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ORIGINAL RESEARCH

High-Sensitivity Cardiac Troponin T and Cognitive Function Over 12 Months After Stroke—Results of the DEMDAS Study

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BACKGROUND: Subclinical myocardial injury in form of hs-cTn (high-sensitivity cardiac troponin) levels has been associated with cognitive impairment and imaging markers of cerebral small vessel disease (SVD) in population-based and cardiovascular cohorts. Whether hs-cTn is associated with domain-specific cognitive decline and SVD burden in patients with stroke remains unknown.

METHODS AND RESULTS: We analyzed patients with acute stroke without premorbid dementia from the prospective multicenter DEMDAS (DZNE [German Center for Neurodegenerative Disease]-Mechanisms of Dementia after Stroke) study. Patients underwent neuropsychological testing 6 and 12 months after the index event. Test results were classified into 5 cognitive domains (language, memory, executive function, attention, and visuospatial function). SVD markers (lacunes, cerebral microbleeds, white matter hyperintensities, and enlarged perivascular spaces) were assessed on cranial magnetic resonance imaging to constitute a global SVD score. We examined the association between hs-cTnT (hs-cTn T levels) and cognitive domains as well as the global SVD score and individual SVD markers, respectively. Measurement of cognitive and SVD-marker analyses were performed in 385 and 466 patients with available hs-cTnT levels, respectively. In analyses adjusted for demographic characteristics, cardiovascular risk factors, and cognitive status at baseline, higher hs-cTnT was negatively associated with the cognitive domains "attention" up to 12 months of follow-up (beta-coefficient, −0.273 [95% CI, −0.436 to −0.109]) and "executive function" after 12 months. Higher hs-cTnT was associated with the global SVD score (adjusted odds ratio, 1.95 [95% CI, 1.27–3.00]) and the white matter hyperintensities and lacune subscores.

CONCLUSIONS: In patients with stroke, hs-cTnT is associated with a higher burden of SVD markers and cognitive function in domains linked to vascular cognitive impairment.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01334749.

Key Words: acute stroke ■ cardiac troponin ■ cognitive impairment ■ heart and brain axis

Cognitive impairment and dementia are common complications following stroke and can lead to significant disability.[1] Previous studies have shown an association between heart disease and cognitive decline as well as incident dementia.[2,3] Additionally, data from the general population have provided

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RESEARCH PERSPECTIVE

What Is New?

- Higher levels of hs-cTnT (high-sensitivity cardiac troponin T) are associated with cognitive outcome in the domains attention and executive function up to 12 months after acute ischemic stroke, suggesting that hs-cTnT is more closely associated with cognitive domains typically affected by vascular cognitive impairment.
- Higher levels of hs-cTnT are associated with a higher burden of cerebral small vessel disease in acute ischemic stroke, which is mainly driven by an association with higher severity of white matter hyperintensities.

What Question Should Be Addressed Next?

- Future studies should address whether hs-cTnT is linked to progression of small vessel disease and long-term cognitive outcome after stroke.

evidence that (subclinical) myocardial injury, reflected by higher levels of hs-cTnT (high-sensitivity cardiac troponin T), is also associated with poor cognitive performance cross-sectionally as well as incident dementia and cognitive decline even in the absence of manifest cardiac comorbidities.[4,5] Hs-cTnT is a sensitive and specific biomarker of myocardial injury. Routine measurement of hs-cTn is currently not recommended as a screening tool for cognitive impairment in the general population or in a memory clinic setting. However, current guidelines by the American Heart Association recommend routine measurement of hs-cTn in patients with ischemic stroke.[6] This recommendation is based on previous studies that have shown an association between hs-cTn and higher mortality and adverse cardiovascular events after stroke.[7,8] At the same time, there is limited evidence on the association between elevated hs-cTn and cognitive function after stroke. In a study with patients with first-ever ischemic stroke, we have previously demonstrated that hs-cTnT is associated with worse cognitive performance at baseline and during follow-up but not with more severe or faster cognitive decline.[6] However, in the PROSCIS (Prospective Cohort with Incident Stroke) study, longitudinal cognitive data were collected using a screening test via telephone interview, which did not allow for domain-specific assessment. Furthermore, data on prestroke cognitive status were not available.[9] Because hs-cTn indicates myocardial injury, one possible explanation for the link between cognitive outcome and hs-cTn levels is that patients with chronic myocardial injury (reflected in higher levels of cardiac biomarkers such as hs-cTnT) may also have chronic vascular damage in the brain (eg, cerebral small vessel disease [SVD]) due to common underlying cardiac and cerebrovascular risk factors.[5] Indeed, hs-cTnT has been associated with white matter hyperintensities (WMH), a marker of cerebral SVD, both in the general population and in patients with acute ischemic stroke.[10,11] However, previous studies of hs-cTnT and SVD have generally examined individual markers rather than the global burden of SVD. The magnetic resonance imaging (MRI)-based global SVD score,[12] which considers 4 different markers of cerebral SVD, has been linked to cognitive performance both in the general population and in patients with stroke.[13–15]

In this study, we aimed to explore the association of hs-cTnT with longitudinal outcome in different cognitive domains and with SVD burden in patients with stroke without prestroke cognitive impairment or dementia. We assessed data from a prospective multicenter study that was specifically designed to identify predictors of long-term cognitive outcomes in different cognitive domains post stroke.[16]

Nonstandard Abbreviations and Acronyms

CERAD	Consortium to Establish a Registry for Alzheimer's Disease Plus
CMB	cerebral microbleeds
DEMDAS	DZNE [German Center for Neurodegenerative Disease]-Mechanisms of Dementia After Stroke study
NIHSS	National Institutes of Health Stroke Scale
PVS	perivascular spaces
SVD	small vessel disease
WMH	white matter hyperintensities

METHODS

Study Population

The anonymized data that support the findings of this study are available from the principal investigator upon reasonable request.

