Cardiac Troponin and Recurrent Major Vascular Events after Minor Stroke or Transient Ischemic Attack

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Objective: This study was undertaken to investigate whether high-sensitivity cardiac troponin T (hs-cTnT) is associated with major adverse cardiovascular events (MACE) in patients with minor stroke or transient ischemic attack (TIA), and whether this association differs after risk stratification based on the Age, Blood Pressure, Clinical Features, Duration of Symptoms, Diabetes ($ABCD^2$) score.

Methods: INSPiRE-TMS was a randomized controlled trial allocating patients with minor stroke or TIA to an intensified support program or conventional care. In this post hoc analysis, participants were categorized using hs-cTnT levels (5th generation; Roche Diagnostics, Manheim, Germany; 99th percentile upper reference limit [URL] = 14ng/l). Vascular risk was stratified using the $ABCD^2$ score (lower risk = 0–5 vs higher risk = 6–7). Cox proportional hazard regression was performed using covariate adjustment and propensity score matching (PSM) for the association between hs-cTnT and MACE (stroke/nonfatal coronary event/vascular death).

Results: Among 889 patients (mean age = 70 years, 37% female), MACE occurred in 153 patients (17.2%) during a mean follow-up of 3.2 years. hs-cTnT was associated with MACE (9.3%/yr, >URL vs 4.4%/yr, ≤URL, adjusted hazard ratio [HR] = 1.63 [95% confidence interval (CI) = 1.13–2.35], adjusted HR [Q_4 vs Q_1] = 2.57 [95% CI = 1.35–4.97], adjusted HR [log-transformed] = 2.31 [95% CI = 1.37–3.89]). This association remained after PSM (adjusted HR = 1.76 [95% CI = 1.14–2.72]). There was a significant interaction between hs-cTnT and $ABCD^2$ category for MACE occurrence ($p_{interaction} = 0.04$). In the lower risk category, MACE rate was 9.5%/yr in patients with hs-cTnT > URL, which was higher than in those ≤URL (3.8%/yr) and similar to the overall rate in the higher risk category.

Interpretation: hs-cTnT levels are associated with incident MACE within 3 years after minor stroke or TIA and may help to identify high-risk individuals otherwise deemed at lower risk based on the $ABCD^2$ score. If confirmed in independent validation studies, this might warrant intensified secondary prevention measures and cardiac diagnostics in stroke patients with elevated hs-cTnT.

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Patients with acute ischemic stroke or transient ischemic attack (TIA) have a high risk of recurrent vascular events.[1] Several clinical prediction schemes such as the Age, Blood Pressure, Clinical Features, Duration of Symptoms, Diabetes ($ABCD^2$) score have been proposed to guide clinical triage of patients.[2] Although initially conceived for early triage purposes after TIA, it has been suggested that higher $ABCD^2$ scores are also associated with an increased risk of recurrent vascular events after ischemic stroke.[1] However, individual stratification of future vascular risk after cerebrovascular events is still limited and the individual risk may vary substantially.[2,3] It is increasingly recognized that blood-based biomarkers may be useful to provide an individual risk estimate beyond conventional risk factors by capturing biologically relevant pathways.[4,5] Recent observations highlight the potential role of high-sensitivity cardiac troponin (hs-cTn) levels for this purpose.[6,7] Myocardial injury with high-sensitivity cardiac troponin T (hs-cTnT) elevation above the assay-specific 99th percentile upper reference limit (URL) is common after stroke and associated with poor long-term outcome.[8] Higher hs-cTn levels are associated with an increased risk of thromboembolic and major adverse cardiovascular events (MACE) in the general population as well as in patients with atrial fibrillation.[9,10] However, this association is less well established in patients with recent ischemic stroke or TIA.[7,11]

Usually, antithrombotic treatment and risk factor control are considered indicated in all patients after stroke, but it remains unknown whether certain patients benefit from intensified secondary prevention measures.[12,13] The recently completed INSPiRE-TMS trial (INtensified Secondary Prevention intending a Reduction of recurrent Events after Transient ischaemic attack and Minor Stroke) demonstrated a significant improvement in risk factor control in patients randomized to a multicomponent secondary prevention support program in comparison to conventional care. Yet this did not transform into a significant reduction of subsequent MACE in these patients.[14] However, subgroup analyses suggested that patients with a higher risk $ABCD^2$score may benefit from the study intervention.[14]

By using data from INSPiRE-TMS, we aimed to investigate (1) whether presence of myocardial injury (hs-cTnT levels above URL) is associated with recurrent MACE in patients with minor stroke or TIA, (2) whether this association is maintained in patients deemed at lower or higher vascular risk based on the $ABCD^2$ score, and (3) whether the effect of the multicomponent support program tested in INSPiRE-TMS is modified by levels of hs-cTnT.

Patients and Methods

Study Population

INSPiRE-TMS was a prospective open-label, multicenter, blinded endpoint, and event-driven international randomized controlled trial that recruited 2,098 patients from August 2011 to October 2017. The protocol for the study received prior approval by the institutional review board (ethics committee) of the Charité–Universitätsmedizin Berlin (EA2/084/11) and was registered online (NCT01586702). Informed consent was obtained from each subject. The details of the protocol and final results of the trial have been published elsewhere.[14,15] In brief, patients aged 18 years or older with nondisabling stroke (ie, modified Rankin Scale (mRS) <3, indicating functional independency) or TIA and at least one modifiable risk factor (ie, arterial hypertension, diabetes, atrial fibrillation, or smoking) within 2 weeks from the index event were eligible to participate. Patients with symptom duration <24 hours but with an ischemic lesion on cerebral imaging were diagnosed as minor stroke patients. The $ABCD^2$ score ranges from 0 to 7 points and assesses age (<60 years = 0 points, ≥60 years = 1 point), blood pressure upon admission (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg = 0 points, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg = 1 point), clinical symptoms (unilateral weakness = 2 points, isolated speech disturbance = 1 point, other symptoms = 0 points), duration of symptoms (<10 minutes = 0 points, 10–59 minutes = 1 point, ≥60 minutes = 2 points), and history of diabetes (no = 0 points, yes = 1 point), with a higher score indicating a higher risk of subsequent stroke.[2] An $ABCD^2$ score ≥6 is considered to indicate a higher risk of recurrent ischemic stroke and MACE.[16] Further refinements to the score have been suggested, such as the $ABCD^3I$ score with addition of a preceding TIA within 7 days before the index TIA (present = 2 points), an ipsilateral >50% stenosis of the carotid artery (present = 2 points), and a possible stroke correlate on brain imaging (present = 2 points).[17] With a range from 0 to 13 points, we used a cutoff at ≥8 points to differentiate between high-risk and low-risk patients as suggested by the literature.[18]

