Aus dem der Klinik für Neurologie
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DISSERTATION

Kardiales Troponin und Schweregrad zerebraler White matter lesions bei akutem ischämischem Schlaganfall

Cardiac Troponin T and severity of cerebral white matter lesions in acute ischemic stroke

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Inhaltsverzeichnis

1. Abstract

In the literature, there is evidence of an association between cardiac diseases and clinical cognitive impairment as well as subclinical brain injury. We examined whether there is a link between elevated cardiac troponin levels (hs-cTnT) as a marker of subclinical myocardial injury and severity of white matter lesions (WML) as a marker of subclinical brain injury in stroke patients since those patients are a high-risk population in terms of both cognitive decline and cardiac comorbidity.

We conducted a retrospective analysis of consecutive acute ischemic stroke patients admitted to Charité-University Hospital, Berlin from 2011-2013. All included participants underwent 3T-cMRI and serial hs-cTnT measurements as part of the clinical routine. Severity of WML was graded using the age- related white matter severity score (ARWMS). Patients with hs-cTnT >52ng/l or dynamic change of hs- cTnT >50%, which may indicate acute myocardial damage, were excluded. We performed unadjusted and adjusted quantile regression models to determine whether there is an association between hs- cTnT (dichotomized at the 99th percentile of a healthy reference population, 14ng/l) and WML.

The data of 860 patients were examined (median age 73 years, 44.8% female, median ARWMS 6). In patients with elevated hs-cTnT, WML were more severe than in patients with normal hs-cTnT (median ARWMS 8 vs. 5, adjusted beta for the 50^{th} percentile 1.12, 95% CI 0.41-1.84). There was a more pronounced association between WML and elevated hs-cTnT in patients with moderate to severe WML (beta 1.77, 95% CI 0.26-3.27 for 80^{th} percentile). Further division of patients with elevated hs- cTnT values showed that the association was independent of the severity of hs-cTnT elevation.

Our data indicate an association between subclinical myocardial injury and severity of white matter lesions. Longitudinal studies are needed to assess the impact of risk-modifying therapy on the prevention of cognitive impairment and the value of hs-cTnT as a parameter for therapy monitoring.

Zusammenfassung

In der Literatur finden sich Hinweise auf einen Zusammenhang zwischen kardialen Erkrankungen und sowohl kognitiver Beeinträchtigung als auch subklinischer Schädigung des Gehirns. In dieser Arbeit wurde untersucht, ob ein Zusammenhang zwischen einer Erhöhung des kardialen Troponins (hs-cTnT) als Marker einer subklinischen Myokardschädigung und dem Schweregrad zerebraler „white matter lesions“ (WML) als Marker einer subklinischen Hirnschädigung bei Schlaganfallpatienten besteht.

Es handelt sich um eine retrospektive Auswertung von Patienten mit akutem ischämischem Schlaganfall, die von 2011-2013 am Campus Benjamin Franklin stationär behandelt worden sind. Bei allen eingeschlossenen Patienten wurden im Rahmen der klinischen Routine ein 3T-cMRT und serielle Bestimmungen der Troponinwerte durchgeführt. Der Schweregrad der zerebraler WML wurde anhand des „age-related white matter severity scores“ (ARWMS) bestimmt. Patienten mit einem hs-cTnT > 52 ng/l oder einer Änderung des hs-cTnT > 50% in seriellen Kontrollen wurden ausgeschlossen, da diese Konstellationen auf einen akuten Myokardschaden hindeuten. Es wurden unadjustierte und adjustierte Quantilsregressionsanalysen durchgeführt, um festzustellen, ob ein Zusammenhang zwischen erhöhtem hs-cTnT (cut-off 14 ng/l, entsprechend der 99. Perzentile einer gesunden Kontrollpopulation) und WML besteht.

Insgesamt wurden die Daten von 860 Patienten untersucht (medianes Alter 73 Jahre, 44.8% weibliches Geschlecht, medianer ARWMS 6). Patienten mit erhöhtem hs-cTnT hatten ein größeres Ausmaß an WML als Patienten mit normwertigem hs-cTnT (medianer ARWMS 8 vs. 5, adjustiertes beta für die 50. Perzentile 1.12, 95% CI 0.41-1.84). Der Zusammenhang zwischen WML und erhöhtem hs-cTnT war stärker bei Patienten mit höherem Schweregrad an WML (beta 1.77, 95% CI 0.26-3.27 für die 80. Perzentile). Eine weitere Aufteilung der Studienpopulation nach hs-cTnT-Werten zeigte, dass der Zusammenhang unabhängig vom Ausmaß der hs-cTnT-Erhöhung war.

Die Ergebnisse weisen auf einen Zusammenhang zwischen subklinischem Myokardschaden und zerebralen WML hin. Es braucht longitudinale Studien, um den Einfluss einer risikomodifizierenden Therapie zur Vorbeugung einer kognitiven Einschränkung und den möglichen Stellenwert von Troponin als Marker eines Therapieerfolgs zu untersuchen.

2. Background and purpose

The increasing prevalence of dementia and cognitive impairment constitutes a major public health problem worldwide [1]. No curative treatment for dementia is available to this date. Therefore, it is of importance to gain knowledge on treatable risk factors and develop possible prevention strategies.

Many cross-sectional and longitudinal studies have demonstrated an association between clinical cognitive impairment and manifest cardiac diseases, such as congestive heart failure or atrial fibrillation [2, 3, 4]. Moreover, data suggest that treatment of heart diseases may lead to an improvement of cognitive function [5].

This link with cardiac diseases has been demonstrated for the development of vascular dementia as well as Alzheimer's dementia [6, 7, 8].

Besides these clinical observations, there is also evidence of a link between cardiac diseases and subclinical brain injury [9, 10]. However, by the time cardiac conditions become clinically apparent, the impact of preventive strategies may already be diminished due to the presence of significant cerebral injury. Furthermore, a relation between subclinical cardiac dysfunction and cognitive impairment has also been shown in patients without clinically apparent cardiac diseases [11]. In order to ensure an effective prevention of cognitive impairment, it may therefore be of benefit to diagnose cardiac damage before the onset of clinical symptoms.

The use of cardiac Troponins is well-established in clinical routine for the diagnosis of myocardial infarction since they are highly sensitive and specific of myocardial damage [12]. Measuring troponin with high-sensitivity assays (hs-cTnT) now enables clinicians to also detect myocardial damage at an early stage [13] when clinical symptoms might not yet be present. Data show that subclinical myocardial injury determined by higher levels of hs-cTnT is associated with poorer cognitive performance and an increased longitudinal risk of hospitalization with an ICD-9 code for dementia in subjects without manifest heart disease [14, 15].

Impairment of executive function can be an early clinical sign of developing dementia [16, 17] and is known to be associated with subcortical vascular damage [18, 19]. White matter lesions (WML) are a useful marker to determine the extent of cerebral small vessel disease [20] and are commonly found in older adults [21]. They are defined as areas of cerebral white matter that appear hyperintense on T2-weighted MRI. Persons with more extensive WML perform worse in cognitive testing and have greater severity of cortical atrophy in cerebral imaging [22, 23]. Moreover, WML progression has also been linked to cognitive decline [24, 25]. Stroke patients with a higher degree of WML have poorer cognitive outcome one year after the event [26]. The exact pathomechanism that explains these observations is not yet fully understood.

We know that progress of WML is largely age-related [27]. However, there is strong evidence for an association between WML severity and common cardiovascular risk factors, such as hypertension [28, 29]. Apart from that, studies have shown a link with cardiac conditions like atrial fibrillation, left- ventricular hypertrophy or low stroke volume [10, 30, 31, 32].

Knowing that there is a link between subclinical myocardial injury and cognitive impairment on the one hand and WML, cardiac diseases and the risk of cognitive decline on the other hand implies that there may also be a connection between subclinical cardiac dysfunction and subclinical brain injury. So far, only few data exist on this matter. Studies that have been conducted to this date yield results in favor of the hypothesized coexistence of subclinical chronic brain and heart injury: Hilal et al. found a significant association between hs-cTnT and cortical cerebral microinfarcts [33]. Analyses of the ARIC (atherosclerosis risk in communities) study revealed a significant association between hs-cTnT and WML on cMRI performed ~ 3 years prior [34]. Moreover, hs-cTnT also seemed to be associated with progression of WML in follow-up MRI ~11 years after the initial brain image [34].