This study is an exploratory analysis of the ongoing DEMDAS (DZNE [German Center for Neurodegenerative Disease]-Mechanisms of Dementia After Stroke) study (NCT01334749). DEMDAS is an investigator-initiated, prospective, multicenter cohort study. The study protocol has been described in detail before.[16] Between January 2014 and January 2019, 600 patients ≥18 years with acute ischemic or hemorrhagic stroke (onset of

symptoms within 5 days before inclusion) were enrolled in 7 stroke centers across Germany. The diagnosis of stroke was confirmed by neuroimaging (ie, a diffusion-weighted imaging-positive lesion on cranial MRI or a new ischemic lesion on a delayed cranial computed tomography or an intracerebral hemorrhage on cranial computed tomographyor MRI). Due to a low number of patients with hemorrhagic stroke, we included only patients with ischemic stroke into our analyses (see Figure S1). Stroke severity at baseline was measured using the National Institutes of Health Stroke Scale (NIHSS).[17] Prestroke level of function was assessed using the modified Rankin Scale. In order to determine the prestroke modified Rankin Scale level, patients and their informants were questioned about the patient's living situation, need for assistance in activities of daily life, and limited physical abilities before the stroke during the baseline study visit. Patients who were not able to undergo cranial MRI or had a preexisting diagnosis of dementia or an Informant Questionnaire on Cognitive Decline in the Elderly score>64 (indicating preexisting cognitive impairment) at baseline were excluded.[18] For this substudy, we additionally excluded all patients with unavailable hs-cTnT values (n=87). For the analysis of imaging data on SVD, we excluded all patients with incomplete MRI assessment (n=33).

Study participants and their informants were invited for in-person follow-up visits 6 and 12 months after the initial event. At each follow-up visit, patients and their informants underwent comprehensive cognitive assessments; details are in Table S1.

The DEMDAS study was conducted according to the Declaration of Helsinki and was approved by local ethics committees of all participating sites. All patients or their legal guardians provided written informed consent before study inclusion. Reporting of this substudy follows the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Blood Tests

Hs-cTnT was measured from the blood samples collected during the baseline visit using the Elecsys assay (Roche Elecsys Troponin Ths, Mannheim, Germany). This test has a cutoff at 14 ng/L as its upper reference limit (based on the 99th percentile of a healthy population) and a limit of blank at 3 ng/L, a limit of detection at 5 ng/L, and a coefficient of variation of 9% at the upper reference limit.[19]

Neurocognitive Testing

During the follow-up visits, a comprehensive battery of neuropsychological tests classified in 5 cognitive domains (executive function, memory, language, attention, visuospatial function) was performed. Classification of cognitive domains has been published earlier.[20] The Trail Making Test Part B from the Consortium to Establish a Registry for Alzheimer's Disease Plus (CERAD-Plus) battery and the Stroop Colour-Word-Interference Test were used to examine executive function.[21,22] Word List Learning/Recall and Recognition and Figure Recall from CERAD-Plus and immediate and delayed recall of the Rey-Osterrieth Complex Figure were used to examine memory function.[23] Semantic and Phonemic Fluency and Boston Naming Test, which were subtests of the CERAD-Plus as well as language items from the Mini-Mental State Examination were used to examine language.[24] The Trail Making Test Part A from CERAD-Plus and the Digit-Symbol-Substitution Test of the Wechsler Intelligence Scale were used to examine attention.[25] The Figure Drawing Test from CERAD-Plus and the copy test of Rey-Osterrieth Complex Figure were used to examine visual spatial function.[21,23]

First, a *Z* score was calculated for each individual test based on published norms corrected for age, sex, and education.[15] In a second step, the test-specific *Z* scores were averaged for each domain to calculate the 5 domain-specific *Z* scores. Lastly, the 5 domain-specific *Z* scores were averaged to calculate the global cognitive score. Cognitive impairment for any given domain was defined as a domain-specific *Z* score lower than –1.5.

At baseline (ie, during the acute in-hospital stay) we performed the Mini-Mental State Examination and the Montreal Cognitive Assessment to screen for global cognitive impairment in the acute poststroke phase.[22,26]

Neuroimaging

Upon study inclusion 3 Tesla cranial MRI imaging (Siemens, Erlangen, Germany) was performed. Details on the neuroimaging protocol may be found in Data S1. The global SVD burden was examined by assembling the individual SVD markers into a global score from 0 to 4.[9] One point is given for each of the following lesions: (1) presence of lacunes, (2) presence of WMH (periventricular WMH Fazekas grade 3 or deep WMH Fazekas grade≥2), (3) presence of cerebral microbleeds (CMB), and (4) presence of moderate to severe perivascular spaces (PVS) (grade≥2).[12,15] SVD markers that were found within the stroke lesion were not incorporated into imaging analysis.[15]

Statistical Analysis

Data are shown as median with interquartile range (25th and 75th percentile) for continuous and as absolute (N) and relative (%) frequencies for categorical variables. In order to examine the association between hs-cTnT and longitudinal cognitive outcome (ie, cognitive trajectories between 6 and 12 months after stroke), we calculated unadjusted and adjusted generalized linear regression

models for continuous cognitive data (ie *Z* scores for global cognitive performance and the 5 individual domains) and logistic regression for dichotomous outcomes (domain-specific *Z* scores dichotomized at <–1.5) using generalized estimating equations. In addition to longitudinal cognitive outcome, we assessed cross-sectional cognitive data at 6 and 12 months separately by performing linear and penalized logistic regression (using the firthlogit command in STATA) analyses. Both longitudinal and cross-sectional analyses were performed with different levels of adjustment: after running an unadjusted analysis (model 1), we performed our analyses after adjusting for age, sex, and years of education (model 2). In the fully adjusted model (model 3), we additionally adjusted for history of hypertension, diabetes, coronary artery disease, atrial fibrillation, baseline NIHSS score, prestroke modified Rankin Scale score, and cognitive impairment at baseline defined as a Montreal Cognitive Assessment score <26 points or a Mini-Mental State Examination score <24 points if no Montreal Cognitive Assessment was performed in the subacute stroke phase. Because hs-cTnT levels were not normally distributed in our study population, we used log-transformed values for all analyses.

As sensitivity analyses, we reran model 3 with (1) additional adjustment for total SVD score to assess whether the link between hs-cTnT levels and cognitive performance may be mediated by SVD burden, (2) additional adjustment for stroke localization in the left anterior territory, and (3) after exclusion of patients with stroke affecting more than 1 territory.

