

JAMA | Original Investigation

Effect of Low-Dose Intracoronary Alteplase During Primary Percutaneous Coronary Intervention on Microvascular Obstruction in Patients With Acute Myocardial Infarction A Randomized Clinical Trial

Peter J. McCartney, MBChB; Hany Eteiba, MD; Annette M. Maznyczka, MBChB; Margaret McEntegart, PhD; John P. Greenwood, PhD; Douglas F. Muir, MBChB; Saqib Chowdhary, PhD; Anthony H. Gershlick, MBBS; Clare Appleby, PhD; James M. Cotton, MD; Andrew Wragg, PhD; Nick Curzen, PhD; Keith G. Oldroyd, MD (Hons); Mitchell Lindsay, MD; J. Paul Rocchiccioli, MD; Aadil Shaukat, MBBS; Richard Good, MD; Stuart Watkins, MD; Keith Robertson, PhD; Christopher Malkin, MD; Lynn Martin, BN; Lynsey Gillespie, PhD; Thomas J. Ford, MBChB; Mark C. Petrie, MBChB; Peter W. Macfarlane, DSc; R. Campbell Tait, MBChB; Paul Welsh, PhD; Naveed Sattar, PhD; Robin A. Weir, MD; Keith A. Fox, MBChB; Ian Ford, PhD; Alex McConnachie, PhD; Colin Berry, PhD; for the T-TIME Group

IMPORTANCE Microvascular obstruction commonly affects patients with acute ST-segment elevation myocardial infarction (STEMI) and is associated with adverse outcomes.

OBJECTIVE To determine whether a therapeutic strategy involving low-dose intracoronary fibrinolytic therapy with alteplase infused early after coronary reperfusion will reduce microvascular obstruction.

DESIGN, SETTING, AND PARTICIPANTS Between March 17, 2016, and December 21, 2017, 440 patients presenting at 11 hospitals in the United Kingdom within 6 hours of STEMI due to a proximal-mid-vessel occlusion of a major coronary artery were randomized in a 1:1:1 dose-ranging trial design. Patient follow-up to 3 months was completed on April 12, 2018.

INTERVENTIONS Participants were randomly assigned to treatment with placebo (n = 151), alteplase 10 mg (n = 144), or alteplase 20 mg (n = 145) by manual infusion over 5 to 10 minutes. The intervention was scheduled to occur early during the primary PCI procedure, after reperfusion of the infarct-related coronary artery and before stent implant.

MAIN OUTCOMES AND MEASURES The primary outcome was the amount of microvascular obstruction (% left ventricular mass) demonstrated by contrast-enhanced cardiac magnetic resonance imaging (MRI) conducted from days 2 through 7 after enrollment. The primary comparison was the alteplase 20-mg group vs the placebo group; if not significant, the alteplase 10-mg group vs the placebo group was considered a secondary analysis.

RESULTS Recruitment stopped on December 21, 2017, because conditional power for the primary outcome based on a prespecified analysis of the first 267 randomized participants was less than 30% in both treatment groups (futility criterion). Among the 440 patients randomized (mean age, 60.5 years; 15% women), the primary end point was achieved in 396 patients (90%), 17 (3.9%) withdrew, and all others were followed up to 3 months. In the primary analysis, the mean microvascular obstruction did not differ between the 20-mg alteplase and placebo groups (3.5% vs 2.3%; estimated difference, 1.16%; 95% CI, -0.08% to 2.41%; $P = .32$) nor in the analysis of 10-mg alteplase vs placebo groups (2.6% vs 2.3%; estimated difference, 0.29%; 95% CI, -0.76% to 1.35%; $P = .74$). Major adverse cardiac events (cardiac death, nonfatal MI, unplanned hospitalization for heart failure) occurred in 15 patients (10.1%) in the placebo group, 18 (12.9%) in the 10-mg alteplase group, and 12 (8.2%) in the 20-mg alteplase group.

CONCLUSIONS AND RELEVANCE Among patients with acute STEMI presenting within 6 hours of symptoms, adjunctive low-dose intracoronary alteplase given during the primary percutaneous intervention did not reduce microvascular obstruction. The study findings do not support this treatment.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: [NCT02257294](https://clinicaltrials.gov/ct2/show/study/NCT02257294)

JAMA. 2019;321(1):56-68. doi:10.1001/jama.2018.19802

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The T-TIME Group members are listed at the end of this article.

Corresponding Author: Colin Berry, PhD, British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, 126 University Pl, University of Glasgow, Glasgow, G12 8TA, Scotland, United Kingdom (colin.berry@glasgow.ac.uk).

Ischemic heart disease is the leading cause of disability¹ and death² worldwide. Acute coronary thrombosis causes ST-segment elevation myocardial infarction (STEMI) and primary percutaneous coronary intervention (PCI) to emergently reopen the occluded coronary artery and secure vessel patency with a stent is the evidence-based standard of care.³ Primary PCI is routinely successful and normalized coronary blood flow is typically achieved in 91% of patients.⁴ However, failed microvascular reperfusion has been estimated to occur in 45% of all treated patients.^{5,6} This complication, described as microvascular obstruction, is independently predictive of an unfavorable cardiac prognosis.⁷ During primary PCI, distal embolization of thrombus from the lumen of the main coronary artery and microvascular thrombosis,⁸⁻¹² notably of fibrin-rich microthrombi,^{9,12} contribute to microvascular obstruction. Clinicians lack the therapeutic tools to treat microvascular obstruction.³

Fibrinolytic therapy is also an effective treatment for acute coronary thrombosis.¹³ A facilitated PCI strategy involving full- or half-dose adjunctive fibrinolytic therapy given before PCI with stenting improves coronary flow acutely.^{14,15} However, combination-facilitated PCI involving either full-dose¹⁶ or half-dose lytic therapy¹⁷ causes paradoxical activation of thrombin, clot formation, and bleeding. Sezer et al¹⁵ modified this strategy by administering adjunctive low-dose thrombolytic therapy with 250 kU of streptokinase at the end of primary PCI. This approach appeared to improve myocardial reperfusion. Since then, fibrin-specific fibrinolytic drugs and antithrombotic pharmacotherapy for STEMI have evolved.

T-TIME investigated whether a therapeutic strategy involving low-dose intracoronary fibrinolytic therapy with alteplase infused early after coronary reperfusion would prevent and reduce microvascular obstruction.

Methods

Trial Design

This was a randomized, double-blind, parallel-group phase 2 clinical trial of low-dose adjunctive alteplase during primary PCI.

Informed Consent and Study Protocol

Screening, witnessed verbal informed consent, study drug administration, and acute assessments of efficacy took place during the standard of care primary PCI. The protocol and statistical analysis plan are provided in [Supplements 1 and 2](#). The trial was reviewed and approved by an ethics committee of the West of Scotland Research Ethics Service (13-WS-0119), adhered to Guidelines for Good Clinical Practice in Clinical Trials,¹⁸ and complied with the Declaration of Helsinki.¹⁹

Participants and Eligibility Criteria

Patients with a clinical diagnosis of acute STEMI with persistent ST-segment elevation or recent left bundle-branch block with a symptom onset to reperfusion time of 6 hours or less were potentially eligible for randomization. Radial artery access was a requirement, and further angiographic criteria in-

Key Points

Question In patients undergoing primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction (STEMI), does adjunctive fibrinolytic therapy with low-dose intracoronary alteplase given after reperfusion and before stent implant reduce microvascular obstruction?

Findings In this randomized clinical trial that included 440 participants randomized to receive alteplase 20 mg, alteplase 10 mg, or placebo, the primary analysis demonstrated that the amount of microvascular obstruction (% left ventricular mass) revealed by magnetic resonance imaging was 3.5% in the alteplase 20-mg group and 2.3% in the placebo group, a difference that was not statistically significant.

Meaning Adjunctive low-dose intracoronary alteplase given early during primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction did not reduce microvascular obstruction.

cluded a proximal-mid coronary artery occlusion (TIMI coronary flow grade 0 or 1) or, impaired coronary flow (TIMI flow grade 2, slow but complete filling) in the presence of definite angiographic evidence of thrombus (TIMI grade ≥ 2) in a major coronary artery. Key exclusion criteria were a functional coronary collateral supply (Rentrop grade ≥ 2) to the infarct-related artery, any contraindication to fibrinolysis, and lack of informed consent. The exclusion criteria are described in [Supplement 3](#).

Race/ethnicity was designated by the patient and recorded by the local investigator to provide information on the participation of individuals with different ethnicity.

Setting

The participants were enrolled in 11 hospitals in the United Kingdom and guideline-based medical and invasive management was recommended.³ Enrollment started on March 17, 2016.

Randomization, Implementation, and Blinding

Participants were randomized by staff in the catheter laboratory using an interactive voice response-based randomization system. The randomization sequence was computer generated, using the method of randomized permuted blocks of length 6, with stratification by location of STEMI (anterior vs nonanterior) and study site ([Figure](#)). The allocation sequence was on a 1:1:1 basis between the placebo and alteplase (10 mg, 20 mg) groups and the sequence was concealed electronically. The participants, staff, and researchers were blinded to the treatment group allocation.