Stroke patients are at higher risk of cognitive impairment or dementia than the general population [35] and often have acute or chronic cardiac diseases [36]. Therefore, our aim was to assess whether an association between subclinical myocardial injury (i.e. elevated hs-cTnT) and subclinical brain injury (i.e. more severe WML) can be found in these patients.

We hypothesized that elevated hs-cTnT levels would be associated with more severe WML on cerebral MRI in stroke patients.

3. Methods

Study population

This cross-sectional study assesses data from a screening list, which includes consecutive stroke patients admitted to the Department of Neurology at Charité-Campus Benjamin Franklin, Berlin between February 2011 and December 2013. The data were recorded anonymously and the list only includes data that were generated during clinical routine. For this study, we defined acute ischemic stroke as an acute focal neurological deficit with onset ≤72 hours prior to admission with confirmation on cerebral imaging (CT or MRI). We did not include patients with a diagnosis of transient ischemic attack.

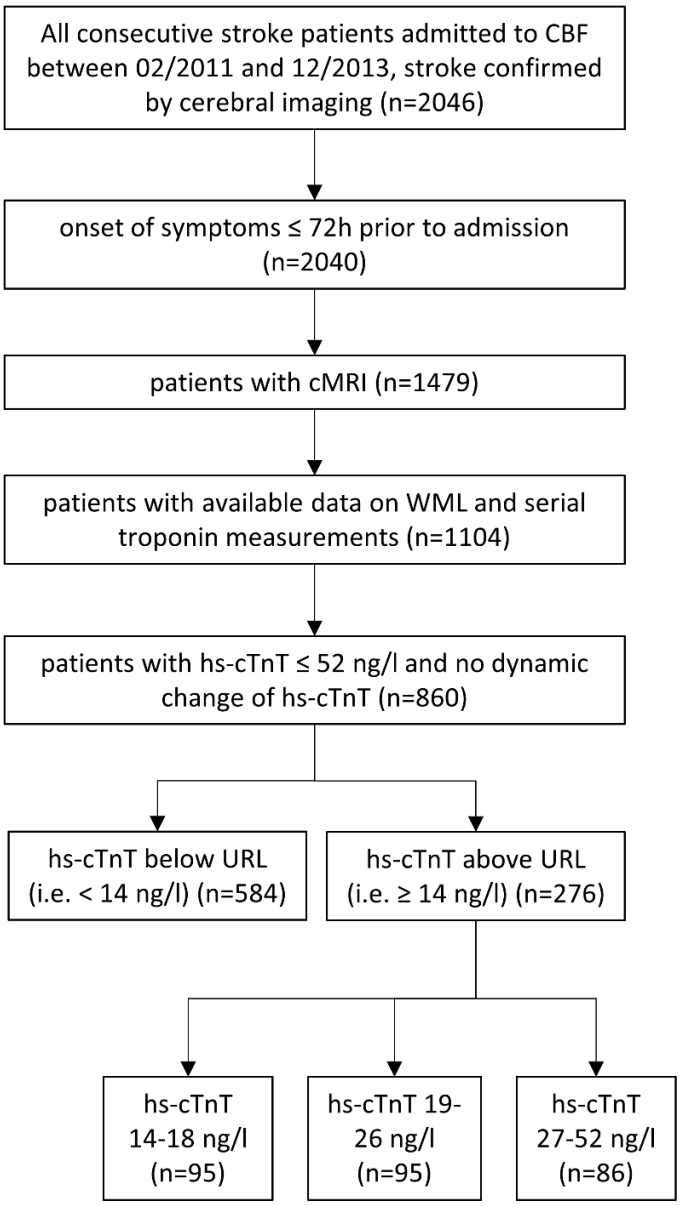
Patient characteristics of interest for this analysis were obtained from medical records. Besides imaging data and hs-cTnT levels, we recorded age, sex, presence of hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, heart failure, diabetes, previous history of stroke and smoking status and patients' medication. Since cognitive testing was not

part of the routine work-up

for acute stroke patients, no data concerning the cognitive status of the study population prior to or after the event were available.

Figure 1 shows inclusion and exclusion criteria. Since CT imaging has lower accuracy and sensitivity concerning the detection of white matter lesions, we evaluated data of those patients that had undergone cerebral MRI (n=1479).

Fig. 1 algorithm for inclusion/exclusion and comparison groups



Abbreviations: CBF = Charité Benjamin Franklin hospital, cMRI = cerebral magnetic resonance imaging, WML = white matter lesions, hs-cTnT = high-sensitivity cardiac troponin T, URL = upper reference limit

This graph is a copy of figure 1 from the publication cited on pp 29-37 of the dissertation [37]

There are various pathophysiologic mechanisms, which may lead to myocardial damage in stroke patients [36]. One can distinguish between acute and chronic myocardial injury by performing serial hs-cTnT measurements [12]. Acute myocardial injury typically leads to a dynamic change in hs-cTnT levels [12]. Stable hs-cTnT levels are indicative of chronic myocardial injury [12], the type of damage, which was of interest for this analysis. With the diagnostic algorithm for suspected myocardial infarction by the European Society of Cardiology as a reference [38], we therefore excluded patients with dynamic change of troponin values > 50 % or a troponin value > 52 ng/l in any measurement (n=244). When less than two hs-cTnT values were available, the patient was excluded (n=375) because we could not differentiate between acute or chronic myocardial injury in this case. No patient included in this analysis had a diagnosis of acute myocardial infarction.

Neuroimaging

All patients included in this study were examined in a 3T MRI (Trim Trio, Siemens AG, Erlangen, Germany). The protocol used in clinical routine includes T2*, diffusion-weighted imaging, time-of-flight MR angiography, fluid attenuated inversion recovery and perfusion imaging. Imaging data were assessed by trained neurologists or neuroradiologists irrespectively of the question addressed in this study. Routine assessment included grading of white matter lesion severity on fluid attenuated inversion recovery using the Age-related white matter severity score (ARWMS) [39].

To determine the score, five regions of the brain are examined with regard to severity of white matter lesions: frontal, parieto-occipital, temporal, infratentorial and basal ganglia. Right and left hemisphere are assessed separately. In each region, severity of white matter lesions is graded on a scale from 0 (no lesions) to 3 (confluent lesions), resulting in a final score from 0 to 30 [38]. Acute infarcts were not included in the rating.

Blood tests

The laboratory of Campus Benjamin Franklin used a high sensitivity Troponin T assay (Roche Elecsys Troponin Ths, Mannheim, Germany) to measure troponin levels. The 99th percentile upper reference limit of a healthy population is 14 ng/l and the limit of detection is 3 ng/l [40]. If hs-cTnT levels were below the upper reference limit, the laboratory did not provide actual values before March 2013.

Acute stroke patients admitted to Campus Benjamin Franklin underwent serial troponin measurements as part of the clinical routine: Initial troponin values were obtained on admission

and subsequent values within 24 hours thereafter. For the statistical analyses, we used the troponin values as measured on admission

Measurement of creatinine values was also part of the routine laboratory work-up on admission. The laboratory estimated glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration equation [41].

Statistical analysis

Mann-Whitney U test for binominal and Spearman correlation analysis for continuous variables were used for univariate analyses of WML and patients' baseline characteristics since the dependent variable (WML) was not normally distributed. The association between hs-cTnT and WML was analyzed by performing quantile regression analysis using three different adjustment models: In the first model, we performed unadjusted analyses. In the second model, we adjusted for age (continuous) and sex (dichotomous). In the third model (full adjustment), additional adjustment was made for comorbidities with a potential influence on WML severity including atrial fibrillation (dichotomous), coronary artery disease (dichotomous), diabetes mellitus (dichotomous), smoking status (dichotomous), heart failure (dichotomous), hypertension (dichotomous), hyperlipidemia (dichotomous) and previous history of stroke (dichotomous).

