac troponin T; and MI, myocardial infarction. *Quartile 1: hs-cTnT <6.01 ng/L; Quartile 2: hs-cTnT ≥6.01 and <11.30 ng/L; Quartile 3: hs-cTnT ≥11.30 and <19.59 ng/L; Quartile 4: hs-cTnT ≥19.59 ng/L. hs-cTnT indicates high-sensitivity cardiac troponin T.

(multivariable adjusted HR 1.96, 95% CI 1.20–3.19). Hs-cTnT above URL was associated with the primary outcome in both women ($n=217$, multivariable adjusted HR, 2.29; 95% CI, 1.02–5.13) and men ($n=345$; multivariable adjusted HR, 2.03; 95% CI, 1.09–3.79). Given the nearly 10-year age difference in patients with and without hs-cTnT above the URL, we applied an exploratory analysis using age matching with a matching margin of 2 years. A total of 175 patients with hs-cTnT above the URL could be matched to patients with hs-cTnT at/below the URL. Hs-cTnT above the URL was similarly associated with the primary outcome ($n=44/175$; multivariable adjusted HR, 2.46; 95% CI, 1.37–4.41). The same held true when comparing the highest and lowest hs-cTnT quartile despite larger CIs because of the smaller event numbers (quartile 4 versus quartile 1; $n=34/111$ versus $n=2/52$, respectively; HR 6.87, 95% CI, 1.59–29.80).

Hs-cTnT and Recurrent Stroke

A total of 40 recurrent ischemic strokes occurred (7.1%) during follow-up. Crude event rates of the subgroup with hs-cTnT above the URL were slightly higher compared with those below the URL (3.8 versus 2.4 events per 100 person-years, respectively; multivariable adjusted HR, 1.14; 95% CI, 0.57–2.28).

As shown in Table 2, a statistically nonsignificant dose-response relationship with higher event rates and HRs in quartile 4 versus quartile 1 was observed (quartile 4 versus quartile 1—4.7 versus 1.3 events per 100 person-years, respectively; multivariable adjusted HR, 2.42; 95% CI, 0.73–8.00; see Table 2). The Kaplan-Meier curves of recurrent stroke are shown in Figure 3.

DISCUSSION

Our study demonstrates that hs-cTnT is associated with a composite outcome of recurrent stroke, MI, and all-cause death in patients with first-ever, mild to moderate ischemic stroke. We observed a dose-response relationship for both recurrent vascular events and death, which was reflected by higher event rates and HR of quartile 4 compared with quartile 1. Furthermore, there was a signal toward higher rates of recurrent strokes in patients with stroke within the highest hs-cTnT quartile compared with the lowest quartile, though to a statistically nonsignificant extent. These findings extend observations of previous studies conducted in the general population and patients with AF to patients with first ischemic stroke, who are at particularly high risk of recurrent vascular events.^{24,25}