To investigate the associations between log-transformed hs-cTnT and SVD, we used the following SVD parameters as dependent variables: (1) the global SVD score (range 0–4), (2) the 4 SVD subscores, and (3) the 5 separate SVD markers (lacune counts, periventricular WMH grade, deep WMH grade, CMB counts, PVS grade). For the association with ordinal-scaled variables (ie, global SVD score, periventricular and deep WMH grade as well as with PVS grade), we calculated ordinal logistic regression models. To assess count variables (ie, lacune count and CMB count), we performed negative binomial regression analyses because both lacune count and CMB count data were overdispersed. Finally, to assess the 4 constituent SVD subscores, we used binary logistic regression analyses. All analyses with regard to SVD markers were performed using 3 models with different levels of adjustment: (1) model 1 unadjusted, (2) model 2 adjusted for age and sex, and (3) model 3 with additional adjustment for hypertension, diabetes, hyperlipidemia, coronary artery disease, atrial fibrillation, smoking status and baseline NIHSS score. In a sensitivity analysis, we reran model 3 after exclusion of patients with stroke affecting more than 1 territory.

To account for multiple comparisons, we calculated corrected *P* values for all analyses using false discovery rate according to the Benjamini–Hochberg method. The false discovery rate adjustment of *P* values was based on the sum total of all the tests. We defined statistical significance as a corrected *P* value <0.05. We performed all statistical calculations using SPSS Statistics 26.0 (IBM, Armonk, NY) and STATA 14.0. The corresponding author had full access to all the data from this substudy and takes responsibility for its integrity and the data analysis.

RESULTS

Baseline Characteristics

We included 385 patients in the analysis of cognitive data and 466 patients in the analysis of imaging data (see Figure S1). The study population included in the analysis of cognitive outcome consisted of patients with mostly mild to moderate strokes (median NIHSS score at baseline=2, interquartile range 1–5), the median age was 68 (interquartile range 59–75) years, and 124 (32.3%) of patients were female. Median hs-cTnT levels in our study population were 7 ng/L (interquartile range 4–12 ng/L). Hs-cTnT values were above the upper reference limit of 14 ng/L in 73 (19.0%) of patients. Median time from stroke symptom onset to hs-cTnT measurement was 1 day (interquartile range 1–2 days). Cognitive impairment at baseline was present in 174 (45.2%) patients with available cognitive follow-up data. Detailed patients' baseline characteristics are shown in Table, including differences with respect to patients who were not included in the analysis of cognitive outcome due to missing data. Patients with missing cognitive follow-up data were older, more often had cognitive impairment at baseline, and more often had a history of coronary artery disease or diabetes (see Table). There were no statistically significant differences in baseline characteristics between patients who were included in the analyses of hs-cTnT and SVD markers and those who were excluded from these analyses due to missing data (see Table S2).

Hs-cTnT and Cognitive Outcome

Overall, cognitive outcomes improved in all domains between month 6 and 12 after stroke. The number of individuals with global cognitive impairment was 112 (29.1%) and 90 (23.4%) at 6 and 12 months, respectively. Hs-cTnT was associated with global cognitive performance in the unadjusted longitudinal analysis as well as in the unadjusted cross-sectional analysis at 12 months after stroke. Both associations were no longer statistically significant after full adjustment.

With regard to specific cognitive domains, hs-cTnT was negatively associated with performance in the

Table. Baseline Characteristics of Patients Included in and Excluded From Cognitive Analyses

	Patients included in cognitive analyses (n=385)	Patients excluded from cognitive analyses (n=215)	*P*
Age, y, median (IQR)	68 (59–75)	71 (62–78)	0.010
Female sex, n (%)	124 (32.3%)	76 (35.3%)	0.434
Years of education, median (IQR)	13 (12–17)	13 (11–15)	0.012
History of hypertension, n (%)	208 (54.0%)	128 (59.5%)	0.165
History of diabetes, n (%)	50 (13.0%)	43 (20.0%)	0.021
History of coronary artery disease, n (%)	17 (4.4%)	18 (8.4%)	0.047
History of atrial fibrillation, n (%)	36 (9.4%)	30 (14.0%)	0.067
Cognitive impairment at baseline, n (%)	174 (45.2%)	130 (60.5%)	<0.001
Hs-cTnT, median (IQR)	7 (4–12)		
Hs-cTnT>upper reference limit, n (%)	73 (19.0%)		
Days from symptom onset to blood draw, median (IQR)	1 (1–2)		
Stroke cause			
Large artery atherosclerosis, n (%)	98 (25.5%)	65 (30.2%)	0.066
Cardioembolism, n (%)	80 (20.8%)	53 (24.7%)	0.110
Small artery occlusion, n (%)	50 (13.0%)	16 (7.4%)	0.074
Other cause, n (%)	50 (13.0%)	15 (7.0%)	0.052
Undetermined cause, n (%)	107 (27.8%)	50 (23.3%)	0.491
Informant Questionnaire on Cognitive Decline in the Elderly score, median (IQR)	48 (48–49)	48 (48–50)	0.538
Baseline National Institutes of Health Stroke Scale score, median (IQR)	2 (1–5)	3 (1–5)	0.332
Cognitive impairment at 6 mo, n (%)	112 (29.1%)		
Language	17 (4.4%)		
Memory	26 (6.8%)		
Executive function	30 (7.8%)		
Attention	35 (9.1%)		
Visuospatial function	69 (17.9%)		
Cognitive impairment at 12 mo, n (%)	90 (23.4%)		
Language	15 (3.9%)		
Memory	20 (5.2%)		
Executive function	21 (5.5%)		
Attention	22 (5.7%)		
Visuospatial function	64 (16.6%)		
Stroke localization			
Anterior left	110 (28.6%)	51 (23.7%)	0.199
Anterior right	90 (23.4%)	56 (26.0%)	0.465
Posterior cerebral artery left	29 (7.5%)	13 (6.0%)	0.494
Posterior cerebral artery right	23 (6.0%)	16 (7.4%)	0.484
Brainstem	36 (9.4%)	18 (8.4%)	0.688
Cerebellum	31 (8.1%)	12 (5.6%)	0.261
Multiple	48 (12.5%)	30 (14.0%)	0.604

Baseline characteristics of patients included in cognitive analyses and excluded from cognitive analyses. Univariable comparisons were performed using chi-square test for dichotomous variables and Mann–Whitney *U* test for linear variables. Patients with missing cognitive follow-up data were older, more often had cognitive impairment at baseline and more often had a history of coronary artery disease or diabetes. hs-cTnT indicates high-sensitivity cardiac troponin T; and IQR, interquartile range.

