High-sensitivity cardiac troponin T is associated with cognitive decline in older adults at high cardiovascular risk

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Abstract

Aims Cardiac troponin T (cTnT), measured with a high-sensitivity (hs) assay, is associated with cognitive decline, but the underlying mechanism is unknown. We investigated the association of hs-cTnT with cognitive function and decline, and studied whether this association was independent of cardiovascular diseases or risk factors, and N-terminal pro-brain natriuretic peptide (NT-proBNP).

Methods and Results We studied 5407 participants (mean age 75.31 years) from the PROspective Study of Pravastatin in the Elderly at Risk, who all had cardiovascular diseases or risk factors thereof. Participants with pre-existent advanced clinical heart failure were excluded. Hs-cTnT and NT-proBNP obtained after 6 months of follow-up were related with cognitive function, tested repeatedly during a mean follow-up of 3.2 years. Participants with higher hs-cTnT performed worse at baseline on Stroop test (mean baseline score (standard error (SE)) lowest vs. highest third 65.91 (1.16) vs. 69.40 (1.10) seconds, p<0.001), Letter-Digit Coding test (23.35 (0.32) vs. 22.40 (0.31) digits coded, p<0.001), immediate Picture-Word Learning test (9.45 (0.09) vs. 9.31 (0.08) pictures remembered, p=0.002) and delayed Picture-Word Learning test (10.33 (0.12) vs. 10.10 (0.12) pictures remembered, p=0.013). Furthermore, participants with higher hs-cTnT had steeper decline on Stroop test (mean annual change (SE) lowest vs. highest third 0.34 (0.12) vs. 1.06 (0.12) seconds, p=0.013), Letter-Digit Coding test (-0.29 (0.03) vs. -0.46 (0.03) digits coded, p<0.001), immediate Picture-Word Learning test (0.01 (0.01) vs. -0.06 (0.01) pictures remembered, p<0.001) and delayed Picture-Word Learning test (-0.03 (0.01) vs. -0.12 (0.02) pictures remembered, p=0.001). Associations were independent of cardiovascular diseases risk factors or apoE genotype. Further adjusting for NT-proBNP levels revealed the same results.

Conclusions Higher levels of hs-cTnT associate with worse cognitive function and steeper cognitive decline in older adults independent of cardiovascular diseases, risk factors and NT-proBNP.

Keywords cardiac troponin T, cognition, cardiovascular diseases, NT-proBNP

Introduction

Cardiac troponin T (cTnT) is a protein that is released in response to cardiomyocyte necrosis, and is routinely used in the diagnosis of acute myocardial infarction.(1) In patients with cardiovascular disease, higher levels of cTnT, measured with a high-sensitivity (hs) assay, are associated with higher risk of incident coronary heart disease, heart failure and stroke.(1, 2) Moreover, in patients free from cardiovascular disease, raised levels of hs-cTnT have also been associated with higher risk of all-cause mortality and myocardial infarction.(3)

Cardiovascular diseases are important risk factors for cognitive impairment and dementia.(4) Recent evidence shows that in subjects without cardiovascular disease, higher levels of hs-cTnT are associated with silent brain infarcts and white matter lesion progression.(5) Hs-cTnT might therefore be a sensitive systemic marker for structural brain damage, which is associated with decreased cognitive function and dementia.(6) Hs-cTnT has recently also been associated with cognitive function, but the underlying mechanism is unknown.(7) Besides the fact that cardiac disease and cognitive dysfunction share common risk factors there may be an alternative explanation. Myocardial ischemia or infarction, as detected by increased hs-cTnT, may lead to clinical heart failure or decreased cardiac function, which in turn leads to cognitive decline.(8) Given the predicted increase in prevalence of cognitive dysfunction in the coming decades, unravelling early predictors of cognitive decline is of importance.(9)

The aims of this study were to investigate 1) whether subjects with higher levels of hs-cTnT are at increased risk of worse cognitive function and steeper cognitive decline; 2) whether this was independent of cardiovascular diseases or its risk factors, and 3) whether this was independent of N-terminal pro-brain natriuretic peptide (NT-proBNP), a marker used in the diagnosis of clinical heart failure.(10-12) We used data from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), which included 5804 older men and women who all had a cardiovascular disease or cardiovascular risk factors thereof.

Methods

Study design and participants

Data were obtained from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a randomized, double-blind, placebo-controlled trial designed to investigate the effect of pravastatin in prevention of vascular events in older individuals with pre-existing cardiovascular disease or risk factors thereof.(13) Briefly, main inclusion criteria were that participants had either pre-existing vascular disease (coronary, cerebral or peripheral) or an elevated level of developing vascular disease because of smoking, diabetes mellitus or hypertension. Furthermore, their total cholesterol level was required to be between 4.0 – 9.0 mmol/L and their triglyceride concentration < 6.0 mmol/L. Participants with congestive heart failure, defined as New York Heart Association functional class III or IV, were not included in the PROSPER study, nor were participants who were previously diagnosed with atrial fibrillation.(13) Furthermore, poor cognitive function at baseline, defined as a Mini-Mental Score Examination below 24 points, was an exclusion criteria. Participants with congestive heart failure, defined as New York Heart Association functional class III or IV, were not included in the PROSPER study, nor were participants who were previously diagnosed with atrial fibrillation.(13) This trial included 5804 men and women aged 70-82 years old who were enrolled from three collaborating centers in Ireland, Scotland and the Netherlands. Approximately 50% of the participants had cardiovascular disease including stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction and/or vascular surgery. The rest of participants had one or more cardiovascular risk factor, defined as hypertension, smoking or diabetes mellitus. Participants with congestive heart failure, defined as New York Heart Association functional class III or IV, were not included in the PROSPER study.(13) The primary outcome of the trial was the combined endpoint of definite or suspect death from coronary heart disease, non-fatal myocardial infarction and fatal or non-fatal stroke during a mean follow-up period of 3.2 years.(14) The institutional ethics committees of the three collaborating centers approved the study and all participants gave written informed consent.

cTnT and NT-proBNP measurements

cTnT and NT-proBNP were measured in blood samples obtained after 6 months of follow-up in EDTA tubes. Both proteins were measured using an electrochemiluminiscence immunoassay on a Roche Modular Analytics E170. The Roche cTnT measurement was performed with a high-sensitivity assay, which has a limit of detection

of 0.003 ug/L and a 99th percentile cutoff of 0.014 ug/L. Furthermore, the Elecsys Troponin T hs assay used had a CV of 10.38% at a cTNT concentration of 0.010 ug/L, thus the assay is able to differentiate reasonably well at lower concentrations. For those patients who had a level below the detection limit, we have assumed these values to be distributed anywhere between zero and 0.003, of which the average is 0.0015. Hs-cTnT levels below detection level were therefore set to 0.0015 ug/L in the statistical analyses. To further investigate whether the association of cTnT with cognitive function and decline was independent of clinical heart failure, we studied participants with low and high NT-proBNP levels more in detail. To be sure that participants had no clinical heart failure, we chose a conservative cut-off of 200 ng/L for NT-proBNP. Furthermore, we stratified our analyses by a less conservative cut-off of low (<400 ng/L) and high (≥ 400 ng/L) NT-proBNP, based on relevant guidelines.(15)

