

## **Type 1 Myocardial Infarction in Patients With Acute Ischemic Stroke**

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**IMPORTANCE** Elevated values of high-sensitivity cardiac troponin (hs-cTn) are common in patients with acute ischemic stroke and are associated with poor prognosis. However, diagnostic and therapeutic implications in patients with ischemic stroke remain unclear.

**OBJECTIVE** To identify factors indicative of myocardial infarction (MI) in patients with acute ischemic stroke and hs-cTn elevation. The primary hypothesis was that a dynamic change of hs-cTn values (>50% change) in patients with acute ischemic stroke indicates MI.

**DESIGN, SETTING, AND PARTICIPANTS** This cross-sectional study was a prospective, observational study with blinded end-point assessment conducted across 26 sites in Germany. Patients were included if they had acute ischemic stroke within 72 hours and either

(1) highly elevated hs-cTn values on admission (>52 ng/L) or (2) hs-cTn levels above the upper limit of normal and a greater than 20% change at repeated measurements. Patients were enrolled between August 2018 and October 2020 and had 1 year of follow-up. Statistical analysis was performed between April 2022 and August 2023.

**EXPOSURE** Standardized electrocardiography, echocardiography, and coronary angiography.

**MAIN OUTCOME AND MEASURES** Diagnosis of MI as adjudicated by an independent end-point committee based on the findings of electrocardiography, echocardiography, and coronary angiography.

**RESULTS** In total, 254 patients were included. End points were adjudicated in 247 patients (median [IQR] age, 75 [66-82] years; 117 were female [47%] and 130 male [53%]). MI was present in 126 of 247 patients (51%) and classified as type 1 MI in 50 patients (20%). Dynamic change in hs-cTn value was not associated with MI in univariable (32% vs 38%;  $\chi^2$   $P = .30$ ) or adjusted comparison (odds ratio, 1.05; 95% CI, 0.31-3.33). The baseline absolute hs-cTn value was independently associated with type 1 MI. The best cutoffs for predicting type 1 MI were at hs-cTn values 5 to 10 times the upper limit normal.

**CONCLUSIONS AND RELEVANCE** This study found that in patients with acute ischemic stroke, a dynamic change in hs-cTn values did not identify MI, underscoring that dynamic changes do not identify the underlying pathophysiological mechanism. In exploratory analyses, very high absolute hs-cTn values were associated with a diagnosis of type 1 MI. Further studies are needed how to best identify patients with stroke who should undergo coronary angiography.

## Key Points

**Question.** Does a “rise and/or fall” pattern (dynamic change) of troponin values in patients with acute ischemic stroke and elevated troponin indicate myocardial infarction?

**Findings.** This cross-sectional study found that a dynamic change in troponin was not associated with myocardial infarction in patients with ischemic stroke whereas baseline absolute troponin value was independently associated with type 1 myocardial infarction. The best cutoffs for predicting type 1 myocardial infarction were 5 to 10 times the upper limit of normal.

**Meaning.** In acute ischemic stroke, a dynamic change in troponin values is not helpful in detecting myocardial infarction, emphasizing that dynamic changes do not reveal the underlying pathophysiological mechanism of myocardial injury.

## Introduction

Elevated values of cardiac troponin (cTn) in patients with acute ischemic stroke are a diagnostic and therapeutic challenge in daily clinical practice. Current guidelines recommend routine measurement of cTn for the early management of patients with acute ischemic stroke.<sup>1</sup> Elevations of cTn above the upper limit of normal (above the 99% percentile) indicate myocardial damage and are detected in approximately 1 in 2 patients with acute ischemic stroke when measured with high-sensitivity assays (hs-cTn).<sup>2</sup> Levels of cTn that meet the European Society of Cardiology (ESC) diagnostic criteria for suspected non-ST-elevation myocardial infarction (MI) are present in about 1 in 7 patients with acute ischemic stroke.<sup>3,4</sup> Elevated values of cTn are strongly associated with poorer outcomes in patients with stroke.<sup>2,5,6</sup> One explanation for the poor outcome could be MI, because cTn elevation in acute ischemic stroke is strongly associated with a higher risk for coronary events and vascular death.<sup>7,8</sup> However, distinguishing MI, in particular type 1 MI, from other pathophysiologies of myocardial injury, such as neurogenic or stress-induced myocardial injury, remains difficult.<sup>2,6,9</sup> Currently, there is limited evidence on how best to diagnose MI in the setting of acute ischemic stroke and, in particular, which patients should undergo coronary angiography.<sup>10</sup> Current guidelines for the early management of patients with acute ischemic stroke do not provide clear recommendations except for the measurement of hs-cTn.<sup>1</sup> The aim of this study was therefore to clarify the significance of hs-cTn elevation and its time course for the diagnosis of MI and type 1 MI in acute ischemic stroke. The prespecified primary hypothesis of this study was that a dynamic change of hs-cTn values (ie, >50% change at repeated measurements) in patients with an acute ischemic stroke is indicative of MI.

## Methods

### Study Design

The Prediction of Acute Coronary Syndrome in Acute Ischemic Stroke (PRAISE) study was a

prospective, multicenter, observational clinical study with external monitoring; central reading by core laboratories; blinded end-point assessment by an endpoint adjudication committee (EAC), data and safety monitoring board, and critical events committee; predefined end points; and sample size calculation. The study protocol was approved by the ethics committee at each participating center and the ethics committee of the lead center, Charité, Berlin (No. EA1/057/18). The protocol was published before the final analysis.<sup>11</sup> A detailed statistical analysis plan was finalized before the statistical analyses were performed.

Eligible patients had to provide written informed consent for study enrollment. The ethics committee approved the method of consent. The study conforms to the Standards for Reporting of Diagnostic Accuracy (STARD) reporting guidelines for diagnostic accuracy studies.<sup>12</sup>

### Setting and Participants

The study was conducted at 26 study sites in Germany. In accordance with current guidelines, the study sites performed hs-cTn testing as part of routine clinical practice in all patients with stroke at the time of admission and after 3 hours.<sup>1</sup> Patients were included if they were 18 years or older and had a clinical diagnosis of acute ischemic stroke (including all subtypes) based on neurological assessment and brain imaging or high-risk transient ischemic attack (TIA, defined as an ABCD2 score  $\geq 4$ ). Time from symptom onset to hospital admission had to be less than 72 hours for study inclusion. Patients were eligible for inclusion if their hs-cTn levels were above the cutoffs recommended by the ESC guidelines for non-ST-elevation (NSTEMI) acute coronary syndrome to prompt early coronary angiography,<sup>4,13</sup> ie, 1 "highly abnormal" hs-cTn value (ie,  $>52$  ng/L if hs-cTnT, Roche Elecsys assay, or  $>52$  ng/L, if hs-cTnI, Abbott Architect assay, or  $>107$  ng/L, if hs-cTnI, Dimension Vista assay) or, alternatively, change greater than 20% at serial measurements and 1 hs-cTn value higher than the upper limit of normal (ULN) depending on assay. Exclusion criteria were severe renal insufficiency (estimated glomerular filtration rate  $<30$  mL/min/1.73 m<sup>2</sup>), uncontrolled thyroid dysfunction, large ischemic brain lesions, pregnancy or breastfeeding, limited life expectancy ( $<1$  year), and a high premorbid degree of disability (defined as a modified Rankin Scale score  $>3$ ).<sup>14</sup> Details were published previously.<sup>11</sup>

### Study Procedures

Patients received repeated 12-lead electrocardiograms (ECGs), transthoracic echocardiography, and coronary angiography following specific standard procedures of the German Centre for Cardiovascular Research (Deutsches Zentrum für Herz-Kreislauf-Forschung).<sup>15</sup> All images were analyzed in separate central academic core laboratories as described earlier.<sup>11</sup> Core laboratories were blinded for clinical information.<sup>11</sup> Blood samples for hs-cTn measurement were deep frozen,

stored, and reanalyzed in an independent core laboratory at the University Heart Center in Hamburg using the Roche Elecsys assay and the Abbott Architect assay.