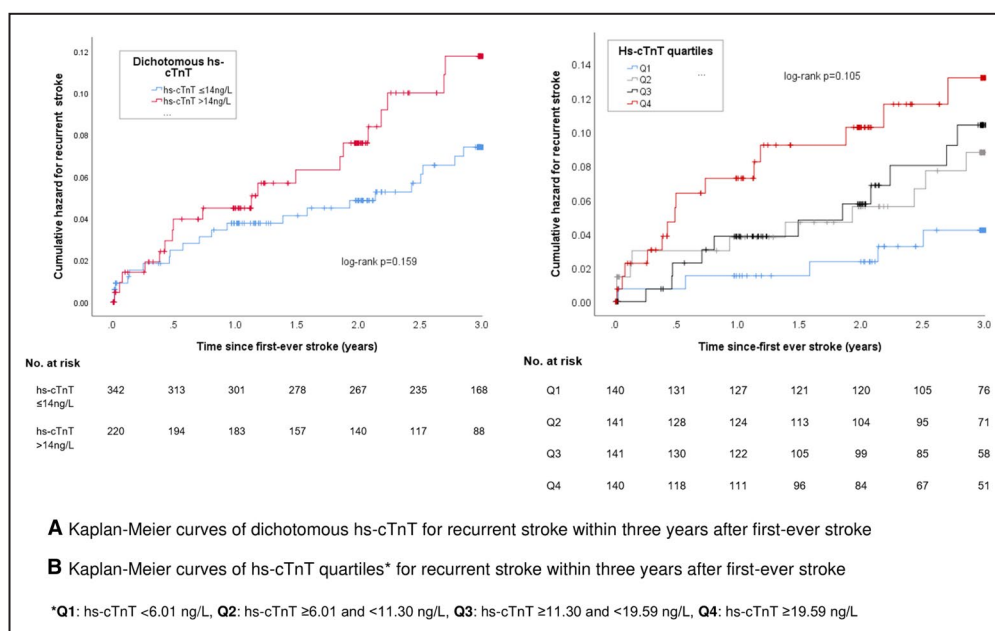


Figure 3. Kaplan-Meier curves of recurrent stroke within 3 years after first stroke according to hs-cTnT.

A, Kaplan-Meier curves of dichotomous hs-cTnT for recurrent stroke within 3 years after first-ever stroke.

B, Kaplan-Meier curves of hs-cTnT quartiles* for recurrent stroke within 3 years after first-ever stroke.

*Quartile 1: hs-cTnT <6.01 ng/L; Quartile 2: hs-cTnT ≥6.01 and <11.30 ng/L; Quartile 3: hs-cTnT ≥11.30 and <19.59 ng/L; Quartile 4: hs-cTnT ≥19.59 ng/L. hs-cTnT indicates high-sensitivity cardiac troponin T.

Table 2. Cox Proportional Hazards Regression: Association Between hs-cTnT and Recurrent Vascular Events and Death, and Recurrent Stroke

	Recurrent Vascular Events and Death			Recurrent Stroke		
	Number of Events, n/N (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Number of Events, n/N (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
hs-cTnT ≤14 ng/L	35/342 (10.2)	1.0 (reference)	1.0	21/342 (6.1)	1.0	1.0
hs-cTnT >14 ng/L	60/220 (27.3)	2.93 (1.90–4.50)	2.03 (1.25–3.29)	19/220 (8.6)	1.56 (0.84–2.90)	1.14 (0.57–2.28)
Quartile 1	7/140 (5.0)	1.0	1.0	5/140 (3.6)	1.0	1.0
Quartile 2*	16/141 (11.4)	2.22 (0.91–5.44)	1.78 (0.69–4.54)	10/141 (7.1)	2.11 (0.72–6.17)	1.76 (0.57–5.46)
Quartile 3†	25/141 (17.7)	3.72 (1.60–8.65)	2.63 (1.06–6.51)	11/141 (7.8)	2.40 (0.83–6.90)	1.84 (0.58–5.88)
Quartile 4‡	47/140 (33.6)	7.43 (3.34–16.53)	4.73 (1.92–11.65)	14/140 (10.0)	3.40 (1.22–9.46)	2.42 (0.73–8.00)

Quartile 1 was used as a reference category, therefore HR=1. Model adjustment was done for age, sex, hypertension, diabetes mellitus, atrial fibrillation, and eGFR (mL/min per 1.73 m²). For recurrent vascular events and death, the model was additionally adjusted for history of coronary artery disease, current smoking, and antiplatelet or anticoagulant therapy before stroke. Quartile 1: hs-cTnT <6.01 ng/L. HR indicates hazard ratio; hs-cTnT, high-sensitivity cardiac troponin T; MI, myocardial infarction.

*Quartile 2: hs-cTnT ≥6.01 and <11.30 ng/L.

†Quartile 3: hs-cTnT ≥11.30 and <19.59 ng/L.

‡Quartile 4: hs-cTnT ≥19.59 ng/L.

