

Elevations in Troponin T and I Are Associated With Abnormal Tissue Level Perfusion

A TACTICS-TIMI 18 Substudy

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Background—Cardiac troponin T (cTnT) and I elevations are associated with a higher risk of adverse events, a higher incidence of multivessel disease, complex lesions, and visible thrombus in the setting of non-ST elevation (NSTEMI) acute coronary syndromes (ACS). Other pathophysiological mechanisms underlying troponin elevation remain unclear.

Methods and Results—We evaluated the relationship between troponin elevation and tissue level perfusion using the TIMI myocardial perfusion grade (TMPG) in 310 patients with NSTEMI-ACS in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction (TACTICS-TIMI) 18 trial. TMPG 0/1 (“closed” microvasculature) was observed more frequently in cTnT-positive patients both before (58.1% versus 42.1%; $P=0.007$) and after percutaneous coronary intervention (55.4% versus 35.6%; $P=0.004$). cTnT levels were higher among patients with TMPG 0/1 versus patients with TMPG 2/3 (0.50 versus 0.31 ng/mL; $P=0.006$). cTnT-positive patients were more likely to have thrombus (42.5% versus 29.3%), tighter stenoses (72.0% versus 64.8%), and higher rates of TIMI flow grade 0/1 (15.6% versus 7.0%; all $P<0.05$). TMPG 0/1 remained independently associated with cTnT elevation (odds ratio, 1.81; $P=0.02$), even after adjusting for epicardial TIMI flow grade, presence of thrombus, and prior myocardial infarction. TMPG 0/1 flow both before and after intervention was associated with increased risk of death or myocardial infarction at 6 months.

Conclusions—Similar to what has been observed in the setting of ST-elevation myocardial infarction, abnormal tissue level perfusion is also associated with adverse outcomes in the NSTEMI-ACS setting. Independent of the presence of thrombus and abnormal flow in the epicardial artery, impaired tissue level perfusion is associated with a 1.8-fold increased risk of cTnT elevation. (*Circulation*. 2002;106:202-207.)

Key Words: angina ■ perfusion ■ troponin ■ angiography ■ thrombosis

Cardiac troponins I and T (cTnI and cTnT) are sensitive and specific biomarkers for myocardial injury. Their elevation is associated with a higher risk of death and reinfarction among patients presenting with non-ST elevation acute coronary syndromes (NSTEMI-ACS).¹⁻⁴ In the setting of NSTEMI-ACS, troponin elevations are also associated with a higher incidence of multivessel disease, complex lesions, and visible thrombus.⁵⁻¹⁰ cTnT elevations have also been associated with abnormal coronary flow reserve after coronary intervention¹¹ and worse angiographic outcomes after primary percutaneous coronary intervention (PCI) for acute ST elevation myocardial infarction (MI).^{5,12}

The aim of this study was to extend previous angiographic observations by examining the relationship between elevations of troponin and tissue level perfusion as assessed using

the TIMI myocardial perfusion grade (TMPG)¹³ in a large cohort of NSTEMI-ACS patients. We hypothesized that elevated troponin levels would be associated with abnormal tissue level perfusion.

Methods

Study Population

The data were drawn from 310 angiographically evaluable patients randomized to the early invasive arm in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction (TACTICS-TIMI 18) trial, which has been described elsewhere.¹⁴ Briefly, TACTICS-TIMI 18 was a randomized controlled trial of patients with NSTEMI-ACS (unstable angina or NSTEMI-MI) that was designed to determine if an early invasive management strategy was superior to conservative (medical) treatment after treatment with the

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glycoprotein IIb/IIIa inhibitor tirofiban. Of the 2200 patients enrolled in TACTICS-TIMI 18, 1114 were randomized to the early invasive arm. All 165 centers in TACTICS-TIMI 18 were invited to participate in the angiographic substudy; there were no prespecified criteria for entry. Overall, 94 centers chose to participate. The current study population was comprised of the 310 patients in the invasive arm (28%) who participated in the angiographic substudy and had full available biomarker data and evaluable angiographic data. Patients randomized to the early invasive strategy were required to undergo coronary angiography within 4 to 48 hours of randomization with revascularization as appropriate. The conservative strategy allowed for coronary angiography only in patients who demonstrated objective evidence of recurrent ischemia, hemodynamic instability, or an abnormal discharge stress test (with or without imaging) after appropriate medical stabilization.