The end point and adjudication process was performed by an independent EAC based on clinical data (including patient symptoms and vital signs) and the reports from the central academic core laboratories. The primary outcome was the presence of MI, which was adjudicated subject to an EAC charter (eMethods in Supplement 1) based on the then-valid third universal definition of MI.<sup>16</sup> MI was considered present if the following criteria were met: the presence of coronary artery disease with stenosis on coronary angiogram and at least 1 of ischemic ECG changes, regional wall motion abnormalities on echocardiography, and/or culprit lesions on coronary angiogram, as reported by the respective central core laboratory. The EAC further differentiated MI into type 1 and type 2 MI based on the coronary angiogram.<sup>16</sup> Type 1 MI was adjudicated when the coronary angiogram revealed a culprit lesion and the clinical presentation concurred. A culprit lesion was defined as a lesion with irregular borders, ulceration, filling defects, or the presence of intraluminal thrombus.<sup>16,17</sup> Type 2 MI was considered if there were no such angiographic findings, but the patient had wall motion abnormalities on echocardiography and/or ischemic ECG changes. If type 1 and 2 MI were not diagnosed and thus MI was excluded, nonischemic myocardial injury was diagnosed.

Secondary end points were major adverse cardiovascular events (MACE) defined as (recurrent) stroke, TIA, MI, and all-cause death. Safety end points included predefined severe adverse events of special interest (SAESI), ie, MI, repeated coronary intervention, ischemic stroke or TIA, peripheral embolic artery occlusion, intracranial hemorrhage, major bleeding (type 3-5 according to the Bleeding Academic Research Consortium [BARC] classification), and death.<sup>18</sup> MACE and SAESI were recorded during the in-hospital stay and at 3 and 12 months. All SAESI were evaluated by the critical events committee regarding a possible causal relationship with coronary angiography. Reports were made to the data and safety monitoring board after the inclusion of 100 and 200 patients as well as after the end of the study. The critical events committee and data and safety monitoring board agreed on a charter defining appropriate conduct and obligation before the beginning of the study (eMethods in Supplement 1).

All data were recorded in an electronic case report form. Remote monitoring was conducted at all sites to ensure data completeness and correctness.

### Statistical Analysis

Sample size calculation and choice of threshold for the definition of dynamic hs-cTn change (>50%) was based on the results of the TRELAS study.<sup>17</sup> The study protocol has already been published.<sup>11</sup> Differences between the 2 diagnostic groups (presence/absence of type 1 MI) were described using the  $\chi^2$  test for dichotomous variables and the Wilcoxon rank sum test for continuous variables.

The primary hypothesis (ie, presence of any MI in relation to a dynamic hs-cTn change >50%) was analyzed by calculation of the diagnostic odds ratio (OR). In an explorative approach, multivariable (adjusted) backwards-stepwise logistic regression was used to identify factors associated with MI overall (primary outcome) and type 1 MI in particular.

In sensitivity analysis, the main analysis was repeated after excluding patients with TIA. In a second sensitivity analyses, the predictive accuracy for different thresholds of relative hs-cTn changes (any cutoff between relative change of 0% and 100%) for the presence of any MI and type 1 MI was evaluated by calculating the area under the receiver operating characteristic curve (ROC-AUC). The best cutoff was determined by the maximum AUC.

This approach was also applied for absolute baseline hs-cTn values using standardized log-transformed hs-cTn values (expressed as multiples of the ULN). Moreover, sensitivity analyses for best cutoff of absolute hs-cTn on admission to predict type 1 MI was performed in the subgroups of patients with hs-cTnT values measured by the Roche Elecsys assay and hs-cTnI values measured by the Abbott Architect assay. Cox regression analysis was used to estimate hazard ratios (HRs) for MACE and mortality at 12 months for patients with stroke with and without a dynamic change in hs-cTn value. All statistical tests were 2-sided and performed using a 5% significance level. All analyses, except for the primary analysis, were conducted in an exploratory manner without adjustment for multiple testing. Statistical analyses were performed using R version 4.0.5 (R Foundation).

## Results

Between August 2018 and October 2020, 254 patients were prospectively enrolled. Of these, 247 patients (97%) underwent coronary angiography (median [IQR] age, 75 [66-82] years; 117 were female [47%] and 130 male [53%]) allowing adjudication of the primary end point (Figure 1). The EAC diagnosed any MI in 126 of 247 patients (51%) and type 1 MI in 50 of 247 patients (20%).

Baseline characteristics of patients with and without MI are shown in Table 1. In unadjusted comparisons, patients with MI were less often female, had shorter times from symptom onset to angiography, were more likely to have dyslipidemia, were more likely to have known coronary artery disease (CAD), and had higher heart rate on admission. In the majority of patients diagnosed with MI, CAD was unknown before the coronary angiography (82/126 [65%]). Patients with type 1 MI had shorter symptom-to-angiography times and higher creatinine values (Table 2). The predefined dynamic change of hs-cTn was detected in 85 of 247 patients (34%). The number of patients with any MI and type 1 MI per study site is shown in eTable 1 in the Supplement 1.

A dynamic hs-cTn change greater than 50% was not associated with the diagnosis of MI (diagnostic OR, 0.76; 95% CI, 0.45-1.28; primary hypothesis). Moreover, sensitivity analyses showed that dynamic hs-cTn changes with a threshold greater than 20% (OR, 0.78; 95% CI, 0.47-1.29) or any

cutoff between 0% and 100% for relative hs-cTn changes did not improve the association with MI (Table 1, Figure 2, and Figure 3). ST depression on ECG, regional wall motion abnormalities on echocardiography (both assessed by core laboratories), a history of CAD, and absence of heart failure were independently associated with the diagnosis of MI (Table 1). There was no interaction between treatment with intravenous thrombolysis and a dynamic change in hs-cTn. The sensitivity analysis after the exclusion of 19 patients with TIA confirmed the results of the main analysis: there was still no association between dynamic change in hs-cTn and diagnosis of any MI (eTable 2 in Supplement 1). Moreover, regional wall motion abnormalities, acute coronary syndrome–typical ECG changes, history of CAD, and absence of heart failure remained associated with a diagnosis of any MI.

Using multiples of the ULN, log-transformed hs-cTn on admission was associated with type 1 MI (OR, 1.35; 95% CI, 1.07- 1.70;  $P = .01$ ). Backward selection of clinical predictors led to an empty model; that is, no additional predictors of type 1 MI were identified. According to the ROC analysis, the best hs-cTn cutoffs to identify type 1 MI were at 5.4 times ULN and 10.4 times ULN with an ROC-AUC of 0.608 (95% CI, 0.535-0.681)

and 0.608 (95% CI, 0.531-0.685), respectively. After exclusion of patients with TIA, the absolute initial hs-cTn value was still the variable with the strongest association with type 1 MI. Similarly to the original analysis, the best cutoff of hs-cTn to predict type 1 MI according to calculation of the ROC-AUC was at 10 times the upper reference limit (eTable 3 and eFigure in Supplement 1).