Hs-cTnT was detectable in >80% of patients, which is higher than in primary prevention studies (~60%) and similar to published stroke populations.^{9,25,26} Hs-cTnT was elevated above the 99th percentile URL in ~40% patients. This was slightly lower than reported by unselected stroke registries, which also included patients with previous stroke and higher stroke severity (~50%).^{8,27} Recurrent events (ie, recurrent stroke, MI, and all-cause death) occurred in ~16%, and recurrent ischemic stroke occurred in ~7% of patients during the

3-year follow-up. This is well in line with vascular event rates observed in minor stroke populations.^{28,29}

Data on the association between cardiac troponin and recurrent vascular events over longer periods of time in stroke populations are scarce. In line with our findings, a Korean cohort study showed that elevated cardiac troponin I levels were associated with a higher risk of major cardiac and cerebrovascular events as well as all-cause mortality during a 2-year follow-up.³⁰ However, this study was confined to an

Asian population and did not use a high-sensitivity troponin assay, which results in a lower accuracy to detect minor myocardial injury and, thus, to assess dose-response effects. In addition, a German single-center study observed that hs-cTnT levels above the median (similar to quartile 1 in our study) was associated with recurrent vascular events and all-cause mortality after ischemic stroke.³¹ However, the study was restricted to patients with ischemic stroke without AF and limited by the overall small sample size (n=197) and consequently event rates (n=31).

A dose-response effect was observed particularly for recurrent vascular events and death and, to a smaller extent, for recurrent stroke. One possible explanation could be that the primary outcome was mainly driven by events of all-cause death. There is strong evidence from several independent cohorts conducted in various populations that hs-cTn is strongly associated with increased all-cause mortality.^{25,32} Our findings extend these observations to a population of patients with first-ever minor stroke. In line with previous studies, excess mortality after stroke linked to high cardiac troponin levels was concentrated in the first year after the index event.^{13,27}

There are several potential explanations for our findings. Stroke patients are at particular risk of developing early cardiac complications in the first days following stroke despite no history of cardiac disease (so-called stroke-heart syndrome). The presumed underlying mechanisms behind myocardial injury and thus hs-cTn elevation in acute stroke are described extensively elsewhere.^{9,33} Also, circulating hs-cTn is indicative of presence and severity of concomitant structural heart disease. Asymptomatic coronary artery disease is common in patients with acute ischemic stroke, with reported prevalence of ≈20%, and correlates with a higher risk of major vascular events.^{34,35} The association between elevated hs-cTnT and recurrent vascular events and death in patients with stroke could also be explained by the presence of silent AF. Elevated baseline hs-cTnT in patients with ischemic stroke has shown to be an independent predictor for detection of previously unknown AF concerning this matter.³⁶

Strengths of our study include the prospective design alongside systematic annual screenings for vascular events with independent end-point validation based on standard definitions. However, several limitations must be considered when interpreting the results. We included only patients with first-ever, mild to moderate ischemic stroke, which does not allow generalizability of our results to patients with severe stroke, prior stroke history, or other stroke types like primary hemorrhage. These patients, however, are even more likely to have elevated hs-cTn.⁸ Despite the overall sample size of our study, event rates of the secondary outcome “recurrent

stroke” was small (n=40), which limited the ability to adjust for all predefined potential confounders in the same way the main analysis was done. Estimates of the association of hs-cTnT levels with recurrent stroke were adjusted only for age, sex, hypertension, diabetes mellitus, AF, and eGFR as potential confounders and may be interpreted with caution. Additionally, we did not collect information about change of comorbidities over time (eg, new diagnosis of AF), and therefore could not use time-varying covariates for model adjustment in the regression analyses. Furthermore, no neuroimaging findings about the acute stroke event were available for analysis. Neuroimaging features, specifically ischemic lesion patterns, have shown to provide prognostic information about recurrent vascular risk as far as 12 months following incident stroke or transient ischemic attack, although their predictive abilities beyond that time is unclear.^{37,38} Vascular imaging to provide detailed information on presence and severity of carotid plaques was not available for analysis in this respect. Since no neuroimaging was performed during follow-up, any potential silent strokes during follow-up remain undetected. Moreover, information about history of congestive heart failure, which is a risk factor for subsequent vascular events, including MI and recurrent stroke, was missing for our stroke cohort. Blood sampling was performed in the acute phase of stroke, and thus the causal interpretation of acute-phase reactants should be done cautiously. Differentiation of the cause of elevated hs-cTnT in patients with stroke is challenging. We made an effort to exclude patients with concomitant acute coronary syndromes and severely impaired kidney function based on medical records. Unfortunately, we do not have serial hs-cTnT measurements, which would have allowed for a distinction between acute or chronic changes of hs-cTn.²¹ Despite systematic screenings during follow-up, we might have missed events that were left either unreported by the patient or treated in hospitals other than the Charité–University Hospital Berlin.

