Low-dose intracoronary alteplase during primary percutaneous coronary intervention in patients with acute myocardial infarction: the T-TIME three-arm RCT

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Declared competing interests of authors: Annette M Maznyczka has received a British Heart Foundation (London, UK) Clinical PhD Fellowship (FS/16/74/32573). James M Cotton has received speaker honoraria from Abbott Vascular (Lake Bluff, IL, USA). Nick Curzen has received an unrestricted research grant and personal fees for lectures and consultancy from Abbott Vascular and Boston Scientific (Marlborough, MA, USA). R Campbell Tait has received personal fees and non-financial support from Bayer Healthcare (Leverkusen, Germany), personal fees from Pfizer Inc. (New York, NY, USA) and Shire Plc (Lexington, MA, USA), personal fees and non-financial support from Novo Nordisk A/S (Bagsværd, Denmark), personal fees from Sanofi SA (Paris, France), personal fees from Swedish Orphan Biovitrum (Stockholm, Sweden) and non-financial support from CSL Behring (King of Prussia, PA, USA). Paul Welsh has received grants from Boehringer Ingelheim (Ingelheim am Rhein, Germany) and Roche Holding AG (Basel, Switzerland) outside the submitted work. Naveed Sattar has received grants and personal fees from Boehringer Ingelheim, personal fees from Amgen Inc. (Thousand Oaks, CA, USA), AstraZeneca PLC (Cambridge, UK), Eli Lilly and Company (Indianapolis, IN, USA), Janssen Pharmaceutica (Beerse, Belgium), Novo Nordisk A/S and Sanofi SA. Keith A Fox has received grants and personal fees from Bayer/Janssen, grants from AstraZeneca and personal fees from Sanofi/Regeneron Pharmaceuticals (Tarrytown, NY, USA) and Verseon Corporation (Fremont, CA, USA). Colin Berry, based on contracts with the University of Glasgow, has held research and/or consultancy agreements with, and has received grants, non-financial support or other support from, Abbott Vascular, AstraZeneca, Boehringer Ingelheim, HeartFlow (Redwood City, CA, USA), GlaxoSmithKline (Brentford, UK), Novartis, Philips (Amsterdam, the Netherlands) and Siemens Healthineers AG (Erlangen, Germany). He has held grants from the National Institute for Health Research Efficacy and Mechanism Evaluation programme (reference 12/170/45) and the British Heart Foundation (reference FS/16/74/32573; RE/18/6/34217) in support of the current study.

Published November 2020
DOI: 10.3310/eme07050

Scientific summary

The T-TIME RCT

Efficacy and Mechanism Evaluation 2020; Vol. 7: No. 5
DOI: 10.3310/eme07050

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Scientific summary

Background

Ischaemic heart disease is the leading cause of disability and death worldwide. Acute coronary thrombosis causes ST-elevation myocardial infarction; the evidence-based standard of care for this is primary percutaneous coronary intervention to emergently reopen the occluded coronary artery and secure vessel patency with a stent. Primary percutaneous coronary intervention is routinely successful and normalised coronary blood flow is typically achieved in most patients. However, failed microvascular reperfusion has been estimated to occur in around half of all treated patients. This complication, described as microvascular obstruction, is independently predictive of an unfavourable cardiac prognosis.

Objective

The overall objective of this Phase II trial is evidence synthesis on the efficacy, safety and related mechanisms of adjunctive, low-dose, intracoronary fibrinolytic therapy during primary percutaneous coronary intervention. The specific objective for efficacy is to determine whether or not a therapeutic strategy involving low-dose intracoronary fibrinolytic therapy with alteplase infused early after coronary reperfusion will reduce microvascular obstruction. The safety objective is to determine whether or not the intervention is associated with an excess of major adverse cardiovascular events and, in particular, bleeds. The objective of the mechanism evaluation is to gather information that will help to explain the main findings for efficacy and safety. We hypothesised that a therapeutic strategy involving low-dose intracoronary fibrinolytic therapy with alteplase infused early after coronary reperfusion will prevent and reduce microvascular obstruction, and be safe.

Methods

This was a randomised, double-blind, parallel-group, Phase II clinical trial of treatment with low-dose adjunctive alteplase during primary percutaneous coronary intervention. During the course of the trial additional exclusion criteria were (1) requirement for immunosuppressive drug therapy at any time during the past 3 months and (2) active or prophylactic treatment with oral or parenteral antibiotic, antifungal or antiviral therapy to prevent or treat infection. This change was implemented to ensure the safety of the participants.