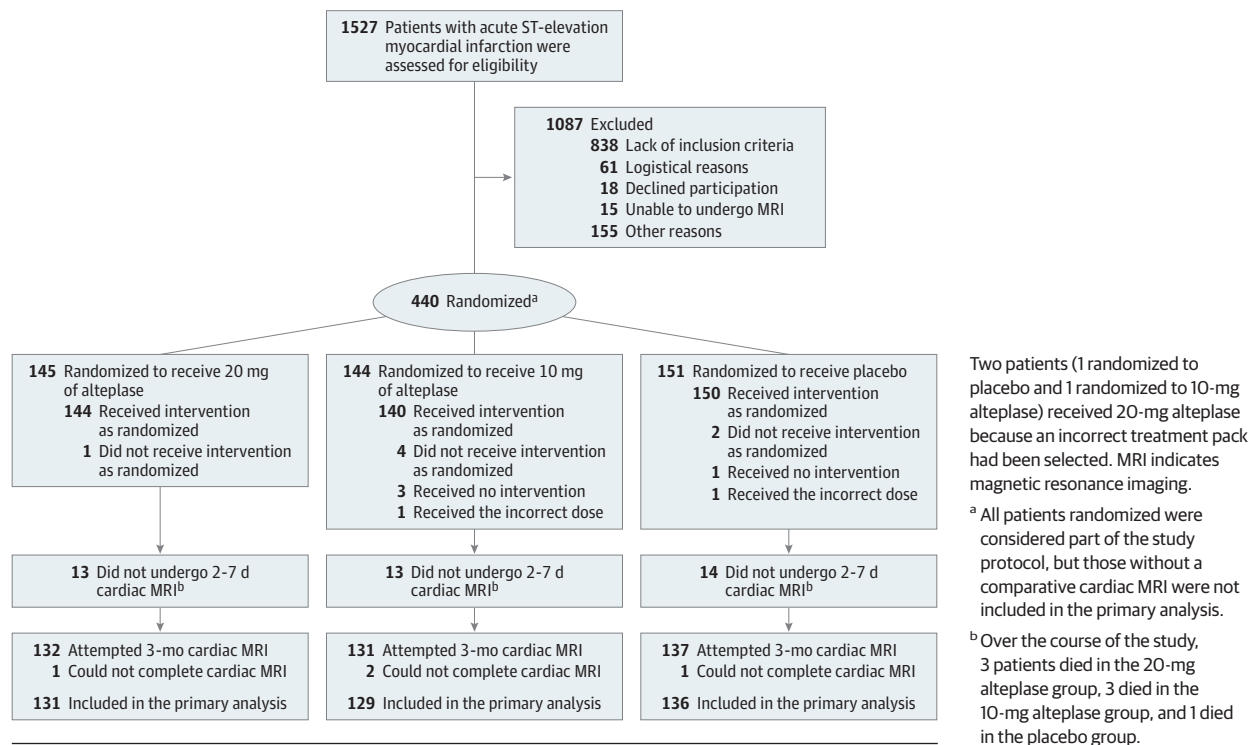
Standard Care

Primary PCI followed contemporary practice guidelines³ ([Supplement 3](#)).

Interventions

After successful reperfusion (TIMI flow grade ≥ 2), the participants received the allocated intervention immediately in the catheter laboratory. The study drug (placebo, alteplase 10 mg, or alteplase 20 mg) was manually infused before implanting

Figure. Patient Recruitment, Randomization, and Flow Through T-TIME Study



the stent. The drug was reconstituted by the clinical staff using 20 mL of sterile water for injection. The cardiologist then infused the solubilized drug over 5 to 10 minutes directly into the infarct-related artery proximal to the culprit lesion using either an intracoronary catheter or the guiding catheter if selectively engaged.

Outcomes

The methods for the assessments of the primary and secondary outcomes are described in Supplement 3.

Primary Outcome

The primary outcome was the amount of microvascular obstruction (% of left ventricular mass) demonstrated by late gadolinium-enhanced magnetic resonance image (MRI) 10 to 15 minutes after administration of contrast media. Cardiac MRI at 1.5 T was scheduled during the index hospitalization, from days 2 through 7 after enrollment.

Secondary Outcomes

Magnetic resonance imaging secondary outcomes included microvascular obstruction (presence/absence), myocardial hemorrhage (presence/absence), and the amount of myocardial hemorrhage expressed as a percentage of left ventricular mass on MRI from days 2 through 7. Infarct size expressed as a percentage of left ventricular mass, myocardial salvage index, left ventricular end-diastolic volume, left ventricular end-systolic volume, and left ventricular ejection fraction were obtained on days 2 through 7 and at 3 months.

Angiographic measures of reperfusion (TIMI coronary flow grade, TIMI myocardial perfusion grade, TIMI frame count) and

TIMI thrombus grade at the end of PCI were predefined secondary outcomes.

The percentage ST-segment resolution on an electrocardiogram (ECG) obtained 60 minutes after reperfusion vs before reperfusion and final infarct size revealed by the Svelster QRS score at 3 months were also calculated.

Troponin T area under the curve (AUC) was measured from blood samples obtained immediately before reperfusion (0 hours) and then again at 2 hours and at 24 hours. N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured from days 2 through 7 and at 3 months after reperfusion, scheduled at the time of MRI.

Health Status

Health-related quality of life (HRQoL; EuroQol 5-Dimensions 3-Level [EQ-5D-3L]) was recorded from days 2 through 7 and 3 months after the MI. The EQ-5D is a standardized instrument used as a measure of health outcome, made up of the following 2 components: first, the health utility score, a descriptive system comprising 5 dimensions—mobility, self-care, usual activities, pain or discomfort, and anxiety or depression; scores for each are combined to give a maximum value of 1. Second, the visual analog scale reports the patient’s self-rated health on a visual analog scale from 0 (worst imaginable) to 100 (best health imaginable).

Bleeding and Coagulation

Fibrinogen and other parameters of coagulation and hemostasis served as surrogate measures of bleeding risk.^{20,21} These parameters were measured in blood samples when site logistics permitted blood sample collection. The sampling time

points were at baseline before reperfusion (0 hours) and 2, and 24 hours after reperfusion. The parameters included fibrinogen and plasminogen (both measures of coagulation and systemic fibrinolysis), fibrin D-dimer (a measure of fibrin lysis), tissue plasminogen activator (a measure of endogenous tissue plasminogen activator and any circulating alteplase), and prothrombin fragment₁₊₂ (a measure of thrombin activation).

Adverse Events

The adverse events and their definitions are listed in [Supplement 3](#). A major adverse cardiovascular event (MACE) was defined as cardiovascular death, nonfatal myocardial infarction, or unplanned hospitalization for heart failure. Acute cerebrovascular and systemic bleeds were defined using the Bleeding Academic Research Consortium (BARC) criteria.²² All of these events were adjudicated by a clinical event committee who were independent of the trial and blinded to the treatment allocation. Longer-term follow-up of health outcomes (12 months, 3 years) blind to treatment group assignment is ongoing.

Trial Coordination

An independent data and safety monitoring committee and a trial steering committee coordinated the trial and communicated with the sponsor.

Sample Size and Statistical Methods

The target sample size was 618, based on obtaining 186 per group who had undergone an MRI within days 2 through 7 after enrollment, allowing for approximately 10% missing data. This was designed to give 90% power at a 5% significance level, to detect a difference between 2 groups of 1.72%, assuming a mean (SD) of 3.2% (5.1%) for the extent of microvascular obstruction in the comparator group. This calculation was based on the amount of microvascular obstruction demonstrated in the subgroup of patients enrolled into the MR-MI cohort study²³ who fulfilled the enrollment criteria for T-TIME.

Efficacy analyses were analyzed according to randomization group, that is, in relation to randomized treatment allocation regardless of treatment received. Safety data were analyzed in relation to treatment received.

The primary outcome (extent of microvascular obstruction on MRI within days 2 through 7, as % of left ventricular mass) was compared between groups using a stratified Wilcoxon test (van Elteren test), stratified by the location of the MI. Ninety-five percent confidence intervals for between-group differences in the mean extent of microvascular obstruction were derived by bootstrap resampling (10 000 replicates), stratified by location of the MI; percentile confidence intervals are reported. The primary analysis was to compare the 20-mg alteplase group with the placebo group; if this was significant at a 5% level, then the 10-mg alteplase group would be compared with the placebo group as a primary analysis. This hierarchical approach was used to preserve the overall type I error rate at 5%. However, if the 20-mg vs placebo comparison was not significant, the 10-mg vs placebo comparison would be considered a secondary analysis. Primary and secondary outcomes were also ana-

lyzed using linear regression (continuous outcomes), logistic regression (binary outcomes), or proportional odds logistic regression (ordinal outcomes). All models were adjusted for the location of the MI. In linear regression models for continuous outcome measures, data were transformed where necessary, to improve model residual distributions, and were further adjusted for the baseline value of the outcome (where appropriate). For the primary outcome, a post hoc analysis was performed with multiple imputation for the missing outcomes. Regression models were used to assess treatment effects within prespecified subgroups through the use of treatment-by-subgroup interactions. Further details are provided in [Supplement 3](#). All tests were 2-tailed and assessed at the 5% significance level. Missing outcome data were not imputed. Because of the potential for type I error in the analyses of secondary end points, these end points should be interpreted as exploratory. All statistical analyses were carried out with R v3.2.4 (R Development Core Team 2015) according to a prespecified statistical analysis plan.

