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One-year outcomes after low-dose intracoronary alteplase during primary percutaneous coronary intervention: the T-TIME randomized trial

Short title: One-year outcomes after alteplase for primary PCI

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Abbreviations

BARC = Bleeding Academic Research Consortium

CI = confidence interval

MACE = major adverse cardiac events

MACCE = major adverse cardiovascular and cardiac events

MVO = microvascular obstruction

OR = odds ratio

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis in Myocardial Infarction

Key words: ST-segment elevation myocardial infarction; fibrinolysis; primary percutaneous coronary intervention; clinical outcomes.
Microvascular obstruction (MVO), which represents failed myocardial reperfusion, occurs in about half of patients treated with standard primary percutaneous coronary intervention (PCI), and predicts a worse prognosis.\(^1\) Distal embolization and microvascular thrombosis contribute to MVO. In the T-TIME trial (NCT02257294),\(^2\) we hypothesized that low-dose intracoronary fibrinolysis with alteplase, in patients with adequate anticoagulation undergoing primary PCI, would reduce MVO extent as assessed by contrast enhanced cardiovascular magnetic resonance imaging. We found that MVO did not differ with alteplase vs. placebo.\(^2\) Here, we report the efficacy and safety of intracoronary alteplase at 1-year.

From August 2016 to December 2017, patients with acute ST-segment elevation myocardial infarction from 11 U.K. hospitals were prospectively enrolled. The trial design and main results have been described previously.\(^2\) T-TIME was an investigator-initiated, double-blind, parallel-group, randomized, placebo-controlled clinical trial. Patients were eligible if they presented with persistent ST-elevation or recent left bundle branch block, ≤6 hours from symptom onset, and either an occluded culprit artery, or impaired flow (TIMI [Thrombolysis in Myocardial Infarction] flow grade 2) with TIMI thrombus grade ≥2. The study was approved by the West of Scotland Research Ethics Committee (reference 13-WS-0119). Informed consent was obtained.

Patients were randomized to placebo, alteplase 10mg, or alteplase 20mg, on a 1:1:1 basis. The intervention was administered before stent implantation by manual infusion of the 20ml volume of study into the culprit artery proximal to the lesion. Serious adverse events with potential relevance to the pre-defined clinical outcomes, were adjudicated by a blinded clinical event committee. Analysis of efficacy outcomes was according to treatment as randomized. Analysis of major bleeds was based on treatment received. Logistic regression
(adjusted for infarct location) was used to assess for treatment effects. Statistical analyses were performed with Rv3.2.4, according to a pre-specified statistical analysis plan.

Four hundred and forty patients (mean age 61±10 years, 85% male) were randomized to placebo (n=151), alteplase 10mg (n=144) and alteplase 20mg (n=145) (Figure). At 1-year, there was no difference in MACE (major adverse cardiac events) with alteplase 20mg (n=15 [10.3%]) vs. placebo (n=16 [10.6%]) (OR [odds ratio]: 0.96 [95% CI (confidence interval): 0.45, 2.04], or with alteplase 10mg (n=22 [15.3%]) vs. placebo (OR: 1.52 [95% CI: 0.76, 3.05]). There was no difference in spontaneous MACE (MACE excluding MI associated with revascularization) at 1-year with alteplase 20mg (n=14 [9.7%]) vs. placebo (n=16 [10.6%]) (OR: 0.89 [95% CI: 0.42, 1.91]), or with alteplase 10mg (n=18 [12.5%]) vs. placebo (OR: 1.19 [95% CI: 0.58, 2.46]). MI associated with revascularization occurred in 2, 4 and 1 patients at 1-year, randomized to placebo, alteplase 10mg and alteplase 20mg respectively (log rank p=0.351).

MACCE (major adverse cardiovascular and cardiac events), defined as cardiovascular death, non-fatal MI, or unplanned hospitalization for stroke, or transient ischemic attack, did not differ between treatment groups at 1-year (alteplase 20mg [n=10 (6.9%)] vs. placebo [n=7 (4.6%)]; OR: 1.54 [95% CI: 0.57, 4.16]; or alteplase 10mg [n=9 (6.3%)] vs. placebo: OR: 1.38 [95% CI: 0.50, 3.83]). Similarly, there was no difference in the composite of all-cause mortality and heart failure hospitalization, with alteplase 20mg (n=13 [9.0%]) vs. placebo (n=14 [9.3%]) (OR: 0.95 [95% CI: 0.43, 2.12]), or with alteplase 10mg (n=19 [13.2%]) vs. placebo (OR: 1.48 [95% CI: 0.71, 3.12]). There was no difference in heart failure hospitalizations at 1-year with alteplase 20mg (n=10 [6.9%]) vs. placebo (n=13 [8.6%]) (OR: 0.76 [95% CI: 0.32, 1.84]), or with alteplase 10mg (n=15 [10.4%]) vs. placebo (OR: 1.22 [95% CI: 0.55, 2.72]). There was no difference in all-cause death at 1-year, with placebo (n=1 [0.7%]), alteplase 10mg (n=6 [4.2%]), or alteplase 20mg (n=3 [2.1%]) (log-
rank \( p=0.127 \). BARC (Bleeding Academic Research Consortium) type 3-5 bleeds occurred in 1, 2 and 2 patients, with placebo, alteplase 10mg and alteplase 20mg (log-rank \( p=0.792 \)).

