

Coronary Angiographic Findings in Acute Ischemic Stroke Patients With Elevated Cardiac Troponin

The Troponin Elevation in Acute Ischemic Stroke (TRELAS) Study

Hans-Christian Mochmann, MD*; Jan F. Scheitz, MD*; Gabor C. Petzold, MD;
Karl Georg Haeusler, MD; Heinrich J. Audebert, MD; Ulrich Laufs, MD;
Christine Schneider, MD; Ulf Landmesser, MD; Nikos Werner, MD; Matthias Endres, MD*;
Bernhard Witzenbichler, MD*; Christian H. Nolte, MD*; for the TRELAS Study Group

Background—A relevant proportion of patients with acute ischemic stroke (AIS) have elevated levels of cardiac troponins (cTn). However, the frequency of coronary ischemia as the cause of elevated cTn is unknown. The aim of our study was to analyze coronary vessel status in AIS patients with elevated cTn compared with patients presenting with non-ST-segment-elevation acute coronary syndrome (NSTEMI-ACS).

Methods and Results—Among 2123 consecutive patients with AIS prospectively screened at 2 tertiary hospitals, 13.7% had cTn elevation (>50 ng/L). According to a prespecified sample size estimation, 29 patients with AIS (median age, 76 years [first–third quartiles, 70–82 years]; 52% male) underwent conventional coronary angiography and were compared with age- and sex-matched patients with NSTEMI-ACS. The primary end point was presence of coronary culprit lesions on coronary angiograms as analyzed by independent interventional cardiologists blinded for clinical data. Median cTn on presentation did not differ between patients with AIS or NSTEMI-ACS (95 versus 94 ng/L; $P=0.70$). Compared with patients with NSTEMI-ACS, patients with AIS were less likely to have coronary culprit lesions (7 of 29 versus 23 of 29; $P<0.001$) or any obstructive coronary artery disease (15 of 29 versus 25 of 29; $P=0.02$; median number of vessels with $>50\%$ stenosis, 1 [first–third quartiles, 0–2] versus 2 [first–third quartiles, 1–3]; $P<0.01$).

Conclusions—Coronary culprit lesions are significantly less frequent in AIS patients compared with age- and sex-matched patients with NSTEMI-ACS despite similar baseline cTn levels. Half of all AIS patients had no angiographic evidence of coronary artery disease. Further studies are needed to clinically identify the minority of patients with AIS and angiographic evidence of a culprit lesion.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01263964.

(*Circulation*. 2016;133:1264–1271. DOI: 10.1161/CIRCULATIONAHA.115.018547.)

Key Words: acute coronary syndrome ■ coronary angiography ■ nervous system ■ stroke ■ troponin

Cardiac troponins (cTns) are sensitive and specific biomarkers for myocardial injury and are widely used in daily clinical practice. In patients presenting with acute coronary syndrome (ACS), cTns allow rapid risk stratification and are critical components of further patient management.^{1–3} Because of the large clinical and pathophysiological overlap of cardiovascular and cerebrovascular disease and the strong impact of cardiac adverse events on the prognosis of acute ischemic stroke (AIS), current American Heart Association/American Stroke Association treatment guidelines recommend the assessment of cTn levels in all patients presenting

with AIS.⁴ Although the vast majority of AIS patients do not clinically present with cardiac symptoms, $\approx 15\%$ show cTn levels above the diagnostic threshold to suspect ongoing myocardial injury when conventional assays are used and up to 60% when high-sensitivity assays are applied.^{5,6} Similar to findings in the general population and in patients with stable and acute cardiac disease,^{7–9} cTn levels provide prognostic information on short- and long-term outcome after AIS.⁵

Editorial, see p 1228
Clinical Perspective on p 1271

Received July 16, 2015; accepted January 28, 2016.

From Klinik für Kardiologie (H.-C.M., U.L.) and Klinik für Neurologie (J.F.S., K.G.H., H.J.A., M.E., C.H.N.), Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Germany; Center for Stroke Research Berlin (J.F.S., K.G.H., H.J.A., M.E., C.H.N.) and ExcellenceCluster NeuroCure (M.E.), Charité-Universitätsmedizin Berlin, Germany; German Center for Neurodegenerative Diseases and Department of Neurology (G.C.P., C.S.) and Department of Internal Medicine II (N.W.), University of Bonn, Germany; Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, Homburg, Germany (U.L.); German Center for Neurodegenerative Diseases, Berlin, Germany (M.E.); Berlin Institute of Health, Germany (M.E.); and Klinik für Kardiologie und Pneumologie, Helios Amper-Klinikum Dachau, Germany (B.W.).

*Drs Mochmann, Scheitz, Endres, Witzenbichler, and Nolte contributed equally.

The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.115.018547/-DC1>.

Correspondence to Christian H Nolte, MD, Department of Neurology, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Hindenburgdamm 30, 12203 Berlin, Germany. E-mail christian.nolte@charite.de

© 2016 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.115.018547

According to current guidelines, ACS patients with elevated cTn (high-risk criterion) and without evidence of ST-segment elevation (NSTEMI-ACS) should undergo invasive evaluation preferably within 72 hours of admission.³ Because of the uncertainty about the cause of cTn elevation in AIS patients and the high risk of secondary hemorrhagic transformation or procedure-related stroke, physicians are left with a clinical dilemma concerning the optimal timing and invasiveness of diagnostic evaluation and treatment. Besides acute coronary artery disease (CAD), stroke-induced myocardial injury, coronary supply-demand imbalance, and other noncoronary causes have been suggested as potential sources of cTn elevation in AIS patients.⁵ Therefore, the aim of the Troponin Elevation in Acute Ischemic Stroke (TRELAS) study was to elucidate the possible coronary cause of cTn elevation in AIS by assessing the frequency of coronary culprit lesions on coronary angiogram. Age- and sex-matched patients presenting with NSTEMI-ACS served as control subjects.