Study participants were randomized in a 1:1 fashion to receive either a multicomponent support program in addition to conventional care or conventional care alone. The support program consisted of 8 outpatient visits at 3, 6, and 12 weeks, then 6, 9, 12, 18, and 24 months after randomization, aiming to improve adherence to secondary prevention targets. Using feedback and motivational interviewing strategies, comprehensive and repeated information on the pathophysiology of the individual's

risk for recurrent vascular events and potential for vascular risk reduction was provided, including changes in lifestyle and adherence to medication. For this biomarker subgroup analysis, we considered patients enrolled at the Charité Campus Benjamin Franklin recruitment site, because measurement of hs-cTnT levels is part of clinical routine upon hospital admission at this center. We did not include patients suffering from intracerebral hemorrhage because of different pathophysiology.

Study Outcomes

The primary outcome of interest was the time to first occurrence of MACE, defined as a composite of vascular events including stroke, nonfatal coronary events (ie, unstable angina pectoris, ST-elevation and non–ST-elevation myocardial infarction), and vascular death. The secondary outcome of interest was time to the first occurrence of stroke, acute coronary syndrome, or vascular death. Stroke was defined as an acute (focal) neurological syndrome caused by a blood supply disorder in the brain with the presence of an ischemic lesion in the corresponding territory on brain imaging, or clinical evidence of an imaging-negative ischemic lesion with symptom duration longer than 24 hours. Nonfatal coronary events were defined as (1) typical clinical symptoms (eg, chest pain, cardiac failure) together with typical electrocardiogram (ECG) abnormalities, (2) typical clinical symptoms with elevation of troponin >2 × the URL, (3) nonspecific symptoms with elevation of troponin >2 × the URL together with typical ECG findings, or (4) so-called silent myocardial infarction as diagnosed on follow-up ECG by comparison with baseline ECG combined with corresponding results in echocardiography or coronary angiography. Vascular death was defined as death within 30 days of stroke, death within 7 days of a nonfatal coronary event, death caused by noncerebral hemorrhage or necrosis following peripheral artery occlusion or pulmonary embolism, or death within 24 hours of a previous good and stable condition and without other identifiable cause. Outcomes were assessed at annual follow-ups, and the endpoint committee adjudicated all possible primary and secondary outcomes using prespecified criteria unaware of treatment allocation.

Biomarker Sampling

As recommended by current guidelines, measurement of hs-cTnT upon hospital admission was performed according to a standardized operating procedure during routine clinical care at the study center Charité Campus Benjamin Franklin.[19,20] hs-cTnT levels were measured using a high-sensitivity electrochemiluminescence immunoassay (Roche Elecsys 2010 5th-generation assay; Roche Diagnostics, Mannheim, Germany) with a URL of 14ng/l corresponding to the 99th percentile of a healthy reference population, a limit of blank set at 3ng/l, and a limit of detection of 5ng/l. The assay properties have been described previously.[21]

Statistical Analysis

Study participants were dichotomized according to the 99th percentile URL of baseline hs-cTnT levels: >14 ng/l (above 99th percentile URL, ie, "elevated") or ≤14 ng/l (reference).[21,22] This cutoff was chosen because it is the established cutoff to define myocardial injury and represented the highest quartile in our cohort.[22] In addition, participants were categorized according to quartiles of hs-cTnT (see sensitivity analyses below). Due to the laboratory reporting system, hs-cTnT values <13 ng/l were not specified until March 2013. Therefore, constitution of hs-cTnT quartiles and log transformation was only possible for participants enrolled after March 18, 2013.

Results are reported as absolute and relative frequencies for categorical variables. In the case of continuous variables, mean and standard deviation (SD) are reported for sufficiently normally distributed data (|skewness|<1) or median and limits of interquartile range (IQR) for variables with skewed distribution or ordinal variables. Continuous variables were compared using a *t*-test or Mann–Whitney *U* test, as appropriate. Categorical variables were compared using Pearson chi-squared test. Unadjusted and adjusted Cox proportional hazards regression analyses were used to explore the association of hs-cTnT levels with the respective outcomes by obtaining hazard ratios (HRs) with their 95% confidence intervals (CIs). The regression models included potential confounders determined a priori based on literature review with known influence on vascular events and/or hs-cTnT levels (age, sex, type of index event [stroke vs TIA], arterial hypertension, diabetes, atrial fibrillation, history of smoking, history of stroke or TIA, coronary artery disease and/or history of myocardial infarction, congestive heart failure, impaired renal function, and treatment arm [intensified secondary prevention program vs conventional care]). Sensitivity analyses were performed by (1) entering hs-cTnT levels as a log-transformed continuous variable (because of skewedness) into the model, (2) categorizing hs-cTnT levels into quartiles and comparing the highest to the lowest quartile, and (3) excluding subgroups of patients considered to have probable hs-cTnT levels above URL (ie, history of myocardial infarction, impaired kidney function, and atrial fibrillation). In case of analyses based on the $ABCD^2$ score, factors already included in the score (age, blood pressure, and diabetes) were not included separately in the adjusted model. If patients had >1 outcome

event, the time leading up to the first event was used for the regression analyses.