In summary, clinical outcomes at 1-year were not improved by adjunctive, low-dose, intracoronary fibrinolysis. Bleeds were uncommon (1.1%) and consistent with what would be expected in a contemporary primary-PCI population. These results should be interpreted as exploratory because the T-TIME trial was designed but not powered to examine 1-year clinical outcomes.

Potential for harm with facilitated PCI, using full- or half-dose fibrinolytic therapy given intravenously pre-PCI, was shown in the ASSENT-4\(^3\) and FINESSE\(^4\) trials.

Intravenous fibrinolytic therapy pre-PCI improved initial culprit artery patency, but increased residual thrombus, ischemic complications and major bleeds, compared to standard primary PCI\(^5\). These results could be explained by inadequate anticoagulation compounded by any paradoxical prothrombotic effects of lytic therapy in P2Y12 inhibitor naive-patients.

Current trials of adjunctive intracoronary fibrinolysis during primary PCI include RESTORE-MI [NCT03998319], STRIVE [NCT0335839], and OPTIMAL [NCT02894138].

Further research should build on the new knowledge arising from T-TIME, to elucidate which patient groups might benefit.

In conclusion, low-dose intracoronary alteplase administered early during primary PCI did not improve clinical outcomes. Further research is warranted to identify new treatments for MVO.
References


Figure. Screening, randomization, treatment, and follow up at one year.

Screening

1527 Patients with acute STEMI were assessed for eligibility

1087 Excluded
838 Lack of inclusion criteria
61 Logistical reasons
18 Declined participation
15 Unable to undergo MRI
155 Other reasons

Randomization

440 Randomized

145 Randomized to receive 20mg of alteplase
1 Did not receive intervention as randomized
1 Received no intervention

144 Randomized to receive 10mg of alteplase
4 Did not receive intervention as randomized
3 Received no intervention
1 Received the incorrect dose (received 20 mg alteplase)

151 Randomized to receive placebo
2 Did not receive intervention as randomized
1 Received no intervention
1 Received the incorrect dose (received 20 mg alteplase)

Treatment

435 Received study drug

146 Received 20mg of alteplase

140 Received 10mg of alteplase

149 Received placebo

Follow up & analysis

Efficacy outcomes:
145 Patients who were randomized to receive 20mg of alteplase had follow up for clinical events at 1 year
0 Loss to follow up for clinical events at 1 year

Efficacy outcomes:
144 Patients who were randomized to receive 10mg of alteplase had follow up for clinical events at 1 year
0 Loss to follow up for clinical events at 1 year

Efficacy outcomes:
151 Patients who were randomized to receive placebo had follow up for clinical events at 1 year
0 Loss to follow up for clinical events at 1 year

MRI = magnetic resonance imaging; STEMI = ST-segment elevation myocardial infarction
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The funder, NIHR-EME, coordinated peer review, approved the design of the study and had oversight of its conduct and management.

Role of Sponsor Statement

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Conflict of Interest Disclosures

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None of the other investigators or committee members have any relevant potential conflict of interest to declare.
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Hany Eteiba, John P. Greenwood, Douglas F. Muir, Saqib Chowdhary, Anthony H Gershlick, Clare Appleby, James M. Cotton, Andrew Wragg, and Nick Curzen, were Local Principal Investigators, obtained informed consent and randomized patients, collected data, interpreted the results and contributed to the manuscript.

Annette M. Maznyczka and Peter J. McCartney contributed to screening and enrolment, collected the data, undertook data analyses and interpreted the data.

Annette M. Maznyczka wrote the original draft of the manuscript.

Annette M. Maznyczka, Thomas J. Ford and Colin Berry served as blinded primary reviewers of serious adverse events, of potential relevance.

Mark C. Petrie helped to design the charter for the clinical event committee, interpreted the data and contributed to the manuscript.

Robin A. Weir chaired the clinical event committee.

Robin A. Weir, Aengus Murphy and Colin J. Petrie adjudicated clinical events, as part of the clinical event committee.

Keith G. Oldroyd, Mitchell Lindsay, Margaret McEntegart, Paul Rocchiccioli, Aadil Shaukat, Richard Good, Stuart Watkins, Keith Robertson, and Christopher Malkin, obtained informed consent and randomized patients, collected data, interpreted the results and contributed to the manuscript.
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Lynsey Gillespie was Project Manager for the trial.

Keith A. Fox chaired the Trial Steering Committee and contributed to the interpretation of the data and the manuscript.

Ian Ford contributed to the study design, data analyses and interpretation, and contributed to the manuscript.

Alex McConnachie, Nitish Ramparsad and Kirsty Wetherall analyzed and interpreted the data and contributed to the manuscript.

Colin Berry conceived the study, obtained the funding, recruited and randomized patients, collected and assessed data blind to treatment group assignment, and interpreted the results.

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