Sensitivity analyses were also performed using absolute hs-cTn values, which were available in 202 of 247 patients (82%) using the Roche Elecsys fifth-generation assay for hs-cTnT and in 159 of 247 patients (64%) patients using the Abbot Architect assays for hs-cTnI. Patients diagnosed with type 1 MI had higher absolute log-transformed hs-cTnT values on admission (median [IQR] hs-cTnT on admission, 117 [52-253] vs 66 [40-143] ng/L;  $P = .007$ ; Roche Elecsys assay). Values for hs-cTnI were numerically higher but did not differ significantly (median [IQR], 326 [64-800] vs 138 [46-717] ng/L;  $P = .27$ ; Abbott Architect assay). Log-transformed hs-cTnT (Roche Elecsys assay) on admission remained independently associated with type 1 MI in adjusted regression analysis (adjusted OR, 3.61; 95% CI, 1.49- 9.51;  $P = .006$ ). According to ROC analysis, the best hs-cTnT cutoff to identify type 1 MI was 76 ng/L for the Roche Elecsys assay (ie, 5.4 times the ULN) with an AUC of 0.625 (95% CI, 0.545-0.705). Overall, 62 of 126 patients (49%) with MI and 39 of 50 (78%) with type 1 MI received immediate percutaneous transluminal coronary angioplasty.

Concerning safety, 7 SAESI in 6 patients were classified as “potentially attributable to coronary intervention” (ie, 1 MI, 1 death, 1 ischemic stroke, 1 TIA, 1 peripheral artery occlusion, and 2 major bleedings [BARC class 3, both of which were groin hematomas], but no intracranial bleeding). No safety concerns were raised by the data and safety monitoring board.

Follow-up at 12 months was available in 229 of 247 patients (91%) with respect to MACE and in 247 of 247 (100%) with respect to vital status. MACE occurred in 60 of 229 patients (26%), and 39 of

247 patients (16%) died. A dynamic change of hs-cTn was not associated with MACE (HR, 0.76; 95% CI, 0.43-1.33; secondary hypothesis). On the contrary, a dynamic change of hs-cTn was associated with reduced mortality at 12 months in unadjusted analyses (HR, 0.46; 95% CI, 0.21-0.99;  $P = .05$ ).

## Discussion

The prospective, multicenter PRAISE study included patients with acute ischemic stroke and elevated hs-cTn values above rule-in cutoffs to suspect NSTEMI and tested the hypothesis that a dynamic hs-cTn change is indicative of MI (including type 1 MI). Elevated cTn values that meet the ESC diagnostic criteria for suspected NSTEMI are present in about 1 in 7 patients with acute ischemic stroke.<sup>3</sup>

The study has the following main findings, First, in this selected population of patients with acute ischemic stroke and elevated hs-cTn, MI (including type 1 MI) is relatively common as assessed by an independent EAC. Second, patients with stroke and elevated hs-cTn values have a high risk of MACE and death over 12 months. Third, coronary angiography carries a decent risk of serious adverse events of 2.4%. Fourth, dynamic hs-cTn changes (ie, a rise and/or fall pattern) alone are not helpful to distinguish MI from other causes of acute myocardial injury and to predict MACE at 12 months. In contrast, the diagnosis of MI was associated with ECG and echocardiography, whereas patients with type 1 MI had higher baseline absolute hs-cTn values.

Based on data from our earlier, much smaller TRELAS study, our prespecified primary hypothesis was that a dynamic change in hs-cTn values would help identify patients with MI. However, we found that neither a prespecified delta of 50% in hs-cTn values nor any dynamic changes were associated with a final diagnosis of any MI or type 1 MI.

In acute ischemic stroke, dynamic hs-cTn changes indicative of acute myocardial injury are therefore not suitable for detecting myocardial infarction, and they do not distinguish between different mechanisms of acute myocardial injury. Alternatively, in patients with acute ischemic stroke, acute myocardial injury may be caused by neurocardiogenic dysregulation rather than acute coronary syndrome.<sup>2,6</sup> This phenomenon has recently obtained much attention, giving birth to the term *stroke-heart syndrome*. For example, ischemic brain lesions in the right anterior dorsal insula (representing the central autonomic network) are associated with dynamic hs-cTn elevation.<sup>19,20</sup>

On the other hand, 1 in 2 patients with stroke and elevated hs-cTn (ie, myocardial injury) was diagnosed with MI and 1 in 5 with type 1 MI, which is in good agreement with the previous TRELAS study.<sup>17</sup> Thus, our study shows that type 1 MI is a common mechanism of myocardial injury in stroke. Of note, the majority of patients did not have known CAD, suggesting a high prevalence of silent CAD in patients with stroke. This apparent underdiagnosis is particularly important for clinical practice because patients with stroke in general (and those with elevated troponin values in

particular) are at increased risk for recurrent vascular events and death.<sup>7,8</sup> Our data suggest that more patients with acute stroke should be evaluated accordingly. Timely evaluation for and treatment of concomitant CAD and MI may help reduce the risk of future cardiovascular events in these patients.

Although stroke severity was not particularly high in patients included in the PRAISE study, 1 in 4 patients had a recurrent event, and 1 in 6 died within 1 year after stroke. In PRAISE, MACE at 12 months occurred in 26% of patients, which is about 3 times as high as in a large Canadian cohort of patients with first ever ischemic stroke and unknown hs-cTn values (9%).<sup>21</sup> Our study suggests that ECG and echocardiography may be helpful to select patients who likely have ischemic myocardial injury (ie, MI). An interesting finding of the PRAISE study is that the baseline value of hs-cTn may be helpful in identifying patients with type 1 MI.

In fact, the baseline hs-cTn level was almost twice as high in patients with type 1 MI compared with those without. This finding was robust in (1) the overall population with multiple hs-cTn assays used, (2) the subgroup testing an hs-cTnT assay (Roche Elecsys), and (3) the subgroup excluding patients with TIA.

In clinical practice, it is important to rapidly identify patients with type 1 MI to allow timely further invasive diagnosis and treatment.<sup>4,13</sup> In contrast, current cardiology guidelines from the ESC do not recommend routinely performing immediate angiography in patients with type 2 MI.<sup>4,13</sup> Preselection of patients with stroke and a higher likelihood of type 1 MI may therefore help triage patients who should undergo urgent coronary angiography. Of note, hs-cTn elevations beyond the 5-fold ULN also have a high positive predictive value for acute type 1 MI in patients with clinically suspected NSTEMI.<sup>4</sup> In the PRAISE study, the best cutoff values for hs-cTn to diagnose type 1 MI were 5.4 and 10.4 times the ULN.

This is considerably higher than the rule-in cutoff values for different assays recommended in the ESC guidelines for suspected NSTEMI.<sup>4</sup> A pragmatic clinical approach might therefore use a higher threshold for hs-cTn values (about 5 times the ULN) to select patients with acute ischemic stroke for urgent coronary angiography. However, based on our results, we cannot yet recommend the use of this cTn threshold to select patients with stroke for coronary angiography in clinical practice. Not only was the discrimination for type 1 MI moderate, but most importantly, it is currently unclear whether patients with acute stroke, elevated hs-cTn, and suspected type 1 MI would benefit from an invasive approach undergoing coronary angiography and potentially percutaneous coronary intervention.