Methods

Study Protocol and Study Population

The protocol of the TRELAS study was previously described in detail (NCT01263964).¹⁰ In summary, TRELAS is a registered, prospective, observational study with blinded end-point assessment that includes AIS patients presenting within 72 hours after symptom onset. AIS was defined as a sudden neurological deficit caused by cerebral ischemia as confirmed by neuroimaging.⁹ Patients with elevated cTn levels (>50 ng/L) on presentation or during the following day underwent diagnostic coronary angiography within 72 hours. cTn was measured with a high-sensitivity troponin T assay (Roche Elecsys, fifth-generation assay, Mannheim, Germany; 99th percentile, 14 ng/L). The cutoff of 50 ng/L with the fifth-generation troponin T assay corresponds to a value of 0.03 ng/mL for the clinical decision limit for myocardial infarction (MI) diagnosis with the fourth-generation troponin T assay.¹¹ Patients with impaired kidney function (creatinine ≥ 1.20 mg/dL [≥ 106 μ mol/L]), severe pre-morbid disability (modified Rankin scale score ≥ 4 , indicating that the patient was unable to attend to own bodily needs without assistance and unable to walk unassisted), ST-segment elevation on ECG, and patients who were unable or not willing to give informed consent were not eligible. Ischemic findings on ECG were defined in accordance with the universal definition of MI: new horizontal or down-sloping ST depression ≥ 0.05 mV in 2 contiguous leads or T inversion ≥ 0.1 mV in 2 contiguous leads with a prominent R wave or R/S ratio >1 .¹² Between February 2011 and August 2013, all consecutive AIS patients admitted to the Stroke Unit of the Department of Neurology at the University Hospital Charité (Campus Benjamin Franklin, Berlin, Germany) were prospectively screened for inclusion. Since July 2012, patients with AIS or NSTEMI-ACS have been additionally enrolled at the University Hospital Bonn (Bonn, Germany). The study was approved by the respective institutional review committees (EA4/118/10). The control group consisted of age- and sex-matched patients presenting with NSTEMI-ACS. Control patients were selected at random from local registries of patients who underwent coronary angiography at the Charité-Universitätsmedizin Berlin ($n=24$) or the University Hospital Bonn ($n=5$). In a first step, a stroke neurologist blinded to coronary angiographic findings (J.F.S., G.P., C.S.) searched the registries for nearest possible age and sex matches. In a second step, the working diagnosis of NSTEMI-ACS at hospital admission was confirmed by medical records.

Outcome Measures

The primary outcome was the presence of a coronary culprit lesion on diagnostic coronary angiography. All diagnostic coronary and left ventricular (LV) angiograms were analyzed independently by 3 experienced interventional cardiologists (H.C.M., B.W., H.Z.M.). Raters

were blinded to clinical data, diagnoses (AIS or NSTEMI-ACS), and further diagnostic procedures. Imaging sequences were anonymized and analyzed at random. A culprit lesion was defined as a lesion with irregular borders, filling defects, or the presence of intraluminal thrombus.¹³ In addition, high-grade stenosis leading to a reduction in Thrombolysis in Myocardial Infarction (TIMI) flow grade was also regarded as a culprit lesion in the absence of the above-mentioned criteria. Because clinical information or additional information from intracoronary imaging is needed for a conclusive statement in some patients, blinded raters had the option to rule for probable or definite culprit lesion. To ensure that the incidence of coronary culprit lesions was not underestimated, both probable and definite culprit lesions were considered in the statistical analysis.

Predefined secondary outcomes were the absence of any obstructive CAD (defined as a coronary stenosis $\geq 50\%$), apical ballooning pattern (indicating Takotsubo cardiomyopathy) on LV angiography, and impaired ejection fraction on LV angiography. Ejection fraction was categorized as normal ($>65\%$), moderately impaired ($45\%–65\%$), or severely impaired ($<45\%$).

Statistical Methods

The McNemar test was used for comparisons of dichotomous variables of baseline characteristics and outcome variables between matched patients with AIS and NSTEMI-ACS. The Wilcoxon signed-rank test was used for comparisons of continuous variables, and the marginal homogeneity test was used for categorical variables. Comparisons within the groups were performed with the Fisher exact test and Mann-Whitney *U* test. Data shown in the tables represent percentages (total numbers) or medians (first–third quartiles [Q1–Q3]). We calculated area under the receiver-operating characteristics curve to evaluate the predictive accuracy of baseline cTn and changes in cTn for the presence of a coronary culprit lesion in AIS patients using the Harrell *c* statistic.

Sample size calculation had shown that an overall sample of 58 patients (29 with AIS and 29 with NSTEMI-ACS) was adequate to detect a difference of 50% (expected frequency of coronary culprit lesions, 35% versus 85%) in angiographic culprit lesions within the matched pairs with a statistical power of 90% at a 2-sided significance level of 5%.¹⁰ All other analyses are explorative. All analyses were performed with SPSS Statistics 22.0 (IBM, Armonk, NY).

Results

Study Population and Baseline Characteristics

Overall, 1568 patients with neuroimaging-confirmed AIS were screened for cTn elevation in Berlin (median age, 75 years; 51.5% male; median National Institutes of Health Stroke Scale [NIHSS] score, 5) and 555 patients were screened in Bonn (median age, 69; 56.0% male; median NIHSS score, 5). Elevated cTn (>50 ng/L) was found in 14.9% and 10.4% of AIS patients, and 46.7% and 32.5% had elevation above the 99th percentile, respectively. Main reasons for exclusion from the TRELAS study were evidence of impaired kidney function (creatinine >1.2 mg/dL, 40.1%), missing informed consent (19.7% unable; 9.0% unwilling), coronary angiography considered contraindicated (eg, severe neurological deficit resulting from a large cerebral infarct, early neurological worsening, hemoglobin-relevant gastrointestinal bleeding, secondary hemorrhagic transformation) or unfavorable pre-morbid condition (prestroke modified Rankin Scale score ≥ 4 , 18.3%), and STE-ACS (2.1%).

Overall, 29 AIS patients and 29 age- and sex-matched patients presenting with NSTEMI-ACS were enrolled and underwent coronary angiography for evaluation of coronary vessel status. Table 1 displays the baseline characteristics of included patients. There were no significant differences in baseline cTn

levels, ECG evidence of myocardial ischemia, or frequency of known vascular risk factors between the AIS patients and control subjects. Patients with AIS were more likely to have atrial fibrillation or a history of congestive heart failure and

had lower estimated glomerular filtration rates compared with NSTEMI-ACS patients.