Patients who had a diagnosis of acute ST-segment elevation myocardial infarction with a symptom onset to reperfusion time of ≤ 6 hours were potentially eligible for randomisation. Access to the radial artery was a requirement, and further angiographic criteria included a proximal-to-middle coronary artery occlusion (Thrombolysis in Myocardial Infarction coronary flow grade of 0 or 1) or impaired coronary flow (Thrombolysis in Myocardial Infarction flow grade of 2: slow but complete filling) in the presence of definite angiographic evidence of a thrombus (Thrombolysis in Myocardial Infarction grade of 2 or more) in a major coronary artery. Key exclusion criteria were a functional coronary collateral supply (Rentrop grade of 2 or 3) to the infarct-related artery, any contraindication to fibrinolysis and lack of informed consent.

Between 17 March 2016 and 21 December 2017, patients who presented at 11 hospitals in the UK were randomised in a 1 : 1 : 1 dose-ranging trial design. Participants were randomly assigned to treatment with placebo ($n = 151$) or 10 mg ($n = 144$) or 20 mg of alteplase ($n = 145$) administered by manual infusion

directly into the infarct-related coronary artery over 5–10 minutes. The intervention was scheduled to happen early during the primary percutaneous coronary intervention procedure: after reperfusion of the infarct-related coronary artery and before stent implantation.

Primary outcome

The primary outcome was the amount of microvascular obstruction (percentage of left ventricular mass) demonstrated by late gadolinium-enhanced magnetic resonance imaging 10–15 minutes after the administration of contrast medium. Cardiac magnetic resonance imaging at 1.5 tesla was scheduled during the index hospitalisation for 2–7 days after enrolment into the trial.

Secondary outcomes

The secondary outcomes were assessed using cardiac magnetic resonance imaging, coronary angiography, electrocardiography, biochemistry and health-related quality-of-life instruments, and health outcomes were evaluated by a blinded clinical event committee.

The cardiac magnetic resonance imaging secondary outcomes included microvascular obstruction (presence/absence), myocardial haemorrhage (presence/absence) and the amount of myocardial haemorrhage expressed as a percentage of left ventricular mass on magnetic resonance imaging at 2–7 days after enrolment. 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 at 2–7 days and 3 months after enrolment into the trial.

Angiographic measures of reperfusion (Thrombolysis in Myocardial Infarction coronary flow grade, Thrombolysis in Myocardial Infarction myocardial perfusion grade and Thrombolysis in Myocardial Infarction frame count) and Thrombolysis in Myocardial Infarction thrombus grade at the end of percutaneous coronary intervention were predefined secondary outcomes. Percentage ST-segment resolution on an electrocardiogram obtained 60 minutes post reperfusion versus pre reperfusion and final infarct size revealed by the Selvester QRS score at 3 months were also calculated. The area under the curve for troponin T (ng/ml) was measured from blood samples that were obtained immediately before reperfusion (0 hours) and then again at 2 hours and 24 hours post reperfusion. NT-pro brain natriuretic peptide concentration (pg/ml) was measured at 2–7 days and 3 months post reperfusion, scheduled at the time of magnetic resonance imaging.

Health-related quality of life (EuroQol 5-Dimensions, three-level version) was recorded at 2–7 days and 3 months post myocardial infarction. The EuroQol 5-Dimensions, three-level version, is a standardised instrument used as a measure of health outcome, which is made up of two components. The first is the health utility score, a descriptive system that is made up of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Scores for each dimension are combined to give a maximum value of 1. Each dimension has three levels: no problems, some problems and extreme problems. Second, the visual analogue scale reports the patient's self-rated health on a visual analogue scale from 0 (worst health imaginable) to 100 (best health imaginable).

Fibrinogen and other parameters of coagulation and haemostasis served as surrogate measures of bleeding risk. 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 at 2 hours and 24 hours post 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 fragment 1 + 2 (a measure of thrombin activation).

Major adverse cardiovascular events were defined as cardiovascular death, non-fatal myocardial infarction or unplanned hospitalisation for heart failure. Acute cerebrovascular and systemic bleeds were defined using the Bleeding Academic Research Consortium criteria. All of these events were

adjudicated by the Clinical Event Committee, the members of which were independent of the trial and blinded to the treatment allocation. Longer-term follow-up of health outcomes (12 months and 3 years) blind to treatment group assignment is ongoing.

