High-Sensitivity Cardiac Troponin T and Cognitive Function in Patients With Ischemic Stroke

Leonie H.A. Broersen, PhD; Bob Siegerink, PhD; Pia S. Sperber; Regina von Rennenberg, MD; Sophie K. Piper, PhD; Christian H. Nolte, MD; Peter U. Heuschmann, MD, MPH; Matthias Endres, MD; Jan F. Scheitz, MD*; Thomas G. Liman, MD, MSc*

Background and Purpose—Our study aim was to assess whether high-sensitivity cardiac troponin T (hs-cTnT), a specific biomarker for myocardial injury, is associated with cognitive function in patients after mild-to-moderate first-ever ischemic stroke.

Methods—We used data from PROSCIS-B (Prospective Cohort With Incident Stroke Berlin). Cognitive function was assessed by Mini-Mental-State-Examination at baseline, and Telephone Interview for Cognitive Status–modified after 1 to 3 years of follow-up. Patients were categorized according to hs-cTnT quartiles. We performed generalized linear regression to calculate risk ratios of cognitive impairment (Mini-Mental-State-Examination <27; Telephone Interview for Cognitive Status–modified <32). Association of hs-cTnT with cognitive function over time was estimated using a linear mixed model.

Results—We included 555 patients (mean age, 67 years, 62% male, median National Institutes of Health Stroke Scale 2 [interquartile range, 1–5], hs-cTnT above upper reference limit 40%, baseline cognitive impairment 28%). Baseline Mini-Mental-State-Examination score and rate of cognitive impairment were lower in patients in the highest versus lowest hs-cTnT quartile (median Mini-Mental-State-Examination 27 versus 29, and 15.3% versus 43.0%, adjusted risk ratio, 1.76 [95% CI, 1.07–2.90], respectively). If anything, cognition seemed to improve in all groups, yet Telephone Interview for Cognitive Status–modified scores were consistently lower in patients within the highest versus lowest hs-cTnT quartile (adjusted β, −1.33 [95% CI, −2.65 to −0.02]), without difference in the rate of change over time.

Conclusions—In patients with mild-to-moderate first-ever ischemic stroke without dementia, higher hs-cTnT was associated with higher prevalence of cognitive impairment at baseline and lower Telephone Interview for Cognitive Status–modified during 3-year follow-up.

Registration—URL: https://www.clinicaltrials.gov; Unique identifier: NCT01363856.

(*Stroke*. 2020;51:1604-1607. DOI: 10.1161/STROKEAHA.119.028410.)

Key Words: biomarker ■ cognition ■ dementia ■ prevalence ■ stroke ■ troponin T

Cognitive decline is a relevant medical problem after stroke with a high impact on quality of life.[1] Until now, individual risk prediction of poststroke cognitive impairment is limited. For this purpose, cardiac troponin is a promising candidate biomarker for more accurate risk estimates of cognitive decline.[2] Higher high-sensitivity cardiac troponin T (hs-cTnT) was associated with incident dementia and cerebral small vessel disease in the general population[2,3] and with worse cognition and faster decline in an elderly outpatient population.[4,5] Hs-cTnT is frequently elevated after stroke and associated with poor long-term outcomes.[6] However, little is known about the association between hs-cTnT and cognitive function over time in stroke patients.

Therefore, we aimed to determine whether hs-cTnT is associated with cognition after stroke at baseline and during 3-year follow-up.

Methods

Data Availability

The data and syntax supporting our findings are available from the principal investigator (Dr Liman) upon reasonable request.

Received September16, 2019; final revision received January 14, 2020; accepted February 12, 2020.

From the Center for Stroke Research Berlin (L.H.A.B., B.S., P.S.S., C.H.N., M.E., J.F.S., T.G.L.), Klinik für Neurologie mit Experimenteller Neurologie (L.H.A.B., P.S.S., R.v.R., C.H.N., M.E., J.F.S., T.G.L.), Berlin Institute of Health (S.K.P., C.H.N., M.E., J.F.S.), and Institute of Biometry and Clinical Epidemiology (S.K.P.), Charité-Universitätsmedizin Berlin, Germany; German Center for Cardiovascular Research (DZHK), partner site Berlin (P.S.S., C.H.N., M.E., J.F.S.); German Center for Neurodegenerative Diseases (DZNE), partner site Berlin, Germany (C.H.N., M.E.); Comprehensive Heart Failure (P.U.H.) and Institute of Clinical Epidemiology and Biometry (P.U.H.), University of Würzburg, Germany; and Center for Clinical Studies, University Hospital Würzburg, Germany (P.U.H.).