In contrast to linear regression analysis, quantile regression compares medians instead of means. Therefore, it is more robust to outliers and is not influenced by skewness in the distribution of the dependent variable [42]. Linear regression analysis relies on the assumption of a linear association between the dependent and the independent variable. In contrast, quantile regression analysis can be performed in different quantiles of the dependent variable [42]. Thus, one is able to assess associations with covariates not only for the median but also for the upper and lower parts of the distribution of the dependent variable. Since there are no well-established clinical cut-offs for the ARWMS, we decided against categorization of the dependent variable to perform logistic regression analyses.

In addition to median quantile regression analysis, we performed quantile regression analysis for the 20^{th}, 40^{th}, 60^{th} and 80^{th} percentile of WML in order to assess whether there was a difference in the association between hs-cTnT and WML depending on the extent of white matter disease. For each regression analysis, we provide the regression coefficient (beta) with 95% confidence interval (CI) and p-value. The regression coefficients indicate the effects of the covariate on the cut-off of the respective quantile of the dependent variable, just like in any other regression model.

For the median quantile regression analysis, we used two different approaches to model hs-cTnT levels: In a first approach, hs-cTnT was dichotomized into either "normal" (i.e. < 14 ng/l) or

"elevated" (≥ 14 ng/l). In a second approach, we assessed if the association with WML depended on the severity of hs-cTnT elevation. Therefore, patients with elevated hs-cTnT were split into tertiles (14-18 ng/l, 19- 26 ng/l and 27-52 ng/l). The reference group for both approaches were the patients with normal hs- cTnT (< 14 ng/l).

To perform quantile regression analysis we used Stata (version 14; StataCorp, College Station, TX). For all other analyses we used SPSS Statistics 23.0 (IBM, Armonk, NY). We conducted all statistical procedures at a 0.05 significance level. No adjustment was made for multiple comparisons.

4. Results

Baseline characteristics

We included 860 patients in this study (figure 1). Detailed information on patient characteristics are shown in Table 1. In our study population, the median age was 73 years (interquartile range = IQR 65- 80 years) with 55.2% male patients. The median ARWMS was 6 (IQR 4-10) and hs-cTnT values on admission were above the upper reference limit (i.e. 14 ng/l) in 32.4% of patients. Univariate analyses revealed that atrial fibrillation, hypertension, diabetes mellitus, hyperlipidemia and history of stroke were positively associated with WML. WML was significantly more severe in women than in men. There was a positive correlation between age and white matter lesions. For all results of univariate analyses, also see Table 1.

Table 1: Univariate analysis of patient characteristics according to WML

Variable		**Spearman's correlation coefficient**	**WML Median (IQR)**	**p**
Age				
years, median, IQR	*73 (65-80)*	*.397*		*<0.001*
Sex				
male	55.2% (n=470)		*5 (4-8)*	*<0.001*
female	44.8% (n=390)		*8 (4-12)*	
hs-cTnT				
normal	67.9% (n=584)		*5 (3-9)*	*<0.001*
elevated	32.1% (n=276)		*8 (4-12)*	
eGFR				
ml/min, median (IQR)	*73.26 (57.71-86.55)*	*-.193*		*<0.001*
Atrial fibrillation				
yes	27.5% (n=236)		*7 (4-12)*	*.003*
no	72.5% (n=624)		*6 (3-10)*	
CAD				
yes	15.9% (n=138)		6.5 (4-10)	.135
no	84.1% (n=722)		6 (4-10)	

Diabetes mellitus				
yes	25.4% (n=219)		*7 (4-11)*	*.002*
no	74.6% (n=641)		*6 (3-10)*	
Heart failure				
yes	6.0% (n=51)		*8 (4-14)*	*.013*
no	94.0% (n=809)		*6 (4-10)*	
History of stroke				
yes	25.4% (n=219)		*8 (4-13)*	*<0.001*
no	74.6% (n=641)		*6 (3-10)*	
Hyperlipidemia				
yes	59.5% (n=512)		*6 (4-10)*	*.042*
no	40.5% (n=348)		*6 (3-10)*	
Hypertension				
yes	82.6% (n=711)		*7 (4-11)*	*<0.001*
no	17.4% (n=149)		*4 (2-6)*	
Medication beta-blockers				
yes	42.9% (n=344)		*8 (4-11)*	*<0.001*
no	57.1% (n=457)		*5 (3-9)*	
Medication RAAS inhibitors				
yes	47.8% (n=383)		*7 (4-11)*	*<0.001*
no	52.2% (n=418)		*5 (3-9)*	
Smoking status				
yes	19.5% (n=168)		*4 (3-8)*	*<0.001*
no	80.5% (n=692)		*6 (4-10)*	

Abbreviations: WML = white matter lesions, IQR = interquartile range, hs-cTnT = high-sensitivity cardiac troponin T, eGFR = estimated glomerular filtration rate, CAD = coronary artery disease

This table is a copy of table 1 from the publication cited on pp 29-37 of the dissertation [37]

Patients who were excluded from this study were older ($p < 0.001$), more often female ($p < 0.001$), more heart failure ($p < 0.001$), more CAD ($p=0.002$), more AFIB ($p < 0.001$), more non-smokers ($p=0.004$), less hyperlipidemia ($p=0.005$), hypertension ($p < 0.001$), lower GFR ($p < 0.001$) No significant difference were found regarding history of stroke and diabetes mellitus. For all characteristics of excluded patients, see table 2.

Table 2: characteristics of excluded patients (n=1186)

Age, years, median (IQR)	78 (70-85)
Sex, female (%)	606 (53.7%)
Wahlund Score, median (IQR)	-
Hs-cTnT, above ULR (%)	63.7% (n=683)
Hs-cTnT, µg/dl, median (IQR)	0.019 (0.013-0.041)
Atrial fibrillation (%)	487 (43.1%)
Hypertension (%)	1008 (89.3%)
Diabetes mellitus (%)	317 (28.1%)
Heart failure (%)	168 (14.9%)
CAD (%)	246 (21.8%)
Hyperlipidemia (%)	607 (43.8%)
Previous history of stroke (%)	327 (29.0%)

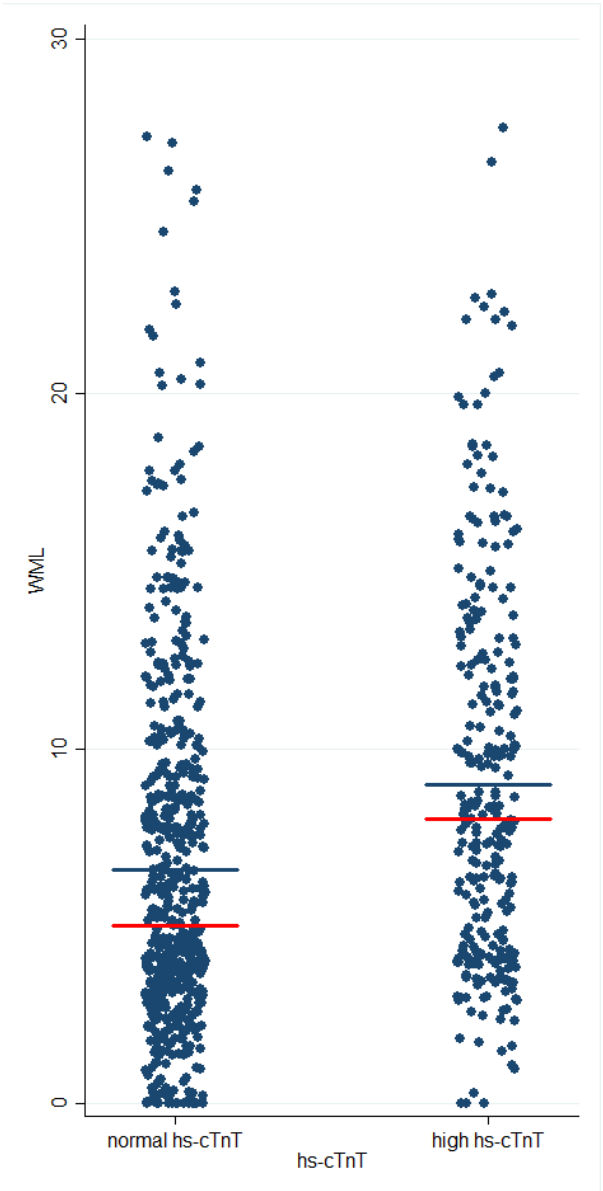
Smoking (%)	162 (14.3%)
GFR, ml/min, median (IQR)	64.61 (48.66-80.47)

Abbreviations: IQR = interquartile range, hs-cTnT = high-sensitivity cardiac troponin T, eGFR = estimated glomerular filtration rate, CAD = coronary artery disease

Hs-cTnT and WML

In unadjusted median quantile regression analysis, patients with hs-cTnT > 14 ng/l had more extensive WML than those with normal hs-cTnT levels (figure 2, table 3). This association was attenuated after adjustment for age and sex as well as in the fully adjusted model but remained statistically significant.