domain "attention" in the longitudinal analysis after adjustment for demographic characteristics, cardiovascular risk factors, and clinical outcome at baseline as well as correction for multiple comparisons (Figure 1). When we examined cognitive outcome at 6 and 12 months separately in cross-sectional analyses, we found an association with the domain "attention" both at 6 and 12 months (Figures 2 and 3) and

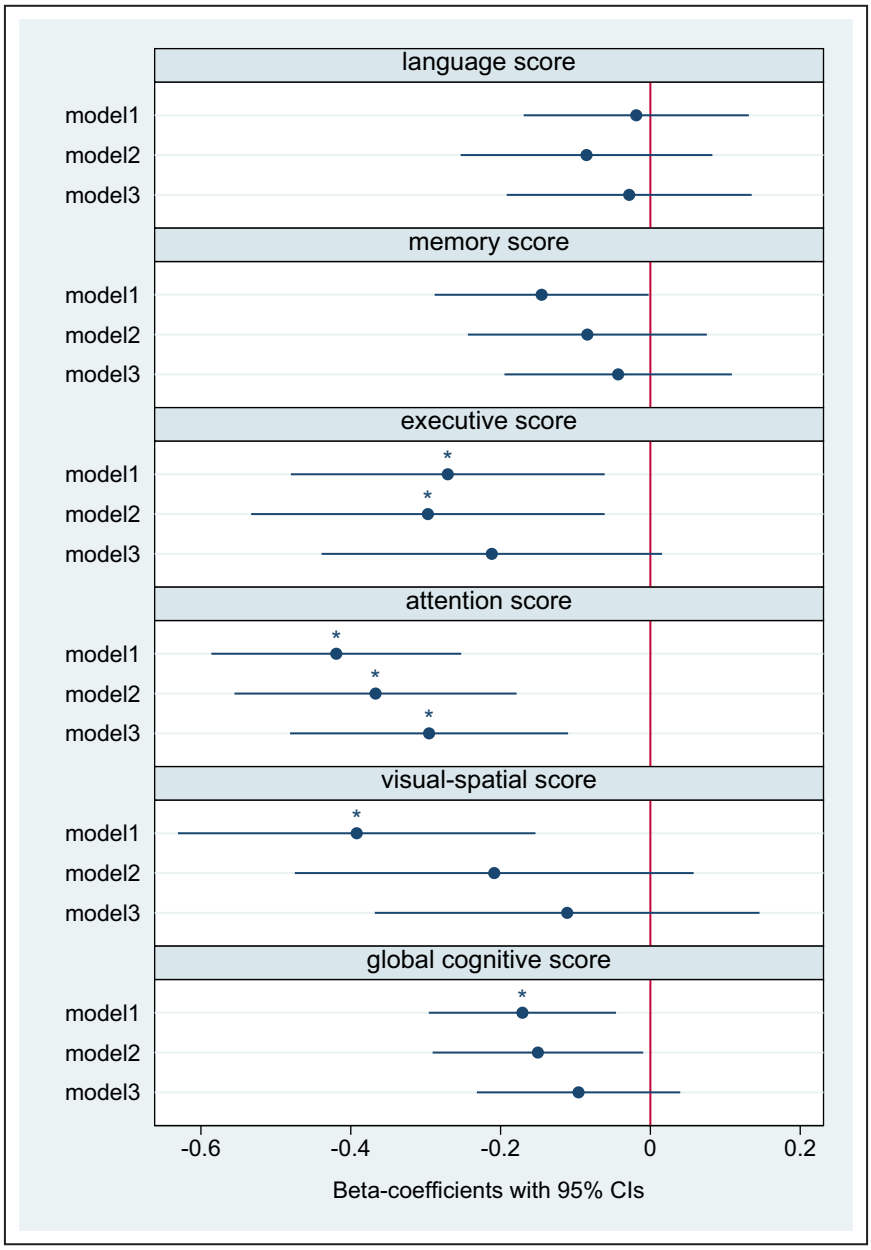

Figure 1. Log-transformed hs-cTnT and cognitive domains (continuous) across 12 months of follow-up according to generalized linear regression models using generalized estimating equations.

The figure displays the respective regression coefficients and 95% CIs. Model 1: unadjusted. Model 2: adjusted for age, sex, and years of education. Model 3: additional adjustment for hypertension, diabetes, coronary artery disease, atrial fibrillation, cognitive impairment at baseline, baseline NIHSS score, and prestroke mRS score. *P_{corr}<0.05. After full adjustment, hs-cTnT was associated with a decline in performance in the cognitive domain "attention" between 6 and 12 months after stroke. Hs-cTnT indicates high-sensitivity cardiac troponin T; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

with executive function at 12 months (Figure 3). The associations we found with the domains "attention" and "executive function" remained significant in the sensitivity analysis after additional adjustment for total SVD burden (see Table S3) and for stroke localization in the left anterior territory (see Table S4). After exclusion of patients with strokes in multiple territories, the association between hs-cTnT and performance in the domain "attention" at 6 months of follow-up was no longer significant (see Table S5). Apart from that, the