To further account for selection bias, we performed propensity score matching (PSM) in a 1:1 fashion without replacement ("optimal matching") to balance baseline characteristics between patients with hs-cTnT below or above URL.[23,24] We used a caliper (ie, the maximum distance that two cases can be apart from each other based on their estimated propensity scores) of 0.2 to prevent matches with very dissimilar estimated propensity scores.[25] Variables used for PSM were age, sex, event type (stroke or TIA), hypertension, diabetes, atrial fibrillation, smoking, prior stroke or TIA, coronary artery disease and/or prior myocardial infarction, congestive heart failure, and renal failure. In the case of missing data, we first tested the data to be missing completely at random using Little's MCAR test. Missing data among covariates used in the model were then imputed using the Expectation–Maximization algorithm. Across all chosen variables for PSM, 1.1% of data were missing. In detail, missing data of individual covariates were prior stroke or TIA (n = 33, 3.7%), coronary artery disease (n = 26, 2.9%), prior myocardial infarction (n = 11, 1.2%), congestive heart failure (n = 36, 4.0%), and renal failure (n = 16, 1.8%). Covariate balance was assessed with standardized mean differences (SMDs). Postmatching SMD <0.1 indicated a good covariate balance between groups.[24,26] After PSM, Cox proportional hazard models were repeated to determine the association between hs-cTnT and recurrent vascular events, also adjusting for the propensity score.[27] PSM was performed using the STATS R35 extension plug-in for SPSS to implement R version 3.5.0 and the PSMATCHING3 custom dialog.[28] Kaplan–Meier plots for dichotomous hs-cTnT and intervention groups were

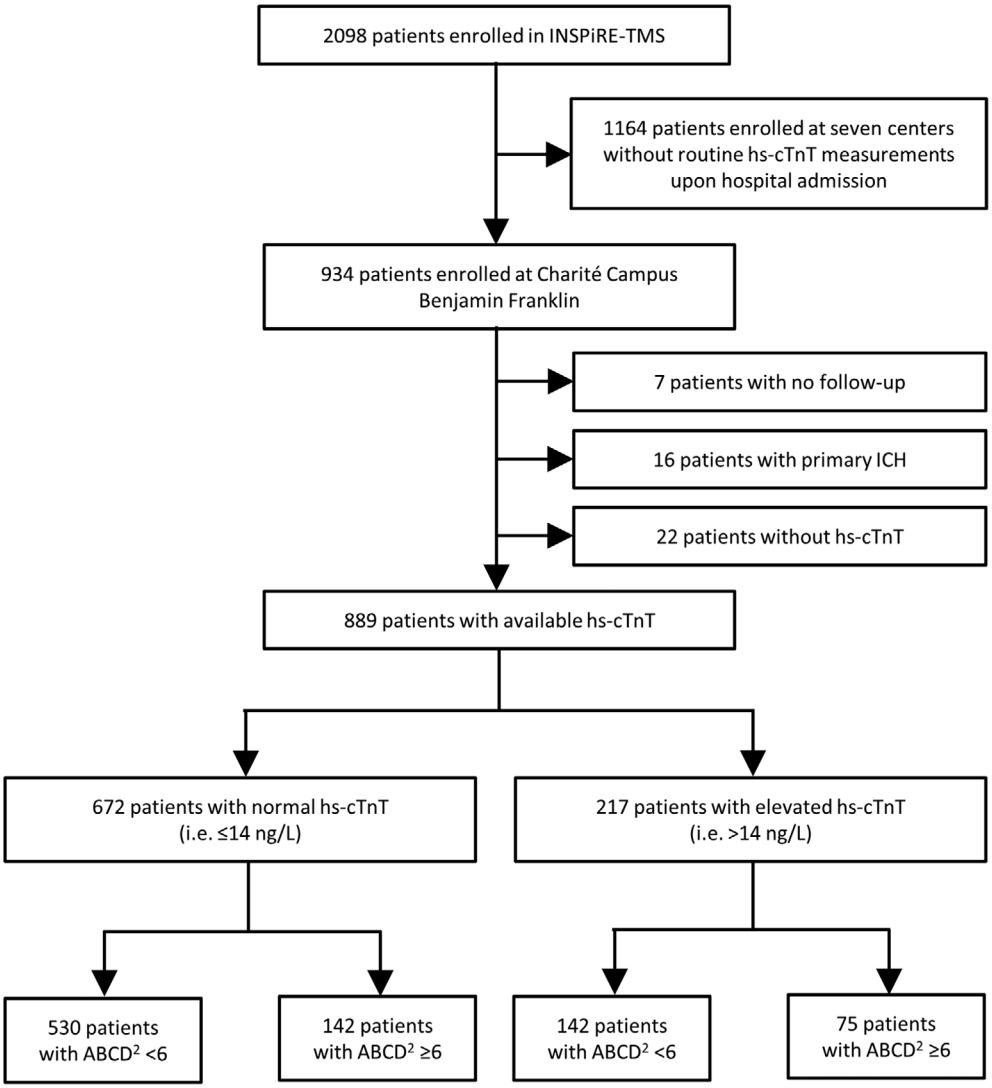

FIGURE 1: Study flowchart. ABCD² (Age, Blood Pressure, Clinical Features, Duration of Symptoms, Diabetes) indicates vascular risk. hs-cTnT = high-sensitivity cardiac troponin T; ICH = intracerebral hemorrhage.

TABLE. Baseline Characteristics[a]