Fig. 2 Extent of white matter lesions according to hs-cTnT status



Distribution of ARWMS in patients with normal (< 14 ng/l, n=584) and elevated (≥ 14 ng/l, n=276) hs-cTnT. The red line indicates the median ARWMS score (5 in patients with normal hs-cTnT, 8 in patients with elevated hs-cTnT). The blue line indicates the mean ARWMS score (7 in patients with normal hs-cTnT, 9 in patients with elevated hs-cTnT). Abbreviations: hs-cTnT = high-sensitivity cardiac troponin T, ARWMS = age-related white matter severity

score

This graph is a copy of figure 2 from the publication cited on pp 29-37 of the dissertation [37]

The unadjusted median quantile regression analysis with hs-cTnT categorized into four groups showed that patients with elevated hs-cTnT had more extensive WML in all tertiles compared to the reference group of patients with normal hs-cTnT levels (table 3). Regression coefficients were similar in all tertiles. Adjusting for age, sex and all other baseline characteristics attenuated the association with WML so that a significant association remained in the first tertile.

Table 3 Median quantile regression analysis with hs-cTnT a) as a dichotomous and b) as a categorical variable

Adjustment	**Model 1**		**Model 2**		**Model 3**	
Stratification model	Beta (95% CI)	p	Beta (95% CI)	P	Beta (95% CI)	p
a)						
hs-cTnT ≥ 14 ng/l	*3.00 (2.00-4.00)*	*<0.001*	*0.90 (0.19-1.61)*	*0.013*	*0.87 (0.13-1.60)*	*.0021*
b)						
hs-cTnT group 2	*3.00 (1.92-4.08)*	*<0.001*	*1.00 (0.11-1.89)*	*0.028*	*1.14 (0.48-1.81)*	*0.001*
hs-cTnT group 3	*3.00 (0.75-5.25)*	*0.009*	1.14 (-0.69-2.97)	0.221	0.96 (-0.86-2.77)	0.301
hs-cTnT group 4	*3.00 (1.33-4.67)*	*<0.001*	0.57 (-0.60-1.75)	0.340	0.44 (-1.09-1.98)	0.569

Quantile regression analysis was performed according to three adjustment models. Model 1: unadjusted regression analysis (n=860). Model 2: adjustment for age and sex (n=860). Model 3: adjustment for age, sex and other baseline characteristics as described in the methods section (n=860). Abbreviations: hs-cTnT = high-sensitivity cardiac troponin T, CI = confidence interval

This table is a copy of table 2 from the publication cited on pp 29-37 of the dissertation [37]

In the quantile regression analysis for the 20th, 40th, 60th and 80th WML percentiles we saw that the association between elevated hs-cTnT and WML was stronger in patients with moderate to severe WML. While the cut-off of 20th percentile of WML was only increased by 0.38 (95% CI -0.27-1.03) for those with hs-cTnT ≥ 14 ng/l after full adjustment the cut-off of the 80th percentile was increased 1.41 (95% CI 0.09-2.74) (see also figure 3 and table 4).

Table 4 Quantile regression analysis in different WML percentiles

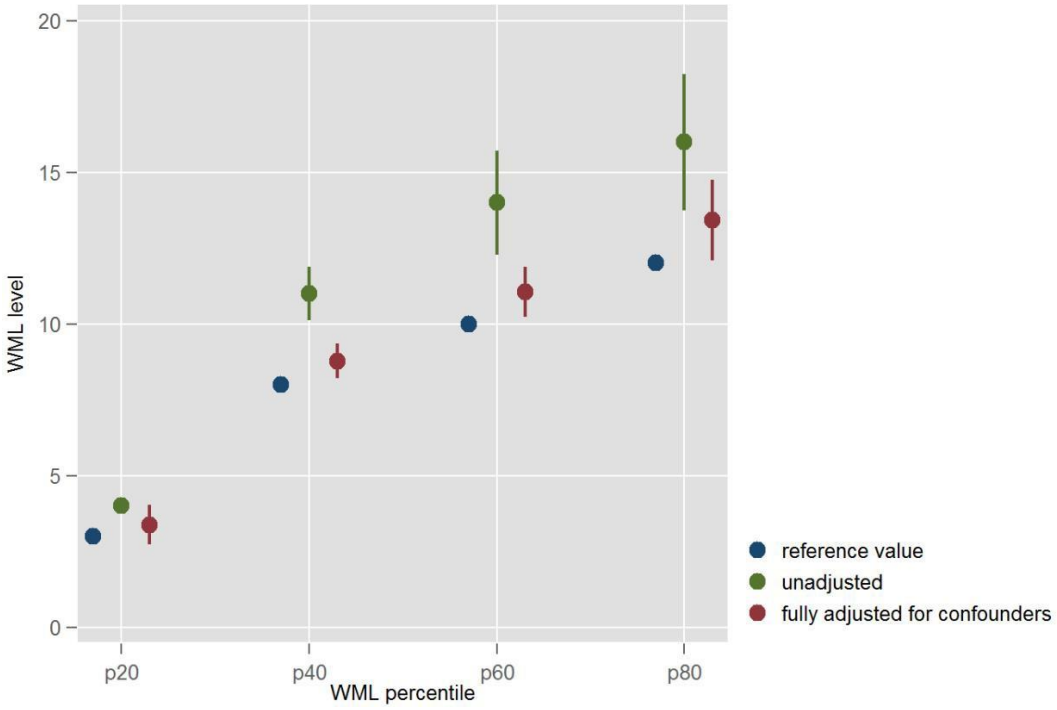
Percentile	**Adjustment model**	**Variable**	**Beta (95% CI)**	**p**
p20	**Model 1**	*hs-cTnT ≥ 14 ng/l*	*1.00 (1.00-1.00)*	*<0.001*
	Model 2	hs-cTnT ≥ 14 ng/l	0.27 (-0.19-0.73)	0.243
	Model 3	hs-cTnT ≥ 14 ng/l	0.38 (-0.27-1.03)	0.246
p40	**Model 1**	*hs-cTnT ≥ 14 ng/l*	*3 (2.13-3.87)*	*<0.001*
	Model 2	*hs-cTnT ≥ 14 ng/l*	*0.38 (0.26-1.74)*	*0.008*
	Model 3	*hs-cTnT ≥ 14 ng/l*	*0.78 (0.21-1.35)*	*0.007*
p60	**Model 1**	*hs-cTnT ≥ 14 ng/l*	*4 (2.28-5.71)*	*<0.001*
	Model 2	*hs-cTnT ≥ 14 ng/l*	*1.17 (0.12-2.22)*	*0.03*

	Model 3	*hs-cTnT ≥ 14 ng/l*	*1.06 (0.24-1.87)*	*0.011*
p80	**Model 1**	*hs-cTnT ≥ 14 ng/l*	*4 (1.75-6.24)*	*<0.001*
	Model 2	hs-cTnT ≥ 14 ng/l	0.93 (-0.46-2.32)	0.19
	Model 3	*hs-cTnT ≥ 14 ng/l*	*1.41 (0.09-2.74)*	*0.037*

Quantile regression analysis was performed for the 20th, 40th, 60th and 80th percentile of WML. Quantile regression analysis was performed according to three adjustment models. Model 1: unadjusted regression analysis (n=860). Model 2: adjustment for age and sex (n=860). Model 3: adjustment for age, sex and and other baseline characteristics as described in the methods section (n=860). Abbreviations: WML=white matter lesions, CI = confidence interval, hs-cTnT = high-sensitivity cardiac troponin T

This table is a copy of table 3 the publication cited on pp 29-37 of the dissertation [37]