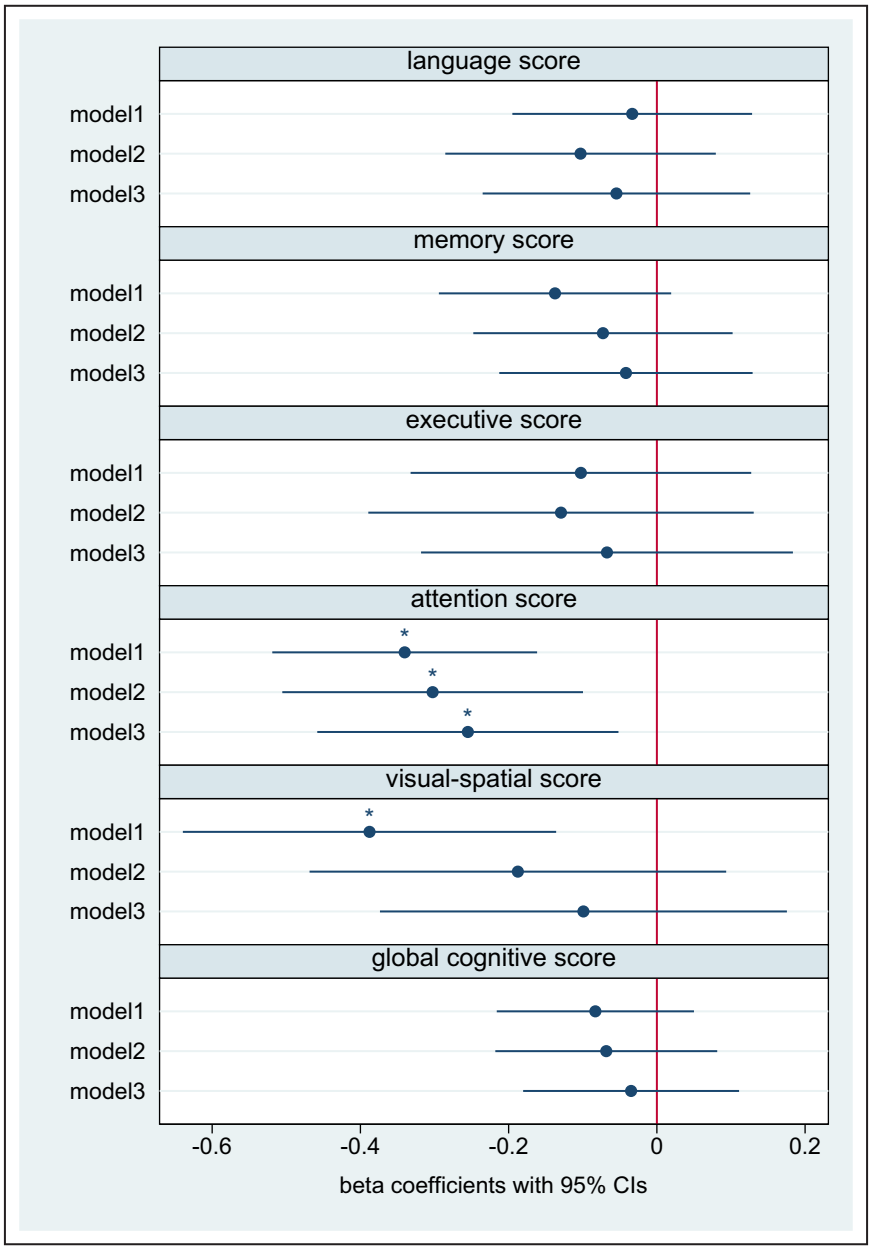

Figure 2. Log-transformed hs-cTnT and cognitive domains (continuous) at 6 months of follow-up according to linear regression models.
The figure displays the respective regression coefficients and 95% CIs. Model 1: unadjusted. Model 2: adjusted for age, sex, and years of education. Model 3: additional adjustment for hypertension, diabetes, coronary artery disease, atrial fibrillation, cognitive impairment at baseline, baseline NIHSS score, and prestroke mRS score. *P_{corr}<0.05. After full adjustment, hs-cTnT was negatively associated with performance in the cognitive domain "attention" in the cross-sectional analyses 6 months after stroke. Hs-cTnT indicates high-sensitivity cardiac troponin T; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

results remained unchanged compared with the main analyses.

There were no statistically significant associations between hs-cTnT and cognitive impairment in any specific domain in the binary outcome models (ie, after dichotomizing cognitive data at a *Z* score of –1.5) both in the longitudinal and in the cross-sectional analyses (see Figures S2 through S4).

Hs-cTnT and SVD Markers

The frequency and burden of SVD markers are displayed in Table S2. Most patients had an SVD score