The median NIHSS score of the AIS patients who underwent coronary angiography was 5 (Q1–Q3, 3–7), which was not

Table 1. Comparison of Baseline Characteristics Between Patients With AIS and NSTEMI-ACS

	AIS Patients (n=29)	NSTEMI-ACS Patients (n=29)	P Value*
Age, median (Q1–Q3), y	76 (70–82)	77 (70–82)	
Male sex, % (n)	51.7 (15)	51.7 (15)	
Stroke severity, NIHSS score, median (Q1–Q3)	5 (3–7)	...	
Time to catheter laboratory, median (Q1–Q3)	48 (28–71)	7 (3–15)	<0.001
GRACE score, median (Q1–Q3)	117 (98–139)	123 (110–136)	0.311
Vascular risk factors, % (n)			
Diabetes mellitus	27.6 (8)	17.2 (5)	0.549
Hypercholesterolemia	65.5 (19)	41.4 (12)	0.092
Hypertension	93.1 (27)	75.9 (22)	0.125
Previous stroke	20.7 (6)	13.8 (4)	0.754
Smoking	17.2 (5)	24.1 (7)	0.754
Medical history, % (n)			
Atrial fibrillation†	41.4 (12)	13.8 (4)	0.039
History of CHF	27.6 (8)	3.4 (1)	0.016
History of CAD	24.1 (7)	34.5 (10)	0.581
History of COPD	3.4 (1)	10.3 (3)	0.625
History of malignant tumor,	6.9 (2)	10.3 (3)	1.0
Laboratory measures, median (Q1–Q3)			
Baseline cTn levels, ng/L	95 (48–227)	94 (32–248)	0.552
Baseline CK, mg/dL	128 (76–243)	140 (81–232)	0.642
Creatinine, mg/dL	1.03 (0.89–1.12)	0.88 (0.72–0.92)	0.002
GFR‡, mL·min ⁻¹ ·1.73 m ⁻²	70 (59–76)	75 (64–92)	0.005
ECG evidence of myocardial ischemia, % (n)	34.5 (10)	60.7 (17)	0.118
Heart rate on admission, median (Q1–Q3), bpm	76 (68–87)	72 (67–91)	0.948
Systolic BP on admission, median (Q1–Q3), mm Hg	152 (140–174)	146 (124–154)	0.124
Diastolic BP on admission, median (Q1–Q3), mm Hg	80 (70–91)	80 (69–89)	0.677
Killip class, % (n)			0.046
1	86.2 (25)	96.6 (28)	
2	10.3 (3)	3.4 (1)	
3	3.4 (1)	0 (0)	
Medication history, % (n)			
Previous antiplatelet use	51.7 (15)	55.6 (15)	1.0
Previous oral anticoagulation	6.9 (2)	3.4 (1)	1.0
Previous statin use	34.5 (10)	29.6 (8)	1.0
Previous use of β -blockers	44.4 (12)	48.1 (13)	0.687

AIS indicates acute ischemic stroke; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CK, creatinine kinase; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; NIHSS, National Institutes of Health Stroke Scale; NSTEMI-ACS, non-ST-segment-elevation acute coronary syndrome; and Q1–Q3, interquartile range.

*McNemar test (dichotomous variables) or Wilcoxon signed-rank test (continuous or ordinal variables).

†Known from medical history (7 of 12) or newly detected during hospital stay (5 of 12).

‡GFR estimated according to *Chronic Kidney Disease Epidemiology Collaboration* formula.

significantly different compared with that of AIS patients who did not fulfill the inclusion criteria (median, 5; Q1–Q3, 2–10; $P=0.933$). AIS patients with elevated cTn (>50 ng/L) had higher baseline stroke severity compared with those without (median NIHSS score, 8; Q1–Q3, 4–16; versus median NIHSS score, 4; Q1–Q3, 2–9; $P<0.001$). Similar findings were observed in patients with cTn elevation above the 99th percentile (14 ng/L; median NIHSS score, 6; Q1–Q3, 3–13; versus median NIHSS score, 4; Q1–Q3, 2–7; $P<0.001$). CTn levels were obtained at a median of 12 hours after onset of stroke-related symptoms (Q1–Q3, 1–27 hours). Follow-up measurements of cTn in AIS patients were obtained at a median of 12 hours (Q1–Q3, 6–21 hours) afterward. Twelve AIS patients (41%) received treatment with intravenous tissue-type plasminogen activator. Seven patients had left anterior circulation stroke; 7 patients had right anterior circulation stroke; 5 patients had posterior circulation stroke; and 10 patients had >1 affected cerebral vascular territory. Involvement of the insular cortex was observed in 7 patients. There was no difference in insular involvement in patients with and without coronary culprit lesion (2 of 7 versus 5 of 22; $P=0.753$). The cause of cerebral ischemia was considered embolic in all 29 patients (cardioembolic in 15 patients, large-artery atherosclerosis in 9 patients, and undetermined or concurrent embolic sources in 5 patients). Of note, only 2 of 7 patients with known atrial fibrillation before AIS were on treatment with oral anticoagulants before the stroke, including 1 patient not in therapeutic range (international normalized ratio <2). The median CHA₂DS₂-VASc score in AIS patients with known atrial fibrillation was 6 (Q1–Q3, 3–7) before the present stroke. None of these patients had a documented contraindication to oral anticoagulants, but 1 patient had a CHA₂DS₂-VASc of 1.

Coronary Angiography Findings

Coronary angiographic findings in patients with AIS and NSTEMI-ACS are summarized in Table 2. Patients with AIS underwent

coronary angiography at a median of 48 hours after hospital admission (Q1–Q3, 28–71 hours) and 72 hours (Q1–Q3 43–91 hours) after stroke symptom onset. Significantly fewer AIS patients had coronary culprit lesions compared with NSTEMI-ACS patients (7 of 29 versus 23 of 29; $P<0.001$; Table 2). Culprit lesions were considered probable in 4 AIS patients and definite in 3 AIS patients. Culprit lesions were located in the left anterior descending artery ($n=2$), in the left circumflex artery ($n=3$), and in venous coronary artery bypass grafts ($n=2$). Blood flow in culprit vessels in AIS patients was graded as TIMI III (complete filling of the coronary bed) in 6 of 7 patients. TIMI III flow in the culprit lesion was found in 11 of 23 patients with NSTEMI-ACS. Time from detection of elevated cTn until sheath insertion was significantly shorter in NSTEMI-ACS patients than in AIS patients (Table 1). Time between detection of elevated cTn until sheath insertion during coronary angiography was not different in patients in whom coronary culprit lesions were identified (Figure 1 in the online-only Data Supplement) in either NSTEMI-ACS patients (7 versus 6 hours; $P=0.979$) or AIS patients (50 versus 48 hours; $P=0.940$).