Cognitive function

The MMSE was used to evaluate global cognitive function; participants with a baseline score below 24 points were not included in PROSPER.(13) Cognitive function was tested at baseline and at 9, 18, 30 months and at the end of the study. The time-point of the measurement at the end of the study varied between 36 and 48 months; therefore, we performed the analysis with their individually varying time point, but report the results for the mean of these time points (at 42 months). Four different neuropsychological tests were used to assess executive function, attention, and immediate and delayed memory. The Stroop-Colour-Word-Test was used to test selective attention and reaction time. Participants were asked to read a color name which was displayed in a color different from the color it actually names. Outcome parameter was the total number of seconds to complete the test; a higher score indicates worse performance. Processing speed was tested by the Letter-Digit Coding Test. Participants had to match certain digits with letters according to a provided key. Outcome variable was the total number of correct entries in 60 seconds, therefore higher scores represented better performance. The Picture-Word Learning Test was used to assess immediate and delayed memory. Fifteen pictures were presented, and participants were asked to recall as many pictures as possible in three trials. After 20 minutes they were asked to repeat the pictures they remembered to measure their delayed recall. Outcome parameter was the accumulated number of correct recalled pictures, immediate and after 20 minutes. Higher scores thus indicate better performance. A detailed description of the cognitive tests has been published previously.(16)

Since treatment with pravastatin did not influence cognitive function during follow-up, we included participants from both pravastatin and placebo groups.(17)

Statistical analyses

We present our results in thirds of cTnT. Baseline characteristics of the study participants are presented as mean (standard deviation) for continuous variables and number (percentage) for categorical variables for each third of cTnT. Differences in continuous variables were tested with linear regression models; differences in categorical variables were tested by Chi-squared tests. Because of the skewed distribution of cTnT levels and log-transformed cTnT levels, all analyses were performed using the square root of cTnT, which was normally distributed (supplemental figure 2). To investigate the cross-sectional association of cTnT with cognitive function, we used linear regression models. The square root levels of cTnT were included as independent variable; outcome variable was the mean baseline score on each of the four cognitive function tests. Linear mixed models were used to examine the association between cTnT and cognitive decline over time. The models included the square root of cTnT level, time (in years) and the interaction term between time and the square root of cTnT level.

We performed our analyses according to two different adjustment models. In the first model, we only adjusted for the variables age, sex, country, education, treatment group and cognitive test version where appropriate (minimally adjusted model). In the second model, we further adjusted for ApoE genotype, history of cerebrovascular and cardiovascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol levels, triglycerides, body mass index and estimated glomerular filtration rate (eGFR), to investigate the potential influence of these factors on the associations. Since the observed associations did not materially differ, we chose to present the results from comprehensive adjusted models. Results from minimally adjusted models are included as supplemental material. Concerning the longitudinal analyses, we further studied the effects of potential confounders on the slope of the association by additionally including the interaction terms between time, square root of troponin level and potential confounder in the linear mixed models. These results did not materially affect the slope of the analyses and we therefore present the results of the simple models. Finally, to explore the influence of cardiovascular diseases and risk factors in more

details, we performed additional analyses in which we stratified for history of cardiovascular diseases and risk factors.

To further investigate whether the association of cTnT with cognitive function and decline was independent of clinical heart failure, we stratified our analyses by low (<200 ng/L) and high (≥ 200 ng/L) NT-proBNP level and calculated a p-value for interaction to test whether the difference was significant. In addition, we 1) further adjusted our analyses for continuous levels of NT-proBNP and 2) stratified our analyses by a less conservative cut-off of low (<400 ng/L) and high (≥ 400 ng/L) NT-proBNP, was based on relevant guidelines.(15) Moreover, we performed additional analyses in which we excluded both participants with heart failure hospitalization during follow-up and participants who used loop diuretics at baseline, since those participants are likely to suffer from clinical heart failure. Furthermore, we performed several sensitivity analyses in which we separately excluded participants who, during follow-up, had 1) a stroke and / or transient ischemic attack (TIA); 2) coronary events; 3) atrial fibrillation; 4) cardiovascular events; and 5) a sign of previous myocardial infarction (defined as pathological Q or QS-waves on their baseline ECG). Finally, we excluded participants with high cTnT levels (defined conform 99th percentile as hs-cTnT levels >0.014 µg/L), to investigate the association of normal levels of cTnT with cognitive function and decline.

Results

Out of the total number of 5804 PROSPER participants, we excluded n=397 participants with missing cTnT measurements. The final sample of the present study included n=5407 participants with a mean (standard deviation) age of 75.31 (3.36) years (supplemental figure 1).

Participants with higher cTnT were older, less frequently female and had a higher prevalence of hypertension, diabetes mellitus, stroke or transient ischemic attack, myocardial infarction and vascular disease (all p-values <0.05) (table 1). No difference in total cholesterol, high-density lipoprotein and low-density lipoprotein levels were found between the thirds of cTnT (all p-values >0.05). Systolic and diastolic blood pressure at baseline were higher in participants with higher cTnT levels (both p-values <0.001). Furthermore, participants with higher cTnT had a lower eGFR and higher NT-proBNP levels (both p-values <0.001).

The association of cTnT with cognitive function at baseline and cognitive decline during follow-up is shown in table 2. At baseline, participants with higher cTnT had worse cognitive function on Stroop test, Letter-Digit Coding test, immediate Picture-Word Learning test and delayed Picture-Word Learning test (all p-values <0.05). Longitudinally, participants with higher cTnT had a steeper decline on Stroop test, Letter-Digit Coding test, immediate Picture-Word Learning test and delayed Picture-Word Learning test (all p-values <0.05). Results were independent of cardiovascular diseases or risk factors, since all analyses were adjusted for histories of cardiovascular diseases and risk factors thereof. Data on the association of cTnT with cognitive function and decline from minimally adjusted models did not materially differ from comprehensive adjusted models (supplemental table 1). Figure 1 shows the results of the association of cTnT with cognitive decline, stratified by cardiovascular diseases and risk factors. Participants with a history of hypertension had a steeper decline on Letter-Digit Coding test and immediate Picture-Word Learning test (both p-values for interaction=0.011).

Figure 2 shows the association of cTnT with cognitive function at baseline in participants with low (<200 ng/L) and high (≥ 200 ng/L) NT-proBNP levels. For participants with low NT-proBNP levels, we observed that higher cTnT was associated with worse cognitive function on the Stroop test, Letter-Digit Coding test, immediate Picture-Word Learning test and delayed Picture-Word Learning test (all p-values <0.05). Although this trend was

less marked on all four cognitive function tests for participants with high NT-proBNP levels, there was no significant difference between low and high NT-proBNP levels in the association of cTnT with cognitive function (all p-values for interaction >0.05). Table 3 shows the longitudinal association of cTnT with cognitive decline in participants with low and high NT-proBNP levels. Again, a trend was found showing that in participants with low NT-proBNP levels, higher levels of cTnT were associated with steeper decline on all four cognitive function tests. This association remained significant for the immediate Picture-Word Learning test. However, this difference between low and high NT-proBNP levels in the association of cTnT with cognitive function was not significant (all p-values for interaction > 0.05). When further adjusting for continuous levels of NT-proBNP and when stratifying our analyses according to the less conservative cut-off of NT-proBNP < and ≥ 400 ng/L, the association between cTnT and cognitive function and decline remained essentially the same (supplemental tables 2 and 3). Furthermore, participants with a history of diabetes mellitus had a steeper decline in immediate Picture-Word learning test. In addition, the observed associations of cTnT with cognitive function and decline did not materially change when excluding participants with heart failure hospitalization during follow-up (n=205) and participants who used loop diuretics (n=588) (supplemental table 4).