Characteristic	hs-cTnT ≤ URL, n = 672		hs-cTnT > URL, n = 217	
	Control, n = 335	Intervention, n = 337	Control, n = 111	Intervention, n = 106
Age, yr	69.3 (9.4)	67.0 (10.2)	73.5 (9.1)	74.4 (8.8)
Sex				
Female	131 (39.1%)	136 (40.4%)	29 (26.1%)	30 (28.3%)
Modifiable risk factors				
Arterial hypertension	305 (91.0%)	289 (85.8%)	103 (92.8%)	97 (91.5%)
Diabetes	76 (22.7%)	64 (19.0%)	39 (35.1%)	44 (41.5%)
Atrial fibrillation	50 (14.9%)	51 (15.1%)	33 (29.7%)	27 (25.5%)
Current tobacco use	67 (20.0%)	60 (17.8%)	11 (9.9%)	18 (17.0%)
History (before index event)				
Stroke	56 (16.7%)	51 (15.1%)	21 (18.9%)	14 (13.2%)
Transient ischemic attack	19 (5.7%)	20 (5.9%)	9 (8.1%)	6 (5.7%)
Myocardial infarction	33 (9.9%)	14 (4.2%)	14 (12.6%)	15 (14.2%)
Peripheral artery disease	11 (3.3%)	13 (3.9%)	15 (13.5%)	6 (5.7%)
Risk factor measurements at baseline				
RR systolic, mmHg	132.9 (25.4)	132.8 (25.0)	137.1 (24.9)	139.0 (22.6)
RR diastolic, mmHg	76.7 (14.5)	77.5 (14.4)	76.4 (13.5)	76.1 (13.0)
HbA1c, mmol/mol	5.9 (0.8)	5.9 (1.0)	6.4 (1.4)	6.3 (1.1)
LDL, mg/dl	125.9 (40.3)	127.9 (41.6)	111.1 (41.8)	115.0 (37.2)
Index event				
Ischemic stroke	176 (52.5%)	176 (52.2%)	74 (66.7%)	71 (67.0%)
Transient ischemic attack	159 (47.5%)	161 (47.8%)	37 (33.3%)	35 (33.0%)
TOAST classification				
Large vessel	32 (9.6%)	36 (10.7%)	13 (11.7%)	15 (14.2%)
Small vessel	35 (10.4%)	23 (6.8%)	7 (6.3%)	9 (8.5%)
Cardioembolic	48 (14.3%)	48 (14.2%)	32 (28.8%)	32 (30.2%)
Other determined	3 (0.9%)	1 (0.3%)	1 (0.9%)	—
Undetermined	217 (64.8%)	229 (68.0%)	58 (52.3%)	50 (47.2%)
Competing mechanisms	27 (8.1%)	24 (7.1%)	6 (5.4%)	6 (5.7%)
Complete investigation	77 (23.0%)	98 (29.1%)	20 (18.0%)	17 (16.0%)
Incomplete investigation	113 (33.7%)	107 (31.8%)	32 (28.8%)	27 (25.5%)
Event to inclusion, days	3.4 (2.5)	3.5 (2.7)	3.9 (2.8)	3.5 (2.4)
NIHSS at hospital admission	1 (0–2)	1 (0–2)	1 (0–3)	1 (0–3)
MOCA	24.9 (3.1)	25.0 (2.9)	23.4 (3.7)	23.1 (4.1)
Physical activity, days/wk	1.2 (1.8)	1.1 (1.6)	0.7 (1.4)	0.9 (1.6)

[a]Data are mean (standard deviation), n (%), or median (interquartile range).

HbA1c = glycated hemoglobin; hs-cTnT = high-sensitivity cardiac troponin T; LDL = low-density lipoprotein; MOCA = Montreal Cognitive Assessment; NIHSS = National Institutes of Health Stroke Scale (indicating stroke severity); RR = blood pressure (method of Riva-Rocci); TOAST = Trial of ORG 10172 in Acute Stroke Treatment (indicating stroke etiology); URL = 99th percentile upper reference limit (14ng/l).

used to determine the cumulative survival and event rate of the subgroups at specified times. To assess a possible association of hs-cTnT levels with the occurrence of MACE after minor stroke or TIA in addition to established risk prediction schemes (ie, $ABCD^2$ score), we dichotomized the cohort based on previously published findings with a cutoff at 6 points or more on the $ABCD^2$ score.[16] To evaluate whether the effect of the intensified support program tested in INSPiRE-TMS on the occurrence of the primary outcome event differed according to hs-cTnT levels, patients were categorized into 4 strata based on hs-cTnT (above vs below URL) and INSPiRE-TMS intervention group (support program vs conventional care). Patients with hs-cTnT below URL and randomized to conventional care were defined as reference (stratum with background risk). Data were analyzed using SPSS statistics 27 (IBM, Armonk, NY) and R version 3.5.0.

Results

From August 2011 to October 2017, 934 patients were enrolled in INSPiRE-TMS at the Charité Campus Benjamin Franklin recruitment site. Seven patients (0.8%) who were lost to follow-up and 16 (1.7%) patients with primary intracerebral hemorrhage were excluded from the analysis. Mean time from onset to study inclusion was 3.5 days (SD = 2.5 days) and did not differ between the conventional care and the intensified support program group (3.5 days [SD = 2.6 days] vs 3.5 days [SD = 2.7 days]). hs-cTnT levels were available in 889 (95.2%) patients (mean age = 70 years [SD = 10, range = 32–92], 37% female). A study flowchart is shown in Figure 1. Compared with the entire INSPiRE-TMS cohort, our population differed in some baseline characteristics, being 2 years older and less frequently smokers, with a slightly higher proportion of patients with TIA as the entry event and a slightly higher proportion of patients with undetermined stroke etiology, mainly due to incomplete workup (Supplementary Table S1). The index event upon study entry was ischemic stroke in 497 (55.9%) and TIA in 392 (44.1%) patients. In total, 443 (49.8%) patients were randomized to the support program and 446 (50.2%) received conventional care. hs-cTnT was obtained within 48 hours after onset of neurological deficits in 80% and within 96 hours in 93.5% of all cases (median = 0 days, IQR = 0–1 days, range = 0–12 days). In total, 217 patients (24.4%) had hs-cTnT above URL (ie, >14 ng/l). Specification of hs-cTnT values <13 ng/l was available for 668 patients (75.1%; median = 9 ng/l, IQR = 6–15 ng/l) and above the limit of detection in 76.2%. The range of hs-cTnT quartiles was 0–5 ng/l (Q_1), 6–8 ng/l (Q_2), 9–14 ng/l (Q_3), and >14 ng/l (Q_4).

Baseline characteristics of the entire cohort, separated by hs-cTnT levels and intervention group, are shown in the Table. In general, patients with hs-cTnT above URL were older, more likely to have a medical history of vascular risk factors, and more likely to have suffered an ischemic stroke (vs TIA) as entry event compared to patients with hs-cTnT levels below URL. Systolic blood pressure and glycated hemoglobin levels were higher, whereas low-density lipoprotein cholesterol levels were lower among patients with an initial hs-cTnT above URL. After PSM, the aforementioned baseline characteristics were well balanced between the two groups.

hs-cTnT and Recurrent Vascular Events

During a mean follow-up of 3.2 years (SD = 1.66, range = 0–6.9), there were 153 patients with the primary outcome of MACE (17.2%; 102 stroke, 31 nonfatal coronary event, 20 vascular death). Rate of MACE was higher in patients with hs-cTnT above URL compared to those below (93 per 1,000 person-years vs 44 per 1,000 person-years, unadjusted HR = 2.04 [95% CI = 1.46–2.84], adjusted HR = 1.63 [95% CI = 1.13–2.35]; Fig 2). After PSM, adjusted HR was 1.76 (95% CI = 1.14–2.72). This association was also present in patients without prior myocardial infarction (n = 802, adjusted HR = 1.57 [95% CI = 1.04–2.36]), without impaired renal function (n = 819, adjusted HR = 1.52 [95% CI = 1.03–2.24]), and without atrial fibrillation (n = 728, adjusted HR = 1.74 [95% CI = 1.16–2.60]). When hs-cTnT