In conclusion, our findings suggest that higher hs-cTnT levels are associated with recurrent vascular events and all-cause death within 3 years after first-ever ischemic stroke with a graded relationship between hs-cTnT levels and vascular event rates. Hence, our findings support the growing body of literature on the potential utility of hs-cTnT for long-term vascular risk prediction. Further studies are needed to determine whether information about hs-cTn levels in patients with acute ischemic stroke improves individualized risk stratification for recurrent vascular events and warrant intensified secondary prevention measures.

ARTICLE INFORMATION

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Affiliations

From the Center for Stroke Research Berlin (CSB), Charité Universitätsmedizin Berlin, Berlin, Germany (J.F.S., L.H.B., R.G., S.H., P.S.S., H.J.A., C.H.N., B.S., M.E., T.G.L.); Klinik für Neurologie mit Experimenteller Neurologie, Charité-Universitätsmedizin Berlin, Berlin, Germany (J.F.S., J.L., L.H.B., R.G., S.H., H.J.A., C.H.N., M.E., T.G.L.); German Center for Cardiovascular Research (Deutsches Zentrum für Herz-Kreislaufforschung, DHZK), partner site Berlin, Germany (P.S.S., C.H.N., M.E.); German Center for Neurodegenerative Diseases (Deutsches Zentrum für Neurodegenerative Erkrankungen), partner site Berlin, Germany (J.F.S., C.H.N., M.E.); Institute of Clinical Epidemiology and Biometry, University of Würzburg, Germany (P.U.H.); Clinical Trial Center, University Hospital Würzburg, Germany (P.U.H.); ExcellenceCluster NeuroCure, Berlin, Germany (M.E.); Berlin Institute of Health (BIH), Germany (S.K.P., C.H.N., M.E.); and Institute of Biometry and Clinical Epidemiology, Charité-Universitätsmedizin Berlin, Berlin, Germany (S.K.P.).

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Supplementary Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of patients stratified according to hs-cTnT quartiles (Q1-Q4).

	Entire Cohort n=562	hs-cTnT <6.01 ng/L Q1 n=140	hs-cTnT ≥6.01 and <11.30ng/L Q2 n=141	hs-cTnT ≥11.30 and <19.59 ng/L Q3 n=141	hs-cTnT ≥19.59 ng/L Q4 n=140
Age, years - mean, (SD)	66.7 (13.0)	56.6 (13.1)	65.4 (10.1)	71.6 (10.5)	73.1 (11.2)
Male sex, N (%)	345 (61.4)	75 (54.0)	95 (67.4)	83 (58.9)	92 (65.3)
NIHSS at admission (median, IQR)	2 (1-4)	2 (1-4)	2 (1-4)	2 (1-5)	3 (2-5)
NIHSS at admission 0-4, N (%)	422 (75.1)	116 (83.5)	106 (75.2)	104 (73.8)	96 (68.1)

NIHSS at admission 5-15, N (%)	140 (24.9)	23 (16.6)	35 (24.8)	37 (26.2)	45 (31.9)
Antiplatelet and/or anticoagulant therapy, N (%)	186 (33.1)	30 (21.4)	34 (24.1)	57 (40.4)	65 (46.4)
TOAST, N (%) *					
Large-artery atherosclerosis	145 (25.8)	25 (17.9)	44 (31.2)	33 (23.4)	43 (30.7)
Cardioembolism	132 (23.5)	17 (12.1)	30 (21.3)	41 (29.1)	44 (31.4)
Small-vessel occlusion	90 (16.0)	26 (18.6)	20 (14.2)	21 (14.9)	23 (16.4)
Stroke of other determined etiology	17 (3.0)	13 (9.3)	2 (1.4)	1 (0.7)	1 (0.7)