*Drs Scheitz and Liman contributed equally.

Presented in part at the European Stroke Organisation Conference, Milan, Italy, May 22–24, 2019.

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.119.028410.

Correspondence to Jan F. Scheitz, MD, Klinik für Neurologie mit Experimenteller Neurologie, Hindenburgdamm 30, 12200 Berlin, Germany. Email jan.scheitz@charite.de

Study Population

The PROSCIS-B (Prospective Cohort With Incident Stroke Berlin) dataset was used for this study. PROSCIS-B was initiated in March 2010 and is described in detail elsewhere.[7] In short, 669 patients aged ≥18 years were recruited within 7 days after first-ever acute stroke. Baseline assessment of cognitive function was conducted at the local stroke unit using Mini-Mental State Examination (cutoff for cognitive impairment <27), and annual follow-up was measured by the Telephone Interview for Cognitive Status–modified (TICS-m, cutoff <32) using structured telephone interviews at 1 to 3 years.

For this substudy, we excluded patients with myocardial infarction within one month before stroke or during hospital admission for stroke, severely impaired kidney function (estimated glomerular filtration rate <30 mL/[min·1.73 m^2]), severe initial stroke (National Institutes of Health Stroke Scale score ≥16), intracerebral hemorrhage or cerebral sinus venous thrombosis, no valid hs-cTnT measurement, and baseline use of dementia medication (Anatomical Therapeutic Chemical code N06D), see the flowchart (Figure I in the Data Supplement).

Statistical Analysis

Study participants were separated into 2 groups according to baseline hs-cTnT: ≥14 ng/L (99th percentile upper reference limit, that is, elevated), or <14 ng/L (reference). Furthermore, we assessed dose-response using quartiles of hs-cTnT, with the lowest quartile as reference.

All statistical analyses were performed using Stata version 14.2 (Stata Corp, College Station, TX). Patients or their legal guardians gave written informed consent before study participation. The study was approved by the local ethics committee. We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[8] Detailed methods and hs-cTnT assay description can be found in the Methods in the Data Supplement.

Results

Study Population

We included 555 patients. Mean age was 67 years (SD, 13, range, 23–99), and 62% were male. Hs-cTnT was obtained at a median of 4 days (interquartile range, 3–5) after stroke. There were 456 patients (82.2%) with detectable hs-cTnT and 219 patients (39.5%) with elevated hs-cTnT. Detailed demographic characteristics are provided in Tables I through III in the Data Supplement. Patients with elevated hs-cTnT were older, had worse renal function, and more comorbidities. During 3-year follow-up, 50 patients died, leading to 103 missing TICS-m measurements (19 in year 1, 35 in year 2, and 49 in year 3).

Hs-cTnT and Cognitive Function

Patients with elevated hs-cTnT had lower baseline Mini-Mental-State-Examination scores than patients with nonelevated hs-cTnT (Figure II and Table IV in the Data Supplement). Cognitive scores were lower in the higher hs-cTnT quartiles compared with lower quartiles (Figure, Table IV in the Data Supplement). Based on Mini-Mental-State-Examination, patients in the highest hs-cTnT quartile had a higher prevalence of baseline cognitive impairment (adjusted risk ratio, 1.76 [95% CI, 1.07–2.90], Table V in the Data Supplement). This was less pronounced in patients with elevated hs-cTnT (adjusted risk ratio, 1.20 [95% CI, 0.89–1.62] Table 1). After 1 year, the adjusted risk ratio for cognitive impairment based on TICS-m was 1.38 (95% CI, 1.01–1.87) for patients with elevated hs-cTnT (Table 1).