In the PRAISE study, all therapeutic decisions were made at the discretion of the treating physician, and there was no control group of patients who did not receive coronary angiography. Therefore, we do not know whether clinical outcome was modified by the procedure. Future studies evaluating an early invasive vs a conservative approach in preselected patients with stroke, elevated hs-cTn values, and high a priori probability of type 1 MI are warranted to address this question. Moreover, potential risks of



coronary angiography need to be taken into account. The most common complication attributable to coronary angiography in our study was major bleeding due to groin hematoma. For this reason, an individual risk-benefit analysis must be carried out for each patient before coronary angiography is performed, taking particular account of the risk of bleeding.

## Strengths and Limitations

The PRAISE study has strengths and limitations. The strengths include its prospective multicenter design with prespecified end points, a prespecified statistical analysis plan, blinded central core laboratories, external monitoring, and its independent EAC. The installation of an independent EAC allowed us to determine a diagnosis of MI while blinded for the variable of interest (ie, hs-cTn levels) to avoid circular reasoning. It should be noted that by definition an invasive investigation is not required for the diagnosis of MI. However, the significance and diagnostic specificity of troponin elevation in patients with stroke is less clear than in patients presenting primarily with chest pain. Therefore, in the PRAISE study, we decided to perform invasive coronary angiography in addition to getting laboratory values, ECG, and echocardiography for diagnosis and end point adjudication. This also made it possible to diagnose type 1 MI.

Limitations include the use of different hs-cTn assays at different study sites. Therefore, we standardized hs-cTn values as multiples of the ULN. Another bias may have been caused by the time interval between hospital admission and coronary angiography. An intracoronary thrombus or embolus may have dissolved in the course of the disease and might have been overlooked because of the time delay. We observed that patients eventually diagnosed with MI underwent angiography somewhat earlier than patients without MI. This could indicate that the treating physicians saw higher urgency in these patients. Moreover, treatment with intravenous thrombolysis for ischemic stroke may have altered the clinical course of MI and thereby hs-cTn values. However, we found no differences in the frequency of intravenous thrombolysis treatment between patients with and without MI or between patients with dynamic hs-cTn values and those without, making this hypothesis unlikely. Patients with severe renal insufficiency were not included in PRAISE, so renal insufficiency cannot serve as an alternative explanation for elevated hs-cTn values in our study population.

Inclusion and exclusion criteria limit the generalizability of our study. Because patients had to be able to provide written informed consent, we included patients with mostly mild to moderate strokes. Since we did not measure hs-cTn levels before the stroke occurred, we cannot exclude the possibility that some patients may have developed MI before the stroke. However, we included no patients in PRAISE who had undergone invasive cardiological treatment (including coronary angiography) within 30 days before the stroke.

## Conclusions

In the PRAISE study, patients with ischemic stroke and elevated hs-cTn underwent standardized diagnostic procedures, including coronary angiography. Based on a blinded review by an EAC, about half of this study population was diagnosed with MI and 1 in 5 with type 1 MI. Dynamic changes in hs-cTn values were not helpful to diagnose MI. In exploratory analyses, only very high absolute hs-cTn values were associated with a diagnosis of type 1 MI. The results of our study highlight the clinical and

pathophysiological relevance of the interplay between heart and brain in acute ischemic stroke. How to select patients with stroke and elevated hs-cTn for coronary angiography requires further exploration.

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## Figure Legends

Figure 1 (Participant Flowchart in the PRAISE study):

Legend for Figure 2 "Diagnostic accuracy of adding hs-cTn changes (0-100%) to predefined regression model for MI":

Figure 2 illustrates the predictive accuracy for different thresholds (x-axis) of relative hs-cTn changes (any cut-off between relative change of 0% and 100%) for the presence of MI as given by area under the curve (AUC). The higher the AUC, the better the predictive accuracy of the respective cut-off.

Legend for Figure 3: "Diagnostic accuracy of adding baseline absolute hs-cTn value to predefined regression model for Typ1 MI"

Figure 3 illustrates the predictive accuracy for different thresholds (x-axis) for hs-cTn on admission (as multiple of ULN) for the presence of MI as given by the area under the curve (AUC). The higher the AUC, the better the predictive accuracy of the cut-off. Optimal cut off hs-Tn to predict type 1 MI is at 5.39 times ULN with AUC = 0.608 (0.535, 0.681) and at 10.42 times ULN with AUC = 0.608 (0.531, 0.685).



**Table 1: Baseline characteristics of patients with and without myocardial infarction (MI)**

N=247	MI (N=126)	No MI (N=121)	p-values of univariable comparisons	OR (95% CI, p-value) from multivariable model
Age (median IQR)	74 (64-82)	76 (67-82)	0.54 <sup>a</sup>	
Age ≥75 years	62/126 (49)	67/121 (55)	0.33 <sup>b</sup>	
Sex (female)	51 / 126 (40)	66 / 121 (55)	<b>0.03</b> <sup>b</sup>	
Symptom-onset-to-coronary angiography (days, median; IQR)	2 (1-4)	3 (2-4)	<b>0.04</b> <sup>a</sup>	
Diabetes mellitus	42 / 126 (33)	28 / 121 (23)	0.08 <sup>b</sup>	
Hypertension	102 / 126 (81)	91 / 121 (75)	0.28 <sup>b</sup>	
Dyslipidemia	61 / 125 (49)	43 / 121 (36)	<b>0.04</b> <sup>b</sup>	
Known CAD	44 / 126 (35)	23 / 121 (19)	<b>&lt;0.005<sup>b</sup></b>	<b>4.74 (1.63-15.3), p=0.006</b>
Atrial fibrillation (N=246)	33 / 126 (26)	36 / 120 (30)	0.51 <sup>b</sup>	
Heart failure (N=246)	13 / 126 (10)	14 / 120 (12)	0.74 <sup>b</sup>	<b>0.10 (0.01-0.54), p=0.02</b>
Previous stroke	34 / 126 (27)	25 / 121 (21)	0.24 <sup>b</sup>	
Current smoker	28 / 122 (23)	31 / 120 (26)	0.87 <sup>b</sup>	
Ex-smoker (N=242)	27 / 122 (22)	25 / 120 (21)		
i.v. thrombolysis (rTPA) (n=246)	49 / 126 (39)	44 / 120 (37)	0.72 <sup>b</sup>	
Heart rate [/min] (median; IQR)	78 (66-88)	72 (64-84)	<b>0.04</b> <sup>a</sup>	0.22 (0.04-1.03), p=0.06 <sup>c</sup>
Systolic blood pressure [mmHg] (median; IQR)	138 (125-150)	135 (120-148)	0.39 <sup>a</sup>	
Diastolic blood pressure [mmHg] (median; IQR)	80 (68-89)	76 (68-85)	0.40 <sup>a</sup>	
Beta blocker (n=245)	62 / 124 (50)	62 / 121 (51)	0.85 <sup>b</sup>	
Statin (n=245)	93 / 124 (75)	87 / 121 (72)	0.58 <sup>b</sup>	
NIHSS Visit day 1 (median; IQR) (n=246)	2 (0-5)	2 (0-3)	0.11 <sup>a</sup>	1.07 (0.94-1.22), p=0.30
GRACE Score (median; IQR)	139.5 (119-158)	137 (118-151)	0.35 <sup>a</sup>	
Creatinine [mg/dL] (median; IQR)	1.00 (0.81-1.20)	0.95 (0.80-1.14)	0.20 <sup>a</sup>	
Hemoglobin [g/dl] (median; IQR)	13.4 (12.0-14.7)	13.4 (12.0-14.8)	0.67 <sup>a</sup>	2.73 (0.98-8.50), p=0.07 <sup>c</sup>
<b>Variables as assessed by the different core laboratories (known to the Endpoint Adjudication Committee (EAC))</b>				
<b>Culprit Lesion present (N=247)</b>	45/126 (36)	2/121 (2)	<b>&lt;0.001<sup>b</sup></b>	
<b>T-Inversion on any ECG (N=243)</b>	45/124 (36)	45/119 (38)	0.81 <sup>b</sup>	
<b>ST Depression in any ECG: (N=243)</b>	12/124 (10)	1/119 (1)	<b>&lt;0.001<sup>b</sup></b>	
<b>ACS-typical ECG changes;</b>	43/95 (45)	30/95 (32)	0.05 <sup>b</sup>	2.37 (0.79-7.55),