Troponin Testing

A baseline blood sample for cardiac markers was obtained, and serum was stored at -20°C or colder at the enrolling site until shipped to the TIMI Biomarker Core Laboratory at Children’s Hospital Medical Center (Boston, Mass), where samples were stored at -80°C. Samples were later analyzed in batch after a single thaw. cTnT was measured on the Elecsys 10/10 (Roche Diagnostics). The manufacturer has reported the minimal detectable concentration as 0.01 ng/mL and a coefficient of variation of 10% at 0.05 ng/mL. cTnI was measured using the ACS:180 Chemiluminescence cTnI Immunoassay (Bayer Diagnostics). The ACS:180 assay for cTnI is

TABLE 1. Clinical and Angiographic Characteristics According to cTnT Status

Variable (%)	Troponin-Positive (>0.01 ng/L)	Troponin-Negative (<0.01 ng/L)	P
n	194	116	
Age, y (mean)	61.8	62.3	
Male sex, %	71.1	53.4	0.002
Coronary risk factors, %			
Hypertension	61.9	69.0	0.21
Diabetes mellitus	23.7	25.0	0.80
Current smoker	34.0	20.7	0.01
Hypercholesterolemia	55.2	77.6	<0.01
Previous cardiac disease, %			
Previous MI	28.4	53.4	<0.01
Previous PCI	21.6	50.0	<0.01
Previous angina	8.2	22.4	<0.01
Admission ECG, %			
ST depression	42.8	25.0	0.02
T-wave inversion	35.5	31.9	0.92
Angiographic characteristics			
TIMI 3 flow, %	61.3	74.1	0.02
TIMI 2/3 flow, %	83.5	92.2	0.03
Median CTFC, No. of frames	36.5	26.5	<0.01
Visible thrombus, %	42.3	29.3	0.02
>70% stenosis in at least one vessel, %	56.8	39.1	<0.01
Number of diseased vessels, %			0.8*
Single vessel	39.2	44.0	
Double vessel	31.4	31.0	
Triple vessel	18.0	16.4	

CTFC indicates corrected TIMI frame count.
*3 way P value.

TABLE 2. Clinical and Angiographic Characteristics According to cTnI Status

Variable (%)	Troponin-Positive (>0.1 ng/L)	Troponin-Negative (<0.1 ng/L)	P
n	205	104	
Age, y (mean)	61.3	62.4	
Male sex, %	68.8	55.8	0.02
Coronary risk factors, %			
Hypertension	62.4	68.3	0.31
Diabetes mellitus	24.9	23.1	0.73
Current smoker	32.4	22.1	0.06
Hypercholesterolemia	57.6	76.0	<0.01
Previous cardiac disease, %			
Previous MI	29.3	54.8	<0.01
Previous PCI	22.9	50.1	<0.01
Previous angina	8.8	23.1	<0.01
Admission ECG, %			
ST depression	42.0	25.0	<0.01
T-wave inversion	31.7	32.7	0.86
Angiographic characteristics			
TIMI 3 flow, %	61.3	77.7	<0.01
TIMI 2/3 flow, %	85.3	92.2	0.08
Median CTFC, No. of frames	35.0	26.0	<0.01
Visible thrombus, %	41.6	29.8	0.05
>70% stenosis in at least one vessel, %	58.6	32.0	<0.01
Number of diseased vessels, %			0.48*
Single vessel	42.9	50.5	
Double vessel	36.4	32.3	
Triple vessel	20.7	17.2	

CTFC indicates corrected TIMI frame count.
*3 way P value.

an automated system using a 2-site sandwich immunoassay and direct chemiluminometric technology. The manufacturer reports the minimum detectable concentration as 0.03 ng/mL. The total imprecision determined in the core laboratory was characterized by a coefficient of variation of 10% at 0.4 ng/mL, 15% at 0.2 ng/mL, and 20% at 0.1 ng/mL.¹⁵ The thresholds used to define a positive cTnT or cTnI test were 0.01 ng/mL and 0.1 ng/mL, respectively as per previously established criteria.⁴ The median time from enrollment to blood sample draw was 3 minutes (25th and 75th percentiles, 28 and 47 minutes).