Hs-cTnT and Cognitive Decline

During 3-year follow-up, patients with elevated hs-cTnT had lower TICS-m scores than patients with nonelevated hs-cTnT (adjusted β, −1.42 [95% CI, −2.33 to −0.51]; Table 2). Patients with hs-cTnT in the higher compared with the lower quartiles had lower TICS-m scores during 3-year follow-up (Table VI in the Data Supplement). TICS-m scores of all patients improved over time (adjusted β, 0.66 [95% CI, 0.40–0.91]), independent from hs-cTnT levels. No distinct interaction of follow-up time and hs-cTnT on cognitive function was observed, meaning that patients with elevated hs-cTnT did not show faster cognitive decline (Table 2). Similar results were obtained if only nondepressed patients were included

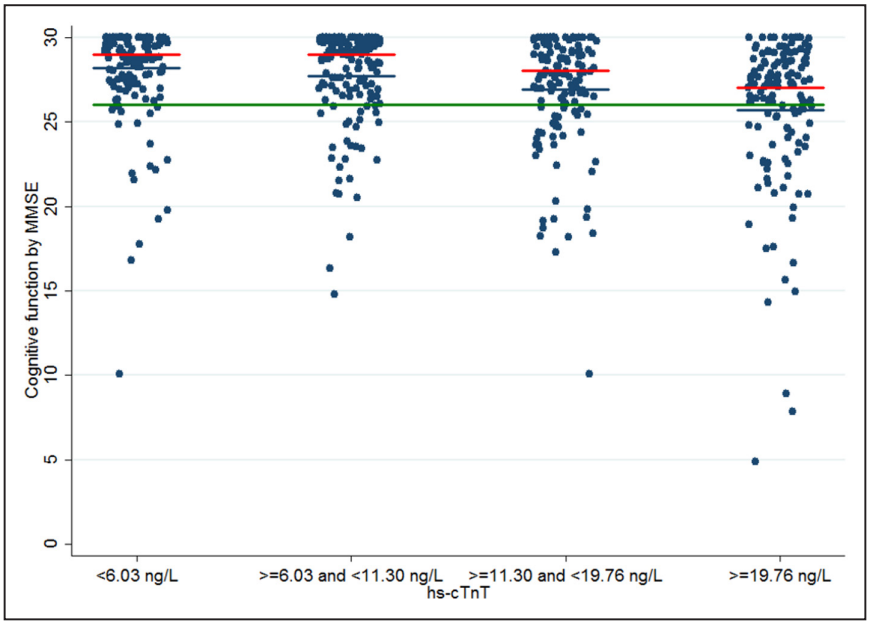

Figure. Cognitive function at baseline by Mini-Mental-State-Examination (MMSE). Detailed legend: Cognitive function measured by MMSE according to quartiles of high sensitivity cardiac troponin T (hs-cTnT). Median: red line, mean: blue line, cutoff for cognitive impairment: green line. MMSE: scale 0–30; cutoff value for cognitive impairment: ≤26; n=544.

Table 1. Association of Dichotomous hs-cTnT With Cognitive Impairment, Baseline, and Year 1

		Frequency of Cognitive Impairment	Model 1	Model 2	Model 3
			Risk Ratio (95% CI)	Risk Ratio (95% CI)	Risk Ratio (95% CI)
Baseline, measured by MMSE	hs-cTnT ≥14 ng/L vs hs-cTnT <14 ng/L	72/329 (21.9%) 78/215 (36.3%)	1.66 (1.26–2.17)	1.25 (0.92–1.70)	1.20 (0.89–1.62)
Year 1, measured by TICS-m	hs-cTnT ≥14 ng/L vs hs-cTnT <14 ng/L	56/228 (24.6%) 69/141 (48.9%)	1.99 (1.50–2.65)	1.45 (1.07–1.98)	1.38 (1.01–1.87)

hs-cTnT, MMSE (scale, 0–30; cutoff for cognitive impairment: ≤26; n=544), TICS-m (scale: 0–50; cutoff for cognitive impairment: ≤31; n=369). Model 1: unadjusted. Model 2: adjusted for age, sex, and education. Model 3: adjusted for age, sex, education, NIHSS, BMI, current smoking, and history of myocardial infarction or coronary heart disease, atrial fibrillation, hypertension, hypercholesterolemia, and diabetes mellitus. For MMSE, 519 patients were included in model 2 and 506 in model 3. For TICS-m, 354 patients were included in model 2 and 347 in model 3. BMI indicates body mass index; hs-cTnT, high-sensitivity cardiac troponin T; MMSE, Mini-Mental State Examination; NIHSS, National Institutes of Health Stroke Scale; and TICS-m, Telephone Interview of Cognitive Status–modified.

and if multiple imputation was used (Tables VII and VIII in the Data Supplement).