(N=190)				p=0.13
<b>Left Ventricular Ejection Fraction [%] (median; IQR) (N=181)</b>	55 (50 – 60)	59 (54 – 64)	<b>&lt;0.001<sup>a</sup></b>	
<b>Left Ventricular Ejection Fraction ≥50% (N=181)</b>	76/99 (77)	73/82 (89)	<b>0.03<sup>b</sup></b>	
<b>Wall Motion Abnormality (N=163 data from core lab)</b>	29/88 (33)	3/75 (4)	<b>&lt;0.001<sup>b</sup></b>	<b>30.89 (6.35-279.5), p&lt;0.001</b>
<b>Wall Motion Abnormality (N=195 incl. data from centers)</b>	34/99 (34)	9/96 (9)	<b>&lt;0.001<sup>b</sup></b>	
<b>Variables of interest (not known to the Endpoint Adjudication Committee (EAC))</b>				
<b>Dynamic hs-cTn change &gt;50% (N=244)</b>	40/126 (32)	45/118 (38)	0.30 <sup>b</sup>	0.72 (0.31-1.61), p=0.42
<b>Dynamic hs-cTn change &gt;20% (N=244)</b>	67/126 (53)	70/118 (59)	0.33 <sup>b</sup>	
<b>hs-cTn on admission (multiples of ULN) (median; IQR) (N=243),</b>	5.98 (3.00-14.86)	5.11 (3-00-11.46)	0.28 <sup>a</sup>	
<b>hs-cTnT [ng/l] on admission Elecsys Roche® Subgroup (median; IQR) (N=202)</b>	76 (38-180)	70 (43-146)	0.71 <sup>a</sup>	
<b>hs-cTnI [ng/l] on admission Abbott Architect® Subgroup (median; IQR) (N=159)</b>	234 (46 – 815)	116 (53 – 614)	0.46 <sup>a</sup>	
<b>Other Variables not known to the Endpoint Adjudication Committee (EAC)</b>				
<b>PTCA-Stent (N=247)</b>	62/126 (49)	8/121 (7)	<b>&lt;0.001<sup>b</sup></b>	
<b>Time from Symptom onset/last known well to first troponin measurement [hours] (median; IQR)</b>	4 (2-9)	4 (2-10)	0.97 <sup>a</sup>	

<sup>a</sup> Wilcoxon rank sum test. <sup>b</sup> Likelihood Ratio Chi-Square-Test. Odds ratios were derived from the fully adjusted logistic regression model after backward selection and inclusion of hs-cTn. <sup>c</sup> heart rate (> 100/min) and hemoglobin (≥ 12 g/dl in women and ≥ 13 g/dl in men) were included as binary variables in the regression model. <sup>d</sup> dynamic hs-cTn change was included as a continuous variable in the regression model. Abbreviations: CAD=coronary artery disease, IVT=intravenous thrombolysis; rTPA=recombinant tissue-type plasminogen activator; NIHSS=National Institutes of Health Stroke Scale (to measure stroke severity); hs-cTn = high sensitivity cardiac troponin, EAC= endpoint adjudication committee; ECG=Electrocardiogram, ULN= upper limit normal.

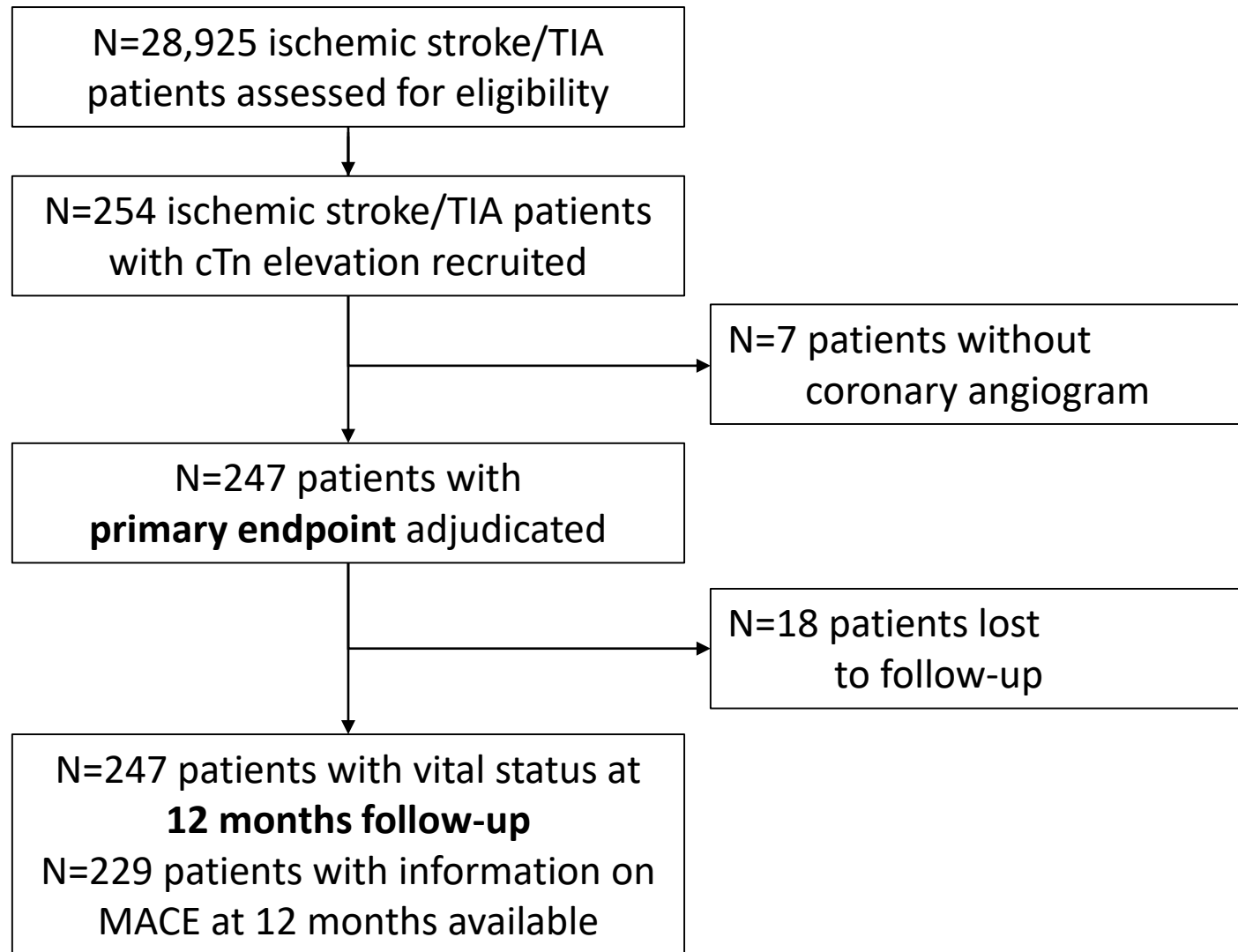
**Table 2: Baseline Characteristics of patients with and without type 1 myocardial infarction (MI)**