Prespecified Futility Analysis

The funder, the Efficacy and Mechanism Evaluation (EME) program of the National Institute for Health Research (NIHR), required an interim analysis for futility and specified the criteria before the start of the trial. This analysis was scheduled for when approximately 40% of patients had been randomized and followed up to 3 months. Considering the primary outcome, each active treatment group was compared with the placebo group, and if the conditional power for showing a benefit over placebo based on the current trend was less than 30%, then a recommendation would be made to halt that group.

Results

On the recommendation of the data and safety monitoring committee, recruitment was discontinued on December 21, 2017, because a prespecified futility criterion for efficacy was met. Specifically, the conditional power for an analysis on the primary efficacy outcome based on 40% of the randomized population ($n = 267$) with follow-up to 3 months was less than 30% in both treatment groups.

By that time, 1527 patients undergoing primary PCI for acute STEMI had been screened (Figure) and 440 patients (mean age, 60.5 years; 15% women) had been randomized (151 placebo, 144 alteplase 10 mg, and 145 alteplase 20 mg) ([Table 1](#)). Seventeen patients (3.9%) withdrew from the study during follow-up. All the other participants were followed up for 3 months. The final follow-up took place on April 12, 2018.

Study Intervention

The standard of care procedure and study intervention are illustrated in [Supplement 3](#) and summarized in [Table 2](#). Adjunctive study drug therapy was administered to 435 patients (98.9%); 5 patients did not receive any drug (Figure). Two patients (1 randomized to placebo and 1 randomized to 10-mg alteplase) received 20-mg alteplase because an incorrect treatment pack had been selected.

Table 1. Baseline Clinical and Treatment Characteristics of the Randomized Participants (N = 440)

Baseline Characteristics	No. (%) of Patients		
	Placebo (n = 151)	Alteplase, 10 mg (n = 144)	Alteplase, 20 mg (n = 145)
Demographics			
Age, mean (SD), y	60.7 (11.0)	59.6 (10.3)	61.2 (9.7)
Men	127 (84.1)	124 (86.1)	123 (84.8)
Women	24 (15.9)	20 (13.9)	22 (15.2)
White	143 (94.7)	134 (93.1)	136 (93.8)
Asian	7 (4.6)	9 (6.3)	8 (5.5)
BMI, mean (SD)	28.4 (5.3)	28.5 (4.8)	27.8 (4.4)
Presenting characteristics, mean (SD)			
Heart rate, beat/min	73.3 (22.5)	71.8 (15.9)	73.5 (17.6)
Systolic blood pressure, mm Hg	132 (26)	135 (25)	134 (25)
Diastolic blood pressure, mm Hg	79 (17)	80 (15)	81 (15)
Infarct location			
Anterior	65 (43.0)	62 (43.1)	64 (44.1)
Inferior	70 (46.4)	67 (46.5)	70 (48.3)
Lateral	1 (0.7)	2 (1.4)	0
Posterior	14 (9.3)	11 (7.6)	8 (5.5)
Other	1 (0.7)	2 (1.4)	3 (2.1)
Medical history			
Hypertension ^a	47 (31.1)	45 (31.2)	49 (33.8)
Renal impairment ^b	2 (1.3)	3 (2.1)	1 (0.7)
Diabetes mellitus ^{a,c}	19 (12.6)	19 (13.2)	18 (12.4)
Hypercholesterolemia ^a	42 (27.8)	28 (19.4)	32 (22.1)
Smoking^a			
Current	75 (49.7)	72 (50.0)	62 (42.8)
Former (stopped >3 mo)	27 (17.9)	22 (15.3)	35 (24.1)
Never	49 (32.5)	50 (34.7)	48 (33.1)
Percutaneous coronary intervention	8 (5.3)	5 (3.5)	7 (4.8)
Angina	6 (4.0)	7 (4.9)	4 (2.8)
Myocardial infarction	6 (4.0)	6 (4.2)	8 (5.5)
Stroke or transient ischemic attack ^a	2 (1.3)	1 (0.7)	2 (1.4)
Peripheral vascular disease ^a	3 (2.0)	3 (2.1)	6 (4.1)
Preexisting maintenance medication			
Aspirin	27 (17.9)	17 (11.8)	22 (15.2)
P2Y₁₂ inhibitor			
Clopidogrel	1 (0.7)	0 (0.0)	1 (0.7)
Ticagrelor or prasugrel	9 (6.0)	4 (2.8)	7 (4.8)
Statin	40 (26.5)	29 (20.1)	28 (19.3)
β-Blocker	17 (11.3)	15 (10.4)	10 (6.9)
ACE inhibitor or ARB	23 (15.2)	28 (19.5)	27 (18.6)
Mineralocorticoid receptor antagonist	1 (0.7)	2 (1.4)	1 (0.7)
Symptom onset to arrival at primary PCI center, median (IQR), h:min	2:05 (1:34-3:01)	2:11 (1:31-3:26)	2:15 (1:32-3:15)
Arrival at primary PCI center to reperfusion, median (IQR), min	24 (19-35)	23 (19-37)	25 (19-34)
Symptom onset to reperfusion, median (IQR) h:min	2:36 (2:03-3:36)	2:50 (1:55-4:06)	2:44 (2:01-3:49)
Initial blood results on admission			
Hemoglobin, mean (SD), g/dL	14.4 (1.4)	14.6 (1.2)	14.7 (1.3)
Platelet count, mean (SD), ×10 ³ /μL	253.7 (59.8)	267.9 (72.0)	260.4 (53.3)
Creatinine, mean (SD), μmol/L	80 (18)	80 (17)	80 (18)
Troponin T, median (IQR), ng/mL	0.06 (0.03-0.13)	0.06 (0.03-0.10)	0.06 (0.03-0.12)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; IQR, interquartile range; PCI, percutaneous coronary intervention.

SI conversion factor: To convert creatinine from μmol/L to mg/dL, divide by 88.4.

^a At least 1 risk factor for coronary artery disease was required for eligibility.

^b Renal impairment was defined according to the estimated glomerular filtration rate (eGFR), with an eGFR <59 mL/min/1.73 m² fulfilling the criteria for renal impairment.

^c Diabetes mellitus was defined as a history of diet-controlled or treated diabetes.

Table 2. Procedure Characteristics and Outcomes^a

Characteristics	No. (%) of Patients Who Underwent Cardiac MRI ^b		
	Placebo (n = 137) ^c	Alteplase, 10 mg (n = 131) ^c	Alteplase, 20 mg (n = 132) ^c
Infarct-related artery			
Left anterior descending coronary	61 (44.5)	61 (46.6)	60 (45.5)
Circumflex	18 (13.1)	15 (11.5)	13 (9.8)
Right	58 (42.3)	55 (42.0)	59 (44.7)
Infarct artery diameter, mean (SD), mm	3.2 (0.4)	3.2 (0.5)	3.2 (0.4)
Mode of reperfusion			
Aspiration thrombectomy	37 (27.0)	42 (32.3)	40 (30.3)
Balloon angioplasty	100 (73.0)	88 (67.7)	91 (68.9)
Primary stent	0 (0.0)	0 (0.0)	1 (0.8)
Balloon angioplasty prestent deployment	129 (94.2)	126 (96.2)	125 (94.7)
PCI with stent implant	136/137 (99.3)	128/130 (98.5)	130/131 (99.2)
Total No. of stents deployed			
0	1 (0.7)	2 (1.4)	1 (0.8)
1	92 (67.2)	88 (67.2)	99 (75.0)
2	40 (29.2)	28 (21.4)	28 (21.2)
≥3	4 (2.9)	10 (7.6)	4 (3.0)
Total length of stents deployed, mean (SD), mm [n = 396]	33.5 (13.8)	35.7 (15.3)	32.0 (14.0)
Poststent dilatation	119 (86.9)	116 (88.5)	115 (87.1)
TIMI flow grade at initial angiography ^d			
0 (no flow)	117 (85.4)	103 (78.6)	103 (78.0)
1 (minimal flow)	3 (2.2)	13 (9.9)	14 (10.6)
2 or 3 (2, slow but complete, 3, normal flow)	17 (12.4)	15 (11.5)	15 (11.4)
TIMI thrombus grade at initial angiography ^e			
0-2 (0, no thrombus, 2, definite, <1/2 vessel diameter)	0 (0.0)	0 (0.0)	0
3 (3, definite, >1/2 but <2 vessel diameters)	4 (2.6)	2 (1.5)	5 (3.8)
4 (definite thrombus ≥2 vessel diameters)	17 (12.4)	25 (19.1)	24 (18.2)
5 (total occlusion)	116 (84.7)	104 (79.4)	103 (78.0)
Acute therapy following the first medical contact			
Aspirin	119 (86.9)	118 (90.1)	112 (84.8)
Loading dose of aspirin, No./total (%), mg			
300	114/119 (95.4)	113/118 (95.8)	109/112 (97.3)
>300	5/119 (4.2)	5/118 (4.2)	3/112 (2.7)
Additional antiplatelet medication			
None	15 (10.9)	10 (7.6)	17 (12.9)
Clopidogrel	43 (31.4)	48 (36.6)	51 (38.6)
Ticagrelor	76 (55.5)	68 (51.9)	60 (45.5)
Prasugrel	3 (2.2)	5 (3.8)	4 (3.0)
Unfractionated heparin, median (IQR), U	10 000 (7000-12 250)	10 000 (7500-13 000)	10 000 (7000-13 000)
Inhaled oxygen, No./total (%)	21/134 (15.5)	22/127 (17.3)	13/129 (10.1)
Intravenous morphine	93 (67.9)	100 (76.3)	104 (78.8)
Intravenous or intracoronary glycoprotein IIb/IIIa antagonist, No./total (%)	13/134 (9.7)	27/127 (21.3)	21/129 (16.3)
Study drug treatment			
Drug administered	137 (100.0)	129 (98.5)	132 (100.0)
Study drug given according to protocol, No./total (%)	136/137 (99.3)	127/129 (98.4)	131/132 (99.2)
Duration of study drug infusion, mean (SD), min	6.4 (1.9)	6.6 (2.0)	6.6 (2.0)