Stroke of undetermined etiology	178 (31.7)	59 (42.1)	45 (31.9)	45 (31.9)	29 (20.7)
Cardiovascular Risk Factors					
Hypertension, N (%)	364 (64.8)	53 (38.1)	101 (71.6)	105 (74.5)	105 (74.5)
Diabetes, N (%)	119 (21.2)	16 (11.5)	27 (19.1)	32 (22.7)	44 (31.2)
Dyslipidemia, N (%)	121 (21.5)	23 (16.6)	33 (23.4)	31 (22.0)	34 (24.1)
Coronary artery disease, N (%)	88 (15.7)	10 (7.2)	16 (11.3)	28 (19.9)	34 (24.1)
Peripheral artery disease, N (%)	39 (6.9)	2 (1.4)	12 (8.5)	10 (7.1)	15 (10.6)

Atrial fibrillation, N (%)	115 (20.5)	7 (5.0)	26 (18.4)	33 (23.4)	49 (34.8)
Current smoker, N (%)[†]	159 (28.3)	54 (39.7)	44 (32.1)	32 (23.0)	29 (20.7)
Physical activity before stroke - No or light physical activity (N, %)	376 (67.6)	77 (55.4)	95 (67.4)	93 (67.9)	111 (79.9)
Laboratory values					
hs-cTnT (ng/L), median (IQR)	11.3 (6-19.8)	4.2 (3 -5.3)	8.4 (7-9.8)	14.4 (13.1-16.6)	28.1 (22.2-43.3)
eGFR, ml/min/1.73 m², mean (SD)	78.3 (19.5)	90.6 (17.3)	81.2 (15.6)	74.2 (16.4)	67.4 (20.4)

Total cholesterol, mg/dL, mean (SD)	199.2 (48.0)	200.6 (40.3)	204.3 (45.7)	197.6 (45.0)	194.2 (59.3)
LDL cholesterol, mg/dL, mean (SD)	122.6 (40.9)	122.8 (34.7)	131.2 (41.6)	120.2 (36.5)	115.9 (48.5)

* Stroke subtypes according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST). The percentages refer to the respective subgroup, i.e. hs-cTnT quartiles Q1-Q4. † Data are missing for <2% of patients

eGFR – estimated glomerular filtration rate, hs-cTnT – high sensitivity cardiac troponin T, IQR – interquartile range, LDL – low density lipoprotein, NIHSS=National Institutes of Health Stroke Scale, Q – quartile, TOAST – Trial of Org 10172 in Acute Stroke Treatment

Table S2. Adverse events during three-year follow-up according to dichotomous hs-cTnT.

	hs-cTnT ≤14ng/L n=342	hs-cTnT >14ng/L n=220
Ischemic Stroke, n (%)	21 (6.1)	19 (8.6)
TIA, n (%)	7 (2.1)	4 (1.8)
MI, n (%)	0	4 (1.8)
Death, n (%)	14 (4.1)	37 (16.8)
Total number of events, n (%) *	42 (12.3)	64 (29.1)

hs-cTnT – high-sensitivity cardiac troponin T, MI – myocardial infarction. *The total number of adverse events (ischemic stroke, TIA, MI, Death) for the respective subgroups do not consider the possibility of one patient having more than one event. Note: the percentages in parentheses refer to the respective subgroup, i.e. hs-cTnT ≤14ng/L and hs-cTnT >14ng/L

Table S3. Adverse events during three-year follow-up according to hs-cTnT quartiles (Q1-Q4).

	hs-cTnT <6.01 ng/L N=140 Q1	hs-cTnT ≥6.01 and <11.30 ng/L N=141 Q2	hs-cTnT ≥11.30 and <19.59 ng/L N=141 Q3	hs-cTnT ≥19.59 ng/L N=140 Q4
Ischemic Stroke, n (%)	5 (3.6)	10 (7.1)	11 (7.8)	14 (10.0)
TIA, n (%)	1 (0.7)	5 (3.6)	2 (1.4)	3 (2.1)
MI, n (%)	0	0	0	4 (2.8)
Death, n (%)	2 (1.4)	6 (4.3)	14 (9.9)	29 (20.7)
Total number of events, n (%) *	8 (5.7)	21 (14.9)	27 (19.2)	50 (35.7)

hs-cTnT – high-sensitivity cardiac troponin T, MI – myocardial infarction

*Total number of adverse events (ischemic stroke, TIA, MI, Death) for the respective subgroups do not take into account the possibility of patients having more than one event