Furthermore, we investigated whether incident cardiovascular diseases might confound our results, by performing sensitivity analyses in which we separately excluded participants who, during follow-up, had 1) a stroke or TIA (n=378); 2) coronary events (n=575); 3) atrial fibrillation (n=507); 4) cardiovascular events (n=872); and finally 5) a sign of previous myocardial infarction (defined as pathological Q or QS-waves on their baseline ECG) (n=1211). In general, exclusion of these participants did not affect the association of cTnT with cognitive function and decline (supplemental tables 5 and 6). In addition, we investigated the association of normal values of cTnT with cognitive function and decline, by excluding participants with cTnT > 0.014 µg/L, conform 99th percentile (n=1002). Results from these analyses did not essentially differ (supplemental table 7).

Discussion

In this large prospective cohort study, we found that among 5407 older men and women, higher levels of hs-cTnT were associated with worse cognitive function at baseline and steeper cognitive decline. Results were independent of cardiovascular diseases or risk factors. Similar trends were observed in participants with lower NT-proBNP levels below levels which might be indicative of clinical heart failure.

Our findings are in line with a previous study by Schneider et al., investigating the association of hs-cTnT with cognitive function.(7) This prospective follow-up study, which included 9472 community-dwelling participants with a mean age of 63 years, showed that higher levels of hs-cTnT were associated with lower scores on a digit symbol substitution test and a word fluency test, indicating worse cognitive function. Furthermore, during a median follow-up period of 13 years, higher baseline concentrations of hs-cTnT were associated with an increased risk for dementia hospitalizations.(7) Although these results did not appreciably alter when analyses were additionally adjusted for left ventricular hypertrophy and carotid intima media thickness, no information on NT-proBNP was available. In addition, this study did not consider apolipoprotein E4 genotype, a well-known risk factor for the development of cognitive impairment, as a potential confounder in the association between hs-cTnT and cognitive function.(18) Another difference between the present study and the study by Schneider et al. was the cognitive test battery. Both studies used measures of delayed word memory and the digit symbol substitution test, which measures processing speed and executive function. The only difference is that the ARIC study used the Word Fluency Test, whereas we used the Stroop test, although both measure executive function and processing speed. We think it is unlikely that this difference in choice of tests is significant enough to make different inferences about the outcome. To our knowledge, our study is the first examining the association of hs-cTnT and cognitive function in older adults at high cardiovascular risk, which tested the potential role of cardiovascular diseases, risk factors and NT-proBNP, and adjusted for apolipoprotein E4 genotype as well.

Several mechanisms can be proposed to explain the association of cTnT with worse cognitive function and steeper cognitive decline. First, cTnT might be a reflection of underlying myocardial injury as well as cerebral damage, rather than being causally related. It is well known that cardiovascular and cerebrovascular disease share the same risk factors, including hypertension, diabetes mellitus and smoking. These risk factors for

cognitive decline clearly also cause myocardial disease, resulting in increased levels of cTnT. The finding that participants with a history of hypertension and diabetes mellitus had a steeper decline on Picture-Word immediate test in stratified analyses, further supports this hypothesis. Second, although our results were found in participants without NYHA functional class stage III or IV, we do not have echocardiography data to rule out the possibility that higher levels of cTnT indicate suboptimal cardiac functioning with subsequent decreased cardiac output and cerebral hypoperfusion.(19, 20) Cerebral hypoperfusion has previously been associated with a higher risk of dementia.(21) However, this explanation is less likely since in the current study, participants with NT-proBNP levels <200 ng/L showed the same results, and additional adjustment for NT-proBNP levels did not change the results. Third, cTnT might have a direct effect in the brain, causing decreased cerebral function. However, no evidence has been provided for this explanation yet. Fourth, although it is generally believed that cTnT is only expressed in striated muscle cells, animal studies have revealed expression of troponin proteins, including troponin T, in smooth muscle cells of rats and mice as well.(22, 23) In addition, a recent report has shown the existence of cTnT in vascular smooth muscle cells of humans, and also found that cTnT contributes to calcium-mediated contraction of smooth muscle cells in mice experiments.(24) Although it has been reported that cTnT is highly specific for cardiomyocytes, these recent findings suggest that cTnT might also be a reflection of smooth muscle cell involvement.(24) Higher levels of cTnT may therefore indicate vascular smooth muscle cell damage in an early stage, before the manifestation of clinical or even subclinical diseases. This might also explain the observation that higher levels of cTnT are associated with subclinical brain disease, including silent brain infarcts and white matter hyperintensities.(5) Speculatively, cTnT is not only released by cardiomyocytes but also by smooth muscle cells in the brain vasculature, and may therefore mark structural brain damage as a cause of cognitive decline.

The magnitude of the association between cTNT and cognitive decline we report, is comparable in magnitude to associations of known risk factors of cognitive decline, such as APOE4 carriership, smoking status and history of diabetes, indicating that the effects are clinically relevant.

A limitation of this study might be that all participants had cardiovascular diseases or risk factors thereof, which might restrict the extrapolation of our findings to a general population of older individuals. However, at the same time this is an advantage of our study, since it allows us to perform several sensitivity analyses to investigate

the influence of cardiovascular diseases and risk factors on the association between cTnT and cognitive function. Second, although we adjusted our analyses for potential confounders, it is uncertain if this fully accounts for the differences between the troponin groups. In addition, there might still be other factors which we did not consider in our analyses. Furthermore, the lack of extensive information on cardiac functioning is a weakness of our study. Strength of this study is the large sample size of 5407 participants, who all underwent repeated extensive neuropsychological examination including four different cognitive function tests, during a mean follow-up period of 3.2 years, and, critically, inclusion and adjustment for NTproBNP measures. Furthermore, cTnT measurements were performed using a high-sensitivity assay, which can detect 10-fold lower concentrations than the usual assay, and therefore allows detection of already very minor damage of the myocardial tissue.

Higher levels of hs-cTnT associate with worse cognitive function and steeper cognitive decline in older adults independent of cardiovascular diseases and risk factors and NT-proBNP.