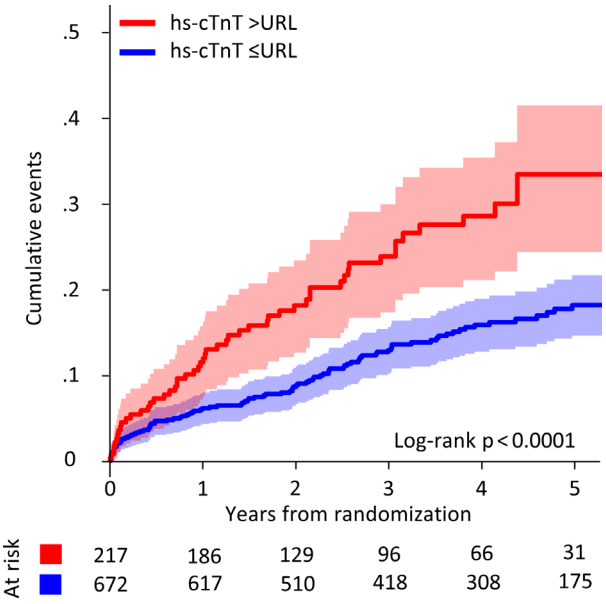

FIGURE 2: Kaplan–Meier plots for the primary outcome (major adverse cardiovascular events) by high-sensitivity cardiac troponin T (hs-cTnT) level (> vs ≤99th percentile upper reference limit [14ng/l; URL]) in the entire cohort.

levels were entered as a log-transformed continuous variable, adjusted HR was 2.31 (95% CI = 1.37–3.89 per log unit; n = 668). Finally, comparing the highest versus the lowest quartile of hs-cTnT values, event rates were 99 per 1,000 person years in Q_4 versus 31 per 1,000 person-years in Q_1 (adjusted HR = 2.59 [95% = CI 1.35–4.97, n = 668]). Figure 3 shows individual unadjusted and adjusted HRs for the composite endpoint MACE and individual vascular events.

Regarding individual vascular events, recurrent stroke occurred in 33 patients with hs-cTnT above URL and in 69 of patients with hs-cTnT below URL (15.2% vs 10.3%; unadjusted HR = 1.73 [95% CI = 1.15–2.61], adjusted HR = 1.49 [95% CI = 0.96–2.33]). A nonfatal coronary event occurred in 12 patients with hs-cTnT above URL and in 19 patients with hs-cTnT below URL (5.5% vs 2.8%; unadjusted HR = 2.53 [95% CI = 1.28–5.02], adjusted HR = 1.79 [95% CI = 0.84–3.81]). Vascular death occurred in 9 patients with hs-cTnT above URL and in 11 patients with hs-cTnT below URL (4.1% vs 1.6%; unadjusted HR = 4.07 [95% CI = 2.05–8.08], adjusted HR = 2.79 [95% CI = 1.28–6.05]; Supplementary Table S2).

hs-cTnT and Risk Stratification for Future Cardiovascular Events

Within the entire cohort, 672 patients (75.6%) had a low estimated vascular risk based on an $ABCD^2$ score of ≤5, and 217 patients (24.4%) had a high estimated vascular risk based on an $ABCD^2$ score of ≥6 after the index event. The rate of MACE was numerically higher in patients with an $ABCD^2$ score of ≥6 compared to those with an $ABCD^2$ score of ≤5 (74 per 1,000 person-years vs 48 per 1,000 person-years, unadjusted HR = 1.53 [95% CI = 1.09–2.16], adjusted HR = 1.38 [95% CI = 0.96–1.97]; Fig 4A).

There was a significant interaction between hs-cTnT levels and $ABCD^2$ risk category for the occurrence of MACE ($p_{interaction} = 0.04$). In the group of patients deemed to be at lower vascular risk (ie, $ABCD^2$ <6), hs-cTnT above URL was associated with the occurrence of MACE (95 per 1,000 person-years vs 38 per 1,000 person-years, adjusted HR = 1.83 [95% CI = 1.17–2.86]), whereas in the group of patients deemed to be at higher risk ($ABCD^2$score ≥6), rate of MACE was similar in patients with hs-cTnT above and below URL (89 per 1,000 person-years vs 67 per 1,000 person-years, adjusted HR = 1.27 [95% CI = 0.65–2.47]; Fig 5A).