Abbreviations: IQR, interquartile range; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction grade.

^a The angiographic parameters are based on central laboratory assessments. None of the patients received intravenous or intracoronary treatment with bivalirudin, metoprolol, nicorandil, or sodium nitroprusside.

^b Unless otherwise noted.

^c Unless otherwise stated.

^d TIMI flow grade is a visual assessment of antegrade coronary artery flow at angiography, graded from 0 (no flow) to 3 (normal flow).

^e TIMI thrombus grade allows the classification of thrombus burden (greatest dimension) revealed during coronary angiography.

Table 3. Primary Outcome for Efficacy Analyses

Outcome	Primary Outcome Analyzed, mean (SD) ^a			Between-Group Comparison			
	Placebo	Alteplase		20 mg vs Placebo		10 mg vs Placebo ^b	
		10 mg (n = 129)	20 mg (n = 131)	% (95% CI)	P Value	% (95% CI)	P Value
Primary outcome ^c							
Microvascular obstruction at 2-7 d, mean (SD), % left ventricular mass	2.3 (4.3)	2.6 (4.5)	3.5 (5.8)	1.16 (-0.08 to 2.41)	.32 ^d	0.29 (-0.76 to 1.35)	.74 ^d
IQR	0.0 to 3.2	0.0 to 3.8	0.0 to 4.8				
Range	0 to 28.8	0 to 27.0	0 to 26.1				
Secondary analysis							
Square root of microvascular obstruction, at 2-7 d				0.23 (-0.09 to 0.55)	.15 ^e	0.07 (-0.25 to 0.39)	.68 ^e

Abbreviation: IQR, interquartile range.

^a Unless otherwise indicated.

^b Given the 20-mg alteplase vs placebo comparison was not significant, the 10-mg alteplase vs placebo comparison became a secondary analysis.

^c Given the high proportion of patients with a 0 value for microvascular obstruction amount (55% of patients), the median value for microvascular

obstruction was 0 for all groups, while the mean (SDs) are not ideal summaries for these data. It has been reported as such for this reason.

^d Between-group comparison *P* values were derived from the stratified Wilcoxon (van Elteren) test. This method does not automatically generate confidence intervals. These were derived by bootstrap resampling (10 000 replicates), stratified by the location of myocardial infarction.

^e Between-group comparison *P* values derived from linear regression model.

Primary and Secondary Outcomes

Magnetic resonance imaging was performed in 400 patients (90.9%) from days 2 through 7 after enrollment and in 367 patients (83.4%) at 3 months. The primary end point was available from 396 patients, meaning there was missing data for the primary end point in 10%. The median time to MRI was 4 days (interquartile range [IQR], 3-6 days); for placebo, 4 days (IQR, 3-5 days); for 10-mg alteplase, 5 days (IQR, 3-6 days); and for 20-mg alteplase, 4 days (IQR, 3-6 days). The median from reperfusion to the 3-month MRI were 91 days (IQR, 86-97 days). Microvascular obstruction was demonstrated in 176 patients (44.4%), and the amount of microvascular obstruction, expressed as the mean percentage of left ventricular mass, was 2.80%. Two clinical case examples are illustrated in eFigure 2 in Supplement 3.

Primary Outcome

In the primary analysis, the amount of microvascular obstruction revealed by MRI did not differ between the 20-mg alteplase group and the placebo group (mean, 3.5% vs 2.3%; estimated difference, 1.16%; 95% CI, -0.08% to 2.41%; van Elteren test, *P* = .32). The comparison of the 10-mg alteplase group and the placebo group then became secondary (mean, 2.6% vs 2.3%; estimated difference, 0.29%; 95% CI, -0.76% to 1.35%; van Elteren test, *P* = .74; Table 3). Similar results were obtained using a linear regression model; with no evidence of a difference in the primary outcome between all patients randomized to alteplase and those randomized to placebo, mean difference on square root scale, 0.15 (95% CI, -0.12 to 0.42; *P* = .28).

A post hoc analysis of the primary outcome including multiple imputation for the missing values was performed, which produced similar results to the primary analysis.

Treatment effect differences on the primary outcome between prespecified subgroups defined by baseline characteristics were assessed. None of the interaction tests were statistically significant (Table 3 and Table 4 and eTable 3 in

Supplement 3). In the subgroup of patients presenting at more than 4 hours, the estimated mean difference in the square root of the amount of microvascular obstruction between the 20-mg alteplase group (*n* = 27) and the placebo group (*n* = 26) was 1.12 (95% CI, 0.42-1.82; *P* = .002); however, the test for interaction was not statistically significant (*P* = .06), so this subgroup finding should not be interpreted as different from the overall effect.

Secondary Outcomes

The AUC for troponin T measured at baseline and at 2 and 24 hours after reperfusion among 317 patients was increased in both treatment groups compared with placebo (eTable 4 in Supplement 3; relative difference, 1.53; 95% CI, 1.16-2.01; *P* = .002) for both alteplase groups combined vs placebo). The troponin T AUC was 35% higher in patients treated with 20 mg of alteplase vs placebo (relative ratio, 1.53; 95% CI, 1.12-2.11; *P* = .008).

Health-related quality of life scores were not significantly different between the groups at 3 months. The EQ-5D health utility scores were 0.88 in both the 20-mg alteplase and placebo groups (mean difference, -0.002; 95% CI, -0.04 to 0.04; *P* = .93; Table 5).

Adverse Events

Compared with placebo, there was a dose-related increase in the systemic concentrations of fibrin D-dimer and prothrombin F₁₊₂, and a slight reduction in plasminogen, in the alteplase groups (eTable 5 in Supplement 3). The systemic concentrations of fibrinogen and hemoglobin were numerically similar between the groups.

Clinical Events

The adverse events are described in eTable 7 in Supplement 3. MACE occurred in 15 patients (10.1%) in the placebo group, 18 (12.9%) in the 10-mg alteplase group, and 12 (8.2%) in the 20-mg alteplase group. Two patients experienced a