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Table 1 Baseline characteristics of study participants by thirds of cardiac troponin T

	Thirds of cardiac troponin T			P-value
	Low	Middle	High	
	0.002-0.004 µg/L	0.005-0.009 µg/L	0.010-1.840 µg/L	
	N=1584	N=1972	N=1851	
Demographics				
Age (years), mean (SD)	74.37 (3.18)	75.17 (3.11)	76.27 (3.44)	<0.001
Female, n (%)	1114 (70.3)	977 (49.5)	693 (37.4)	<0.001
Education (age left school), mean (SD)	15.14 (1.99)	15.16 (2.22)	15.12 (2.15)	0.829
Pravastatin treatment, n (%)	778 (49.1)	983 (49.8)	921 (49.8)	0.898
Vascular risk factors				
History of hypertension, n (%)	952 (60.2)	1202 (61.0)	1199 (64.8)	0.011
History of diabetes mellitus, n (%)	120 (7.6)	209 (10.6)	247 (13.3)	<0.001
History of stroke or TIA, n (%)	147 (9.3)	207 (10.5)	248 (13.4)	<0.001
History of myocardial infarction, n (%)	140 (8.8)	252 (12.8)	330 (17.8)	<0.001
History of vascular disease, n (%)	620 (39.1)	861 (43.7)	916 (49.5)	<0.001
Current smoker, n (%)	451 (28.5)	535 (27.1)	441 (23.8)	0.006
Body mass index (kg/m$^{2)}$, mean (SD)*	26.12 (4.38)	26.82 (4.00)	27.41 (4.30)	<0.001
Total cholesterol (mmol/L), mean (SD)*	5.71 (0.80)	5.65 (0.89)	5.66 (0.86)	0.112
High density lipoprotein* (mmol/L), mean (SD)	1.29 (0.40)	1.28 (0.44)	1.27 (0.43)	0.404
Low density lipoprotein* (mmol/L), mean (SD)	3.83 (0.80)	3.76 (0.89)	3.77 (0.86)	0.083
Systolic blood pressure (mmHg), mean (SD)*	151.17 (22.29)	155.11 (21.32)	157.39 (22.37)	<0.001
Diastolic blood pressure (mmHg), mean (SD)*	82.76 (11.94)	84.02 (11.55)	84.44 (11.62)	<0.001
Blood pressure lowering medication, n (%)				
Diuretics	572 (36.1)	755 (38.3)	851 (46.0)	<0.001
ACE-inhibitors	185 (11.7)	292 (14.8)	409 (22.1)	<0.001
Beta-blockers	408 (25.8)	523 (26.5)	462 (25.0)	0.544
Calcium channel blockers	413 (26.1)	475 (24.1)	476 (25.7)	0.334
ApoE genotype				0.783
E2 carriers	14 (0.9)	12 (0.6)	9 (0.5)	
E3/E3 carries	984 (62.1)	1226 (62.2)	1123 (60.7)	
E4 carriers	389 (24.6)	482 (24.4)	452 (24.4)	
Biochemistry, mean (SD)				
eGFR (ml/min/m1.73m^2)	61.07 (14.33)	60.86 (14.65)	58.24 (14.63)	<0.001
NT-proBNP level (ng/L)* $^{\#}$	159.39 (549.23)	230.77 (525.78)	475.51 (542.09)	<0.001
Fasting glucose level (mmol/L)*^	5.41 (1.49)	5.45 (1.25)	5.49 (1.58)	0.362

Abbreviations: SD, standard deviation; n, number; TIA, transient ischemic attack; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide.

P-values were calculated using the continuous value of the square root of troponin levels for continuous variables and Chi-squared tests for categorical variables.

*adjusted p-value for age and sex $^{\#}$measured at 6 months ^missing data for n=716 participants.

Table 2 Association of cardiac troponin T with cognitive function at baseline and during follow-up

		Thirds of cardiac troponin T			P-value*
		Low	Middle	High	
		0.002-0.004 µg/L	0.005-0.009 µg/L	0.010-1.840 µg/L	
Cognitive tests (mean, SE)					
Stroop, seconds	Baseline score	65.91 (1.16)	67.26 (1.10)	70.09 (1.10)	<0.001
	Annual change	0.34 (0.12)	0.59 (0.11)	1.06 (0.12)	0.013
LDCT, digits coded	Baseline score	23.36 (0.32)	22.94 (0.30)	22.28 (0.30)	<0.001
	Annual change	-0.29 (0.03)	-0.34 (0.02)	-0.46 (0.03)	<0.001
PLTi, pictures remembered	Baseline score	9.45 (0.09)	9.36 (0.08)	9.28 (0.08)	0.002
	Annual change	0.01 (0.01)	-0.02 (0.01)	-0.06 (0.01)	<0.001
PLTd, pictures remembered	Baseline score	10.31 (0.12)	10.09 (0.12)	10.05 (0.11)	0.013
	Annual change	-0.03 (0.01)	-0.06 (0.01)	-0.12 (0.02)	0.001

Data represent model-based adjusted means (standard error) of each cognitive function test concerning the baseline associations. For the longitudinal analyses, data represent model-based adjusted mean annual change (standard error) per 1 square root (ng/L) increase of cardiac troponin T for each cognitive function test. Cardiac troponin T was measured after 6 months of follow-up.

*Adjusted p-values were calculated using the continuous value of the square root of troponin levels.

Abbreviations: SE, standard error; LDCT, Letter-Digit Coding test; PLTi, Picture-Word Learning test, immediate; PLTd, Picture-Word Learning test, delayed.

Data are adjusted for age, sex, country, education, treatment group, test version for LDCT and PLT, ApoE genotype, history of vascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, body mass index, eGFR.

Table 3 Association of cardiac troponin T and NT-proBNP with cognitive decline during follow-up

	Thirds of cardiac troponin T			P-value*
	Low 0.002-0.004 µg/L	Middle 0.005-0.009 µg/L	High 0.010-1.840 µg/L	
NT-proBNP				
Low (<200 ng/L)	N=1254	N=1279	N=826	
Stroop, seconds	0.27 (0.13)	0.64 (0.13)	0.71 (0.17)	0.076
LDCT, digits coded	-0.27 (0.03)	-0.34 (0.03)	-0.38 (0.04)	0.287
PLTi, pictures remembered	0.01 (0.01)	-0.01 (0.01)	-0.05 (0.02)	0.001
PLTd, pictures remembered	-0.02 (0.02)	-0.06 (0.02)	-0.09 (0.02)	0.176
High (≥ 200 ng/L)	N=330	N=693	N=1025	
Stroop, seconds	0.59 (0.29)	0.45 (0.21)	1.48 (0.19)	0.540
LDCT, digits coded	-0.37 (0.06)	-0.34 (0.04)	-0.53 (0.04)	0.001
PLTi, pictures remembered	0.01 (0.02)	-0.04 (0.02)	-0.07 (0.02)	0.070
PLTd, pictures remembered	-0.06 (0.04)	-0.06 (0.03)	-0.14 (0.02)	0.120