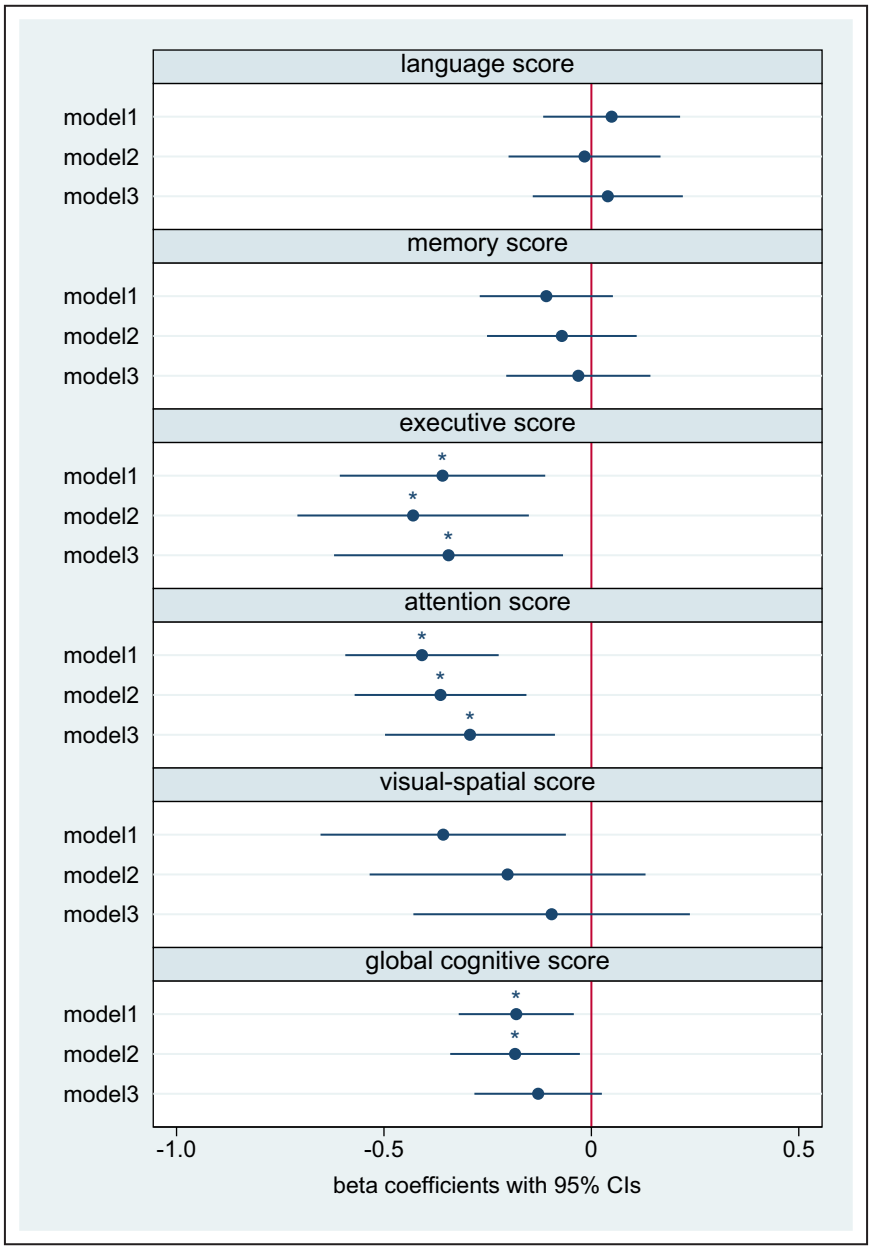

Figure 3. Log-transformed hs-cTnT and cognitive domains (continuous) at 12 months of follow-up according to linear regression models.
The figure displays the respective odds ratios and 95% CIs. Model 1: unadjusted. Model 2: adjusted for age, sex, and years of education. Model 3: additional adjustment for hypertension, diabetes, coronary artery disease, atrial fibrillation, cognitive impairment at baseline, baseline NIHSS score, and prestroke mRS score. *P_{corr}<0.05. After full adjustment, hs-cTnT was negatively associated with performance in the domains "attention" and "executive function" in the cross-sectional analyses 6 months after stroke. Hs-cTnT indicates high-sensitivity cardiac troponin T; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

of either 0 (40.1%, no lesions fulfilling the score criteria) or 1 (29.4%, one lesion type fulfilling the score criteria). The SVD marker most frequently found to fulfill the score criteria was WMH (see Table S2).

Levels of hs-cTnT were associated with the global SVD score (see Figure 4). This association remained statistically significant after full adjustment and correction for multiple testing (adjusted odds ratio for model 3, 1.87 [95% CI, 1.21–2.89], see Figure 4). In the unadjusted models, hs-cTnT was associated with all 4 constituent SVD subscores except for the CMB subscore (see Figure 4). After full adjustment and correction for

multiple testing, the association remained statistically significant for the WMH subscore and the lacune subscore (see Figure 4). However, after exclusion of patients with strokes in multiple territories, the association between hs-cTnT and the lacune subscore was no longer statistically significant (see Table S6). When assessing individual SVD markers in their entire severity range, we found a statistically significant association with deep WMH grade after adjustment for potential confounders and correction for multiple testing (see Figure 5).

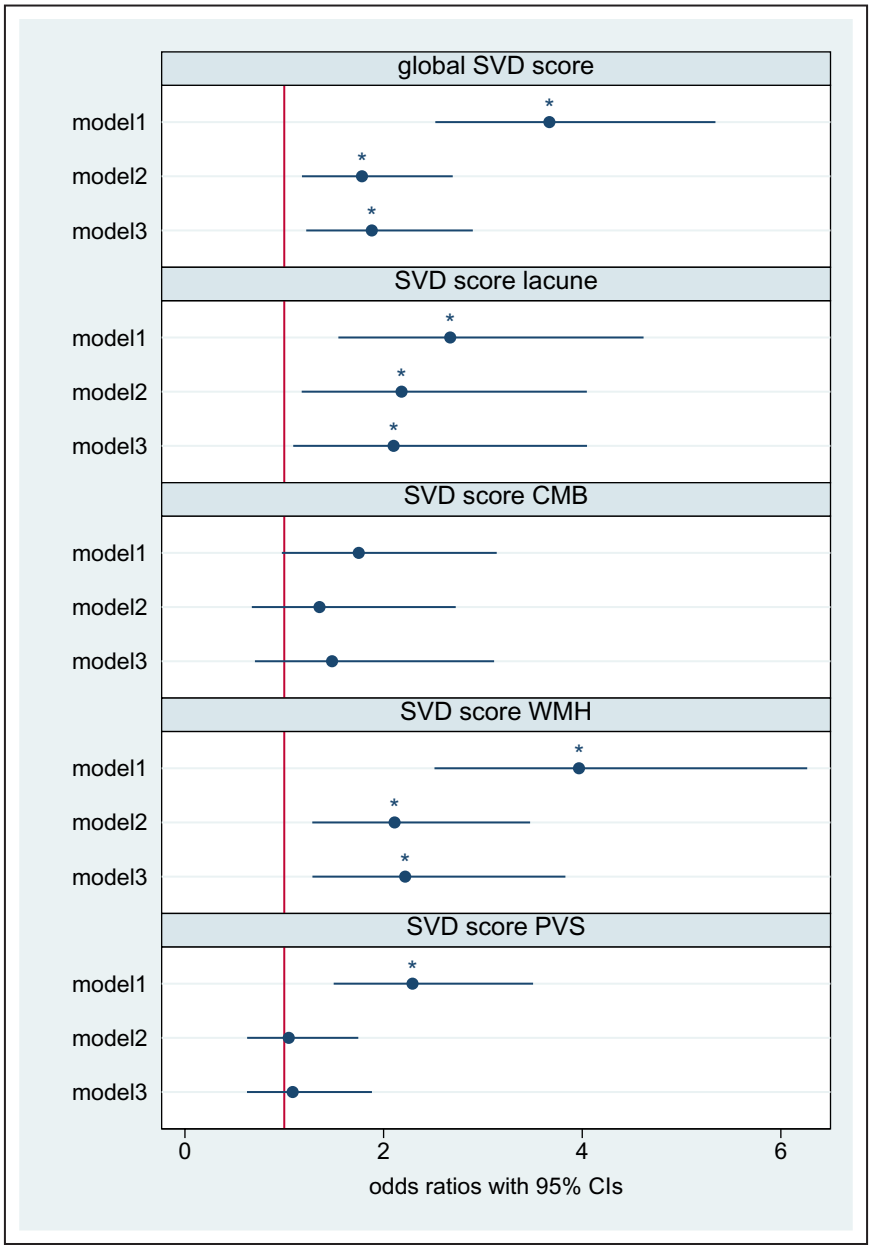

Figure 4. Log-transformed hs-cTnT and global cerebral small vessel disease score as well as 4 constituent SVD subscores.
The figure displays odds ratios and 95% CIs derived from ordinal logistic regression models for the global SVD score and binary logistic regression models for each constituent subscore, respectively. Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: additional adjustment for hypertension, diabetes, hyperlipidemia, coronary artery disease, atrial fibrillation, smoking status, and baseline NIHSS score. After full adjustment, hs-cTnT was associated with higher global SVD scores as well as the WMH and lacune subscores. *P_{corr}<0.05. CMB indicates cerebral microbleeds; hs-cTnT, high-sensitivity cardiac troponin T; NIHSS, National Institutes of Health Stroke Scale; PVS, perivascular spaces; SVD, small vessel disease; and WMH, white matter hyperintensities.