Discussion

In our study, higher hs-cTnT was associated with worse cognitive function at baseline and during 3-year follow-up after first-ever ischemic stroke. We did not observe considerable differences in poststroke cognitive function over time in any group, indicating that cognitive function after follow-up depended mainly on baseline cognitive performance.

Our study demonstrates that, although all groups improved in cognition over time, elevated hs-cTnT was associated with poorer cognitive outcome after stroke than non-elevated hs-cTnT. Our findings expand previous observations that hs-cTnT is associated with worse cognitive function in the general population to the high-risk population of ischemic stroke patients.[2,4] There are at least 3 potential underlying mechanisms to consider. First, that heart disease may lead to brain ischemia. This is supported by evidence that atrial fibrillation leads to ischemic stroke via embolism and that oral anticoagulation prevents cognitive decline in atrial fibrillation,[9] and heart failure is linked to white matter damage.[10] The second mechanism leads from the brain to the heart, which is also known as the stroke-heart syndrome, involving impaired autonomic cardiac function with myocardial damage after stroke.[11] Finally, vascular risk factors may lead to damage of both organs simultaneously as small vessel disease.[12]

In contrast to studies in the general population, we did not find faster cognitive decline among stroke patients with elevated hs-cTnT.[4,5] Cognitive function varied little over time and, therefore, seemed to be largely dependent on baseline cognitive function. This is in line with the literature, in which baseline Montreal Cognitive Assessment after stroke was a predictor of long-term cognitive outcome.[13] The lack of cognitive decline might be explained by the relatively short follow-up and comparatively mild nature of the ischemic stroke. Additionally, a learning effect for TICS-m could have interfered with measurement of cognitive decline, which is supported by the slight improvement in cognitive function observed in our study. The lack of difference in rate of change over time between exposure groups might be due to the little change in cognitive function in our cohort. However, it might mean that there is no differential association between hs-cTnT and cognitive decline over time, which would reduce potential usefulness of hs-cTnT as predictor for cognitive decline.

Strengths of this study include the large sample size and the assessment of both baseline and follow-up cognitive function. However, the following study limitations need to be

Table 2. Association of Dichotomous hs-cTnT With Cognitive Function During 3 Years of Follow-Up

			Model 1	Model 2	Model 3
			Beta (95% CI)	Beta (95% CI)	Beta (95% CI)
Model without interaction	Group effect	Change in TICS-m for hs-cTnT ≥14 ng/L vs hs-cTnT <14 ng/L	−2.73 (−3.68 to −1.78)	−1.57 (−2.52 to −0.61)	−1.42 (−2.33 to −0.51)
	Time effect	Change in TICS-m during follow-up per year*	0.64 (0.39 to 0.89)	0.65 (0.40 to 0.90)	0.66 (0.40 to 0.91)
Model with interaction	Group effect	Change in TICS-m for hs-cTnT ≥14 ng/L vs hs-cTnT <14 ng/L	−3.54 (−4.92 to −2.16)	−2.34 (−3.74 to −0.93)	−2.05 (−3.43 to −0.67)
	Time effect	Change in TICS-m during follow-up per year*	0.49 (0.19 to 0.80)	0.51 (0.20 to 0.83)	0.54 (0.23 to 0.86)
	Interaction	Follow-up time in years×hs-cTnT ≥14 ng/L	0.42 (−0.10 to 0.94)	0.39 (−0.13 to 0.92)	0.32 (−0.20 to 0.85)