Obstructive CAD (stenosis $>50\%$) was significantly less frequent in AIS patients compared with patients with NSTEMI-ACS (8 of 29 versus 25 of 29; $P=0.021$). Moreover, the extent of CAD was lower in AIS patients compared with NSTEMI-ACS patients (Table 3), and patients with AIS were less likely to have multivessel CAD (≥ 2 vessels diseased, 28% versus 62%; $P=0.013$). Ejection fraction on LV angiography did not differ between the AIS and NSTEMI-ACS patients ($P=0.853$), nor did presence of Takotsubo cardiomyopathy (7 versus 7; $P=1.0$).

Sensitivity analyses were performed because of the potential effect of fibrinolysis on coronary lesions; 5 AIS patients with stable coronary lesions (all had stenosis $<80\%$) were treated with tissue-type plasminogen activator before coronary angiography. The main results remained unchanged if these lesions were considered to be possible culprit lesions (41% [12

Table 2. Diagnostic Coronary Angiographic Findings in AIS Patients With Elevated cTn Compared With NSTEMI-ACS Patients

	AIS Patients (n=29)	NSTEMI-ACS Patients (n=29)	P Value
Coronary culprit lesion, % (n)	24.1 (7)	79.3 (23)	<0.001
Absence of any obstructive CAD, % (n)	48.3 (14)	13.8 (4)	0.021
Vessels diseased, median (Q1–Q3), n*	1 (0–2)	2 (1–3)	0.003
Multivessel disease, ≥ 2 vessels diseased, % (n)	27.6 (8)	62.1 (18)	0.013
Chronic total occlusion, % (n)	17.2 (5)	6.9 (2)	0.453
Ejection fraction, % (n)†			0.720‡
Normal, $>65\%$	63.0 (17)	57.1 (14)	
Moderately reduced, 40%–65%	14.8 (3)	35.7 (10)	
Severely reduced, $<40\%$	22.2 (6)	7.1 (2)	
Takotsubo cardiomyopathy	7.1 (2)	7.4 (2)	1.0
Ejection fraction in TTC patients, mean $\pm$ SD, %	44 $\pm$ 11	58 $\pm$ 13	

AIS indicates acute ischemic stroke; CAD, coronary artery disease; cTn, cardiac troponin; NSTEMI-ACS, non-ST-segment-elevation acute coronary syndrome; and TTC, Takotsubo cardiomyopathy.

*With stenosis $>50\%$.

†Left ventricular angiography available in 55 patients (26 pairs).

‡P for categorical variable.

Table 3. Severity of CAD Among AIS Patients With Elevated cTn and Patients Presenting With NSTEMI-ACS

	AIS Patients (n=29), % (n)	NSTEMI-ACS Patients (n=29), % (n)	P Value*
No CAD, % (n)	48.3 (14)	13.8 (4)	0.003
1-Vessel CAD, % (n)	24.1 (7)	24.1 (7)	
2-Vessel CAD, % (n)	13.8 (4)	20.7 (6)	
3-Vessel CAD, % (n)	13.8 (4)	41.4 (12)	

AIS indicates acute ischemic stroke; CAD, coronary artery disease with evidence of angiographic evidence of coronary stenosis >50%; cTn, cardiac troponin; and NSTEMI-ACS, non-ST-segment-elevation acute coronary syndrome.

*Wilcoxon signed-rank test.

of 29] versus 79% [23 of 29]; $P<0.01$). Similar results were found when thrombolized AIS patients were excluded from the analysis (35% [6 of 17] versus 65% [11 of 17]; $P=0.180$).

Therapeutic Consequences and Safety of Coronary Angiography

Angioplasty with stenting of the culprit lesion was performed in the same session in 3 AIS patients. In 3 other AIS patients, a staged intervention after neurological rehabilitation was recommended (Table 4). In contrast, 20 patients with NSTEMI-ACS received immediate revascularization, and 3 underwent coronary artery bypass graft surgery. Among AIS patients who underwent coronary angiography, 1 patient experienced an inguinal hematoma and 1 had nonsustained postinterventional atrial fibrillation. None of the AIS patients had neurological worsening or clinical evidence of hemorrhagic transformation. There were no adverse events during coronary angiography in the NSTEMI-ACS group.

Characteristics of AIS Patients With Coronary Culprit Lesion and With Evidence of CAD

One AIS patient with angiographic evidence of a culprit lesion had chest pain, and 3 patients had ischemic findings on ECG (other than ST-segment elevation). AIS patients with evidence of a coronary culprit lesion were more likely to have a history of CAD (4 of 7 versus 3 of 22; $P=0.036$), but other baseline characteristics and laboratory findings did not differ significantly (Table I in the online-only Data Supplement). Baseline cTn was 170 ng/L (Q1–Q3, 36–863 ng/L) in AIS patients with coronary culprit lesions compared with 90 ng/L (Q1–Q3, 53–152 ng/L) in those without ($P=0.629$; c statistic, 0.57; 95% confidence interval, 0.26–0.87). Median absolute increase in cTn between baseline and follow-up measurements was 74 ng/L (Q1–Q3, 46–171 ng/L) in AIS patients with coronary culprit lesions compared with 26 ng/L in those without (Q1–Q3, 12–178 ng/L; $P=0.161$; c statistic, 0.68; 95% confidence interval, 0.46–0.89). Six of 7 AIS patients with coronary culprit lesions had a change in cTn levels of at least 4 times the 99th percentile (14 ng/L). When AIS patients with history of CAD were excluded ($n=7$), all 3 patients with culprit lesions had a baseline cTn level ≥ 347 ng/L and an increase of cTn ≥ 100 ng/L.