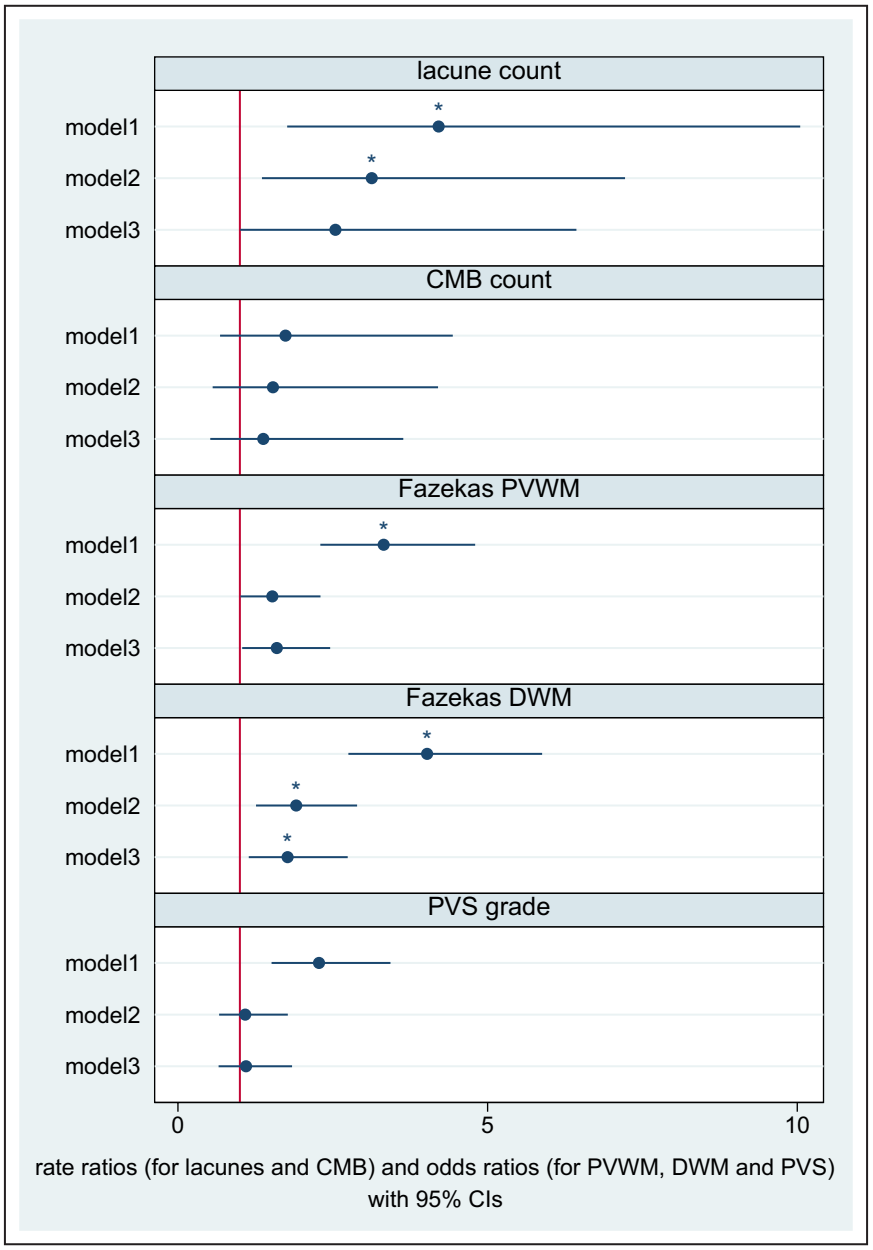

Figure 5. Hs-cTnT and individual cerebral small vessel disease markers in their entire range.
The figure displays odds ratios derived from ordinal regression models for periventricular WMH grade, deep WMH grade, and PVS grade. The figure displays rate ratios calculated using negative binomial regression models for lacune count and CMB count. Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: additional adjustment for hypertension, diabetes, hyperlipidemia, coronary artery disease, atrial fibrillation, smoking status, and baseline NIHSS score. After full adjustment, hs-cTnT remained associated with higher deep WMH grade. *P_{corr}<0.05. CMB indicates cerebral microbleeds; DWM, deep white matter; hs-cTnT, high-sensitivity cardiac troponin T; NIHSS, National Institutes of Health Stroke Scale; PVS, perivascular spaces; PVWM, periventricular white matter; SVD, small vessel disease; and WMH, white matter hyperintensities.

DISCUSSION

This exploratory analysis of the prospective multicenter DEMDAS study contains several important findings. First, hs-cTnT levels were associated with poorer cognitive performance and decline in the domain "attention" up to 12 months of follow-up. Associations were found in both longitudinal and cross-sectional analyses

and remained stable after adjustment for potential confounders, including prevalent cardiovascular risk factors, and after correction for multiple comparisons. Second, hs-cTnT levels were associated with poorer performance in executive function at 12 months after the index stroke. Third, we found that hs-cTnT levels were associated with cerebral SVD burden in patients with stroke, which was driven by the subscores of WMH burden and (to a lesser degree) lacunes. This highlights the potential interplay between subclinical myocardial injury, arteriolosclerotic SVD, and features of vascular dementia. However, because the association between hs-cTnT levels and cognitive function remained statistically significant even after adjustment for SVD burden, the link between hs-cTnT and cognition in patients with stroke seems to also be independently mediated by pathophysiological factors other than SVD.

To our knowledge, our study is the first to examine the association between hs-cTnT levels and different cognitive domains in patients with stroke. Our results are in line with studies from the general population showing an association between hs-cTnT levels and performance in the Digit-Symbol-Substitution Test, which tests mainly attention and processing speed and was also part of the cognitive tests used to assess attention in our study.[4,5,27] Attention and processing speed have typically been attributed to vascular pathology and vascular dementia.[28] Therefore, our results suggest that hs-cTnT is associated with vascular pathology rather than the cognitive domains typically affected in Alzheimer's disease, such as memory or language.[29]

Of note, we did not find a statistically significant association between hs-cTnT levels and cognitive impairment when using the logistic model dichotomizing each score at –1.5. However, only a small percentage of patients (<10% in all cognitive domains except visual spatial function) had cognitive impairment for any given domain. Therefore, we might have missed a statistically significant association due to limited statistical power.