Table 4. Primary Outcome for Prespecified Analyses

	Primary Outcome Analyzed, Mean (SD) ^a				Between-Group Comparison				P Value for Interaction ^d
	No. (%) of Patients	Placebo (n = 136)	Alteplase		20 mg vs Placebo		10 mg vs Placebo ^b		
			10 mg (n = 129)	20 mg (n = 131)	% (95% CI)	P Value ^c	% (95% CI)	P Value ^c	
Ischemic time, h									
<2	98 (24.7)	1.4 (2.7)	1.5 (2.7)	2.7 (5.0)	0.25 (-0.43 to 0.92)	.48	0.09 (-0.55 to 0.73)	.78	.09
2-4	215 (54.3)	3.0 (5.0)	3.1 (5.3)	3.2 (5.7)	-0.06 (-0.47 to 0.35)	.79	-0.01 (-0.45 to 0.42)	.95	
>4	83 (21.0)	1.1 (2.6)	3.1 (4.6)	5.2 (6.9)	1.12 (0.42 to 1.82)	.002	0.53 (-0.15 to 1.22)	.13	
Sex									
Men	338 (85.4)	2.4 (4.5)	2.8 (4.6)	4.0 (6.2)	0.34 (0.00 to 0.68)	.05	0.11 (-0.23 to 0.45)	.51	.27
Women	58 (14.6)	1.8 (2.8)	1.7 (4.0)	0.8 (1.6)	-0.39 (-1.20 to 0.43)	.35	-0.22 (-1.06 to 0.61)	.60	
Age, y									
<55	113 (28.5)	1.8 (2.9)	3.2 (5.2)	3.1 (4.7)	0.21 (-0.42 to 0.85)	.51	0.34 (-0.22 to 0.91)	.23	.68
55-65	168 (42.4)	3.0 (5.6)	2.3 (3.8)	3.6 (6.4)	0.14 (-0.35 to 0.63)	.58	-0.19 (-0.71 to 0.33)	.47	
>65	115 (29.0)	2.1 (3.8)	2.5 (4.5)	3.5 (5.5)	0.33 (-0.25 to 0.91)	.27	0.10 (-0.50 to 0.69)	.75	
MI location									
Anterior	178 (44.9)	3.4 (5.6)	2.8 (4.0)	4.7 (6.9)	0.26 (-0.21 to 0.74)	.28	-0.08 (-0.55 to 0.39)	.74	.57
Nonanterior	221 (55.1)	1.5 (2.7)	2.5 (4.8)	2.5 (4.6)	0.20 (-0.22 to 0.63)	.35	0.19 (-0.24 to 0.62)	.38	
Smoking status									
Never	137 (34.6)	2.4 (4.0)	1.9 (3.7)	4.7 (7.5)	0.36 (-0.18 to 0.90)	.19	-0.25 (-0.79 to 0.30)	.38	.22
Former	74 (18.7)	1.3 (3.4)	1.8 (2.9)	3.2 (5.7)	0.57 (-0.12 to 1.27)	.10	0.28 (-0.52 to 1.07)	.50	
Current	185 (46.7)	2.6 (4.8)	3.3 (5.2)	2.6 (3.8)	0.00 (-0.48 to 0.47)	.99	0.19 (-0.26 to 0.64)	.41	
Initial TIMI coronary flow grade									
0 (none)	320 (80.8)	2.6 (4.5)	3.1 (4.9)	3.9 (6.2)	0.21 (-0.13 to 0.56)	.23	0.06 (-0.28 to 0.41)	.73	.71
1 (minimal)	30 (7.6)	0.0 (0.0)	1.4 (2.3)	3.5 (4.8)	1.37 (-0.24 to 2.98)	.10	0.87 (-0.76 to 2.50)	.29	
≥2 (2, slow but complete to 3, normal flow)	46 (11.6)	0.7 (2.9)	0.5 (1.0)	0.8 (2.9)	0.07 (-0.83 to 0.97)	.88	0.06 (-0.86 to 0.97)	.90	
Preexisting antiplatelet medication									
Yes	58 (14.6)	2.4 (3.5)	1.4 (4.0)	3.9 (6.3)	0.31 (-0.48 to 1.11)	.44	-0.46 (-1.32 to 0.40)	.30	.31
No	338 (85.4)	2.3 (4.5)	2.8 (4.5)	3.4 (5.8)	0.22 (-0.13 to 0.56)	.22	0.14 (-0.20 to 0.49)	.31	

Abbreviations: MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction grade.

^a Unless otherwise indicated.

^b Given the 20-mg alteplase vs placebo comparison was not significant, the 10-mg alteplase vs placebo comparison became a secondary analysis.

^c Between-group comparison P values are derived from linear regression model.

^d Interaction test P values reported from regression models with treatment included as a 3-level categorical variable.

stroke. Aspiration thrombectomy was used in 1 of these patients who developed a homonymous hemianopia after the procedure. Major bleeds were uncommon, occurring in 1 patient in each of the 10-mg and 20-mg alteplase groups.

Discussion

Among patients with acute STEMI presenting within 6 hours of symptom onset, adjunctive low-dose intracoronary al-

teplase given during the primary PCI compared with placebo did not reduce microvascular obstruction.

This trial has several strengths. Comparable in scale with other pivotal trials involving cardiac MRI,²⁴ including the INFUSE-AMI⁴ and AIDA STEMI^{24,25} trials, the trial design selected patients with presenting characteristics that increase infarct size, eg, proximal occlusion of a thrombus-laden coronary artery. Mean infarct size (27% of left ventricular mass) was almost 2-fold larger than that observed in an unselected population of patients with STEMI.^{5,6} By limiting eligibility to an

Table 5. Secondary Outcomes for Efficacy and Health Outcomes

Outcome	No. of Patients	Treatment Group ^a			Between-Group Comparison			
		Placebo (n = 151)	Alteplase		20 mg vs Placebo		10 mg vs Placebo	
			10 mg (n = 144)	20 mg (n = 145)	% (95% CI)	P Value	% (95% CI)	P Value
Coronary Angiogram								
TIMI flow grade after PCI								
0 (no flow)		0 (0.0)	1 (0.7)	1 (0.7)	0.73 (0.41 to 1.29)	.28 ^b	0.83 (0.46 to 1.49)	.52 ^b
1 (minimal flow)		6 (4.0)	6 (4.2)	3 (2.1)				
2 (slow but complete)		20 (13.2)	22 (15.3)	29 (20.0)				
3 (normal flow)		125 (82.8)	115 (79.9)	112 (77.2)				
TIMI myocardial perfusion grade after PCI ^c								
0 (no blush)		46 (30.5)	62 (43.1)	49 (33.8)	0.93 (0.61 to 1.41)	.73 ^b	0.70 (0.46 to 1.08)	.11 ^b
1 (incomplete clearance)		11 (7.3)	2 (1.4)	9 (6.2)				
2 (persistent)		51 (33.8)	48 (33.3)	49 (33.8)				
3 (normal blush and clearance)		43 (28.5)	32 (22.2)	38 (26.2)				
Corrected TIMI frame count after PCI ^d	438	20 (14 to 27)	20 (15 to 28)	22 (14 to 30)	1.07 (0.94 to 1.23)	.31 ^e	1.10 (0.96 to 1.25)	.19 ^e
TIMI thrombus grade after PCI								
0 (no thrombus)		147 (97.4)	137 (95.1)	141 (97.2)	1.04 (0.25 to 4.23)	.96 ^f	1.87 (0.53 to 6.53)	.33 ^f
1 (possible thrombus)		2 (1.3)	4 (2.8)	3 (2.1)				
2 (definite, <1/2 vessel diameter)		1 (0.7)	2 (1.4)	0 (0.0)				
3 (definite, >1/2 but <2 vessel diameters)		0 (0.0)	0 (0.0)	0 (0.0)				
4 (definite, >2 vessel diameters)		1 (0.7)	0 (0.0)	0 (0.0)				
5 (occluded artery)		0 (0.0)	1 (0.7)	1 (0.7)				
Electrocardiogram (acute)								
ST-segment resolution 60 min, mean (SD), %	396	49.6 (38.9)	43.7 (45.0)	44.2 (46.0)	-5.0 (-15.1 to 5.2)	.34 ^e	-5.8 (-16.2 to 4.6)	.27 ^e
Biochemistry (Acute), Mean (SD)								
Troponin T, AUC	317	2.80 (1.10 to 5.32)	2.94 (1.57 to 5.98)	3.80 (1.56 to 6.63)	1.53 (1.12 to 2.11)	.008 ^e	1.52 (1.10 to 2.09)	.01 ^e
NT-proBNP in 2-7 d, pg/mL	394	784 (386 to 1350)	849 (417 to 1586)	791 (412 to 1355)	1.00 (0.78 to 1.27)	.98 ^e	1.12 (0.88 to 1.42)	.35 ^e
Cardiac MRI (2-7 d)								
Microvascular obstruction, No. (%)	396	59/136 (43.4)	58/129 (45.0)	59/131 (45.0)	1.07 (0.66 to 1.73)	.80 ^f	1.06 (0.65 to 1.73)	.81 ^f
Myocardial hemorrhage, No. (%)	378	52/128 (40.6)	54/121 (44.6)	56/129 (43.4)	1.12 (0.68 to 1.84)	.65 ^f	1.17 (0.71 to 1.94)	.54 ^f
Myocardial hemorrhage, mean (SD), % left ventricular mass	360	1.56 (3.78)	1.98 (3.68)	2.45 (4.80)	0.86 (-0.17 to 1.88)	.10 ^e	0.36 (-0.69 to 1.41)	.50 ^e
Infarct size, mean (SD), % left ventricular mass	396	26.3 (13.7)	27.3 (12.4)	26.6 (13.4)	0.23 (-2.64 to 3.11)	.87 ^e	0.80 (-2.08 to 3.69)	.58 ^e
Extent of myocardial edema, mean (SD), % left ventricular mass	397	40.4 (11.4)	41.9 (11.4)	41.0 (11.5)	0.44 (-1.72 to 2.60)	.69 ^e	1.17 (-0.99 to 3.33)	.29 ^e
Myocardial salvage index, mean (SD)	396	0.37 (0.25)	0.36 (0.23)	0.36 (0.24)	-0.01 (-0.07 to 0.05)	.68 ^e	-0.01 (-0.07 to 0.04)	.64 ^e
Left ventricular end-diastolic volume, median (IQR), mL	400	166 (144 to 195)	177 (157 to 208)	166 (143 to 195)	1.00 (0.95 to 1.05)	.94 ^e	1.06 (1.01 to 1.12)	.02 ^e
Left ventricular end-systolic volume, median (IQR), mL	400	90 (77 to 112)	96 (80 to 124)	95 (79 to 110)	1.00 (0.94 to 1.08)	.93 ^e	1.08 (1.01 to 1.16)	.03 ^e
Left ventricular ejection fraction, mean (SD), %	400	44.5 (8.8)	43.6 (8.1)	44.2 (8.4)	-0.27 (-2.16 to 1.63)	.78 ^e	-0.76 (-2.66 to 1.14)	.44 ^e