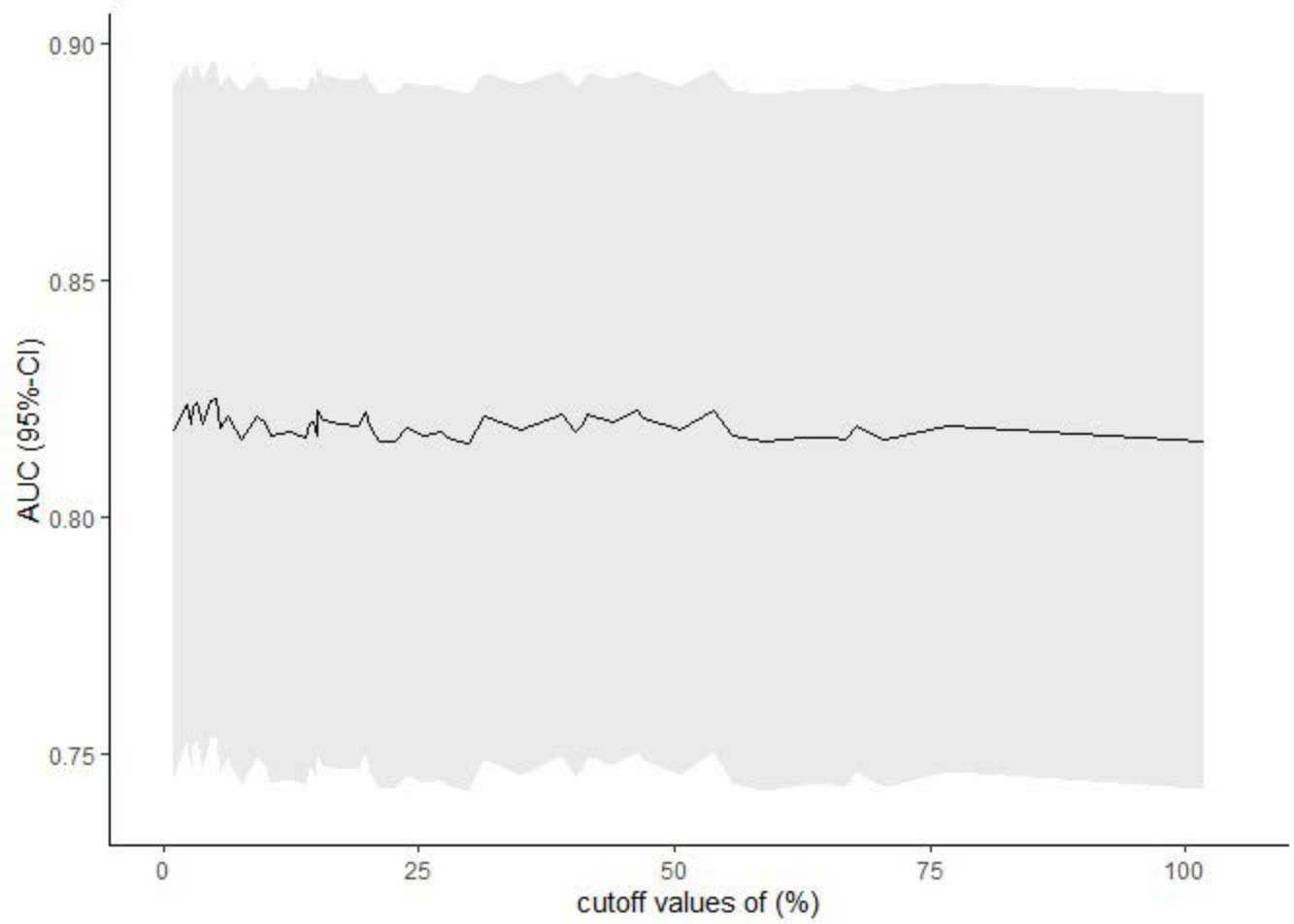
<b>N=247</b>	<b>Type 1 MI; N=50</b>	<b>No type 1 MI; N=197</b>	<b>p-values of univariable comparisons</b>	<b>OR (95% CI, p- value) from multivariable model</b>
<b>Age (median; IQR)</b>	77 (66-82)	75 (65-82)	0.50 <sup>a</sup>	
<b>Age ≥75 years</b>	27/50 (54)	102/197 (52)	0.78 <sup>b</sup>	
<b>Sex (female)</b>	22/50 (44)	95/197 (48)	0.59 <sup>b</sup>	
<b>Symptom-onset-to-angio [days] (median; IQR)</b>	2 (0-4)	2 (1-4)	<b>0.02</b> <sup>a</sup>	
<b>Diabetes mellitus</b>	17/50 (32)	53/197 (27)	0.33 <sup>b</sup>	
<b>Hypertension</b>	41/50 (82)	152/197 (77)	0.45 <sup>b</sup>	
<b>Dyslipidemia</b>	24/49 (49)	80/197 (41)	0.29 <sup>b</sup>	
<b>Known CAD</b>	13/50 (26)	54/197 (27)	0.84 <sup>b</sup>	
<b>Atrial fibrillation (N=246)</b>	12/50 (24)	57/196 (29)	0.47 <sup>b</sup>	
<b>Heart failure (N=246)</b>	5/50 (10)	22/196 (11)	0.80 <sup>b</sup>	
<b>Previous stroke</b>	16/50 (32)	43/197 (22)	0.14 <sup>b</sup>	
<b>Current smoker</b>	12/49 (25)	47/193 (24)	0.98 <sup>b</sup>	
<b>Ex-Smoker (N=242)</b>	11/49 (22)	41/193 (21)		
<b>i.v. thrombolysis (rTPA) (N=246)</b>	21/50 (42)	72/196 (37)	0.50 <sup>b</sup>	
<b>Heart rate [/min] (median; IQR)</b>	80 (68-85)	74 (64-86)	0.31 <sup>a</sup>	
<b>Systolic blood pressure [mmHg] (median; IQR) (N=240)</b>	137 (126-145)	136 (122-150)	0.75 <sup>a</sup>	
<b>Diastolic blood pressure [mmHg] (median; IQR) (N=240)</b>	77 (70-85)	78 (68-86)	0.97 <sup>a</sup>	
<b>Beta blocker (N=245)</b>	23/49 (47)	101/196 (52)	0.57 <sup>b</sup>	
<b>Statin (N=245)</b>	34/49 (69)	146/196 (75)	0.47 <sup>b</sup>	
<b>NIHSS Visit 1 (N=246)</b>	2 (1-6)	2 (0-4)	0.24 <sup>a</sup>	
<b>GRACE Score (median; IQR)</b>	146 (122-164)	136 (118-151)	0.05 <sup>a</sup>	
<b>Creatinine [mg/dL] (median; IQR)</b>	<b>1.10 (1.00-1.27)</b>	<b>0.95 (1.0-1.13)</b>	<b>0.01</b> <sup>a</sup>	
<b>Hemoglobin [g/dl] (median; IQR)</b>	13.6 (12.0-14.9)	13.4 (12.0-14.7)	0.58 <sup>a</sup>	
<b>Variables as assessed by the different core laboratories (known to the Endpoint Adjudication Committee (EAC))</b>				
<b>Culprit Lesion present</b>	<b>42/50 (84)</b>	<b>5/197 (3)</b>	<b>&lt;0.001<sup>b</sup></b>	
<b>T-Inversion on any ECG; N=243</b>	15/50 (30)	75/193 (39)	0.24 <sup>b</sup>	
<b>ST Depression in any ECG; (N=243)</b>	4/50 (8)	9/193 (5)	0.37 <sup>b</sup>	
<b>ACS-typical changes in any ECG; (N=190)</b>	13/34 (38)	60/156 (38)	0.98 <sup>b</sup>	
<b>Left Ventricular Ejection Fraction [%] (median; IQR) (N=181)</b>	56 (50-61)	58 (52-62)	0.29 <sup>a</sup>	