In 14 patients with AIS (48%), there was no evidence of obstructive CAD at all. Detailed characteristics of AIS patients with and without presence of CAD on angiograms are shown in Table I in the online-only Data Supplement. AIS patients without obstructive CAD were younger (median age,

71 versus 79 years; $P=0.026$), had lower scores on the Global Registry of Acute Coronary Events (GRACE) score (median, 102 versus 127 points; $P=0.018$), and less often had ECG signs of ischemia (2 of 14 versus 8 of 15; $P=0.050$). In terms of other baseline characteristics, AIS patients with proven CAD did not differ from those without CAD. Among AIS patients without known history of CAD ($n=22$), coronary angiography showed evidence of obstructive CAD in 8 patients (36%).

Discussion

Elevation of cTn in AIS is a common finding and presents a quandary for physicians. A better understanding of the underlying mechanism of cTn elevation would help to guide clinical decision making. The findings of our study suggest that the majority of AIS patients with elevated cTn do not have coincident ACS and about half of patients had no evidence of obstructive CAD at all. As expected, angiographic evidence of coronary culprit lesions is observed significantly less often in AIS patients compared with age- and sex-matched patients presenting with NSTEMI-ACS. Moreover, the overall burden of coronary lesions is lower in AIS patients than in NSTEMI-ACS patients despite similar baseline cTn levels and GRACE scores (both correlating with severity of coronary lesions and TIMI flow rates in ACS patients).^{14–16}

Despite the angiographic evidence of a coronary culprit lesion in $\approx 25\%$ of AIS patients, all but 1 patient had TIMI III flow beyond the culprit artery, and the majority were treated conservatively during the acute phase after ischemic stroke. Given that there is substantial overlap between the plaque anatomy of putatively stable and acute coronary disease,^{17,18} the context of clinical complaints and typical ECG findings is needed to establish the diagnosis of an ACS. Because only 1 of 7 AIS patients with culprit lesions had clinical symptoms (ie, chest pain) and just 3 patients had typical ECG changes, one could argue that cTn release might not be mediated by type I MI in all AIS patients despite angiographic evidence of a coronary culprit lesion.

Clinical conditions provoking coronary demand ischemia (ie, type 2 MI) and noncoronary causes are more likely to be the source of cTn release in the majority of AIS patients. The higher prevalence of atrial fibrillation and congestive heart failure and the overall lower glomerular filtration rate

Table 4. Therapeutic Consequences of Conventional Coronary Angiograms in Patients Presenting With AIS With Elevated cTn Compared With Patients Presenting With NSTEMI-ACS

	AIS Patients (n=29), % (n)	NSTEMI-ACS Patients (n=29), % (n)	P Value*
No intervention	79.3 (23)	13.8 (4)	<0.001
Staged intervention	10.3 (3)	0 (0)	
Urgent revascularization	10.3 (3)	75.9 (22)	
Urgent CABG	0 (0)	10.3 (3)	

AIS indicates acute ischemic stroke; CABG, coronary artery bypass graft; cTn, cardiac troponin; and NSTEMI-ACS, non-ST-segment-elevation acute coronary syndrome.

*Wilcoxon signed-rank test.

in AIS patients compared with NSTEMI-ACS patients support this hypothesis. Furthermore, there was a relatively high rate of chronic total vessel occlusion on angiography and severely impaired LV function in AIS patients. In addition, neurogenic mechanisms are likely to contribute to cTn elevation in patients with AIS. AIS is frequently followed by a shift in autonomic balance, leading to an increased sympathetic tone and subsequent release of catecholamines.^{19,20} The so-called neurogenic heart syndrome can promote coronary demand ischemia or provoke diffuse myocyte necrosis (contraction band necrosis).^{5,19} One variation of neurogenic heart syndrome is Takotsubo cardiomyopathy.²¹ We did not find a difference in the frequency of Takotsubo cardiomyopathy among AIS and NSTEMI-ACS patients, but our study was not powered to detect a significant difference. Further studies are needed to define the impact and the therapeutic implications of noncoronary and, especially, neurogenic mechanisms of cTn elevation.

A dynamic pattern of cTn levels may help to differentiate acute from chronic CAD.^{11,22} Six of 7 AIS patients with coronary culprit lesions had a delta change in cTn of at least 4 times the 99th percentile. This may be considered an argument that higher relative changes in serial cTn levels may increase the pretest probability to detect a culprit lesion by coronary imaging procedures in AIS patients also. Unfortunately, patient numbers were too small in our cohort to derive reliable clinical predictors and reliable cutoffs of cTn for the prediction of acute CAD in the clinical setting of AIS. Moreover, the sampling interval in AIS patients was longer than usually recommended in patients presenting with suspected MI. Thus, the reported kinetics of cTn in AIS patients are not easily comparable with the available literature.

Given the strong overlap between cerebrovascular and cardiovascular risk factors,²³ diagnostic workup for CAD is generally required after AIS. In AIS patients with cTn elevation but unknown history of CAD before stroke, we detected significant coronary stenosis in about one third. This finding is higher than in previous studies that did not stratify according to cardiac biomarkers.^{24,25} Higher cTn levels were associated with the extent of CAD in patients with suspected CAD and the general population.²⁶ Because silent CAD has prognostic relevance for future cardiovascular events and death,²⁷ cTn levels may be used as a surrogate biomarker for concomitant silent CAD. Hence, cTn levels might be useful to identify AIS patients who need earlier workup for CAD and more intensified secondary prevention. As primary diagnostic workup, cardiac imaging could be performed by less invasive procedures such as cardiac computed tomography or magnetic resonance imaging.

Importantly, the frequency of oral anticoagulation in patients with known atrial fibrillation before the index stroke was low despite a Class 1 recommendation for treatment with oral anticoagulants in patients with a CHA₂DS₂-VASc score ≥ 2 .²⁸ This reinforces the continued need to overcome the underuse of oral anticoagulation in patients with atrial fibrillation.