(continued)

Table 5. Secondary Outcomes for Efficacy and Health Outcomes (continued)

Outcome	No. of Patients	Treatment Group ^a		Between-Group Comparison				
		Placebo (n = 151)	Alteplase 10 mg (n = 144)	20 mg (n = 145)	20 mg vs Placebo % (95% CI)	P Value	10 mg vs Placebo % (95% CI)	P Value
Electrocardiogram (3 mo)								
Final infarct size (Selvester score), mean (SD) ^a	368	10.3 (9.0)	12.1 (10.6)	12.1 (9.9)	1.70 (-0.64 to 4.03)	.15 ^e	1.69 (-0.69 to 4.08)	.16 ^e
Biochemistry (3 mo)								
NT-proBNP, pg/mL	372	228 (94 to 521)	260 (100 to 442)	239 (119 to 528)	0.99 (0.76 to 1.28)	.93 ^e	0.98 (0.75 to 1.27)	.88 ^e
Ratio of NT-proBNP at 3 mo, d 2-7	354	0.32 (0.20 to 0.58)	0.33 (0.18 to 0.51)	0.34 (0.22 to 0.49)	0.95 (0.79 to 1.15)	.63 ^e	8.69 (-316.94 to 334.32)	.45 ^e
Cardiac MRI (3 mo)								
Infarct size, mean (SD), % left ventricular mass	364	18.7 (12.5)	18.5 (11.2)	19.3 (12.2)	0.79 (-2.00 to 3.58)	.58 ^e	-0.21 (-3.02 to 2.61)	.89 ^e
Myocardial salvage index, mean (SD) ^b	358	0.56 (0.24)	0.58 (0.21)	0.55 (0.23)	-0.02 (-0.08 to 0.04)	.52 ^e	0.01 (-0.05 to 0.07)	.67 ^e
Left ventricular end-diastolic volume, median (IQR), mL	367	164 (144-192)	173 (152-206)	170 (142-195)	1.00 (0.94 to 1.06)	.87 ^e	1.06 (1.00 to 1.12)	.06 ^e
Left ventricular end-systolic volume, median (IQR), mL	367	79 (64-103)	88 (71-110)	88 (67-108)	1.03 (0.94 to 1.12)	.57 ^e	1.08 (0.99 to 1.18)	.09 ^e
Left ventricular ejection fraction, mean (SD), %	367	49.8 (8.8)	48.5 (8.0)	48.6 (8.5)	-1.25 (-3.30 to 0.80)	.23 ^e	-1.30 (-3.38 to 0.77)	.22 ^e
Health-Related Quality of Life at 3 mo, Mean (SD)								
EQ-5D health utility score ⁱ	391	0.88 (0.16)	0.89 (0.15)	0.88 (0.16)	-0.002 (-0.04 to 0.04)	.93 ^e	0.008 (-0.03 to 0.05)	.68 ^e
Change from baseline	378	0.07 (0.17)	0.08 (0.23)	0.06 (0.18)	-0.005 (-0.05 to 0.04)	.83 ^e	0.014 (-0.03 to 0.06)	.55 ^e
EQ-5D visual analog ⁱ	396	78.0 (17.5)	79.8 (15.2)	81.8 (15.1)	3.89 (0.07 to 7.71)	.05 ^e	1.89 (-1.97 to 5.75)	.34 ^e
Change from baseline	392	5.6 (19.9)	8.2 (17.2)	6.7 (18.4)	1.0 (-3.45 to 5.59)	.66 ^e	2.50 (-2.00 to 7.01)	.28 ^e

Abbreviations: EQ-5D, EuroQol 5-dimension scale; MRI, magnetic resonance imaging; NTproBNP, N-terminal probrain natriuretic peptide; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction grade.

^a Unless otherwise indicated.

^b Between-group comparison *P* values derived from proportional odds logistic regression model.

^c TIMI myocardial perfusion grade provides a score for ground-glass appearance "blush" of contrast entering the microvasculature and contrast washout.

^d Corrected TIMI frame count is an objective continuous variable index of coronary blood flow, representing the time (in cine frames) for contrast to reach a standardized landmark, corrected for vessel length (normal value, <27 frames).

^e Between-group comparison *P* values derived from linear regression model.

^f Between-group comparison *P* values derived from a logistic regression model.

^g Selvester score translates subtle changes in ventricular depolarization on the

electrocardiogram to a surrogate measure of infarct size; there is a maximum score of 32 points with 1 point corresponding to 3% of the left ventricle.

^h Myocardial salvage index is calculated by subtracting the infarct size from the extent of myocardial edema (represents jeopardized myocardium) and then indexing by dividing by the extent of myocardial edema, values range from 0 (no salvage) to 1 (complete salvage).

ⁱ EQ-5D is a standardized instrument used as a measure of health outcome, made up of 2 components: (1) the health utility score, a descriptive system comprised of 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Scores for each are combined to give a maximum value of 1; (2) the visual analog scale reports the patient's self-rated health on a visual analog scale from 0 (worst imaginable) to 100 (best health imaginable). Baseline health status was assessed using the EQ-5D, which was completed by patients at the time of their 2- to 7-day follow-up visit. Each patient had 1 blood sample available for each time point. Data summarized as mean (SD) or median (interquartile range) for normal and nonnormally distributed data, respectively.

ischemic time of 6 or fewer hours, the aim was to include participants with salvageable myocardium. Alteplase was used within its licensed indication and at doses that are available in the clinic. Bias was minimized through a double-blind design and use of core laboratory analyses. The increase in systemic concentrations of fibrin D-dimers without any change in fibrinogen indicates that fibrinolysis or fibrin generation were localized to the heart.

The potential for harm with facilitated PCI was highlighted in the ASSENT-4 (Assessment of the Safety and Effi-

cacy of a New Treatment Strategy with Percutaneous Coronary Intervention 4)¹⁶ and FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events)¹⁷ trials. In ASSENT-4,¹⁶ compared with primary PCI (standard care), full-dose tenecteplase combined with PCI was associated with an increase in the primary end point of death, congestive heart failure, or shock within 90 days. Ischemic cardiac complications and ischemic stroke were also increased in the intervention group. Despite more initial patency in the infarct-related artery, residual thrombus burden was higher

in the facilitated PCI group and tissue reperfusion and clinical outcomes were worse.²⁶ These results may be explained by comparatively inadequate anticoagulation and, potentially, formation of fibrin and thrombus in the group treated with tenecteplase.^{26,27} The importance of effective anticoagulation to mitigate the prothrombotic effects of fibrinolytic therapy with alteplase has been reported previously.²⁷

The targeted, intracoronary infusion of the study drug was intended to minimize the systemic release of alteplase and minimize bleeding events. Alteplase was selected because it is a fibrin-specific fibrinolytic drug with a brief circulating half-life (≈ 5 minutes). In order to further reduce the possibility of harmful remote bleeds, patients with risk factors for bleeding were excluded and the PCI procedures were performed via the radial artery. The rates of bleeding events were within the expected range for primary PCI.²⁸

The increase in troponin T in the alteplase groups may provide mechanistic insights. The troponin T AUC is distinct from the other measures of infarct size that were obtained at single time points. An alternative explanation such as biomarker washout after fibrinolysis may explain why this rise in troponin was not associated with an increase in MRI measures of infarction. The dose-related increase in the systemic concentrations of fibrin D-dimer indicates that clot lysis had occurred. An increase in prothrombin F_{1+2} concentrations was observed in the alteplase groups, despite achieving therapeutic anticoagulation with unfractionated heparin. The undesired procoagulant effect of fibrinolytic therapy through thrombin activation²⁷ may have led to microvascular thrombosis, limiting the efficacy of the intervention.

Contemporary practice guidelines call for more research to identify new treatments for microvascular obstruction.³

There is growing interest in the potential efficacy of adjunctive intracoronary fibrinolytic therapy during primary PCI. Two phase 3 trials are investigating the efficacy of reduced doses of either alteplase (STRIVE, NCT03335839) or tenecteplase (RESTORE-MI; ACTRN12618000778280) (Supplement 3).

Limitations

The study had several limitations. First, the study presents short-term findings up to 3 months. Second, the trial was discontinued when prespecified futility criteria were met. The interim analysis and related stopping criteria had been required and specified by the funder. The objectives of this phase 2 trial included evidence synthesis for mechanisms evaluation as well as efficacy. To an extent, premature discontinuation limits the mechanisms evaluation. Third, because of the large number of secondary end points and the potential for type I error, all of these findings should be interpreted as only exploratory. Fourth, study drug administration was focused at a single time point before stent implant when coronary blood flow was variable. Alternatively, in the STRIVE and RESTORE-MI trials, the intervention is scheduled at the end of primary PCI, after stent implant.

Conclusions

Among patients with acute STEMI presenting within 6 hours of symptoms, adjunctive low-dose intracoronary alteplase given during the primary percutaneous intervention compared with placebo did not reduce microvascular obstruction. The study findings do not support this treatment.