The randomisation sequence was computer generated by the University of Glasgow Clinical Trials Unit, using the method of randomised permuted blocks of length 6, with stratification by location of ST-segment elevation myocardial infarction (anterior vs. non-anterior) and study site. The allocation sequence was on a 1 : 1 : 1 basis between the placebo, 10 mg of alteplase and 20 mg of alteplase groups and the sequence was concealed electronically. The projected sample size was 618 patients (minimum 558 patients).

The participants, staff and researchers were blinded to the treatment group allocation. The primary outcome (extent of microvascular obstruction on magnetic resonance imaging at 2–7 days, as the percentage of left ventricular mass) was compared between groups using a stratified Wilcoxon test (van Elteren test), stratified by the location of the myocardial infarction.

Results

Recruitment was discontinued on 21 December 2017 given that conditional power for the primary outcome based on a prespecified analysis of the first 267 randomised participants was < 30% in both treatment groups (futility criterion). By that time, 1527 patients undergoing primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction were screened and 440 patients (mean age of 60.5 years, 15% female) had been randomised (placebo, $n = 151$; 10 mg of alteplase, $n = 144$; 20 mg of alteplase, $n = 145$). Seventeen (3.9%) patients withdrew from the study during follow-up and seven patients died. All of the other participants were followed up for 3 months; final follow-up took place on 12 April 2018.

Study intervention

Adjunctive study drug therapy was administered to 435 (98.9%) patients; five patients did not receive any drug. Two patients (one randomised to the placebo group and one randomised to the 10 mg of alteplase group) received 20 mg of alteplase because an incorrect treatment pack had been selected.

Primary and secondary outcomes

Cardiac magnetic resonance imaging was carried out in 400 (90.9%) patients at 2–7 days and in 367 (83.4%) patients at 3 months after enrolment. The primary end point was available in 396 patients, which meant that there were missing data for the primary end point in 10% of patients. The median time to magnetic resonance imaging was 4 days (3–6 days) [placebo: 4 days (3–5 days); 10 mg of alteplase: 5 days (3–6 days); 20 mg of alteplase: 4 days (3–6 days)] and 91 days (86–97 days), respectively. Microvascular obstruction was demonstrated in 176 (44.4%) patients and the amount of microvascular obstruction, expressed as the mean percentage of left ventricular mass, was 2.8%.

Primary outcome

In the primary analysis, the mean amount of microvascular obstruction revealed by magnetic resonance imaging did not differ between the 20 mg of alteplase group and the placebo group [3.5% vs. 2.3%, estimated difference 1.16%, 95% confidence interval −0.08% to 2.41%; Wilcoxon test (van Elteren test) $p = 0.32$]. The comparison of the 10 mg of alteplase group with the placebo group then became secondary [2.6% vs. 2.3%, estimated difference 0.29%, 95% confidence interval −0.76% to 1.35%; Wilcoxon test (van Elteren test) $p = 0.74$]. Similar results were obtained using a linear regression model, with no evidence of a difference in the primary outcome between patients randomised to alteplase and patients randomised to placebo (mean difference on square-root scale 0.15, 95% confidence interval −0.12 to 0.42; $p = 0.28$).

Post hoc analysis

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

Prespecified subgroup analyses of the primary outcome

Treatment effect differences on the primary outcome between prespecified subgroups defined by baseline characteristics were assessed. The subgroups were:

- ischaemic time [< 2 hours, $n = 98$ (24.7%); 2–4 hours, $n = 215$ (54.3%); ≥ 4 hours, $n = 83$ (21.0%)]
- sex [male, $n = 338$ (85.4%); female, $n = 58$ (14.6%)]
- age [< 55 years, $n = 113$ (28.5%); 55–65 years, $n = 168$ (42.4%); ≥ 65 years, $n = 115$ (29.0%)]
- myocardial infarction location [anterior, $n = 178$ (44.9%); non-anterior, $n = 221$ (55.1%)]
- smoking status [never, $n = 137$ (34.6%); former, $n = 74$ (18.7%); current, $n = 185$ (46.7%)]
- initial Thrombolysis in Myocardial Infarction coronary flow grade [0 (no flow), $n = 320$ (80.8%); 1 (minimal flow), $n = 30$ (7.6%); 2 or more (2 = slow but complete, 3 = normal flow), $n = 47$ (11.6%)]
- pre-existing antiplatelet medication [yes, $n = 58$ (14.6%); no, $n = 341$ (85.4%)].