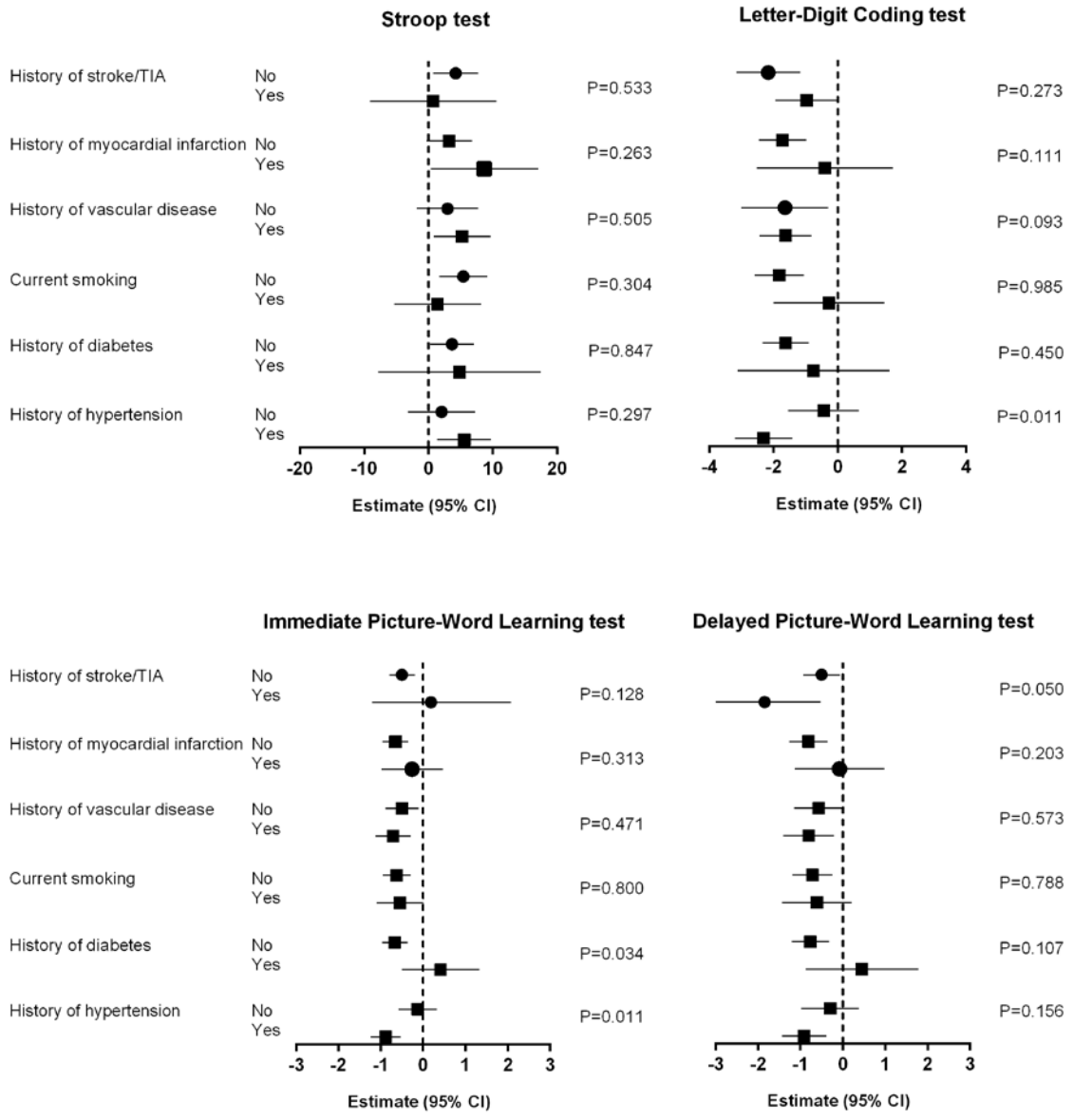
Abbreviations: SE, standard error; n, number; LDCT, Letter-Digit Coding test; PLTi, Picture-Word Learning test, immediate; PLTd, Picture-Word Learning test, delayed.

Data represent model-based adjusted mean annual change (standard error) per 1 square root (ng/L) increase of cardiac troponin T for each cognitive function test. Cardiac troponin T and NT-proBNP were measured after 6 months of follow-up.

*Adjusted p-values were calculated using the interaction term of time x square root of troponin levels.

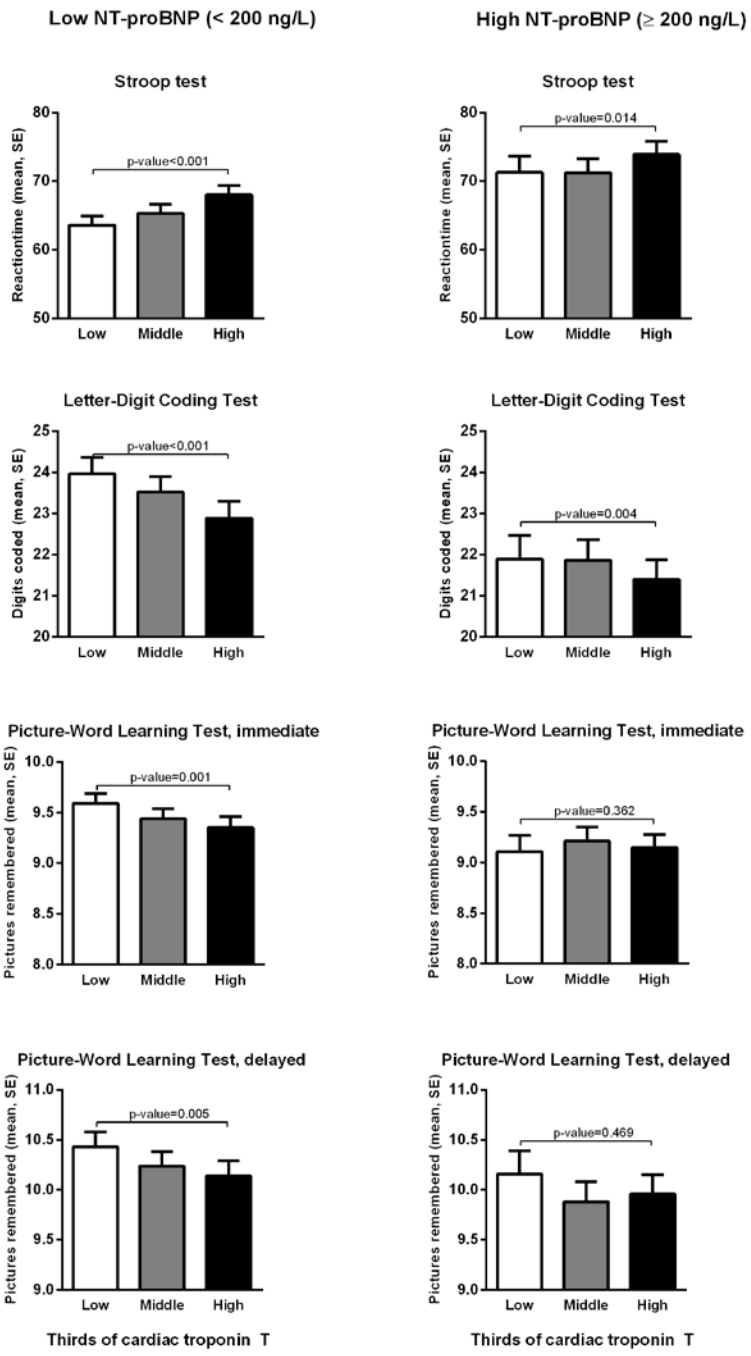
Adjusted for age, sex, country, education, treatment group, test version for LDCT and PLT, ApoE genotype, history of cerebrovascular and cardiovascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, body mass index and eGFR.

Figure 1 Association of cardiac troponin T with cognitive decline during follow-up, stratified by cardiovascular diseases and risk factors



Legend: Data represent mean annual change (95% confidence interval) per 1 square root (ng/L) increase of cardiac troponin T for each cognitive test, stratified by cardiovascular diseases. Higher annual change indicates less decline in cognitive function over time; expect for the Stroop test, where higher annual change means more decline in cognitive function over time. P-values were calculated using the interaction term of cardiovascular disease, square root of cardiac troponin T, and time. They represent the statistical difference in annual change in cognitive function between participants with and without cardiovascular disease or risk factors. Adjusted for age, sex, country, education, treatment group and test version where appropriate.