Angiographic Analysis

All coronary angiograms were evaluated at the TIMI Angiographic Core Laboratory without knowledge of clinical or troponin status. Flow in the epicardial arteries was assessed for TIMI flow grade¹⁶ and corrected TIMI frame count¹⁷ using previously described methods. The TMPG was used to assess myocardial tissue level perfusion.¹³ TMPG was previously defined as follows: grade 0, no angiographic blush; grade 1, stain or prolonged persistence of dye on next contrast injection; grade 2, slow dye transit, dye bright at the end of injection, gone by next injection; and grade 3, normal ground glass appearance of blush. A “closed” microvasculature was defined as either TMPG 0 or 1, with TMPG 2 or 3 representative of an “open” microvasculature. TMPG was assessed only in the area supplied by the culprit vessel. The culprit vessel was identified by the on-site operator; interventions were performed on the vessel

TABLE 3. Comparison Between Patients in Angiographic Substudy and Remaining Patients in TACTICS Trial

	Angiographic Substudy (n=310)	Not in Substudy (n=1910)	P
Age, y (mean)	61.7	61.8	0.82
Male sex, %	64.5	66.1	0.58
Coronary risk factors, %			
Hypertension	64.5	66.3	0.53
Diabetes mellitus	24.2	28.2	0.15
Current smoker	29.1	27.3	0.51
Hypercholesterolemia	63.6	60.2	0.26
Previous cardiac disease, %			
Previous MI	37.7	39.2	0.62
Previous angina	13.6	12.8	0.63
Admission ECG, %			
ST depression	36.1	38.7	0.38
T-wave inversion	32.3	35.2	0.32
Troponin status, %			
Troponin I >0.1 ng/mL	66.4	58.4	0.009
Troponin T >0.01 ng/mL	62.6	52.3	0.001

when judged clinically appropriate given the patient's angiographic, ECG, and clinical data.

Statistical Analysis

Continuous variable values were reported as the mean±SD. ANOVA or the Wilcoxon rank sum test were used to analyze continuous variables. The corrected TIMI frame count was analyzed using the Wilcoxon rank sum test with a frame count of 100 given to patients with an occluded vessel. Other categorical variables were compared using the χ^2 test. The primary analysis in this study was based on the dichotomous comparison of patients with positive or negative troponin results using the cut points of 0.1 ng/mL and 0.01 ng/mL for cTnI and cTnT, respectively.⁴ Multivariable evaluation of the association between TMPG and cTnT and cTnI was performed using logistic regression. All analyses were performed using Stata version 7.0.¹⁸

Results

Baseline Clinical Characteristics

Clinical and angiographic characteristics of the 310 evaluable patients according to baseline cTnT and cTnI are summarized

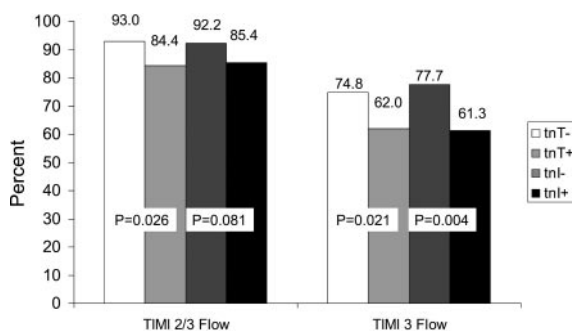


Figure 1. Pre-PCI epicardial flow characteristics stratified by cTnT and cTnI status. Patients with elevated cTnT and cTnI had lower rates of both TIMI 2/3 and TIMI 3 grade flow.