hs-cTnT, TICS-m (scale: 0–50; cutoff for cognitive impairment: ≤31; n=211 with 3 cognitive tests, n=116 with 2 cognitive tests, and n=84 with 1 cognitive test during 3-year follow-up). Model 1: unadjusted. Model 2: adjusted for age, sex, and education. Model 3: adjusted for age, sex, education, NIHSS, BMI, current smoking, and history of myocardial infarction or coronary heart disease, atrial fibrillation, hypertension, hypercholesterolemia, and diabetes mellitus. There are 411 patients with 1-3 cognitive tests in Model 1, 396 in model 2, and 387 in model 3. BMI indicates body mass index; hs-cTnT, high-sensitivity cardiac troponin T; NIHSS, National Institutes of Health Stroke Scale; and TICS-m, Telephone Interview of Cognitive Status–modified.

*Beta represents the change in TICS-m score for each year that a patient is in follow-up after stroke.

taken into account. A major limitation is the lack of TICS-m measurement at baseline, preventing us from performing a longitudinal analysis from baseline. Furthermore, although previously used in stroke patients, TICS-m has not been validated specifically in a stroke population. We included patients with mild-to-moderate (median National Institutes of Health Stroke Scale 2) first-ever ischemic stroke, which may limit the generalizability of our results. Prevalence of cognitive impairment and elevation of hs-cTnT depend on stroke severity.[1,11] Without assessment of prestroke cognition and burden of cerebral small vessel disease on brain magnetic resonance imaging,[6] it remains unclear whether the association between hs-cTnT and cognition might be due to a preexisting heart-brain disorder. Moreover, stroke can induce cardiac dysfunction, peaking within 72 hours after stroke.[11] This could have led to acute hs-cTnT elevation of a different pathophysiological origin than we aimed to assess. In addition, the applied cognitive tests were screening tests for global cognitive impairment. Thus, it remains uncertain whether the observed associations are more pronounced in certain cognitive domains. Potential residual confounding cannot be excluded, for example, if a chronic underlying disease affects hs-cTnT and cognitive function. After full adjustment, we still showed differences regarding cognitive function based on hs-cTnT. The lack of difference between patients with and without any TICS-m measurements suggests a low risk of bias through missing data and selective loss to follow-up.

In conclusion, based on our results, elevated hs-cTnT is associated with worse cognitive function at baseline and during 3-year follow-up in patients with mild-to-moderate first-ever ischemic stroke. Further research is needed to investigate whether cardiac biomarkers can be used to predict poststroke cognitive impairment.

Sources of Funding

PROSCIS-B (Prospective Cohort With Incident Stroke Berlin) received funding from the Federal Ministry of Education and Research (grant: Center for Stroke Research Berlin, 01 EO 0801) until May 2018. Additional funding (for salary of Dr Broersen) was obtained from the Corona-Stiftung via a research grant of Dr Scheitz.

Disclosures

Dr Sperber reports funding from FAZIT-STIFTUNG March 2018 to March 2020. Dr Nolte reports research grants from German Ministry of Research and Education, German Center for Neurodegenerative Diseases, German Center for Cardiovascular Research and receives Speaker honoraria or consultation fees from Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer Pharma, and W.L. Gore and Associates. Dr Heuschmann reports research grants from German Ministry of Research and Education, German Research Foundation, European Union, Charité, Berlin Chamber of Physicians, German Parkinson Society, University Hospital Würzburg, Robert-Koch-Institute, German Heart Foundation, Federal Joint Committee (Gemeinsamer Bundesausschuss) within the Innovationfond, Charité-Universitätsmedizin Berlin (MonDAFIS [Impact of Standardized Monitoring for Detection of Atrial Fibrillation in Ischemic Stroke]; unrestricted research grant from Bayer), University Göttingen (FIND-AF randomized [Finding Atrial Fibrillation in Stroke]; unrestricted research grant from Boehringer-Ingelheim), University Hospital Heidelberg (RASUNOA-prime [Registry of Acute Stroke Under Novel Oral Anticoagulants - Prime]; unrestricted research grant from Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi Sankyo), outside submitted work. Dr Endres reports grants from Bayer, German Research Foundation, German Federal Ministry of Education and Research, German Center for Neurodegenerative Diseases, German Centre for Cardiovascular Research, European Union, Corona Foundation, Fondation Leducq; fees paid to Charité-Universitätsmedizin Berlin from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, Amgen, GlaxoSmithKline, Sanofi, Covidien, Novartis, outside submitted work. Dr Scheitz receives Speaker honoraria from Bristol-Myers Squibb, Stryker GmbH & Co.KG; research grant from CORONA-Stiftung. The other authors report no conflicts.