ARTICLE INFORMATION

Accepted for Publication: November 20, 2018.

Author Affiliations: British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (McCartney, Eteiba, Maznyczka, McEntegart, Oldroyd, Lindsay, Rocchiccioli, Shaukat, Good, Watkins, Robertson, T. J. Ford, Petrie, Welsh, Sattar, Berry); West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank, Clydebank, United Kingdom (McCartney, Eteiba, Maznyczka, McEntegart, Martin, Petrie, Berry); Leeds University and Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom (Greenwood, Malkin); James Cook University Hospital NHS Trust, Middlesbrough, United Kingdom (Muir); South Manchester Hospitals NHS Trust, Manchester, United Kingdom (Chowdhary); Leicester University Hospitals NHS Trust, Leicester, United Kingdom (Gershlick); Liverpool Heart and Chest Hospital NHS Foundation Trust, Liverpool, United Kingdom (Appleby); Royal Wolverhampton University Hospital NHS Trust, Wolverhampton, United Kingdom (Cotton); Barts and the London Hospital, London, United Kingdom (Wragg); University Hospital Southampton Foundation Trust, Southampton, United Kingdom (Curzen); Greater Glasgow and Clyde Health Board, Glasgow, United Kingdom (Gillespie); Electrocardiography Core Laboratory, University of Glasgow, Glasgow,

United Kingdom (Macfarlane); Department of Haematology, Royal Infirmary, Glasgow, United Kingdom (Tait); University Hospital Hairmyres, East Kilbride, United Kingdom (Weir); University of Edinburgh, Edinburgh, United Kingdom (Fox); Robertson Centre for Biostatistics, Institute of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom (I. Ford, McConnachie).

Author Contributions: Dr Berry had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Eteiba, Greenwood, Chowdhary, Lindsay, Sattar, I. Ford, Berry.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: McCartney, Muir, Gershlick, Berry.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: McConnachie.

Obtained funding: Greenwood, Sattar, I. Ford, Berry.

Administrative, technical, or material support: McCartney, Eteiba, Maznyczka, McEntegart, Greenwood, Chowdhary, Gershlick, Cotton, Wragg, Curzen, Rocchiccioli, Good, Martin, Gillespie, T. Ford, Petrie, Macfarlane, Tait, Welsh, Weir, Berry.

Supervision: Eteiba, McEntegart, Muir, Oldroyd, Lindsay, Good, Watkins, Petrie, Fox, I. Ford, Berry.

Other: Malkin.

Conflict of Interest Disclosures: Dr Maznyczka reported participating in the British Heart Foundation Clinical Research Training Fellowship (FS/16/74/32573) during the conduct of the study. Dr Curzen reported receiving unrestricted research grants and fees for lectures and consultancy from Abbott Vascular and Boston Scientific, personal fees from HeartFlow and Haemonetics, and grants from Beckman Coulter, outside the submitted work. Dr Tait reported receiving grants from National Institute for Health Research (NIHR) during the conduct of the study; consultancy fees and honoraria from Boehringer-Ingelheim, personal fees and nonfinancial support from Bayer Healthcare, personal fees from Pfizer and Shire, and nonfinancial support from NovoNordisk. Dr Welsh reported receiving grants from the Chief Scientist Office, Boehringer-Ingelheim, and Roche. Dr Sattar reported receiving grants and personal fees from Boehringer-Ingelheim, personal fees from Amgen, Eli Lilly, Janssen, and AstraZeneca outside the submitted work. Dr Fox reported receiving grants and personal fees from Bayer/Janssen, Sanofi/Regeneron, and Verseeon and grants from AstraZeneca. Drs I. Ford and McConnachie reported receiving grants from the NIHR Efficacy and Mechanism Evaluation (EME) Programme during the conduct of the study. Dr Berry reported receiving research grants from the NIHR EME Programme and British Heart Foundation; receiving nonfinancial support from Boehringer-Ingelheim

during the conduct of the study; receiving research support to his institution from Abbott Vascular, AstraZeneca, Boehringer-Ingelheim, HeartFlow, GlaxoSmithKline, Novartis, Philips, and Siemens Healthcare; serving as chair of the clinical trials committee of the Society for Cardiovascular Magnetic Resonance and treasurer of the British Society of Cardiovascular Magnetic Resonance. Dr McCartney reported receiving grants from National Institute for Health Research (NIHR) during the conduct of the study. No other disclosures were reported.

Funding/Support: This work was supported by grant 12/170/45 from the NIHR EME, and Boehringer-Ingelheim provided the study drugs. Dr Maznyczka was funded by a fellowship from the British Heart Foundation (FS/16/74/32573). Drs Berry, Petrie, and Sattar are supported by grant RE/18/6/34217 from the British Heart Foundation. The research was in part supported by the NIHR infrastructure at Leeds.

Role of the Funder/Sponsor: The funder, NIHR-EME, coordinated peer review, approved the design of the study and had oversight of its conduct and management. The University of Glasgow and Greater Glasgow and Clyde Health Board were independent cosponsors of the trial. The cosponsors shared oversight and responsibility for the design and conduct of the study; collection, management, research governance, analysis, and final approval of the manuscript; the sponsor did not have the right to preclude submission of the manuscript.

T-TIME Group Collaborators

Responsible Individual at Data Coordinating Centre: Alex McConnachie.

Data Coordinating Centre(s): Robertson Centre for Biostatistics, Glasgow Clinical Trials Unit, University of Glasgow.

Participating Sites: *West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank, UK;* David Corcoran, MRCP; Andrew Davie, FRCP; Stuart Hood, FRCP; Joanne Kelly, RN; Tom Krysztofiak, MRCP; Victoria McNulty, MPharm (Hons); Vanessa Orchard, HCPC; and Jackie Wales, FIBMS; *Liverpool Heart and Chest Hospital NHS Foundation Trust:* Suneil Aggarwal, FRCP; Turab Ali, FRCP; Fiona Andrews, BN; Nicola Browning, PhD; Timothy A. Fairbairn, FRCP; Ruth Hardwick, MPharm; J Hasleton, FRCP; Babu Kunadian, FRCP; Pradeep Magapu, FRCP; Nick Palmer, FRCP; Rodney Stables, FRCP; Clive Taylerson; Hoi Tong, HCPC; Sophie Twiss, BN; and Periaswamy Velavan, FRCP; *University Hospital Southampton Foundation Trust:* Karen Banks, RN; Simon Corbett, FRCP; Michael Mahmoudi, FRCP; Zoe Nicholas, BSc; and James Wilkinson, FRCP; *Leeds University Hospitals NHS Trust:* Matthew Allan, MRCP; Michelle Anderson, RN; Daniel J Blackman, MD, MRCP; Jonathan Blaxill, FRCP; Michael Cunnington, MD; Vivek Kodoth, FRCP; John Kurian, FRCP; Steven Lindsay, FRCP; Christopher Malkin, FRCP; Jim McLenahan, FRCP; Kathryn Somers, RN; and Murgugapathy Veerasamy, FRCP; *Leicester Biomedical Research Centre, University Hospitals of Leicester NHS Trust:* Reenamol Abraham, RN; David Adlam, FRCP; Stephen Coleman, BPharm; Ian Hudson, FRCP; Andrew Ladwiniec, MRCP; Gerald P. McCann, MD; Emma Parker, RN; Elved Roberts, MD; and Joanne Wormleighton, DCR(R); *Wythenshawe Hospital, Manchester University NHS Foundation Trust:*

Eltigani Abdelaal, MRCP; Hussain Contractor, FRCP; Beatriz Duran, BS Pharm; Robin Egdel, FRCP; Susan Ferguson, BN; Sarra Giannopoulou, BN; Sanjay Sastry, FRCP; Jaydeep Sarma, FRCP; Matthias Schmitt, FRCP; and Sophie Quinn, BN; *Barts Health NHS Trust, London:* Andrew Archbold, FRCP; Mervyn Andiapien, DN; Charity Ewverhoma, BN; Ajay Jain, FRCP; Dan Jones, FRCP; Simon Kennon, FRCP; James Moon, FRCP; Anthony Mathur, FRCP; Amy Richards, BSc; and Alexander Sirker, FRCP; *The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough:* David Austin, FRCP; Mark de Belder, FRCP; Justin Carter, MRCP; Nicola Cunningham, BSc (Hons); Rachel Dale, HCPC; Jim Hall, FRCP; Stephanie Mack, BSc (Hons); Tracy Manders, RN; Neil Medredia, MD; Karen McLeod, BSc (Hons); Luca Settimo, PhDPharm; Andrew Sutton, FRCP; Neil Swanson, FRCP; Paul Williams, FRCP; and Robert Wright, FRCP; *New Cross Hospital, Wolverhampton University Hospital NHS Trust:* Victoria Cottam, BN; Elizabeth Radford; and Ben Wrigley, FRCP; *Freeman Hospital, The Newcastle Upon Tyne Hospital NHS Foundation Trust:* Rajiv Das, FRCP; Samantha Jones, BN; and Vera Wealleans, BN; *Royal Infirmary of Edinburgh, NHS Lothian:* Nick Cruden, FRCP; Laura Flint, BN; and Ruairidh Buchan, MPharm; *University Hospitals Bristol NHS Foundation Trust:* Chiara Bucciarelli-Ducci, FRCP; Tom Johnson, FRCP; Vincy Johny, BN; and Liz McCullagh, BPharm.