Figure 2 Association of cardiac troponin T with baseline cognitive function, stratified by NT-proBNP



Legend: Abbreviations: SE, standard error. Adjusted for age, sex, country, education, treatment group, test version for LDCT and PLT, ApoE genotype, history of cerebrovascular and cardiovascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, body mass index and eGFR. Higher scores indicate better cognitive performance; expect for the Stroop test, where a higher score indicates worse performance.

Supplemental table 1 Association of cardiac troponin T with cognitive function at baseline and during follow-up (minimally adjusted models)

Cognitive tests (mean, SE)		Thirds of cardiac troponin T			P-value*
		Low	Middle	High	
		0.002-0.004 µg/L	0.005-0.009 µg/L	0.010-1.840 µg/L	
Stroop, seconds	Baseline score	63.06 (0.65)	64.44 (0.56)	67.30 (0.61)	<0.001
	Annual change	0.34 (0.12)	0.58 (0.11)	1.05 (0.12)	0.015
LDCT, digits coded	Baseline score	24.18 (0.18)	23.77 (0.15)	23.17 (0.17)	<0.001
	Annual change	-0.29 (0.03)	-0.34 (0.02)	-0.46 (0.03)	<0.001
PLTi, pictures remembered	Baseline score	9.56 (0.05)	9.47 (0.04)	9.39 (0.04)	0.001
	Annual change	0.01 (0.01)	-0.02 (0.01)	-0.06 (0.01)	<0.001
PLTd, pictures remembered	Baseline score	10.50 (0.07)	10.26 (0.06)	10.22 (0.06)	0.004
	Annual change	-0.03 (0.02)	-0.06 (0.02)	-0.12 (0.02)	0.001

Abbreviations: SE, standard error; LDCT, Letter-Digit Coding test; PLTi, Picture-Word Learning test, immediate; PLTd, Picture-Word Learning test, delayed. Data represent model-based adjusted means (standard error) of each cognitive function test concerning the baseline associations. For the longitudinal analyses, data represent model-based adjusted mean annual change (standard error) per 1 square root (ng/L) increase of cardiac troponin T for each cognitive function test. Cardiac troponin T was measured after 6 months of follow-up. Data are adjusted for age, sex, country, education, treatment group, test version for LDCT and PLT. *Adjusted p-values were calculated using the continuous value of the square root of troponin levels.

Supplemental table 2 Association of cardiac troponin T with cognitive function at baseline and during follow-up, additionally adjusted for NT-proBNP

		Thirds of cardiac troponin T			P-value*
		Low	Middle	High	
		0.002-0.004 µg/L	0.005-0.009 µg/L	0.010-1.840 µg/L	
Cognitive tests (mean, SE)					
Stroop, seconds	Baseline score	66.22 (1.16)	67.38 (1.10)	69.43 (1.11)	0.013
	Annual change	0.34 (0.12)	0.59 (0.11)	1.07 (0.12)	0.010
LDCT, digits coded	Baseline score	23.32 (0.32)	22.92 (0.30)	22.37 (0.30)	<0.001
	Annual change	-0.29 (0.03)	-0.34 (0.02)	-0.47 (0.03)	<0.001
PLTi, pictures remembered	Baseline score	9.44 (0.09)	9.36 (0.08)	9.28 (0.08)	0.005
	Annual change	0.01 (0.01)	-0.02 (0.01)	-0.06 (0.01)	<0.001
PLTd, pictures remembered	Baseline score	10.30 (0.12)	10.09 (0.12)	10.06 (0.12)	0.041
	Annual change	-0.03 (0.02)	-0.06 (0.01)	-0.12 (0.02)	0.001

Abbreviations: SE, standard error; LDCT, Letter-Digit Coding test; PLTi, Picture-Word Learning test, immediate; PLTd, Picture-Word Learning test, delayed. Data represent model-based adjusted means (standard error) of each cognitive function test concerning the baseline associations. For the longitudinal analyses, data represent model-based adjusted mean annual change (standard error) per 1 square root (ng/L) increase of cardiac troponin T for each cognitive function test. Cardiac troponin T was measured after 6 months of follow-up. Data are adjusted for age, sex, country, education, treatment group, test version for LDCT and PLT, ApoE genotype, history of vascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, body mass index, eGFR and NT-proBNP level. *Adjusted p-values were calculated using the continuous value of the square root of troponin levels.

Supplemental table 3 Association of cardiac troponin T and NT-proBNP with cognitive function at baseline and during follow-up (stratified by NT-proBNP < and ≥ 400 ng/L)

		Thirds of cardiac troponin T			P-value*
		Low	Middle	High	
		0.002-0.004 µg/L	0.005-0.009 µg/L	0.010-1.840 µg/L	
Cognitive tests (mean, SE)					
NT-proBNP < 400 ng/L		N=1496	N=1713	N=1265	
Stroop, seconds	Baseline score	64.75 (1.20)	65.99 (1.15)	68.55 (1.19)	<0.001
	Annual change	0.33 (0.12)	0.60 (0.11)	0.85 (0.14)	0.130
LDCT, digits coded	Baseline score	23.67 (0.34)	23.27 (0.33)	22.71 (0.34)	<0.001
	Annual change	-0.28 (0.03)	-0.33 (0.03)	-0.43 (0.03)	0.085
PLTi, pictures remembered	Baseline score	9.54 (0.09)	9.43 (0.09)	9.38 (0.09)	0.006
	Annual change	-0.23 (0.11)	-0.08 (0.08)	-0.13 (0.05)	0.001
PLTd, pictures remembered	Baseline score	10.43 (0.13)	10.17 (0.13)	10.22 (0.13)	0.016
	Annual change	-0.03 (0.02)	-0.05 (0.02)	-0.10 (0.02)	0.042
NT-proBNP ≥ 400 ng/L		N=88	N=259	N=586	
Stroop, seconds	Baseline score	73.81 (4.28)	75.94 (3.37)	76.56 (3.05)	0.291
	Annual change	0.40 (0.69)	0.37 (0.43)	1.79 (0.30)	0.744
LDCT, digits coded	Baseline score	20.83 (0.98)	20.97 (0.76)	20.47 (0.69)	0.054
	Annual change	-0.37 (0.12)	-0.38 (0.07)	-0.53 (0.05)	0.004
PLTi, pictures remembered	Baseline score	8.76 (0.27)	9.02 (0.21)	8.82 (0.19)	0.395
	Annual change	0.10 (0.05)	-0.06 (0.03)	-0.09 (0.02)	0.126
PLTd, pictures remembered	Baseline score	9.81 (0.37)	9.72 (0.29)	9.36 (0.26)	0.372
	Annual change	0.01 (0.08)	-0.10 (0.05)	-0.17 (0.03)	0.445

Abbreviations: SE, standard error; LDCT, Letter-Digit Coding test; PLTi, Picture-Word Learning test, immediate; PLTd, Picture-Word Learning test, delayed. Data represent model-based adjusted means (standard error) of each cognitive function test concerning the baseline associations. For the longitudinal analyses, data represent model-based adjusted mean annual change (standard error) per 1 square root (ng/L) increase of cardiac troponin T for each cognitive function test. Cardiac troponin T was measured after 6 months of follow-up. Data are adjusted for age, sex, country, education, treatment group, test version for LDCT and PLT, ApoE genotype, history of vascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, body mass index, eGFR. *Adjusted p-values were calculated using the continuous value of the square root of troponin levels.