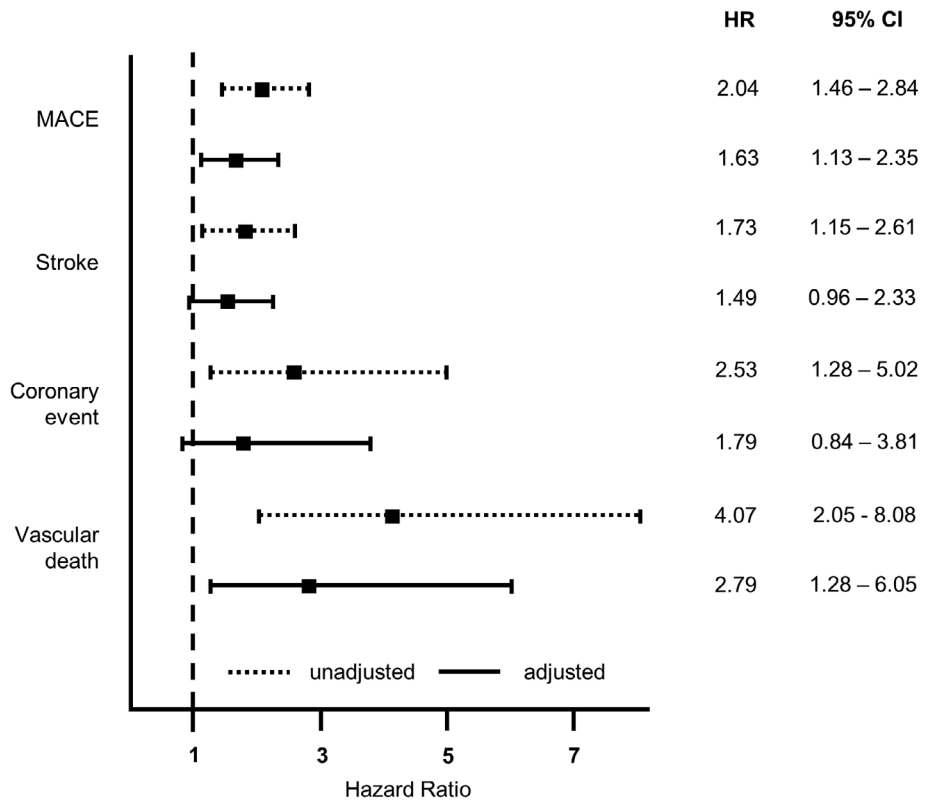

FIGURE 3: Forest plot depicting unadjusted and adjusted hazard ratios (HRs) for the primary outcome (major adverse cardiovascular events [MACE]) as well as secondary outcome measures (stroke, nonfatal coronary event, vascular death) in patients with high-sensitivity cardiac troponin T above the 99th percentile upper reference limit compared to those below. CI = confidence interval.

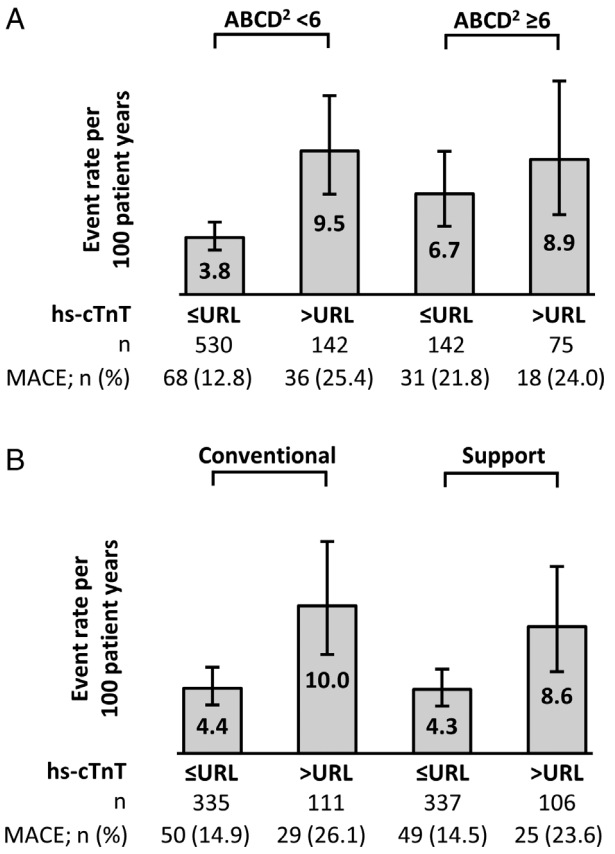

FIGURE 4: Event rates per 100 patient-years, according to Age, Blood Pressure, Clinical Features, Duration of Symptoms, Diabetes ($ABCD^2$; indicates vascular risk) category (lower risk vs higher risk; A) and intervention group (conventional care vs support program; B). "Conventional" indicates conventional care group. "Support" indicates support program group. hs-cTnT = high-sensitivity cardiac troponin T; MACE = major adverse cardiovascular events; URL = 99th percentile upper reference limit.

With respect to the $ABCD^3I$ score, 704 patients (79.2%) had a score of ≤7 (ie, lower risk group) and 185 patients (20.8%) had a score of ≥8 (ie, higher risk group). As with the $ABCD^2$ score, hs-cTnT above URL was associated with a higher rate of MACE in the lower risk group (adjusted HR = 1.67 [95% CI = 1.08–2.57]). In the higher risk group, there was no statistically significant difference in the rate of MACE between those with hs-cTnT above and below URL (adjusted HR = 1.57 [95% CI = 0.79–3.13]; see Fig 5B).

hs-cTnT and Intensified Support Program

Randomization to the intensified support program was not associated with reduced rate of MACE (adjusted HR = 0.99 [95% CI = 0.72–1.36]). Event rates were higher in patients with hs-cTnT above URL, both in the group of patients randomized to conventional care (100 per 1,000 person-years vs 42 per 1,000 person-years) and in those randomized to the intensified support program (86 per 1,000 person-years vs 43 per 1,000 person-years; see Fig 4B). Patients presenting with hs-cTnT above URL who were randomized to conventional care had the highest risk of the primary outcome (adjusted HR = 1.79 [95% CI = 1.11–2.87]) compared with patients with hs-cTnT below URL and conventional care (Fig 6). There was no statistically significant difference with regard to the occurrence of MACE in patients with hs-cTnT above URL and participation in the support program compared with those receiving conventional care (100 per 1,000 patient years vs 86 per 1,000 patient years, log-rank $p = 0.589$).

Discussion

In this post hoc analysis of INSPiRE-TMS, a randomized controlled trial with blinded endpoint assessment, we report 3 major findings regarding the potential utility of hs-cTnT testing in ischemic stroke and TIA. First, presence of myocardial injury as indicated by hs-cTnT levels above URL was independently associated with the occurrence of MACE within 3 years after minor ischemic stroke or high-risk TIA. This association remained robust after PSM, in sensitivity analyses excluding patient subgroups with higher probability of vascular events and higher probability of hs-cTnT elevation, and was more pronounced when the highest hs-cTnT quartile was compared with the lowest. Second, in patients presumed to be at lower risk for recurrent MACE based on their $ABCD^2$ score, annual event rates were more than 2× higher in patients with hs-cTnT above URL than in those below. In this group with lower $ABCD^2$ score and hs-cTnT above URL, the annual MACE rate was similar to the rate observed in the higher risk $ABCD^2$ category, irrespective of hs-cTnT levels. This held true also for categorization based on the $ABCD^3I$ score. Third, participation in the support program had no significant impact on the risk of MACE, irrespective of the hs-cTnT status.