We found that hs-cTnT levels were associated with the global SVD burden measured by the MRI-based SVD score. Our results are in line with 2 previous studies in patients with hypertension and lacunar stroke, respectively, that found an association between NT-proBNP (N-terminal pro–brain natriuretic peptide) and global SVD burden.[30,31] We are, however, not aware of any other studies assessing the link between global SVD burden and hs-cTnT.

When examining the four constituent SVD subscores and the respective SVD markers in their entire severity range, we found that the association with hs-cTnT levels is largely driven by WMH, which was also the most common pathological SVD marker in our study population. Previous studies have also shown a link between hs-cTnT levels and WMH both in the general population and in patients with ischemic stroke.[10,11,32] The association between cardiac biomarkers and other markers of SVD (ie, CMB, PVS, and lacunes) is less well described. We found an association between hs-cTnT levels and the lacune subscore but not with lacune count as a linear variable. A possible explanation is that only a small proportion of our study population had lacunes and that lacune count as a linear variable was highly skewed. This may also be the reason why the association between hs-cTnT and lacune subscore was no longer significant in the sensitivity analysis excluding patients with stroke in more than 1 territory. Concerning the PVS and CMB subscores, we did not find a statistically significant association with hs-cTnT levels after full adjustment and correction for multiple testing. In line with our findings, Gyanwali et al. did not find an association between hs-cTnT and incident CMBs on repeated MRI scans in 343 memory clinic patients.[33]

The pathogenetic mechanisms that explain the association between markers of myocardial injury such as hs-cTnT and cerebral SVD as well as cognitive function have not been fully elucidated. Importantly, it is unlikely that troponin itself causes cognitive impairment or SVD. Hs-cTn is released into the bloodstream as a result of cardiomyocyte injury.[19] Both myocardial injury as well as SVD may result from common underlying vascular risk factors and vascular disease.[34,35] Apart from that, higher levels of hs-cTn may also result from structural heart disease leading to chronic cerebral hypoperfusion.[36,37] Finally, acute stroke has been linked to autonomic cardiac dysfunction and stroke-induced heart injury (so called stroke-heart syndrome) that would explain increased cardiac biomarkers, too.[38] Stroke-heart syndrome typically occurs in the (subacute) stroke phase.[38] It occurs more frequently in patients with higher stroke severity but also depending on stroke localization, for example, in strokes affecting the insular region.[38,39] Because blood draws for hs-cTn measurement were taken relatively early after symptom onset in our study population, both chronic myocardial injury and stroke-induced acute myocardial injury have likely contributed to hs-cTnT levels measured in this study.

Our results suggest that hs-cTnT levels may provide a more accurate determination of the cardiovascular-associated risk for cognitive decline and SVD in patients with stroke than clinical history alone. Indeed, previous research has shown that although a history of cardiovascular comorbidities (such as ischemic heart disease, hypertension, or diabetes) is significantly associated with WMH, cardiovascular risk factors accounted for only a small amount of WMH variability.[40] Hs-cTnT may be a useful parameter to identify patients at risk of cognitive decline because it is a sensitive biomarker for myocardial injury and can be measured in

everyday clinical practice.[41] Moreover, current guidelines for the management of patients with acute ischemic stroke recommend the routine measurement of hs-cTn.[8] Thus, hs-cTn levels are widely available in patients with stroke in particular.

Our study benefits from the multicenter prospective design with the predefined aim to determine factors of cognitive impairment after stroke. To this end, patients underwent repeated face-to-face follow-up examinations including detailed neuropsychological testing that provided an extensive, multidomain, and standardized assessment of cognitive performance. In addition, patients underwent 3T MRI imaging using a standardized protocol in accordance with the Standards for Reporting Vascular Changes on Neuroimaging recommendations for neuroimaging of SVD.[42] Interpretation of MRI was performed centralized and blinded to clinical data.

However, our study also has certain limitations: patients eligible for inclusion in DEMDAS had to be able to give informed consent and be willing and motivated to participate in a study with several years of follow-up including repeated and extensive neuropsychological examinations and cerebral MRI. Therefore, the majority of our study population had mild stroke (median NIHSS score 2). In addition, most of our study population was highly educated (median 13 years of education) and had overall good cognitive outcome resulting in a low number of patients with cognitive impairment for every examined domain. This may have attenuated the association between hs-cTnT levels and cognition, particularly in the dichotomous models and restricts the generalizability to more severely affected patients with stroke. Because hs-cTnT levels were measured only once during the acute phase, we were not able to differentiate between acute and chronic myocardial injury and their respective associations with cognitive performance. Moreover, insular involvement was not systematically recorded in DEMDAS but may also have affected hs-cTn levels in our study population. Stroke localization and the initial neurological deficit may affect the performance in cognitive tests. To account for this, we adjusted our analysis for initial NIHSS score and presence of global cognitive impairment at baseline. In addition, we performed a sensitivity analysis with additional adjustment for stroke located in the left anterior territory, which has been associated with an increased risk of poststroke cognitive impairment.[43] However, we cannot exclude residual confounding of our results due to stroke localization.

In addition, there was a considerable rate of loss to follow-up in our study population. Because patients with poor cognitive function are less likely to take part in repeated follow-up examinations, this might have led to selective attrition bias from loss to follow-up. The analyses we report here were exploratory and not part of the prespecified DEMDAS study protocol. The DEMDAS study was not specifically powered to detect an association between hs-cTnT and cognitive outcome. The long-term follow-up period of the DEMDAS study is still ongoing. Therefore, our current analysis on imaging data is restricted to the MRI at baseline and we were not able to examine the association between hs-cTnT levels and SVD progression. However, the study protocol of DEMDAS includes repeated MRI imaging[16] during the follow-up period so that this question may be addressed in future substudies.

CONCLUSIONS

Our results from this multicenter prospective study with comprehensive neuropsychological assessment show that hs-cTnT levels at baseline is associated with performance in the cognitive domain “attention” and “executive function” in patients with stroke with up to 12 months of follow-up. This suggests that hs-cTnT is associated with vascular pathology and vascular dementia rather than the cognitive domains typically affected in Alzheimer’s disease in patients with stroke. In this cohort, hs-cTnT levels are also associated with the global SVD burden in general and severity of WMH as a marker of arteriolosclerotic atheropathy in particular.

APPENDIX

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Supplemental Material

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