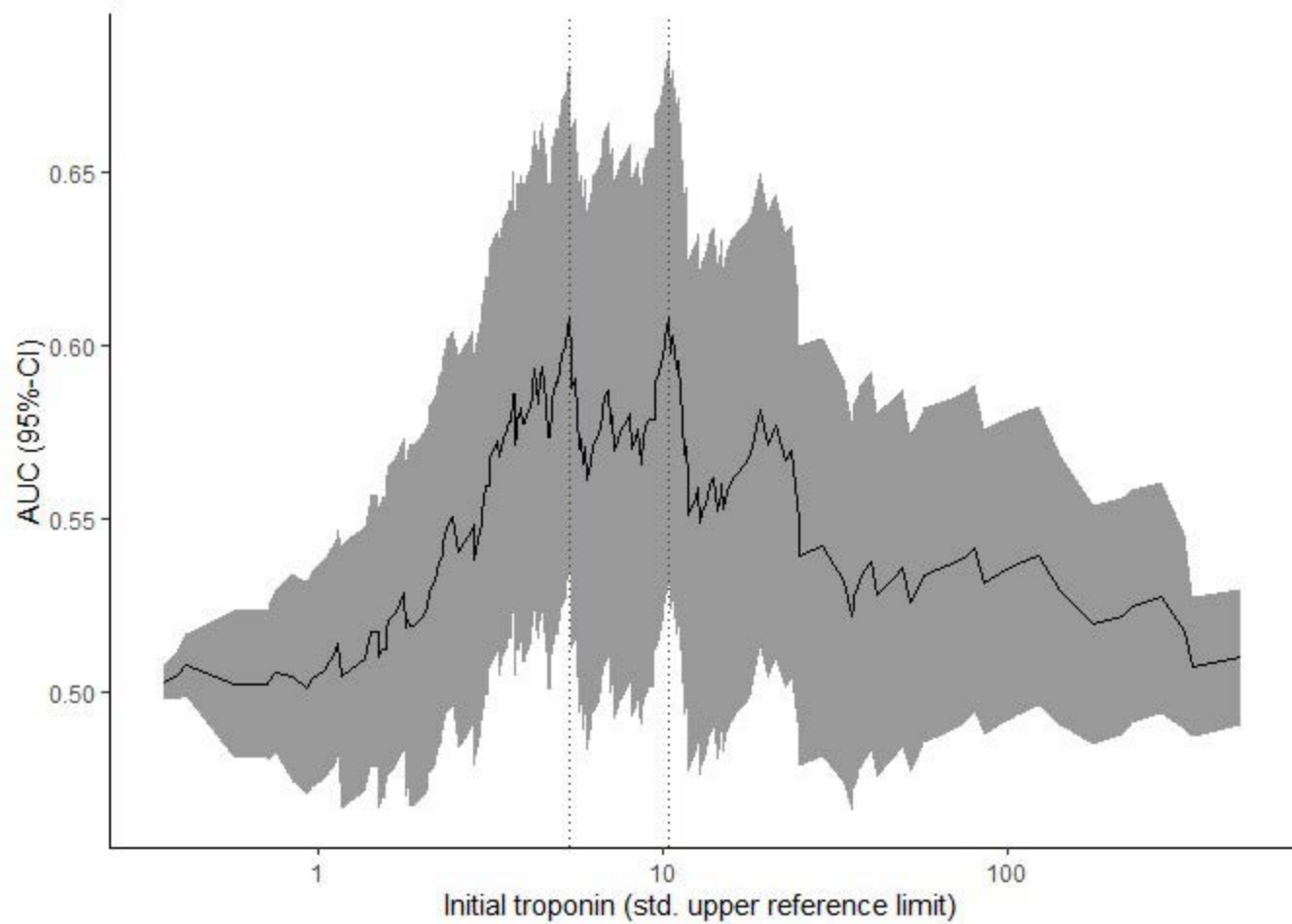
<b>Left Ventricular Ejection Fraction <math>\geq</math>50% (N=181)</b>	35/41 (85)	114/140 (81)	0.55 <sup>b</sup>	
<b>Wall Motion Abnormality (N=163 data from core lab)</b>	10/38 (26)	22/125 (18)	0.25 <sup>b</sup>	
<b>Wall Motion Abnormality (N=195 incl. data from centers)</b>	12/41 (29)	31/154 (20)	0.22 <sup>b</sup>	
<b>Variables of interest (not known to the Endpoint Adjudication Committee (EAC))</b>				
<b>Dynamic hs-cTn change <math>&gt;</math>50% (N=244)</b>	18/50 (36)	67/194 (35)	0.85 <sup>b</sup>	
<b>Dynamic hs-cTn change <math>&gt;</math>20% (N=244)</b>	23/50 (46)	114/194 (59)	0.11 <sup>b</sup>	
<b>hs-cTn on admission (multiples of ULN) (median; IQR) (N=243)</b>	9.56 (4.00-23.26)	5.19 (3.00-12.00)	<b>0.01</b> <sup>a</sup>	<b>1.35 (1.07-1.70)</b> <b>p=0.01</b> <sup>c</sup>
<b>hs-cTnT on admission Roche Elecsys<sup>®</sup> Subgroup (median; IQR) (N=202)</b>	117 (52-253)	66 (40-143)	<b>0.007<sup>a</sup></b>	<b>3.61 (1.49-9.51), p=0.006<sup>d</sup></b>
<b>hs-cTnI on admission Abbott Architect<sup>®</sup> Subgroup (median IQR) (N=159)</b>	326 (64 – 800)	138 (46 – 717)	0.28 <sup>a</sup>	1.10 (0.89-1.37), p=0.38 <sup>e</sup>
<b>Other Variables not known to the Endpoint Adjudication Committee (EAC)</b>				
<b>PTCA-Stent (N=247)</b>	<b>39/50 (78)</b>	<b>31/197 (16)</b>	<b>&lt;0.001<sup>b</sup></b>	
<b>Time from Symptom onset/last known well to first troponin measurement [hours]; (median; IQR)</b>	3 (2-8)	4 (2-10)	0.47	

<sup>a</sup>Wilcoxon rank sum test. <sup>b</sup>Likelihood Ratio Chi-Square-Test. Odds ratios were derived from the fully adjusted logistic regression model after backward selection and inclusion of hs-cTn. <sup>c</sup>Troponin was entered as multiples of ULN (thereby all assays could be used) and logarithmized, continuous variable into the model. <sup>d</sup>Troponin was entered as absolute value [ng/l] as measured by Elecsys<sup>®</sup> Roche Assay and log-transformed, continuous variable into the model. <sup>e</sup>Troponin was entered as absolute value [ng/l] as measured by Architect<sup>®</sup> Abbott Assay and log-transformed, continuous variable into the model. Abbreviations: CAD=coronary artery disease, IVT=intravenous thrombolysis; rTPA=recombinant tissue-type plasminogen activator; NIHSS=National Institutes of Health Stroke Scale (to measure stroke severity); EAC= endpoint adjudication committee; ECG=Electrocardiogram, ULN=upper limit normal.