Supplemental table 4 Association of cardiac troponin T with cognitive function at baseline and during follow-up (participants with heart failure hospitalization (n=205) and participants using loop diuretics (n=588) excluded)

		Thirds of cardiac troponin T			P-value*
		Low	Middle	High	
		0.002-0.004 µg/L	0.005-0.009 µg/L	0.010-1.840 µg/L	
Cognitive tests (mean, SE)					
Stroop, seconds	Baseline score	65.33 (1.22)	67.09 (1.17)	68.11 (1.19)	<0.001
	Annual change	0.37 (0.13)	0.55 (0.12)	1.00 (0.13)	<0.001
LDCT, digits coded	Baseline score	23.38 (0.34)	22.96 (0.33)	22.46 (0.33)	<0.001
	Annual change	-0.30 (0.03)	-0.33 (0.03)	-0.45 (0.03)	<0.001
PLTi, pictures remembered	Baseline score	9.51 (0.09)	9.44 (0.09)	9.39 (0.09)	0.028
	Annual change	0.02 (0.01)	-0.02 (0.01)	-0.05 (0.01)	<0.001
PLTd, pictures remembered	Baseline score	10.37 (0.13)	10.20 (0.13)	10.22 (0.13)	0.051
	Annual change	-0.02 (0.02)	-0.06 (0.02)	-0.11 (0.02)	<0.001

Abbreviations: SE, standard error; LDCT, Letter-Digit Coding test; PLTi, Picture-Word Learning test, immediate; PLTd, Picture-Word Learning test, delayed. Data represent model-based adjusted means (standard error) of each cognitive function test concerning the baseline associations. For the longitudinal analyses, data represent model-based adjusted mean annual change (standard error) per 1 square root (ng/L) increase of cardiac troponin T for each cognitive function test. Data are adjusted for age, sex, country, education, treatment group, test version for LDCT and PLT, ApoE genotype, history of vascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, body mass index, eGFR. *Adjusted p-values were calculated using the continuous value of the square root of troponin levels.

Supplemental table 5 Association of cardiac troponin T with baseline cognitive function

	Thirds of cardiac troponin T			P-value*
	Low	Middle	High	
Cognitive tests (mean, SE)	0.002-0.004 µg/L	0.005-0.009 µg/L	0.010-1.840 µg/L	
Exclusion of participants with stroke/tia (N=378)	**N=1497**	**N=1838**	**N=1694**	
Stroop, seconds	65.19 (1.21)	66.97 (1.15)	69.68 (1.15)	<0.001
LDCT, digits coded	23.52 (0.33)	23.01 (0.31)	22.30 (0.31)	<0.001
PLTi, pictures remembered	9.48 (0.09)	9.41 (0.08)	9.31 (0.08)	0.001
PLTd, pictures remembered	10.36 (0.13)	10.15 (0.12)	10.10 (0.12)	0.014
Exclusion of participants with coronary events (N=575)	**N=1495**	**N=1809**	**N=1528**	
Stroop, seconds	65.44 (1.18)	66.96 (1.12)	69.08 (1.13)	<0.001
LDCT, digits coded	23.62 (0.34)	23.19 (0.32)	22.55 (0.32)	<0.001
PLTi, pictures remembered	9.44 (0.09)	9.36 (0.09)	9.27 (0.09)	0.015
PLTd, pictures remembered	10.33 (0.13)	10.07 (0.12)	10.05 (0.12)	0.008
Exclusion of participants with AF (N=507)	**N=1507**	**N=1814**	**N=1579**	
Stroop, seconds	65.32 (1.21)	66.79 (1.15)	69.46 (1.16)	<0.001
LDCT, digits coded	23.38 (0.34)	22.97 (0.32)	22.44 (0.32)	<0.001
PLTi, pictures remembered	9.44 (0.09)	9.38 (0.09)	9.26 (0.09)	0.005
PLTd, pictures remembered	10.29 (0.13)	10.13 (0.12)	10.04 (0.12)	0.042
Exclusion of participants with cardiovascular events (N=872)	**N=1421**	**N=1694**	**N=1420**	
Stroop, seconds	64.36 (1.22)	66.20 (1.16)	68.10 (1.17)	<0.001
LDCT, digits coded	23.76 (0.35)	23.33 (0.33)	22.64 (0.33)	<0.001
PLTi, pictures remembered	9.50 (0.09)	9.41 (0.09)	9.34 (0.09)	0.037
PLTd, pictures remembered	10.37 (0.13)	10.13 (0.13)	10.11 (0.13)	0.035
Exclusion of participants with path. Q waves (N=1211)	**N=1339**	**N=1513**	**N=1344**	
Stroop, seconds	65.98 (1.26)	67.14 (1.20)	68.54 (1.22)	0.144
LDCT, digits coded	23.41 (0.36)	23.16 (0.34)	22.76 (0.34)	0.005
PLTi, pictures remembered	9.44 (0.10)	9.38 (0.09)	9.30 (0.09)	0.029
PLTd, pictures remembered	10.32 (0.13)	10.12 (0.13)	10.10 (0.13)	0.080

Abbreviations: SE, standard error; LDCT, Letter-Digit Coding test; PLTi, Picture-Word Learning test, immediate; PLTd, Picture-Word Learning test, delayed. Data represent model-based adjusted means (standard error) of each cognitive function test. Analyses were adjusted for sex, age, country, education, treatment code, test version for LDCT and PLT, ApoE genotype, history of vascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, body mass index and eGFR. *Adjusted p-values were calculated using the continuous value of the square root of troponin levels.

Supplemental table 6 Association of cardiac troponin T with cognitive decline during follow-up