Certain limitations in our study have to be discussed. First, AIS patients unable to give informed consent (eg, because of aphasia) or with unfavorable premorbid status were not included in the study for ethical reasons. Because the frequency and extent of cTn elevation increase with older age, overall burden of comorbidities, and higher stroke severity,²⁹ it might be possible that the presence of coronary culprit lesions in AIS patients

is underestimated in our cohort. However, general characteristics (age, sex, vascular risk factors, and stroke severity) of the included patients are well representative of general stroke cohorts.^{30,31}

Second, a dynamic pattern of cTn was not mandatory for inclusion. However, we applied a diagnostic threshold for diagnosis of MI that is markedly higher than the recommended 99th percentile to increase the positive predictive value of a coronary pathomechanism, and we excluded patients with impaired kidney function or unfavorable premorbid status. Higher absolute cTn levels entail a higher positive predictive value of coronary causes of cTn elevation, whereas differential diagnosis of mildly elevated cTn levels with values close to the 99th percentile is broad.^{32,33} Hence, the choice of a lower cutoff might have resulted in an even lower frequency of coronary culprit lesions in AIS patients. Therefore, we believe that the findings of a lower frequency of coronary culprit lesions in AIS compared with NSTEMI-ACS patients and that nearly half of AIS patients had no evidence of obstructive CAD are strengthened. Moreover, the cutoff of high-sensitivity cTn that was applied in our study exceeds age- and sex-specific cutoffs that have been advocated for diagnosis of MI.^{34–36}

Third, 41% of the enrolled AIS patients received intravenous thrombolysis before coronary angiography, which may lead to improved TIMI flow rates. In the Strategic Reperfusion Early After Myocardial Infarction (STREAM) trial, a significantly higher rate of TIMI III flow was found in patients with ST-segment elevation MI randomized to fibrinolysis before percutaneous coronary intervention.³⁷ However, the observed difference in the frequency of coronary culprit lesions between AIS and NSTEMI-ACS patients remained when stable coronary lesions in thrombolized AIS patients were considered possible culprit lesions.

Fourth, the average time to the catheter laboratory was longer in AIS patients than in NSTEMI-ACS patients. Given that previous studies reported a slightly higher rate of percutaneous coronary interventions in NSTEMI-ACS patients randomized to early invasive compared with those receiving delayed invasive treatment strategies ($\approx 5\%$),^{38,39} the timing of angiography may have influenced our findings. However, our observed difference between AIS and NSTEMI-ACS patients markedly exceeds these observations and may not be explained by the timing of angiography alone.

Fifth, intracoronary imaging (intravascular ultrasound or optical coherence tomography) would have provided additional information on underlying pathomechanisms (plaque erosion versus rupture).^{40,41} However, this imaging requires administration of antithrombotic agents, which increase the risk of hemorrhagic transformation in AIS patients.

Conclusions

The major finding of this prospective observational case-control study with blinded end-point assessment is that AIS patients are significantly less likely to have coronary culprit lesions than age- and sex-matched patients with NSTEMI-ACS despite similar baseline cTn levels. Angiographic evidence of coronary culprit lesion is found in up to one quarter of all patients with AIS and elevated cTn, but in the majority of AIS patients, no underlying culprit lesion is present in coronary angiography. Further studies are needed to define clinical algorithms for better risk

stratification and to evaluate the necessity of invasive and non-invasive diagnostic procedures. Given that the frequency of underlying culprit lesions is low in AIS patients with elevated cTn and is not accompanied by chest pain or typical ECG changes in most cases, one should consider less invasive cardiac imaging procedures such as cardiac computed tomography or magnetic resonance imaging as the primary diagnostic workup.

Acknowledgments

We thank Regina Chmielnik (Berlin) and Dr Serdar Tütüncü (Center for Stroke Research Berlin, Berlin, Germany) for help with data acquisition, as well as Dr Ulrike Grittner (Clinical Epidemiology and Health Services Research in Stroke [Cehris], Charité, Center for Stroke Research Berlin) for statistical advice, and Dr Hedda von zur Mühlen (Helios Amper-Klinikum Dachau, Dachau, Germany) for blinded evaluation of coronary angiograms.

Sources of Funding

The TRELAS study was funded by the Bundesministerium für Bildung und Forschung (Center for Stroke Research Berlin). Dr Scheitz is a participant in the Charité Clinical Scientist Program funded by the Charité Universitätsmedizin Berlin and the Berlin Institute of Health. Drs Schneider and Petzold were supported by the German Center for Neurodegenerative Diseases.

Disclosures

None.