Fig. 3 Association between hs-cTnT and ARWMS in different WML percentiles



The Figure shows WML scores for each quintile of WML depending on hs-cTnT status. WML levels for patients with normal hs-cTnT are the reference group (blue). Clinically elevated hs-cTnT was significantly associated with higher ARWMS scores in all WML quintiles (green) with the effect being more pronounced in patients with higher WML levels (60th and 80th percentile). Full adjustment for confounders attenuated these effects, but remained statistically significant for the 40th, 60th and 80th WML percentile (red).
Abbreviations: WML = white matter lesions, ARWMS = age-related white matter severity score hs-cTnT = high-sensitivity cardiac troponin T

This graph is a copy of figure 3 from the publication cited on pp 29-37 of the dissertation [37]

5. Discussion

In this study, we found that elevation of hs-cTnT as a marker of myocardial injury was significantly associated with more severe WML as a marker of chronic brain injury. This association remained significant after adjustment for age, sex and vascular diseases that have also been linked to the development of WML. In our study population, the association between elevated hs-cTnT levels

and WML was more pronounced in patients with more extensive white matter disease. Therefore, measurement of hs-cTnT might be useful to identify individuals with more severe cerebral small vessel disease and at greater risk of cognitive impairment, and vice versa, assessment of WML severity might help in detecting (subclinical) myocardial injury, thus identifying patients who should undergo a more detailed cardiological work-up.

In accordance with our findings, other studies conducted in different populations have shown a link between hs-cTnT and different markers of cerebral small vessel disease. In memory clinic patients, there was an association between hs-cTnT and cortical cerebral microinfarcts that was described by Hilal et al [33]. Analyses of the ARIC (atherosclerosis risk in communities) study showed that hs-cTnT is associated with WML on cMRI in the general population [34]. However, participants in the ARIC study underwent cMRI approximately 3 years prior to the hs-cTnT measurements. Therefore, it remains unclear whether myocardial injury was already present when the extent of WML was assessed. Both studies mentioned recruited participants either from the general population [34] or from a memory clinic [33]. Our study, however, was the first to examine the association between subclinical cardiac and cerebral injury in patients with manifest cerebrovascular disease, who are at a particularly high risk of both cognitive impairment and cardiac complications.

Since our study was conducted in stroke patients, a population with high cardiac comorbidity, the average baseline hs-cTnT levels in our cohort were higher in the ARIC study, which recruited participants from the general population [34]. Moreover, there was a significantly higher proportion of patients with elevated hs-cTnT levels in our study (> 30%) compared to the ARIC study (10%) [34]. While the ARIC investigators chose to categorize patients with normal hs-cTnT levels [34], we did an additional analysis after splitting patients with elevated hs-cTnT into tertiles. Furthermore, the ARIC study performed a volume-based assessment of WML [34], whereas in our study, WML was assessed based on a visual rating scale. These differences regarding the study population, imaging assessment and statistical analysis might explain why (in contrast to the ARIC study) we did not find significantly greater WML severity with increasing hs-cTnT levels when we performed the analysis after further categorization.

Studies utilizing other markers of subclinical cardiac disease have also produced evidence of a link between cardiac and cerebral damage: NT-proBNP as a marker of cardiac volume overload is associated with WML as well as reduced grey matter volume in the general population [43, 44]. Furthermore, Russo et al. found a connection between echocardiographic determinants of subclinical cardiac damage, such as increased left atrial volume or left ventricular dysfunction, and subclinical cerebral damage [45, 46].

The pathogenic mechanisms underlying the link between subclinical myocardial and cerebral

injury are not fully understood. However, it is likely that their etiology is multifactorial. Currently, several hypotheses are discussed that may explain these findings: One theory states that cerebral hypoperfusion due to reduced cardiac output may lead to chronic cerebral ischemia and small vessel disease. Animal research has shown that chronic cerebral hypoperfusion following bilateral carotid artery occlusion can lead to cerebral white matter lesions and neurodegenerative diseases [47]. Saosh et al. found that EC-IC bypass performed in patients with hemodynamic cerebral ischemia results in better cerebral perfusion as well as better performance in cognitive tests [48]. One might argue that cerebral autoregulation should provide some protection from hypoperfusion due to cardiac dysfunction. However, data show that cerebral autoregulation cannot compensate sufficiently for systemic hypoperfusion resulting from reduced cardiac output [49]. One possible explanation is impairment of cerebral autoregulation resulting from cardiovascular disease [49].

The second suggested mechanism underlying cerebral small vessel disease is cardioembolism. Cardiac injury is known to be associated with atrial fibrillation, which can cause recurrent cerebral ischemia [50].

Thirdly, it has been proposed that the association between cardiac and cerebrovascular disease is mediated by a common underlying pathomechanism, such as atherosclerosis. There is compelling evidence for the co-occurrence of atherosclerosis and cerebral injury [51, 52, 53]. For instance, data show that aortic stiffness, a marker of atherosclerosis, leads to increased pressure and flow in cerebral microvasculature, which subsequently impairs cerebral autoregulation and causes vascular damage [51, 52]. Apart from pressure- and flow-induced vascular damage, atherosclerosis is also associated with chronic inflammatory activity [53].

Pase et al. found that aortic stiffness is associated with more severe WML in the general population [54]. Moreover, there also seems to be a link between arterial stiffness and cognitive impairment [51]. Coronary artery calcification is considered a marker of subclinical atherosclerosis and provides information on the future risk of coronary artery disease as well as cerebrovascular disease [55]. However, research has revealed that it is also associated with endothelial dysfunction and the development of cerebral white matter disease [56].

All three theories outlined above have been supported by scientific evidence and arguably complement one another. Moreover, they imply that vascular risk prevention strategies might also be effective in primary prevention of WML and, subsequently, cognitive impairment.

Lastly, the association between hs-cTnT and WML might also be caused by subclinical brain injury, which in turn leads to myocardial damage. Data suggest that the localization of brain injury might play an important role in neurogenic myocardial injury. A stroke in certain regions of the brain, such as the insular cortex, can lead to myocardial injury and hs-cTnT elevation [57]. This

implies that the interaction between heart and brain is in fact bidirectional.

The actual connection between WML and cognitive impairment, however, is still only partly understood. It has been suggested that the effect may be mediated by cortical atrophy [22, 23]. Apart from that, imaging studies indicate that, in white matter with close proximity to WML, tissue integrity may already be impaired even though standard MRI sequences do not show any structural damage yet. Studies using diffusion tensor imaging (DTI) to assess white matter integrity have shown that those damages of microstructure in cerebral white matter are associated with poorer cognitive performance in non-demented subjects [58, 59]. Moreover, they seem to be associated with later development of WML [20]. This suggests that there are in fact several stages of development of WML and that structurally visible lesions may only represent the tip of the iceberg of cerebral white matter damage.

Strengths of this study include the large sample size as well as standardized cMRI evaluation. Quantile regression analysis is suitable especially if the dependent variable is not normally distributed, which was also the case in our study population. For linear regression analysis, one assumes that in the equation $Y_i = \beta_0 + \beta_1 X_i + \varepsilon_i$ the error term ε_i is normally distributed with a mean of 0 [60]. However, quantile regression is of a semiparametric nature and therefore does not rely on the normal distribution of errors and is also invariant to monotonic transformations (e.g. logarithmic transformation) [60]. If the assumptions underlying linear regression analysis are not met, data are often log-transformed to achieve a normal distribution [60]. However, this complicates interpretation of the results. Moreover, one still does not resolve the issue of a non-linear relationship between the dependent variable and the predictor since linear regression analysis only provides information on the average effect of a predictor on the outcome variable [42]. If the relationship is non-linear (e.g. if there is a floor or ceiling effect), important information about the relationship between the outcome variable and a predictor may be missed [42].
Another way of analyzing non-normally distributed data is to categorize the variable in question and perform logistic regression analysis, which does not necessarily assume a linear relationship between the variables analyzed [42]. However, categorizing a variable comes with a loss of information, especially when there is no clinically defined cut-off [42]. Quantile regression analysis works with a continuous outcome variable and does not require a prior definition of cut-off values.
Nevertheless, our study also has certain limitations. First of all, our study is cross-sectional, leaving it impossible to make any inference about the direction of the effect captured in our analyses. Second, we were not able to obtain exact hs-cTnT values below the URL in the majority

of patients. Therefore, we were confined to performing our statistical analyses with hs-cTnT as a categorical variable, which may have attenuated the association with WML. Third, acute elevation of hs-cTnT is not uncommon in acute ischemic stroke [61]. To account for this, we excluded patients with dynamic change of hs-cTnT or hs-cTnT > 52 ng/l. However, the exact pathomechanism of myocardial damage could not be determined in each patient since not all patients undergo a systematic cardiological work-up.