	Thirds of cardiac troponin T			P-value*
	Low	Middle	High	
Cognitive tests (mean, SE)	0.002-0.004 µg/L	0.005-0.009 µg/L	0.010-1.840 µg/L	
Exclusion of participants with stroke/tia (N=378)				
Stroop, seconds	0.26 (0.12)	0.47 (0.11)	0.93 (0.12)	0.033
LDCT, digits coded	-0.27 (0.03)	-0.31 (0.02)	-0.42 (0.03)	<0.001
PLTi, pictures remembered	0.02 (0.01)	-0.02 (0.01)	-0.05 (0.01)	<0.001
PLTd, pictures remembered	-0.02 (0.02)	-0.06 (0.01)	-0.11 (0.02)	0.002
Exclusion of participants with coronary events (N=575)				
Stroop, seconds	0.28 (0.12)	0.58 (0.11)	0.98 (0.13)	0.040
LDCT, digits coded	-0.28 (0.03)	-0.35 (0.03)	-0.44 (0.03)	0.003
PLTi, pictures remembered	0.01 (0.01)	-0.02 (0.01)	-0.06 (0.01)	<0.001
PLTd, pictures remembered	-0.03 (0.02)	-0.06 (0.02)	-0.11 (0.02)	0.018
Exclusion of participants with AF (N=507)				
Stroop, seconds	0.31 (0.12)	0.53 (0.11)	0.96 (0.13)	0.042
LDCT, digits coded	-0.29 (0.03)	-0.31 (0.03)	-0.45 (0.03)	<0.001
PLTi, pictures remembered	0.01 (0.01)	-0.02 (0.01)	-0.04 (0.01)	<0.001
PLTd, pictures remembered	-0.02 (0.02)	-0.05 (0.01)	-0.10 (0.02)	0.002
Exclusion of participants with cardiovascular events (N=872)				
Stroop, seconds	0.24 (0.12)	0.47 (0.11)	0.83 (0.13)	0.129
LDCT, digits coded	-0.26 (0.03)	-0.32 (0.03)	-0.41 (0.03)	0.003
PLTi, pictures remembered	0.02 (0.01)	-0.01 (0.01)	-0.06 (0.01)	<0.001
PLTd, pictures remembered	-0.02 (0.02)	-0.05 (0.02)	-0.10 (0.02)	0.008
Exclusion of participants with path. Q waves (N=1211)				
Stroop, seconds	0.32 (0.13)	0.55 (0.12)	1.09 (0.14)	0.005
LDCT, digits coded	-0.29 (0.03)	-0.36 (0.03)	-0.46 (0.03)	<0.001
PLTi, pictures remembered	0.01 (0.01)	-0.02 (0.01)	-0.05 (0.01)	<0.001
PLTd, pictures remembered	-0.03 (0.02)	-0.05 (0.02)	-0.12 (0.02)	0.003

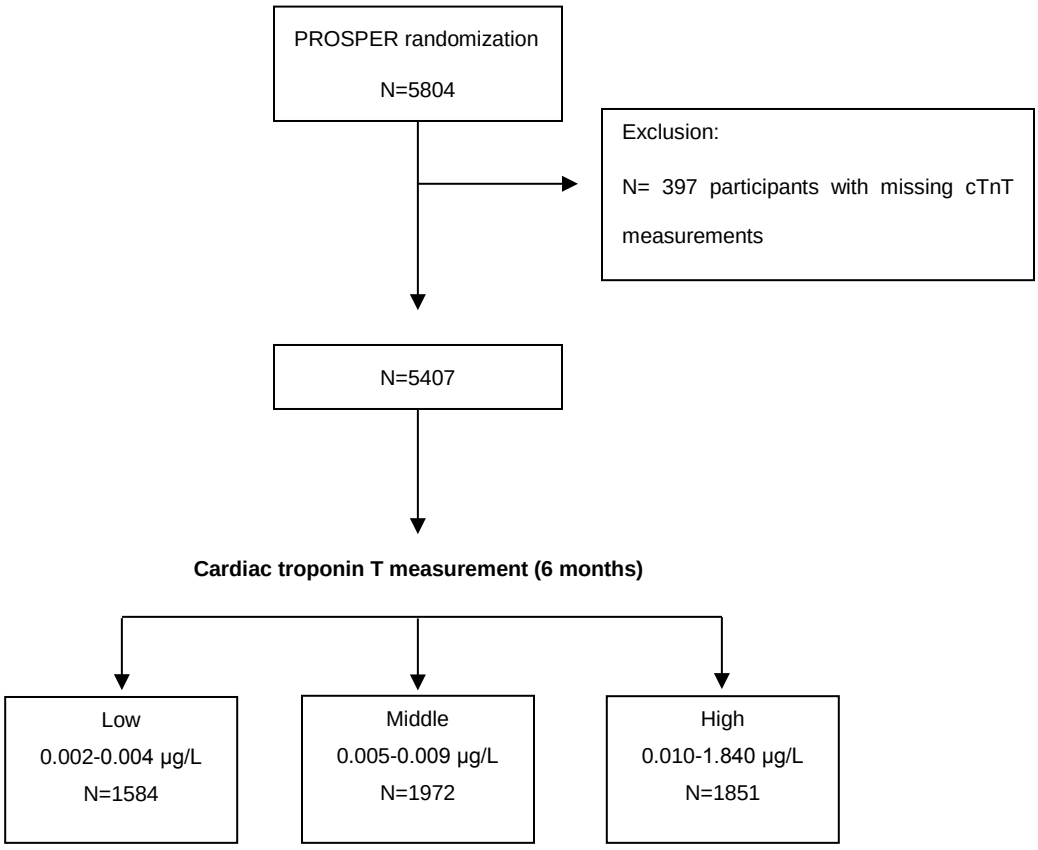
Abbreviations: SE, standard error; LDCT, Letter-Digit Coding test; PLTi, Picture-Word Learning test, immediate; PLTd, Picture-Word Learning test, delayed. Data represent model-based adjusted mean annual change (standard error) per 1 square root (ng/L) increase of cardiac troponin T for each cognitive function test. Adjusted for age, sex, country, education, treatment group, test version for LDCT and PLT, ApoE genotype, history of cerebrovascular and cardiovascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, body mass index and eGFR. *Adjusted p-values were calculated using the interaction term of time x square root of troponin levels.

Supplemental table 7 Association of cardiac troponin T with cognitive function at baseline and during follow-up (exclusion of participants with cTnT >0.014 µg/L)

		Thirds of cardiac troponin T			P-value*
		Low	Middle	High	
		0.002-0.004 µg/L	0.005-0.009 µg/L	0.010-0.013 µg/L	
Cognitive tests (mean, SE)		N=1584	N=1972	N=849	
Stroop, seconds	Baseline score	65.04 (0.40)	66.80 (0.38)	68.03 (0.43)	0.001
	Annual change	0.34 (0.12)	0.59 (0.11)	1.18 (0.17)	<0.001
LDCT, digits coded	Baseline score	23.46 (0.11)	23.02 (0.11)	22.86 (0.12)	0.002
	Annual change	-0.29 (0.03)	-0.34 (0.02)	-0.43 (0.04)	0.003
PLTi, pictures remembered	Baseline score	9.45 (0.03)	9.37 (0.03)	9.33 (0.03)	0.033
	Annual change	0.01 (0.01)	-0.02 (0.01)	-0.04 (0.02)	<0.001
PLTd, pictures remembered	Baseline score	10.35 (0.04)	10.12 (0.04)	10.12 (0.05)	0.002
	Annual change	-0.03 (0.02)	-0.06 (0.01)	-0.10 (0.02)	0.016

Abbreviations: SE, standard error; LDCT, Letter-Digit Coding test; PLTi, Picture-Word Learning test, immediate; PLTd, Picture-Word Learning test, delayed. Data represent model-based adjusted means (standard error) of each cognitive function test concerning the baseline associations. For the longitudinal analyses, data represent model-based adjusted mean annual change (standard error) per 1 square root (ng/L) increase of cardiac troponin T for each cognitive function test. Data are adjusted for age, sex, country, education, treatment group, test version for LDCT and PLT, ApoE genotype, history of vascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, body mass index, eGFR. *Adjusted p-values were calculated using the interaction term of time x square root of troponin levels.

Supplemental figure 1



Supplemental figure 2 Distribution of hs-cTnT levels