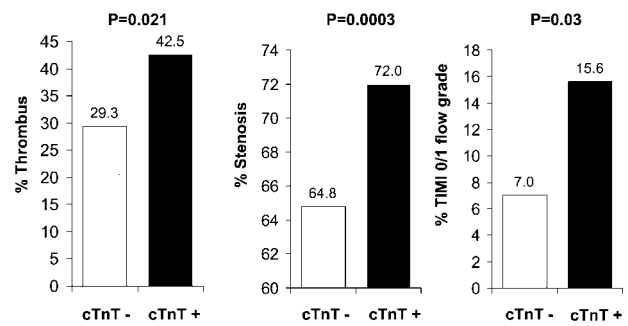


Figure 2. Rate of angiographically evident thrombus, percent stenosis of the disease-related epicardial artery, and the rate of TIMI 0/1 epicardial flow before PCI stratified by cTnT status. cTnT-positive patients had more severe epicardial disease than cTnT-negative patients.

in Tables 1 and 2, respectively. There was no difference in the duration of tirofiban therapy before angiography between troponin-positive and troponin-negative patients. Troponin-positive patients were more often male and were less likely to have a history of MI, percutaneous coronary transluminal angiography, and angina before enrollment. ST segment depression at presentation was observed more frequently among troponin-positive patients. Patients enrolled in the angiographic substudy had clinical and electrocardiographic characteristics similar to other patients in the TACTICS-TIMI 18 trial (Table 3), although patients in the substudy were more likely to have elevated cTnT and cTnI.

Angiographic Findings and Troponin Levels

A total of 258 of the 310 patients (83.2%) underwent PCI, and 226 patients (87.6%) had TIMI 3 flow after PCI. cTnT-positive patients were less likely to have patent (TIMI 2/3) epicardial arteries before intervention (84.4% versus 93.0%; $P=0.026$) or normal epicardial (TIMI 3) flow (62.0% versus 74.8%; $P=0.021$) compared with cTnT-negative patients (Figure 1). cTnT-positive patients also had a higher incidence of thrombus (42.5%; [82 of 193] versus 29.3% [34 of 116]; $P=0.021$); tighter percent stenoses (72.0±16.3% versus 64.8±17.1%; $P=0.0003$), and higher rates of vessel occlusion (TIMI epicardial grade 0/1 flow: 15.6% [30 of 192] versus 7.0% [8 of 115]; $P=0.026$) compared with cTnT-

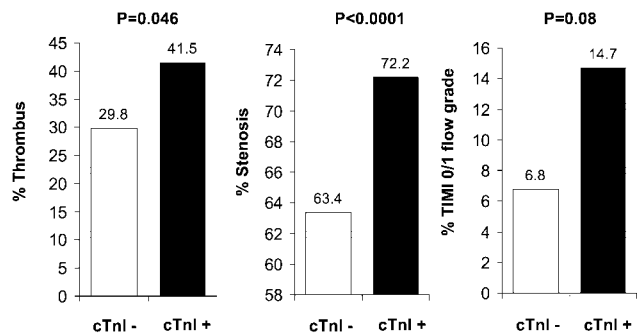


Figure 3. Percent stenosis of the disease-related epicardial artery and rates of angiographically evident thrombus and TIMI 0/1 epicardial flow before PCI stratified by cTnI status. cTnI-positive patients had more severe epicardial disease than cTnI-negative patients.

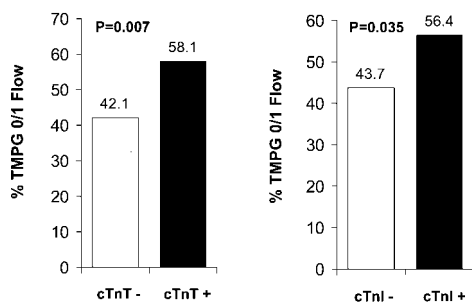


Figure 4. Rate of pre-PCI TMPG 0/1 flow, stratified by cTnT and cTnI status. Abnormal tissue level perfusion before PCI was more frequent among patients with elevated cTnT and cTnI.

negative patients (Figure 2). Similar findings were observed in relation to cTnI (Figure 3). cTnI-positive patients were also significantly more likely than cTnI-negative patients to have angiographically evident thrombus (41.5% versus 29.8%; $P=0.046$), tighter percent epicardial stenoses ($72.2 \pm 15.8\%$ versus $63.4 \pm 17.7\%$; $P<0.0001$), and a trend toward higher rates of TIMI flow grade 0/1 flow (14.7% versus 6.8%; $P=0.08$).