None of the interaction tests on the primary outcome was statistically significant. In the subgroup of patients who presented > 4 hours after symptom onset, the estimated mean difference in the square root of the amount of microvascular obstruction between the 20 mg of alteplase group ($n = 27$) and the placebo group ($n = 26$) was 1.12 (95% confidence interval 0.42 to 1.82; $p = 0.002$); however, the test for interaction was not statistically significant ($p = 0.06$) and so this subgroup finding should not be interpreted as different from the overall effect.

Secondary outcomes

Blood chemistry

The area under the curve for troponin T concentration (ng/ml) measured at baseline and at 2 hours and 24 hours post reperfusion in 317 patients was increased in both treatment groups compared with placebo (relative difference 1.53, 95% confidence interval 1.16 to 2.01, $p = 0.002$, for both alteplase groups combined vs. placebo). The area under the curve for troponin T was 35% higher in patients treated with 20 mg of alteplase than in patients who received placebo (relative ratio 1.53, 95% confidence interval 1.12 to 2.11; $p = 0.008$).

Health-related quality of life

In unadjusted analyses, health-related quality-of-life scores were not significantly different between the groups at 3 months. The EuroQol-5 Dimensions, three-level version, health utility score was 0.88 in both the 20 mg of alteplase group and the placebo group (mean difference −0.002, 95% confidence interval −0.04 to 0.04; $p = 0.93$).

Adverse events

Haematology and coagulation

Compared with placebo, there was a dose-related increase in the systemic concentrations of fibrin D-dimer and prothrombin fragment 1 + 2 and a slight reduction in plasminogen in the alteplase groups. The systemic concentrations of fibrinogen and haemoglobin were numerically similar between the groups.

Clinical events

Major adverse cardiac events occurred in 15 (10.1%) of the placebo, 18 (12.9%) of the 10 mg of alteplase and 12 (8.2%) of the 20 mg of alteplase group patients. Major bleeds were uncommon, occurring in only one patient in both the 10 mg of alteplase and the 20 mg of alteplase groups.

Conclusions

Among patients with acute ST-segment elevation myocardial infarction presenting within 6 hours of symptoms, adjunctive low-dose intracoronary alteplase given during the primary percutaneous intervention did not reduce microvascular obstruction compared with placebo. In patients who present > 4 hours after symptom onset, treatment with 20 mg of alteplase may increase the amount of microvascular obstruction. The study findings do not support this treatment as designed. This trial presents new knowledge about lytic therapy when administered as an adjunctive treatment early after reperfusion during primary percutaneous coronary intervention. On the one hand, fibrinolytic therapy is an evidence-based primary reperfusion therapy for ST-segment elevation myocardial infarction. The intervention using low-dose fibrinolytic therapy given as designed, immediately after coronary reperfusion and before stent implantation, was neither effective nor harmful. This trial has provided information on efficacy, safety and relevant mechanisms, and the trial has answered the primary research questions. Future research studies should consider alternative designs for targeted lytic therapy in ST-segment elevation myocardial infarction. Future trial designs may focus on (1) eligibility criteria (e.g. ischaemic time of < 4 hours), (2) administration of the study drug at the end of primary percutaneous coronary intervention when antegrade blood flow in the infarct-related artery is secured by a stent and (3) optimal concomitant antithrombotic therapy.

Trial registration

This trial is registered as ClinicalTrials.gov NCT02257294.

Funding

This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a Medical Research Council (MRC) and National Institute for Health Research (NIHR) partnership. This will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 7, No. 5. See the NIHR Journals Library website for further project information.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

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The EME programme is funded by the Medical Research Council (MRC) and the National Institute for Health Research (NIHR), with contributions from the Chief Scientist Office (CSO) in Scotland and National Institute for Social Care and Health Research (NISCHR) in Wales and the Health and Social Care Research and Development (HSC R&D), Public Health Agency in Northern Ireland.

This report

The research reported in this issue of the journal was funded by the EME programme as project number 12/170/45. The contractual start date was in November 2015. The final report began editorial review in July 2019 and was accepted for publication in January 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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