Since patients' cognitive status was not systematically evaluated, we could not draw any conclusions regarding a possible association with clinical symptoms of cognitive impairment or the development of cognitive decline. However, the primary aim of this study was to assess cardiac and cerebral damage at the subclinical level.

Compared to the overall population of stroke patients treated at the Campus Benjamin Franklin, the patients included in our study were younger and a history of cardiac diseases was less common, which limits the generalizability of our results. However, this also highlights that the association between hs- cTnT and WML that we found in our study cannot solely be explained by the presence of clinically apparent cardiac diseases.

6. Conclusions

In our study, we showed that elevated levels of hs-cTnT were associated with more extensive WML in patients with acute ischemic stroke. In conjunction with previous studies, this suggests a link between subclinical heart and brain injury. Therefore, evidence of myocardial injury might be useful in identifying subjects at increased risk of cognitive impairment and dementia at a subclinical stage.

The effect that early treatment of risk factors, such as hypertension or hyperlipidemia, may have on cognitive outcome is still unknown. Further longitudinal studies are needed to assess the impact of risk-modifying therapy on the prevention of cognitive impairment. In addition, further might look at the potential value of hs-cTnT as a marker for monitoring therapeutic effects.

7. References

[1] Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005;366(9503): 2112–7

[2] Rusanen M, Kivipelto M, Levälahti E, Laatikainen T, Tuomilehto J, Soininen H, Ngandu T. Heart diseases and long-term risk of dementia and Alzheimer's disease: a population-based CAIDE study. J Alzheimers Dis. 2014;42(1):183-91

[3] Stefanidis KB, Askew CD, Greaves K, Summers MJ. The Effect of Non-Stroke Cardiovascular Disease States on Risk for Cognitive Decline and Dementia: A Systematic and Meta-Analytic Review. Neuropsychol Rev. 2018;28(1):1-15

[4] Cannon JA, Moffitt P, Perez-Moreno AC, Walters MR, Broomfield NM, McMurray JJV, Quinn TJ. Cognitive Impairment and Heart Failure: Systematic Review and Meta-Analysis. J Card Fail. 2017;23(6):464-475

[5] de Roos A, van der Grond J, Mitchell G, Westenberg J. Magnetic Resonance Imaging of Cardiovascular Function and the Brain: Is Dementia a Cardiovascular-Driven Disease? Circulation. 2017;135(22):2178-2195

[6] Hoth KF, Poppas A, Moser DJ, Paul RH, Cohen RA. Cardiac dysfunction and cognition in older adults with heart failure. Cogn Behav Neurol. 2008;21(2):65-72

[7] Wiesmann M, Kiliaan AJ, Claassen JA. Vascular aspects of cognitive impairment and dementia. J Cereb Blood Flow Metab. 2013;33(11):1696-706

[8] Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Jolles J, Koudstaal PJ, Hofman A, Breteler MM. Cerebral small vessel disease and decline in information processing speed, executive function and memory. Brain. 2005;128(Pt 9):2034-41

[9] Todoroki K, Ikeya Y, Fukui S, Yanagimachi N, Okazaki T, Tanaka C, Tanaka E, Shizuma T, Fukuyama N, Mori H. Severity of white matter hyperintensities in older adults aged in their mid 80s and its relationship with hemodynamic and cardiac parameters. Geriatr Gerontol Int. 2015;15 Suppl 1:66-73

[10] Jeerakathil T, Wolf PA, Beiser A, Massaro J, Seshadri S, D'Agostino RB, DeCarli C. Stroke risk profile predicts white matter hyperintensity volume: the Framingham Study. Stroke. 2004;35(8):1857-61

[11] de Bruijn RF, Portegies ML, Leening MJ, Bos MJ, Hofman A, van der Lugt A, Niessen WJ, Vernooij MW, FrancoOH, Koudstaal PJ, Ikram MA . Subclinical cardiac dysfunction increases the risk of stroke and dementia: The Rotterdam Study. Neurology. 2015;84(8):833-40

[12] Twerenbold R, Boeddinghaus J, Nestelberger T, Wildi K, Rubini Gimenez M, Badertscher P, Mueller C. Clinical Use of High-Sensitivity Cardiac Troponin in Patients With Suspected Myocardial Infarction. J Am Coll Cardiol. 2017;70(8):996-1012
[13] Lee GR, Jhanji S, Tarrant H, James S, Pearse RM, Fitzgibbon M. Peri-operative troponin monitoring using a prototype high-sensitivity cardiac troponin I (hs-cTnI) assay: comparisons with hs- cTnT and contemporary cTnI assays. Ann Clin Biochem. 2014;51(Pt 2):258-68.
[14] Wijsman LW, de Craen AJ, Trompet S, Sabayan B, Muller M, Stott DJ, Ford I, Welsh P, Westendorp RG, Jukema JW, Sattar N, Mooijaart SP. High-sensitivity cardiac troponin T is associated with cognitive decline in older adults at high cardiovascular risk. Eur J Prev Cardiol. 2016;23(13):1383- 92
[15] 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(1):235-242
[16] Hankee LD, Preis SR, Beiser AS, Devine SA, Liu Y, Seshadri S, Wolf PA, Au R. Qualitative neuropsychological measures: Normative data on executive functioning tests from the Framingham offspring study. Exp. Aging Res. 2013;39(5):515-35
[17] Harrington MG, Chiang J, Pogoda JM, Gomez M, Thomas K, Marion SD, Miller KJ, Siddarth P, Yi X Zhou F, Lee S, Arakaki X, Cowan RP, Tran T, Charleswell C, Ross BD, Fonteh AN. Executive function changes before memory in preclinical Alzheimer's pathology: A prospective, cross-sectional, case- control study. PLoS One. 2013;8(11):e79378
[18] Scuteri A. Brain injury as end-organ damage in hypertension. Lancet Neurol. 2012;11:1015-7
[19] Viscogliosi G, Andreozzi P, Manzon L, Ettorre E, Cacciafesta M. Metabolic syndrome, executive dysfunction, and late-onset depression: Just a matter of white matter? J. Am. Geriatr. Soc. 2014;62(8):1607-9
[20] de Groot M, Verhaaren BF, de Boer R, Klein S, Hofman A, van der Lugt A, Ikram MA, Niessen WJ, Vernooij MW. Changes in normal-appearing white matter precede development of white matter lesions. Stroke. 2013;44(4):1037-42
[21] Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ. 2010;341:c3666
[22] Knopman DS, Griswold ME, Lirette ST, Gottesman RF, Kantarci K, Sharrett AR, Jack CR Jr, Graff- Radford J, Schneider AL, Windham BG, Coker LH, Albert MS, Mosley TH Jr. Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: atherosclerosis risk in communities-neurocognitive study. Stroke. 2015;46(2):433-40

[23] Schmidt R, Ropele S, Enzinger C, Petrovic K, Smith S, Schmidt H, Matthews PM, Fazekas F. White matter lesion progression, brain atrophy, and cognitive decline: the Austrian stroke prevention study. Ann Neurol 2005;58(4):610-6

[24] Schmidt R, Berghold A, Jokinen H, Gouw AA, van der Flier WM, Barkhof F, Scheltens P, Petrovic K, Madureira S, Verdelho A, Ferro JM, Waldemar G, Wallin A, Wahlund LO, Poggesi A, Pantoni L, Inzitari D, Fazekas F, Erkinjuntti T. White matter lesion progression in LADIS: frequency, clinical effects, and sample size calculations. Stroke. 2012;43(10):2643-7

[25] Kloppenborg RP, Nederkoorn PJ, Geerlings MI, van den Berg E. Presence and progression of white matter hyperintensities and cognition: a meta-analysis. Neurology. 2014;82(23):2127-38