Figure 1. Participant Flowchart in the PRAISE Study







# Acute myocardial infarction in acute ischemic stroke - the prospective, observational multicenter PRAISE study

## Supplement material

### emethods

Statistical analysis plan

STARD checklist

Charter of the critical events committee (CEC)

Charter of the Data and Safety Monitoring Board (DSMB)

### etables

etable 1

Study site #	Number of patients included (N)	Patients with MI	Patients with type 1 MI
1	28	14 (50.0%)	8 (28.6%)
2	10	3 (30.0%)	2 (20.0%)
3	27	15 (55.6%)	8 (29.6%)
4	9	2 (22.2%)	2 (22.2%)
5	12	6 (50.0%)	2 (16.7%)
6	7	6 (85.7%)	4 (57.1%)
7	9	4 (44.4%)	1 (11.1%)
8	8	5 (62.5%)	0 (0.0%)
9	12	8 (66.7%)	3 (25.0%)
10	8	4 (50.0%)	0 (0.0%)
11	6	2 (33.3%)	0 (0.0%)
12	9	4 (44.4%)	3 (33.3%)
13	3	2 (66.7%)	1 (33.3%)
14	5	3 (60.0%)	1 (20.0%)
15	1	0 (0.0%)	0 (0.0%)
16	3	2 (66.7%)	2 (66.7%)
17	33	16 (48.5%)	5 (15.2%)
18	17	9 (52.9%)	2 (11.8%)
19	12	6 (50.0%)	3 (25.0%)
20	4	4 (100.0%)	1 (25.0%)
21	2	0 (0.0%)	0 (0.0%)
22	9	4 (44.4%)	1 (11.1%)
23	1	1 (100.0%)	1 (100.0%)
24	2	1 (50.0%)	0 (0.0%)
25	7	3 (42.9%)	0 (0.0%)
26	3	2 (66.7%)	0 (0.0%)

The table shows the number of patients included as well as the number of patients with MI and type 1 MI per study site.

eTable 2. Patient characteristics associated with a diagnosis of myocardial infarction (MI) after exclusion of patients with TIA

N=228	OR (95% CI, p-value)
Known CAD	4.00 (1.49-11.63), p=0.008
Heart failure	0.09 (0.01-0.53), p=0.014
Heart rate > 100/min	0.15 (0.03-0.62), p=0.012
NIHSS Visit day 1	1.10 (0.97-1.26), p=0.147



Hemoglobin	2.00 (0.73-5.85), p=0.188
ACS-typical ECG changes	3.79 (1.44-10.94), p=0.009
Wall motion abnormality	38.18 (8.32-315.56), p<0.001
Dynamic hs-cTn change > 50%	0.76 (0.32-1.78), p=0.527

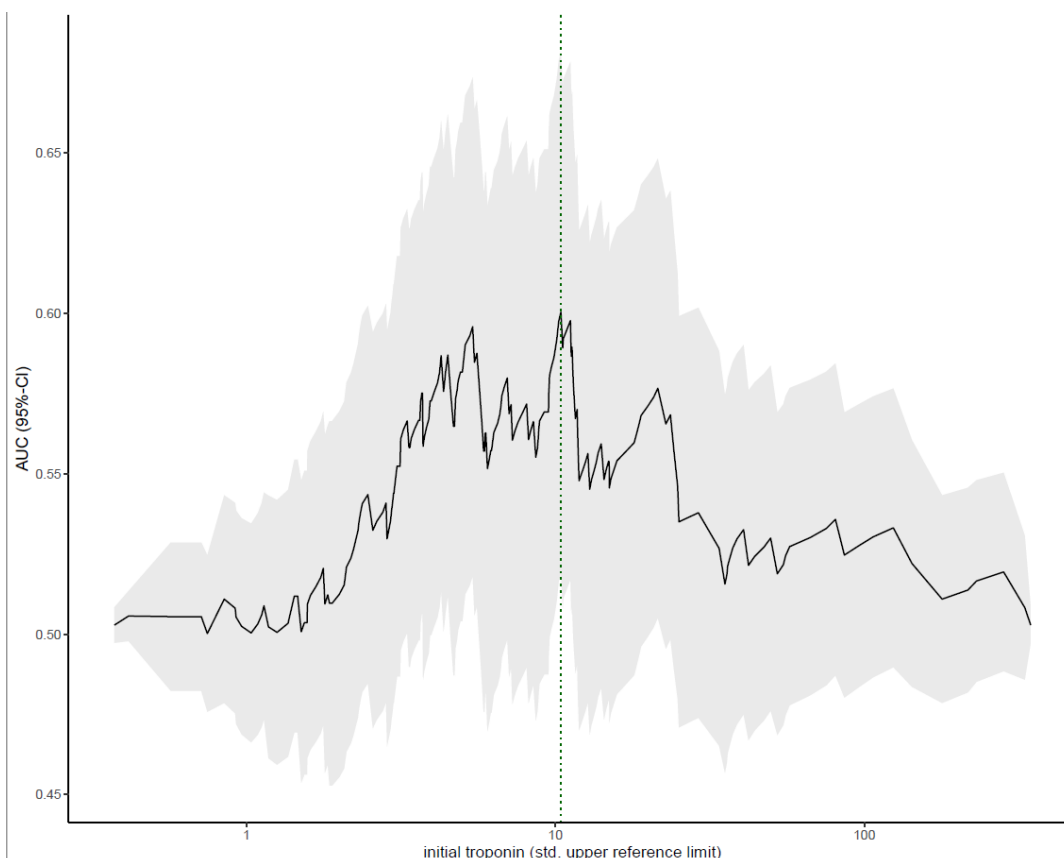
Odds ratios (OR) and 95% confidence intervals (CI) were derived from multivariable logistic regression using backward selection. Hemoglobin ( $\geq 12$  g/dl in women and  $\geq 13$  g/dl in men) was included as a binary variable in the regression model. Abbreviations: CAD = coronary artery disease. NIHSS = National Institutes of Health Stroke Scale. ACS = acute coronary syndrome.

**eTable 3. Patient characteristics associated with a diagnosis of type 1 myocardial infarction (MI) after exclusion of patients with TIA**

N=228	OR (95% CI, p-value)
hs-cTn on admission (multiples of ULN)	1.79 (1.02-3.15), p=0.042

Odds ratios (OR) and 95% confidence intervals (CI) were derived from multivariable logistic regression using backward selection. Abbreviations: hs-cTn = high-sensitivity cardiac troponin, ULN = upper limit normal

**eFigure 1. Diagnostic accuracy of adding hs-cTn changes (0-100%) to predefined regression model for MI after exclusion of patients with TIA**



The figure illustrates the predictive accuracy for different thresholds (x-axis) for hs-cTn on admission (as multiple of ULN) for the presence of MI as given by the area under the curve (AUC) after exclusion of N=19 patients with TIA. The higher the AUC, the better the predictive accuracy of the cut-off.