Clinical Event Committee: Robin A. Weir, MRCP; University Hospital Hairmyres Hospital, NHS Lanarkshire, UK; Aengus Murphy, MD; University Hospital Monklands, NHS Lanarkshire, UK; Colin J. Petrie, PhD; University Hospital Monklands, NHS Lanarkshire, UK; and Eleanor Dinnett, MBChB; Robertson Centre for Biostatistics, University of Glasgow.

Independent Data and Safety Monitoring Committee: Gary A. Ford, MB, BChir, University of Oxford, UK; Chim C. Lang, FRCP, University of Dundee, UK; and John Norrie, MSc, University of Edinburgh, UK.

Trial Steering Committee: Keith A. Fox, FRCP, University of Edinburgh; Colin Berry, FRCP, British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow; Rajesh Kharbanda, FRCP, Oxford University Hospitals NHS Foundation Trust; Catherine Labinjoh, FRCP, Forth Valley Royal Hospital, NHS Forth Valley; Gordon Baird, MRCP, Stranraer; Sandra Pairman, BN, Golden Jubilee National Hospital; David Jamieson, PhD, Robertson Centre for Biostatistics, University of Glasgow; Sarah Weeden, PhD, Robertson Centre for Biostatistics, University of Glasgow; Jorgen Van-Melckebeke, BSc, Project Management Unit, Glasgow Clinical Research Facility, Greater Glasgow and Clyde Health Board; Elizabeth Douglas, PhD, Clinical Trials Pharmacy, Clinical Research and Development, Greater Glasgow and Clyde Health Board; Pamela Surtees, Clinical Trials Pharmacy, Clinical Research and Development, Greater Glasgow and Clyde Health Board; Barbara Ross, BSc (Hons), Clinical Research and Development, Greater Glasgow and Clyde Health Board; Gemma Brindley, PhD, Clinical Research and Development, Greater Glasgow and Clyde Health Board; Sheila McGowan, PhD, Clinical Research and Development, Greater Glasgow and Clyde Health Board; Emma Jane Gault, MA (Hons), College of Medical, Veterinary and Life Sciences, University of Glasgow; Debra Stuart, PhD, College of Medical,

Veterinary and Life Sciences, University of Glasgow; Maureen Travers, PhD, R&D Office, Clinical Research and Development, Greater Glasgow and Clyde Health Board; Marc Jones, PhD, Pharmacovigilance Office, Clinical Research and Development, Greater Glasgow and Clyde Health Board; Sharon Kean, Robertson Centre for Biostatistics, Institute of Health and Wellbeing, University of Glasgow; Caroline Watson, PhD, R&D Governance, Clinical Research and Development, Greater Glasgow and Clyde Health Board; Emma Miller, Project Management Unit, Glasgow Clinical Research Facility, Greater Glasgow and Clyde Health Board; Eamonn Bolger, BSc, College of Medical, Veterinary and Life Sciences, University of Glasgow; Gillian Thomson, Project Management Unit, Glasgow Clinical Research Facility, Greater Glasgow and Clyde Health Board; Elaine Butler, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow; Josephine Cooney, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow; Julie Kennedy, MSc, Electrophysiology Core Laboratory, University of Glasgow; Emma Leishman, BSc, Department of Haematology, Royal Infirmary, Glasgow; Jaclyn Carberry, MBChB (Hons), Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow; David Corcoran, MRCP, West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank; and Aleksandra Radjenovic, PhD, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We thank all of the other clinical staff and the patients who participated in this project.

REFERENCES

- GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1859-1922. doi:10.1016/S0140-6736(18)32335-3
- GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736-1788. doi:10.1016/S0140-6736(18)32203-7
- Ibanez B, James S, Agewall S, et al; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119-177. doi:10.1093/eurheartj/ehx393
- Stone GW, Maehara A, Witzenbichler B, et al; INFUSE-AMI Investigators. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *JAMA*. 2012;307(17):1817-1826. doi:10.1001/jama.2012.421
- Wu KC, Zerhouni EA, Judd RM, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute

- myocardial infarction. *Circulation*. 1998;97(8):765-772. doi:10.1161/01.CIR.97.8.765
6. Carrick D, Haig C, Ahmed N, et al. Myocardial hemorrhage after acute reperfused ST-segment-elevation myocardial infarction: relation to microvascular obstruction and prognostic significance. *Circ Cardiovasc Imaging*. 2016;9(1):e004148. doi:10.1161/CIRCIMAGING.115.004148
 7. de Waha S, Patel MR, Granger CB, et al. Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials. *Eur Heart J*. 2017;38(47):3502-3510. doi:10.1093/eurheartj/ehx414
 8. Schwartz RS, Burke A, Farb A, et al. Microemboli and microvascular obstruction in acute coronary thrombosis and sudden coronary death: relation to epicardial plaque histopathology. *J Am Coll Cardiol*. 2009;54(23):2167-2173. doi:10.1016/j.jacc.2009.07.042
 9. Zaleski J, Undas A, Godlewski J, Stepień E, Zmudka K. No-reflow phenomenon after acute myocardial infarction is associated with reduced clot permeability and susceptibility to lysis. *Arterioscler Thromb Vasc Biol*. 2007;27(10):2258-2265. doi:10.1161/ATVBAHA.107.149633
 10. Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. *J Clin Invest*. 1974;54(6):1496-1508. doi:10.1172/JCI107898
 11. Henriques JP, Zijlstra F, Ottervanger JP, et al. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. *Eur Heart J*. 2002;23(14):1112-1117. doi:10.1053/eurhj.2001.3035
 12. Robbers LF, Eerenberg ES, Teunissen PF, et al. Magnetic resonance imaging-defined areas of microvascular obstruction after acute myocardial infarction represent microvascular destruction and haemorrhage. *Eur Heart J*. 2013;34(30):2346-2353. doi:10.1093/eurheartj/ehi100
 13. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. (Second International Study of Infarct Survival) Collaborative Group. *Lancet*. 1988;2(8607):349-360.
 14. Hillis WS, Jones CR, Been M, Campbell BC, Fulton WF. Intracoronary thrombolytic therapy performed within a coronary care unit: one year's experience. *Scott Med J*. 1986;31(1):25-29. doi:10.1177/003693308603100106
 15. Sezer M, Oflaz H, Gören T, et al. Intracoronary streptokinase after primary percutaneous coronary intervention. *N Engl J Med*. 2007;356(18):1823-1834. doi:10.1056/NEJMoa054374
 16. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet*. 2006;367(9510):569-578. doi:10.1016/S0140-6736(06)68147-6
 17. Ellis SG, Tendera M, de Belder MA, et al; FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med*. 2008;358(21):2205-2217. doi:10.1056/NEJMoa0706816
 18. Good clinical practice for clinical trials. Gov.UK website. <https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials>. Accessed October 22, 2018.
 19. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053
 20. Huang X, Moreton FC, Kalladka D, et al. Coagulation and fibrinolytic activity of tenecteplase and alteplase in acute ischemic stroke. *Stroke*. 2015;46(12):3543-3546. doi:10.1161/STROKEAHA.115.011290
 21. Rao AK, Pratt C, Berke A, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial—phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol*. 1988;11(1):1-11. doi:10.1016/0735-1097(88)90158-1
 22. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123(23):2736-2747. doi:10.1161/CIRCULATIONAHA.110.009449
 23. Detection and significance of heart injury in ST-elevation myocardial infarction (BHF MR-MI). <https://clinicaltrials.gov/ct2/show/NCT02072850>. Accessed October 22, 2018.
 24. Thiele H, Wöhrle J, Hambrecht R, et al. Intracoronary versus intravenous bolus abciximab during primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction: a randomised trial. *Lancet*. 2012;379(9819):923-931. doi:10.1016/S0140-6736(11)61872-2
 25. Eitel I, Desch S, Fuernau G, et al. Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. *J Am Coll Cardiol*. 2010;55(22):2470-2479. doi:10.1016/j.jacc.2010.01.049
 26. Zaleski J, Bogaerts K, Desmet W, et al. Intraluminal thrombus in facilitated versus primary percutaneous coronary intervention: an angiographic substudy of the ASSENT-4 PCI (Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention) trial. *J Am Coll Cardiol*. 2011;57(19):1867-1873. doi:10.1016/j.jacc.2010.10.061
 27. Rapold HJ. Promotion of thrombin activity by thrombolytic therapy without simultaneous anticoagulation. *Lancet*. 1990;335(8687):481-482. doi:10.1016/0140-6736(90)90720-P
 28. Kwok CS, Khan MA, Rao SV, et al. Access and non-access site bleeding after percutaneous coronary intervention and risk of subsequent mortality and major adverse cardiovascular events: systematic review and meta-analysis. *Circ Cardiovasc Interv*. 2015;8(4):e001645. doi:10.1161/CIRCINTERVENTIONS.114.001645