[26] Kliper E, Ben Assayag E, Tarrasch R, Artzi M, Korczyn AD, Shenhar-Tsarfaty S, Aizenstein O, Hallevi H, Mike A, Shopin L, Bornstein NM, Ben Bashat D. Cognitive state following stroke: the predominant role of preexisting white matter lesions. PLoS One. 2014;9(8):e105461

[27] Bokura H, Yamaguchi S, Iijima K, Nagai A, Oguro H. Metabolic syndrome is associated with silent ischemic brain lesions. Stroke. 2008 May;39(5):1607-9

[28] Rozanski M, Richter TB, Grittner U, Endres M, Fiebach JB, Jungehulsing GJ. Elevated levels of hemoglobin A1c are associated with cerebral white matter disease in patients with stroke. Stroke. 2014;45(4):1007-11

[29] van Dijk EJ, Breteler MM, Schmidt R, Berger K, Nilsson LG, Oudkerk M, Pajak A, Sans S, de Ridder M, Dufouil C, Fuhrer R, Giampaoli S, Launer LJ, Hofman A. The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study.
Hypertension. 2004;44(5):625-30

[30] Watts A, Honea RA, Billinger SA, Rhyner KT, Hutfles L, Vidoni ED, Burns JM. A combined measure of vascular risk for white matter lesions. J Alzheimers Dis. 2015;45(1):187-93

[31] Takami T, Yamano S, Okada S, Sakuma M, Morimoto T, Hashimoto H, Somekawa S, Saito Y. Major risk factors for the appearance of white-matter lesions on MRI in hypertensive patients with controlled blood pressure. Vasc Health Risk Manag. 2012;8:169-76

[32] Shimizu A, Sakurai T, Mitsui T, Miyagi M, Nomoto K, Kokubo M, Bando YK, Murohara T, Toba K. Left ventricular diastolic dysfunction is associated with cerebral white matter lesions (leukoaraiosis) in elderly patients without ischemic heart disease and stroke. Geriatr Gerontol Int. 2014;14 Suppl 2:71-6

[33] Hilal S, Chai YL, van Veluw S, Shaik MA, Ikram MK, Venketasubramanian N, Richards AM, Biessels GJ, Chen C. Association Between Subclinical Cardiac Biomarkers and Clinically Manifest

Cardiac Diseases With Cortical Cerebral Microinfarcts. JAMA Neurol. 2017;74(4):403-410
[34] Dadu RT, Fornage M, Virani SS, Nambi V, Hoogeveen RC, Boerwinkle E, Alonso A, Gottesman RF, Mosley TH, Ballantyne CM. Cardiovascular biomarkers and subclinical brain disease in the atherosclerosis risk in communities study. Stroke. 2013;44(7):1803-8
[35] Savva GM, Stephan BC. Epidemiological studies of the effect of stroke on incident dementia: a systematic review. Stroke;41(1):e41-6
[36] Kumar S, Selim MH, Caplan LR. Medical complications after stroke. Lancet Neurol 2010;9(1):105- 118
[37] von Rennenberg R, Siegerink B, Ganeshan R, Villringer K, Doehner W, Audebert HJ, Endres M, Nolte CH, Scheitz JF. High-sensitivity Cardiac Troponin T and Severity of Cerebral White Matter Lesions in Patients With Acute Ischemic Stroke. Journal of Neurology 2019 Jan;266(1):37-45.
[38] Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(3):267-315
[39] Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren M, Wallin A, Ader H, Leys D, Pantoni L, Pasquier F, Erkinjuntti T, Scheltens P. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001;32(6):1318-1322
[40] Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high- sensitivity cardiac troponin T assay. Clin Chem. 2010;56(2):254-61
[41] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612.
[42] Beyerlein A (2014) Quantile regression – opportunities and challenges from a user's perspective. Am J Epidemiol 180(3):330-331
[43] Park CM, Williams ED, Chaturvedi N, Tillin T, Stewart RJ, Richards M, Shibata D, Mayet J, Hughes AD. Associations Between Left Ventricular Dysfunction and Brain Structure and Function: Findings From the SABRE (Southall and Brent Revisited) Study. J Am Heart Assoc. 2017;6(4)
[44] Zonneveld HI, Ikram MA, Hofman A, Niessen WJ, van der Lugt A, Krestin GP, Franco OH, Vernooij MW: N-Terminal Pro–B-Type Natriuretic Peptide and Subclinical Brain Damage in the

General Population. Radiology. 2017;283(1):205-214
[45] Russo C, Jin Z, Liu R, Iwata S, Tugcu A, Yoshita M, Homma S, Elkind MS, Rundek T, Decarli C, Wright CB, Sacco RL, Di Tullio MR. LA Volumes and Reservoir Function Are Associated With Subclinical Cerebrovascular Disease. The CABL (Cardiovascular Abnormalities and Brain Lesions) Study. JACC Cardiovasc Imaging. 2013;6(3):313-23
[46] Russo C, Jin Z, Homma S, Elkind MS, Rundek T, Yoshita M, DeCarli C, Wright CB, Sacco RL, Di Tullio MR. Subclinical Left Ventricular Dysfunction and Silent Cerebrovascular Disease: The Cardiovascular Abnormalities and Brain Lesions (CABL) Study. Circulation. 2013;128(10):1105-11
[47] Farkas E, Luiten PG, Bari F. Permanent, bilateral common carotid artery occlusion in the rat: a model for chronic cerebral hypoperfusion-related neurodegenerative diseases. Brain Res Rev 2007;54(1):162–180
[48] Sasoh M, Ogasawara K, Kuroda K, Okuguchi T, Terasaki K, Yamadate K, Ogawa A. Effects of EC-IC Bypass Surgery on Cognitive Impairment in Patients with Hemodynamic Cerebral Ischemia. Surg Neurol. 2003;59(6):455-60; discussion 460-3
[49] De la Torre JC. Cardiovascular Risk Factors Promote Brain Hypoperfusion Leading to Cognitive Decline and Dementia. Cardiovasc Psychiatry Neurol. 2012;2012:367516
[50] Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. Circulation1997;96:2455– 61
[51] Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson Ó, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility - Reykjavik study. Brain. 2011;134(Pt 11):3398-407
[52] O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension. 2005;46(1):200-4
[53] Gür M, Sahin DY, Elbasan Z, Kalkan GY, Yıldız A, Kaya Z, Özaltun B, Çaylı M. Uric acid and high sensitive C-reactive protein are associated with subclinical thoracic aortic atherosclerosis. J Cardiol. 2013;61(2):144-8
[54] Pase MP, Himali JJ, Mitchell GF, Beiser A, Maillard P, Tsao C, Larson MG, DeCarli C, Vasan RS, Seshadri S. Association of Aortic Stiffness with Cognition and Brain Aging in Young and Middle-Aged Adults. The Framingham Third Generation Cohort Study. Hypertension. 2016;67(3):513-9
[55] Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events:

The St. Francis heart study. J Am Coll Cardiol. 2005;46(1):158-65
[56] Kim BJ, Lee SH, Kim CK, Ryu WS, Kwon HM, Choi SY, Yoon BW. Advanced Coronary Artery Calcification and Cerebral Small Vessel Diseases in the Healthy Elderly. Circ J. 2011;75(2):451-6
[57] Krause T, Werner K, Fiebach JB, Villringer K, Piper SK, Haeusler KG, Endres M, Scheitz JF, Nolte CH. Stroke in right dorsal anterior insular cortex is related to myocardial injury. Ann Neurol. 2017;81(4):502-511
[58] van Norden AG, van Uden IW, de Laat KF, van Dijk EJ, de Leeuw FE. Cognitive function in small vessel disease: the additional value of diffusion tensor imaging to conventional magnetic resonance imaging: the RUN DMC study. J Alzheimers Dis. 2012;32(3):667-76
[59] Vernooij MW, Ikram MA, Vrooman HA, Wielopolski PA, Krestin GP, Hofman A, Niessen WJ, Van der Lugt A, Breteler MM. White matter microstructural integrity and cognitive function in a general elderly population. Arch Gen Psychiatry. 2009;66(5):545-53
[60] Petscher Y, Logan JAR. Quantile regression in the study of developmental sciences. Child Dev. 2014;85(3):861-881
[61] Scheitz JF, Nolte CH, Laufs U, Endres M. Application and interpretation of high-sensitivity cardiac troponin assays in patients with acute ischemic stroke. Stroke. 2015;46(4):1132-40

8. Eidesstattliche Versicherung

„Ich, Regina von Rennenberg, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Kardiales Troponin und Schweregrad zerebraler White matter lesions bei akutem ischämischem Schlaganfall / Cardiac Troponin T and severity of cerebral white matter lesions in acute ischemic stroke“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Erstbetreuer angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Anteilserklärung an den erfolgten Publikationen

Regina von Rennenberg hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Regina von Rennenberg, Bob Siegerink, Ramanan Ganeshan, Kersten Villringer, Wolfram Doehner, Heinrich J. Audebert, Matthias Endres, Christian H. Nolte, Jan F. Scheitz. High-sensitivity cardiac Troponin T and severity of cerebral white matter lesions in patients with acute ischemic stroke. Journal of Neurology 2018.