cTnT-positive patients were more likely to have a closed microvasculature (TMPG 0/1 perfusion) before intervention than cTnT-negative patients (58.1% [111 of 191] versus 42.1% [48 of 114]; $P=0.007$) (Figure 4). TMPG 0/1 perfusion was also observed more frequently among cTnI-positive patients compared with cTnI-negative patients (56.4% [114 of 202] versus 43.7% [45 of 103]; $P=0.035$) (Figure 4). After successful PCI (the achievement of TIMI 3 flow), patients who were troponin-positive were at higher risk for having a closed myocardium (TMPG 0/1) after the procedure (cTnT: 55.4% versus 35.6%, $P=0.004$; cTnI: 54.1% versus 36.7%, $P=0.013$) (Figure 5). Quantitatively, cTnT levels were significantly higher in patients with TMPG 0/1 perfusion (mean, 0.50; median, 0.14) compared with those with TMPG 2/3 perfusion (mean, 0.31; median, 0.03; $P=0.006$) (Figure 6). A similar association was observed with cTnI.

Patients with TMPG 0/1 flow before and after successful PCI were at increased risk of death or MI at 6 months ($P=0.026$) compared with patients with TMPG 2/3 flow at either time (Figure 7). A multivariate model demonstrated that the presence of a closed microvasculature (TMPG 0/1)

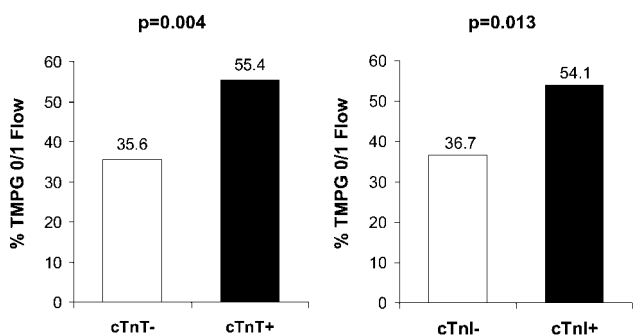


Figure 5. Rate of TMPG 0/1 flow among patients with TIMI flow grade 3 after PCI, stratified by cTnT and cTnI status. Abnormal tissue level perfusion after successful PCI was more frequent among patients with elevated troponins.

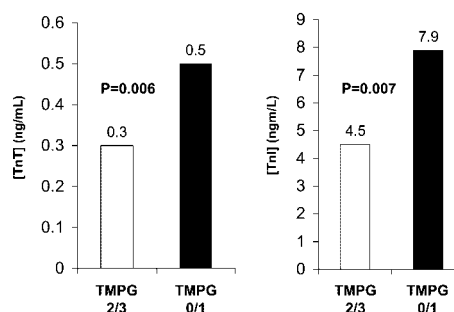


Figure 6. Peak cTnT and cTnI levels stratified by TMPG status. Patients with abnormal tissue level perfusion had higher levels of cTnT and cTnI compared with patients with normal tissue level perfusion.

was independently associated with cTnT elevation >0.01 ng/mL (odds ratio, 1.81; $P=0.02$) after adjusting for epicardial TIMI flow grade ($P=0.19$), thrombus ($P=0.25$), and prior MI ($P<0.001$). A similar trend was also seen for cTnI (odds ratio, 1.56; $P=0.082$) after adjusting for TIMI flow grade ($P=0.34$), presence of thrombus ($P=0.27$), and prior MI ($P<0.001$).

Discussion

Elevations in cardiac troponins identify a high-risk subgroup of patients who present with unstable angina or MI without ST elevation.¹⁻³ These patients have more extensive coronary artery disease, more complex and severe coronary lesions, and a greater burden of intracoronary thrombus⁵⁻¹⁰ on coronary arteriography.

The present report is consistent with these previous observations: a greater impairment of epicardial flow and a greater thrombus burden was present among cTnT- and cTnI-positive patients. However, these data also demonstrate that elevations in troponin are associated with angiographically abnormal tissue level perfusion, which persisted even after controlling for epicardial flow grade and presence of thrombus. Thus, these data extend previous observations relating troponin elevations to disease in the epicardial arteries to demonstrate an additional impairment in tissue level perfusion on diag-