Our findings add to the growing evidence supporting an association between hs-cTn levels and increased risk of cardiovascular events and extend previous observations to the population of patients with minor ischemic stroke or TIA.[7,9] Elevation of hs-cTn has been linked to cardiovascular events in both the general population and different patient populations.[6,9] In patients with cerebrovascular disease, such an association is less clear. It is well established that hs-cTnT levels after stroke are associated with increased mortality.[19] However, a recent meta-analysis concluded that there are insufficient data regarding the question of whether hs-cTn is associated with recurrence of ischemic stroke in stroke patients.[7] So far, a small subgroup analysis of the Find-AF trial suggested a

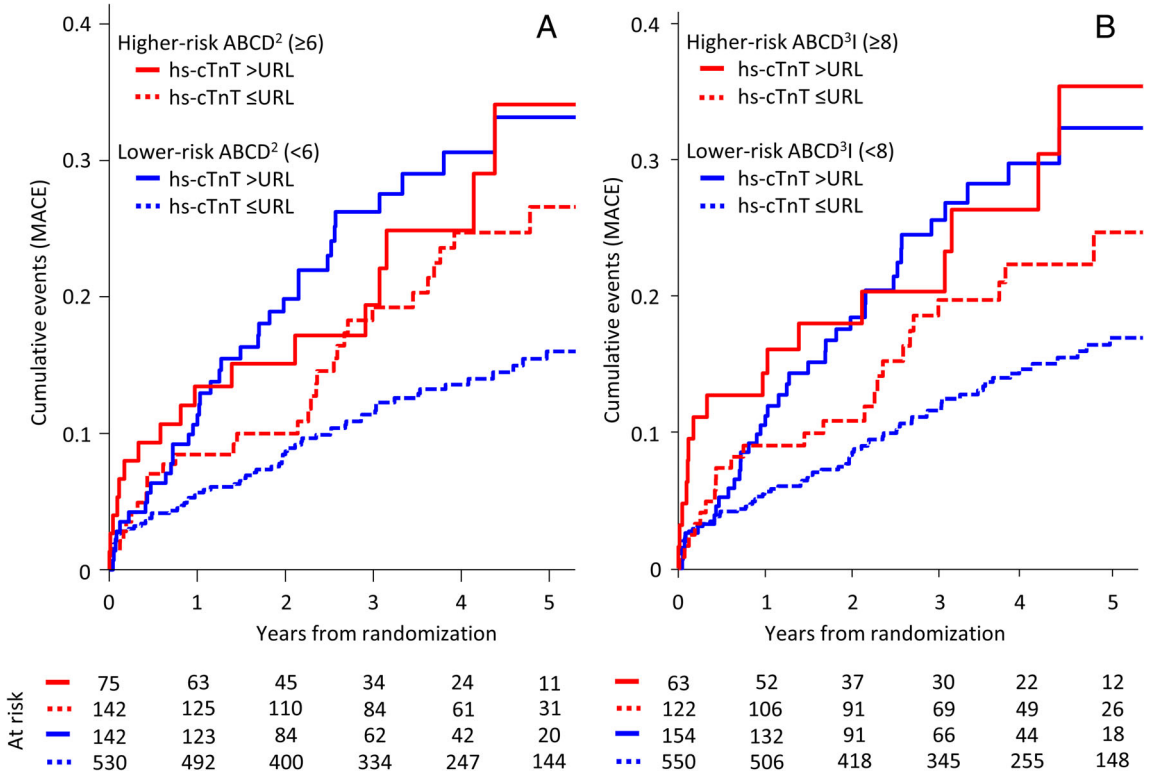

FIGURE 5: Reclassification of cardiovascular risk as assessed with the Age, Blood Pressure, Clinical Features, Duration of Symptoms, Diabetes ($ABCD^2$) score (A) and the $ABCD^3I$ score (B) with addition of high-sensitivity cardiac troponin T (hs-cTnT) levels (> vs ≤99th percentile upper reference limit [14ng/l; URL]). $ABCD^2$/$ABCD^3I$ indicate cardiovascular risk group. MACE = major adverse cardiovascular events.

possible association between hs-cTnT levels above URL and vascular events (n = 23) during a 1-year follow-up.[29] In a cohort of patients with recent embolic stroke of undetermined source enrolled in the NAVIGATE ESUS trial, hs-cTnT above URL was associated with a higher crude rate of MACE within approximately 1 year after the event, albeit not being statistically significant.[11] A possible explanation for the stronger association observed in our cohort than in previous studies might be the longer duration of follow-up and higher number of outcome events.

Individual stratification of vascular risk after minor stroke or TIA is challenging and usually based on presence or absence of traditional vascular risk factors. The $ABCD^2$ score has been proposed and validated to identify patients who have an increased risk of vascular events. Although initially conceived for early triage purposes after TIA, it has been suggested that higher $ABCD^2$ scores are also associated with increased longer term stroke risk within 5 years after TIA or minor stroke, although the specificity of the $ABCD^2$ score was only moderate in previous studies.[1–3] One long-discussed limitation of the $ABCD^2$ score is that a relevant proportion of patients diagnosed with TIA may not actually have suffered a cerebrovascular event, but rather a mimic (migraine with aura, carpal tunnel syndrome, etc). INSPiRE-TMS only included patients without hints of an alternative diagnosis (eg, subsequent headache, sensory march). In our study, we confirmed a 1.5-fold increase in the annual MACE rate in patients estimated to be at higher risk according to the $ABCD^2$ score, with event rates of approximately 7%/yr. These numbers are well in line with those observed in the recently published TIA registry.[1] In contrast, annual event rates in patients with presumably lower risk based on the $ABCD^2$ score were markedly different after stratification for hs-cTnT. Patients deemed to be at lower risk but with elevated hs-cTnT had similar annual event rates as patients with presumed higher risk based on the $ABCD^2$ score. This suggests that hs-cTnT levels may help to identify a subgroup of high-risk individuals with a relevant risk of MACE after stroke or TIA who are not captured by the $ABCD^2$ score alone. This could be of relevance, as current guidelines recommend triage of patients with TIA on the basis of the risk estimated by the $ABCD^2$ score alone.[20] There is evidence that biomarker-based risk models including hs-cTnT may be superior to traditional risk factor–based models.[4,10,30,31] Recently, a subgroup analysis of the PEGASUS-TIMI54 trial observed that addition of hs-cTn levels to guideline-derived risk groups resulted