Ich habe gemeinsam mit Jan Scheitz und Christian Nolte die Fragestellung und das Studienprotokoll erstellt. Bei den für die Publikation verwendeten Daten handelt es sich ausschließlich um Daten, welche im Rahmen der klinischen Routine erhoben werden, sodass der Datensatz bereits vorlag. Unter der Supervision von Bob Siegerink und Jan Scheitz habe ich sämtliche statistische Analysen durchgeführt, welche die Arbeit enthält. Das Manuskript sowie alle enthaltenen Tabellen und Grafiken habe ich erstellt und unter Supervision aller o.g. Co-Autoren überarbeitet. Den gesamten Publikationsprozess (Submission, Draft einer Revision, kritische Antworten an die Reviewer, Resubmission) habe ich selbstständig durchgeführt.

Unterschrift, Datum und Stempel des erstbetreuenden Hochschullehrers

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Unterschrift der Doktorandin

9. Auszug Journal Summary List

Journal Data Filtered By: **Selected JCR Year: 2017** Selected Editions: SCIE,SSCI Selected Categories: **"CLINICAL NEUROLOGY"** Selected Category
Scheme: WoS
Gesamtanzahl: 197 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	LANCET NEUROLOGY	28,671	27.138	0.069040
2	Nature Reviews Neurology	8,095	19.819	0.028090
3	ACTA NEUROPATHOLOGICA	18,783	15.872	0.041490
4	Alzheimers & Dementia	10,423	12.740	0.030040
5	JAMA Neurology	6,885	11.460	0.035270
6	BRAIN	52,061	10.840	0.075170
7	SLEEP MEDICINE REVIEWS	6,080	10.602	0.010720
8	ANNALS OF NEUROLOGY	37,251	10.244	0.053390
9	NEURO-ONCOLOGY	10,930	9.384	0.030350
10	Epilepsy Currents	790	9.333	0.001600
11	MOVEMENT DISORDERS	26,511	8.324	0.037980
12	Translational Stroke Research	2,202	8.266	0.005260
13	NEUROLOGY	88,493	7.609	0.115530
14	NEUROSCIENTIST	4,738	7.461	0.008730
15	JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY	29,695	7.144	0.032980
16	STROKE	65,854	6.239	0.088520
17	BRAIN PATHOLOGY	4,952	6.187	0.007750
18	Brain Stimulation	4,263	6.120	0.014510
19	NEUROPATHOLOGY AND APPLIED NEUROBIOLOGY	3,654	6.059	0.006350
20	Neurotherapeutics	3,973	5.719	0.008980
21	PAIN	36,132	5.559	0.038000
22	Multiple Sclerosis Journal	10,675	5.280	0.021890
23	SLEEP	20,547	5.135	0.025870
24	EPILEPSIA	26,301	5.067	0.032490
25	Alzheimers Research & Therapy	2,192	5.015	0.008470
26	JOURNAL OF NEUROTRAUMA	14,508	5.002	0.021130
27	JOURNAL OF PAIN	9,264	4.859	0.016890
28	Journal of Stroke	694	4.750	0.002880
28	Therapeutic Advances in Neurological Disorders	1,004	4.750	0.002800
30	JOURNAL OF PSYCHOPHARMACOLOGY	5,808	4.738	0.010900
31	PARKINSONISM & RELATED DISORDERS	8,967	4.721	0.019910
32	NEUROREHABILITATION AND NEURAL REPAIR	5,032	4.711	0.009850
33	Annals of Clinical and Translational Neurology	1,377	4.649	0.006450
34	EUROPEAN JOURNAL OF NEUROLOGY	10,206	4.621	0.019350
35	BIPOLAR DISORDERS	5,070	4.490	0.007870
36	NEUROSURGERY	28,592	4.475	0.025930
37	JOURNAL OF NEUROSURGERY	34,561	4.318	0.030750
38	CNS DRUGS	4,364	4.206	0.007540

39	PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY	9,823	4.185	0.013170
40	EUROPEAN NEUROPSYCHOPHARMACOLOGY	6,920	4.129	0.015110
41	CURRENT OPINION IN NEUROLOGY	5,344	4.010	0.010200
42	INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY	6,259	3.981	0.014550
43	CEPHALALGIA	8,721	3.882	0.013940
44	International Journal of Stroke	3,825	3.859	0.014880
45	NEUROGASTROENTEROLOGY AND MOTILITY	7,401	3.842	0.014960
46	JOURNAL OF AFFECTIVE DISORDERS	26,957	3.786	0.053380
47	JOURNAL OF NEUROLOGY	14,359	3.783	0.025160
48	NEUROEPIDEMIOLOGY	3,261	3.697	0.005640
49	Expert Review of Neurotherapeutics	3,888	3.692	0.006910
50	AMERICAN JOURNAL OF NEURORADIOLOGY	22,667	3.653	0.029840
51	Journal of Neurologic Physical Therapy	964	3.633	0.001530
52	EUROPEAN ARCHIVES OF PSYCHIATRY AND CLINICAL NEUROSCIENCE	3,837	3.617	0.005400
53	CLINICAL NEUROPHYSIOLOGY	18,399	3.614	0.023070
54	Frontiers in Neurology	4,272	3.508	0.015580
55	CNS SPECTRUMS	2,200	3.504	0.003180
56	Journal of Neurodevelopmental Disorders	1,106	3.500	0.003410
57	JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY	9,252	3.490	0.008680
58	Current Neurology and Neuroscience Reports	2,770	3.478	0.007410
59	Journal of Neurogastroenterology and Motility	1,207	3.438	0.002930
60	JOURNAL OF SLEEP RESEARCH	5,092	3.433	0.007460
61	JOURNAL OF HEAD TRAUMA REHABILITATION	4,282	3.406	0.005540
62	JOURNAL OF HEADACHE AND PAIN	2,624	3.403	0.005510
63	Journal of Clinical Sleep Medicine	5,329	3.396	0.011800
64	SLEEP MEDICINE	9,130	3.395	0.016270
65	Current Alzheimer Research	3,740	3.289	0.007910
65	DEVELOPMENTAL MEDICINE AND CHILD NEUROLOGY	11,671	3.289	0.013680
67	JOURNAL OF PAIN AND SYMPTOM MANAGEMENT	9,734	3.249	0.013980

10. Original-Publikation

Regina von Rennenberg, Bob Siegerink, Ramanan Ganeshan, Kersten Villringer, Wolfram Doehner, Heinrich J Audebert, Matthias Endres, Christian H Nolte, Jan F Scheitz. High-sensitivity cardiac troponin T and severity of cerebral white matter lesions in patients with acute ischemic stroke. Journal of Neurology 2019;266(1):37-45.
https://doi.org/10.1007/s00415-018-9085-3

11. Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

12. Publikationsliste

1. Regina von Rennenberg, Bob Siegerink, Ramanan Ganeshan, Kersten Villringer, Wolfram Doehner, Heinrich J Audebert, Matthias Endres, Christian H Nolte, Jan F Scheitz. High-sensitivity Cardiac Troponin T and Severity of Cerebral White Matter Lesions in Patients With Acute Ischemic Stroke. Journal of Neurology 2019 Jan;266(1):37-45.doi: 10.1007/s00415-018-9085-3.

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