References

- Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, Biedert S, Schaub N, Buergel C, Potocki M, Noveanu M, Breidthardt T, Twerenbold R, Winkler K, Bingisser R, Mueller C. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med*. 2009;361:858–867. doi: 10.1056/NEJMoa0900428.
- Body R, Carley S, McDowell G, Jaffe AS, France M, Cruickshank K, Wibberley C, Nuttall M, Mackway-Jones K. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. *J Am Coll Cardiol*. 2011;58:1332–1339. doi: 10.1016/j.jacc.2011.06.026.
- Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:e344–e426. doi: 10.1161/CIR.0000000000000134.
- Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demerschall BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:870–947. doi: 10.1161/STR.0b013e318284056a.
- Scheitz JF, Nolte CH, Laufs U, Endres M. Application and interpretation of high-sensitivity cardiac troponin assays in patients with acute ischemic stroke. *Stroke*. 2015;46:1132–1140. doi: 10.1161/STROKEAHA.114.007858.
- Kerr G, Ray G, Wu O, Stott DJ, Langhorne P. Elevated troponin after stroke: a systematic review. *Cerebrovasc Dis*. 2009;28:220–226. doi: 10.1159/000226773.
- de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, Hashim I, Berry JD, Das SR, Morrow DA, McGuire DK. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA*. 2010;304:2503–2512. doi: 10.1001/jama.2010.1768.
- Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, Tjora S, Domanski MJ, Gersh BJ, Rouleau JL, Pfeffer MA, Braunwald E; Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial Investigators. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med*. 2009;361:2538–2547. doi: 10.1056/NEJMoa0805299.
- Lindahl B, Diderholm E, Lagerqvist B, Venge P, Wallentin L; FRISC II (Fast Revascularization during Instability in CAD) Investigators. Mechanisms behind the prognostic value of troponin T in unstable coronary artery disease: a FRISC II substudy. *J Am Coll Cardiol*. 2001;38:979–986.
- Scheitz JF, Mochmann HC, Nolte CH, Haeusler KG, Audebert HJ, Heuschmann PU, Laufs U, Witzendichler B, Schultheiss HP, Endres M. Troponin elevation in acute ischemic stroke (TRELAS): protocol of a prospective observational trial. *BMC Neurol*. 2011;11:98. doi: 10.1186/1471-2377-11-98.
- Twerenbold R, Jaffe A, Reichlin T, Reiter M, Mueller C. High-sensitive troponin T measurements: what do we gain and what are the challenges? *Eur Heart J*. 2012;33:579–586. doi: 10.1093/eurheartj/ehr492.
- Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atan D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020–2035. doi: 10.1161/CIR.0b013e31826e1058.
- Ambrose JA, Israel DH. Angiography in unstable angina. *Am J Cardiol*. 1991;68:78B–84B.
- Laufer EM, Mingels AM, Winkens MH, Joosen IA, Schellings MW, Leiner T, Wildberger JE, Narula J, Van Dieijen-Visser MP, Hofstra L. The extent of coronary atherosclerosis is associated with increasing circulating levels of high sensitive cardiac troponin T. *Arterioscler Thromb Vasc Biol*. 2010;30:1269–1275. doi: 10.1161/ATVBAHA.109.200394.
- Wong GC, Morrow DA, Murphy S, Krammer N, Pai R, James D, Robertson DH, Demopoulos LA, DiBattiste P, Cannon CP, Gibson CM. Elevations in troponin T and I are associated with abnormal tissue level perfusion: a TACTICS-TIMI 18 substudy: Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction. *Circulation*. 2002;106:202–207.
- Beigel R, Matetzky S, Gavrielov-Yusim N, Fefer P, Gottlieb S, Zahger D, Atar S, Finkelstein A, Roguin A, Goldenberg I, Kornowski R, Segev A; ACSIS and ACSIS-PCI 2010 Investigators. Predictors of high-risk angiographic findings in patients with non-ST-segment elevation acute coronary syndrome. *Catheter Cardiovasc Interv*. 2014;83:677–683. doi: 10.1002/ccd.25081.
- Dong L, Mintz GS, Witzendichler B, Metzger DC, Rinaldi MJ, Duffy PL, Weisz G, Stuckey TD, Brodie BR, Yun KH, Xu K, Kirtane AJ, Stone GW, Maehara A. Comparison of plaque characteristics in narrowings with ST-elevation myocardial infarction (STEMI), non-STEMI/unstable angina pectoris and stable coronary artery disease (from the ADAPT-DES IVUS Substudy). *Am J Cardiol*. 2015;115:860–866. doi: 10.1016/j.amjcard.2015.01.008.
- Maehara A, Mintz GS, Bui AB, Walter OR, Castagna MT, Canos D, Pichard AD, Satler LF, Waksman R, Suddath WO, Laird JR Jr, Kent KM, Weissman NJ. Morphologic and angiographic features of coronary plaque rupture detected by intravascular ultrasound. *J Am Coll Cardiol*. 2002;40:904–910.
- Samuels MA. The brain-heart connection. *Circulation*. 2007;116:77–84. doi: 10.1161/CIRCULATIONAHA.106.678995.
- Oppenheimer SM, Hachinski VC. The cardiac consequences of stroke. *Neurol Clin*. 1992;10:167–176.
- Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J*. 2008;155:408–417. doi: 10.1016/j.ahj.2007.11.008.
- Newby LK, Jesse RL, Babb JD, Christenson RH, De Fer TM, Diamond GA, Fesmire FM, Geraci SA, Gersh BJ, Larsen GC, Kaul S, McKay CR, Philippides GJ, Weintraub WS. ACCF 2012 expert consensus document on practical clinical considerations in the interpretation of troponin elevations: a report of the American College of Cardiology Foundation task force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2012;60:2427–2463. doi: 10.1016/j.jacc.2012.08.969.

23. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, Goto S, Liao CS, Richard AJ, Röther J, Wilson PW; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA*. 2006;295:180–189. doi: 10.1001/jama.295.2.180.
24. Amarenco P, Lavallée PC, Labreuche J, Ducrocq G, Juliard JM, Feldman L, Cabrejo L, Meseguer E, Guidoux C, Adraï V, Ratani S, Kusmirek J, Lapergue B, Klein IF, Gongora-Rivera F, Jaramillo A, Mazighi M, Touboul PJ, Steg PG. Prevalence of coronary atherosclerosis in patients with cerebral infarction. *Stroke*. 2011;42:22–29. doi: 10.1161/STROKEAHA.110.584086.
25. Calvet D, Touzé E, Varenne O, Sablayrolles JL, Weber S, Mas JL. Prevalence of asymptomatic coronary artery disease in ischemic stroke patients: the PRECORIS study. *Circulation*. 2010;121:1623–1629. doi: 10.1161/CIRCULATIONAHA.109.906958.
26. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, Folsom AR, Heiss G, Coresh J, Ballantyne CM. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation*. 2011;123:1367–1376. doi: 10.1161/CIRCULATIONAHA.110.005264.
27. Amarenco P, Lavallée PC, Labreuche J, Ducrocq G, Juliard JM, Feldman L, Cabrejo L, Meseguer E, Guidoux C, Adraï V, Ratani S, Kusmirek J, Lapergue B, Klein IF, Gongora-Rivera F, Jaramillo A, Abboud H, Olivet JM, Mazighi M, Touboul PJ, Steg PG. Coronary artery disease and risk of major vascular events after cerebral infarction. *Stroke*. 2013;44:1505–1511. doi: 10.1161/STROKEAHA.111.000142.
28. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:2071–2104. doi: 10.1161/CIR.0000000000000040.
29. Scheitz JF, Mochmann HC, Erdur H, Tütüncü S, Haeusler KG, Grittner U, Laufs U, Endres M, Nolte CH. Prognostic relevance of cardiac troponin T levels and their dynamic changes measured with a high-sensitivity assay in acute ischaemic stroke: analyses from the TRELAS cohort. *Int J Cardiol*. 2014;177:886–893. doi: 10.1016/j.ijcard.2014.10.036.
30. Koennecke HC, Belz W, Berfelde D, Endres M, Fitzek S, Hamilton F, Kreitsch P, Mackert BM, Nabavi DG, Nolte CH, Pöhls W, Schmehl I, Schmitz B, von Brevern M, Walter G, Heuschmann PU; Berlin Stroke Register Investigators. Factors influencing in-hospital mortality and morbidity in patients treated on a stroke unit. *Neurology*. 2011;77:965–972. doi: 10.1212/WNL.0b013e31822dc795.
31. Irie F, Kamouchi M, Hata J, Matsuo R, Wakisaka Y, Kuroda J, Ago T, Kitazono T; FSR Investigators. Sex differences in short-term outcomes after acute ischemic stroke: the Fukuoka Stroke Registry. *Stroke*. 2015;46:471–476. doi: 10.1161/STROKEAHA.114.006739.
32. Wildi K, Twerenbold R, Mueller C. How acute changes in cardiac troponin concentrations help to handle the challenges posed by troponin elevations in non-ACS-patients. *Clin Biochem*. 2015;48:218–222. doi: 10.1016/j.clinbiochem.2014.09.003.
33. Reichlin T, Twerenbold R, Wildi K, Rubini Gimenez M, Bergsma N, Haaf P, Druey S, Puelacher C, Moehring B, Freese M, Stelzig C, Krivoshei L, Hillinger P, Jäger C, Herrmann T, Kreutzinger P, Radosavac M, Weidmann ZM, Pershyna K, Honegger U, Wagener M, Vuillomenet T, Campodarve I, Bingisser R, Miró Ö, Rentsch K, Bassetti S, Osswald S, Mueller C. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. *CMAJ*. 2015;187:E243–E252. doi: 10.1503/cmaj.141349.
34. Gore MO, Seliger SL, Defilippi CR, Nambi V, Christenson RH, Hashim IA, Hoogeveen RC, Ayers CR, Sun W, McGuire DK, Ballantyne CM, de Lemos JA. Age- and sex-dependent upper reference limits for the high-sensitivity cardiac troponin T assay. *J Am Coll Cardiol*. 2014;63:1441–1448. doi: 10.1016/j.jacc.2013.12.032.
35. Omland T, de Lemos JA, Holmen OL, Dalen H, Benth JS, Nygård S, Hveem K, Røsjø H. Impact of sex on the prognostic value of high-sensitivity cardiac troponin I in the general population: the HUNT study. *Clin Chem*. 2015;61:646–656. doi: 10.1373/clinchem.2014.234369.
36. Twerenbold R, Wildi K, Jaeger C, Gimenez MR, Reiter M, Reichlin T, Walukiewicz A, Gugala M, Krivoshei L, Marti N, Moreno Weidmann Z, Hillinger P, Puelacher C, Rentsch K, Honegger U, Schumacher C, Zurbriggen F, Freese M, Stelzig C, Campodarve I, Bassetti S, Osswald S, Mueller C. Optimal cutoff levels of more sensitive cardiac troponin assays for the early diagnosis of myocardial infarction in patients with renal dysfunction. *Circulation*. 2015;131:2041–2050. doi: 10.1161/CIRCULATIONAHA.114.014245.
37. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Rosell Ortiz F, Ostojic M, Welsh RC, Carvalho AC, Nanay J, Arntz HR, Halvorsen S, Huber K, Grajek S, Fresco C, Bluhmki E, Regelin A, Vandenberghe K, Bogaerts K, Van de Werf F; STREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;368:1379–1387. doi: 10.1056/NEJMoa1301092.
38. Thiele H, Rach J, Klein N, Pfeiffer D, Hartmann A, Hambrecht R, Sick P, Eitel I, Desch S, Schuler G; LIPSIA-NSTEMI Trial Group. Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: the Leipzig Immediate versus early and late Percutaneous coronary Intervention trial in NSTEMI (LIPSIA-NSTEMI Trial). *Eur Heart J*. 2012;33:2035–2043. doi: 10.1093/eurheartj/ehr418.
39. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, Afzal R, Chrolavicius S, Jolly SS, Widimsky P, Avezum A, Rupprecht HJ, Zhu J, Col J, Natarajan MK, Horsman C, Fox KA, Yusuf S; TIMACS Investigators. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med*. 2009;360:2165–2175. doi: 10.1056/NEJMoa0807986.
40. Reith S, Battermann S, Hoffmann R, Marx N, Burgmaier M. Optical coherence tomography derived differences of plaque characteristics in coronary culprit lesions between type 2 diabetic patients with and without acute coronary syndrome. *Catheter Cardiovasc Interv*. 2014;84:700–707. doi: 10.1002/ccd.25267.
41. Madder RD, Smith JL, Dixon SR, Goldstein JA. Composition of target lesions by near-infrared spectroscopy in patients with acute coronary syndrome versus stable angina. *Circ Cardiovasc Interv*. 2012;5:55–61. doi: 10.1161/CIRCINTERVENTIONS.111.963934.

CLINICAL PERSPECTIVE

Current American Heart Association/American Stroke Association treatment guidelines recommend assessing cardiac troponin (cTn) levels in all patients presenting with acute ischemic stroke (AIS) to identify concurrent myocardial ischemia and to evaluate cardiovascular status. Because the underlying pathophysiology of cTn elevation in AIS is not necessarily acute coronary ischemia and aggressive antiplatelet therapy may cause harm, the treating physician is left in a clinical dilemma about the optimal timing and invasiveness of diagnostics and treatment. Here, we report the results of the Troponin Elevation in Acute Ischemic Stroke (TRELAS) study, a prospective, observational study with blinded end-point evaluation. The aim of the TRELAS study was to display the frequency of angiographic evidence of a coronary culprit lesion and of obstructive coronary artery disease in patients with AIS and cTn elevation (>50 ng/L) compared with age- and sex-matched patients with non-ST segment–elevation acute coronary syndrome. The major finding of the presented analysis is that patients with AIS were significantly less likely to have coronary culprit lesions compared with patients with non-ST segment–elevation acute coronary syndrome (24% versus 79%; $P < 0.001$) despite similar baseline cTn levels. Moreover, fewer patients with AIS had evidence of any obstructive coronary artery disease (52% versus 87%; $P = 0.021$) or multivessel disease (≥ 2 vessels diseased, 28% versus 62%; $P = 0.013$). Therefore, routine invasive diagnostic procedures in AIS patients with elevated cTn do not seem warranted. Further research is needed to define clinical or imaging predictors that allow better identification of AIS patients with elevated cTn resulting from potentially unstable coronary artery disease.