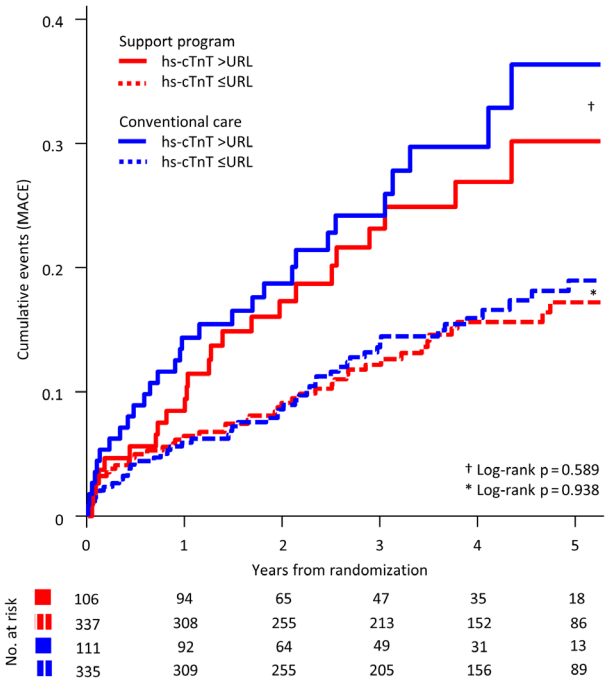

FIGURE 6: Kaplan–Meier plots for the primary end point (major adverse cardiovascular events [MACE]) according to treatment allocation in INSPiRE-TMS (ie, participation in the intensified secondary prevention support program vs conventional care) and subclassification according to high-sensitivity cardiac troponin T (hs-cTnT) levels. URL = 99th percentile upper reference limit (14ng/l).

in substantial reclassification of vascular risk.[32] If confirmed and validated in other cohorts, our findings may have implications for the design of future trials and informing clinical practice with regard to triage purposes of patients with minor stroke or TIA. As a potential consequence, intensified secondary prevention measures and advanced cardiac workup should be considered in stroke patients with elevated hs-cTnT. A relevant proportion of patients with ischemic stroke or TIA remain without a definitive cause of stroke after routine clinical workup.[33] Routine measurement of hs-cTnT in patients with acute ischemic stroke or TIA might help to identify individuals who should receive echocardiography at high priority, especially because there appears to be an association between elevated troponin and cardioembolic stroke etiology.[34,35]

Previous studies suggested that hs-cTn levels may identify individuals who benefit from intensified secondary prevention measures.[36,37] For instance, the absolute and relative benefit of statin treatment was markedly higher in individuals with high versus low hs-cTn levels in the PROVE-IT trial and LIPID study.[36,37] Therefore, we hypothesized that there might be an effect of the intensified secondary prevention support program tested in the INSPiRE-TMS trial on patients with hs-cTnT above URL. In our analyses, there was no clear evidence of a benefit of the intensified support program in patients with hs-cTnT above URL. This is in line with the overall INSPiRE-TMS trial results, which showed no statistically significant impact of the intensified support program on the occurrence of MACE, although significantly more patients achieved the predefined secondary prevention targets.[14] A possible explanation might be that the absolute difference of risk factor control in the groups was smaller than anticipated and control of modifiable risk factors was already at a high standard in the conventional care group. Moreover, numbers and overall event rates in our stratified analyses were too low to finally reject our hypothesis. Of note, INSPiRE-TMS observed a signal toward a benefit of the support program in patients with a higher ABCD^2 score.[14] This suggests that certain high-risk groups may benefit from more aggressive stroke prevention. Our findings encourage further investigation regarding the effect of more rigorous risk factor control in stroke patients with elevated hs-cTnT.

Per study protocol of the INSPiRE-TMS trial, our analyses included patients with minor, nondisabling stroke or TIA. Therefore, the results may not be generalizable to the population of more severely affected stroke patients. This may have reduced our power to detect relevant differences, as hs-cTn elevation above URL is associated with higher stroke severity, severity of vascular risk factors, and cardioembolic stroke etiology, and the risk of recurrent vascular events is higher in patients suffering major ischemic stroke. Second, our analysis was restricted to trial participants enrolled at the coordinating trial center only, because other centers did not routinely measure hs-cTnT in all patients admitted with suspected stroke or TIA. Due to these limitations, the overall number of events in this study was too low to allow for in-depth risk prediction analyses (eg, reclassification improvement of risk scores), especially in the analyses of combined exposures. hs-cTnT was measured in the acute phase after stroke, and transient hs-cTnT elevation as a stroke-associated phenomenon cannot be excluded.[8] Time from symptom onset to measurement of hs-cTnT was only documented in days and not in hours. Because hs-cTnT levels might have changed over time, this could have an impact on possible cutoff values for the prediction of MACE. Thus, we cannot draw definite conclusions on the ideal time point and relevance of serial hs-cTnT measurements for risk stratification. Although this affects the biological interpretation of hs-cTnT, it does not negate our observation that the effect of elevated hs-cTnT is different per treatment group. There is evidence that hs-cTnT levels rise during the first few days after stroke and might be lower in the postacute phase.[8,11] Therefore, it remains to be proven whether our

findings are generalizable to patients with hs-cTnT measurements during the postacute phase. Moreover, there is evidence that the extent of myocardial injury is relatively stable over time in the majority of patients with ischemic stroke.[8] Lastly, hs-cTnT is only one candidate biomarker that may be useful for risk stratification after ischemic stroke or TIA. Future studies should test the additive prognostic performance of other biomarkers such as NTproBNP or MRproANP (among others).

In conclusion, there was a robust association between myocardial injury (hs-cTnT levels above URL) and an increased risk of recurrent cardiovascular events in this population of patients with minor stroke or TIA. If these results are validated in confirmatory studies, stratification for hs-cTnT may help to identify patients at high risk for recurrent cardiovascular events among patients otherwise considered to be at lower risk based on their $ABCD^2$ score. Further studies are warranted to address the question whether hs-cTnT can be used for risk stratification after stroke and whether hs-cTnT is useful to identify stroke patients who especially benefit from advanced cardiac workup and intensified secondary prevention measures.

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Author Contributions

J.F.S, S.H., and H.J.A. contributed to the concept and design of the study; S.H., T.I., R.G., I.L., M.A., and M.S. contributed to the acquisition and analysis of data; J.F.S., S.H., J.E.W., M.E., and H.J.A. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

H.J.A. reports speaker fees and consultancy honoraria received during the conduct of the study from Pfizer (Pfizer was involved as a funding source of the study). All other authors reported no relationships with commercial firms whose products could be affected by the present study.

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