References

1. Pendlebury ST, Rothwell PM; Oxford Vascular Study. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study. *Lancet Neurol*. 2019;18:248–258. doi: 10.1016/S1474-4422(18)30442-3
2. Schneider AL, Rawlings AM, Sharrett AR, Alonso A, Mosley TH, Hoogeveen RC, et al. High-sensitivity cardiac troponin T and cognitive function and dementia risk: the atherosclerosis risk in communities study. *Eur Heart J*. 2014;35:1817–1824. doi: 10.1093/eurheartj/ehu124
3. Dadu RT, Fornage M, Virani SS, Nambi V, Hoogeveen RC, Boerwinkle E, et al. Cardiovascular biomarkers and subclinical brain disease in the atherosclerosis risk in communities study. *Stroke*. 2013;44:1803–1808. doi: 10.1161/STROKEAHA.113.001128
4. Bertens AS, Sabayan B, de Craen AJM, Van der Mast RC, Gussekloo J. High sensitivity cardiac troponin T and cognitive function in the oldest old: the Leiden 85-Plus Study. *J Alzheimers Dis*. 2017;60:235–242. doi: 10.3233/JAD-170171
5. Wijsman LW, de Craen AJ, Trompet S, Sabayan B, Muller M, Stott DJ, et al. High-sensitivity cardiac troponin T is associated with cognitive decline in older adults at high cardiovascular risk. *Eur J Prev Cardiol*. 2016;23:1383–1392. doi: 10.1177/2047487316632364
6. von Rennenberg R, Siegerink B, Ganeshan R, Villringer K, Doehner W, Audebert HJ, et al. High-sensitivity cardiac troponin T and severity of cerebral white matter lesions in patients with acute ischemic stroke. *J Neurol*. 2019;266:37–45. doi: 10.1007/s00415-018-9085-3
7. Liman TG, Zietemann V, Wiedmann S, Jungehuelsing GJ, Endres M, Wollenweber FA, et al. Prediction of vascular risk after stroke - protocol and pilot data of the Prospective Cohort with Incident Stroke (PROSCIS). *Int J Stroke*. 2013;8:484–490. doi: 10.1111/j.1747-4949.2012.00871.x
8. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12:1495–1499. doi: 10.1016/j.ijsu.2014.07.013
9. Friberg L, Rosenqvist M. Less dementia with oral anticoagulation in atrial fibrillation. *Eur Heart J*. 2018;39:453–460. doi: 10.1093/eurheartj/ehx579
10. Vogels RL, van der Flier WM, van Harten B, Gouw AA, Scheltens P, Schroeder-Tanka JM, et al. Brain magnetic resonance imaging abnormalities in patients with heart failure. *Eur J Heart Fail*. 2007;9:1003–1009. doi: 10.1016/j.ejheart.2007.07.006
11. Scheitz JF, Nolte CH, Doehner W, Hachinski V, Endres M. Stroke-heart syndrome: clinical presentation and underlying mechanisms. *Lancet Neurol*. 2018;17:1109–1120. doi: 10.1016/S1474-4422(18)30336-3
12. Berry C, Sidik N, Pereira AC, Ford TJ, Touyz RM, Kaski JC, et al. Small-vessel disease in the heart and brain: current knowledge, unmet therapeutic need, and future directions. *J Am Heart Assoc*. 2019;8:e011104. doi: 10.1161/JAHA.118.011104
13. Zietemann V, Georgakis MK, Dondaine T, Müller C, Mendyk AM, Kopczak A, et al. Early MoCA predicts long-term cognitive and functional outcome and mortality after stroke. *Neurology*. 2018;91:e1838–e1850. doi: 10.1212/WNL.0000000000006506