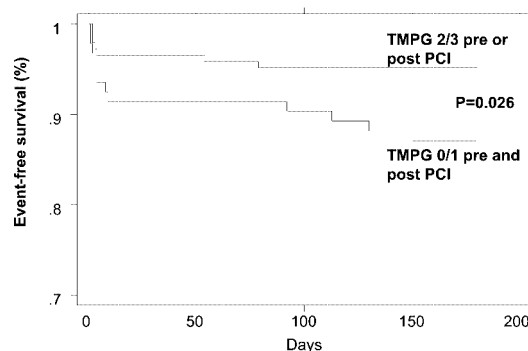


Figure 7. Event-free survival (death or MI) through 6 months of follow-up, stratified by TMPG flow. The presence of TMPG 0/1 flow before and after successful PCI ($n=93$) was associated with higher rates of death or MI through 6 months compared with patients without TMPG 0/1 flow before or after PCI ($n=145$).

nostic angiography. Abnormal tissue perfusion before and after successful PCI was in turn associated with a higher incidence of death or MI at 6 months.

The findings relating abnormal tissue level perfusion on diagnostic angiography extend our recent report regarding the release of creatine kinase (CK)-MB after PCI in the Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrillin Therapy (ESPRIT) substudy.¹⁹ The post-PCI release of CK-MB was not explained by TIMI grade 3 flow, because 100% of patients had TIMI grade 3 flow at the completion of PCI. In contrast, tissue level perfusion using TMPG was related to postintervention CK-MB release: only 4.2% of patients with normal tissue level perfusion had CK-MB leak >2 times the upper limit of normal, compared with 41.2% of patients with impaired tissue level perfusion ($P=0.002$). Thus, abnormalities in tissue level perfusion rather than epicardial artery perfusion seem to explain the release of CK-MB after PCI. Taken together, these 2 studies indicate that troponin elevation on presentation is related to impaired tissue level perfusion on the diagnostic angiogram and, after PCI, impaired tissue level perfusion is related to the release of CK-MB. In both studies, impaired tissue level perfusion was related to long-term clinical outcomes.

The principal mechanism underlying the pathophysiology of impaired myocardial perfusion in the setting of ACS remains unclear. Impaired myocardial perfusion may be explained by embolization of platelet aggregates to the microvasculature.²⁰ Supportive evidence of platelet-dependent microembolization of thrombi has come from both animal²¹ and human necropsy studies.²² Insofar as the relationship of troponin release to tissue level perfusion was independent of other angiographic features such as thrombus and epicardial flow, mechanisms other than mechanical embolization, such as capillary edema, inflammation, and vasospasm mediated by the release of vasoconstrictors, may play at least some role. Release of vasoactive products such as serotonin, thromboxane, and endothelin from activated platelets may be associated with microcirculatory spasm, continued thrombosis, and further deterioration of microvascular flow.²³ Significant impairment of myocardial flow may eventually lead to irreversible myocardial necrosis, which is detectable with serum biomarkers such as troponin.

Alternatively, impaired myocardial flow may result from reperfusion injury. Coronary occlusion that is associated with significant myocardial damage may also be associated with disruption of the surrounding microvascular integrity.^{24,25} A complex process involving platelets, neutrophils, oxygen radicals, complement, and other inflammatory mediators may then result in localized inflammation and worsening of microvascular obstruction.²³ The inflammatory consequences of microvascular dysfunction may then further limit the extent of blood flow at the tissue level after epicardial reperfusion, leading to further myocardial necrosis. Accordingly, the no-reflow phenomenon has been associated with more extensive necrosis and is associated with regional and global ventricular dysfunction.^{25,26}

Limitations

This data were drawn from a substudy of a randomized trial, and the analysis of tissue level perfusion was performed

retrospectively because this parameter of perfusion was developed after the initiation of the trial. Analyses pertaining to epicardial flow and troponin release were, however, prospectively defined. Troponin data were available at baseline only. It is not known if patients who were troponin negative initially may have had troponin elevation at a later time point.

Conclusions

Independent of the presence of thrombus and abnormal flow in the epicardial artery, impaired tissue level perfusion is associated with a 1.8-fold increased risk of cTnT elevation. Impaired tissue level perfusion before and persisting after successful PCI was associated with an increased risk of death or MI at 6 months. Future studies into strategies to reduce troponin elevation and improve myocardial perfusion in the setting of NSTEMI-ACS are warranted.

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