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

First Author: Maznyczka

Authors: Annette M. Maznyczka[1,2] MBChB(Hons), Peter J. McCartney[1,2] MBChB, Hany Eteiba[2] MD, John P. Greenwood[3] PhD, Douglas F. Muir[4] MBChB, Saqib Chowdhary[5] PhD, Anthony H. Gershlick[6] MBBS, Clare Appleby[7] PhD, James M. Cotton[8] MD, Andrew Wragg[9] PhD, Nick Curzen[10] PhD, Keith G. Oldroyd[1,2] MD(Hons), Mitchell Lindsay[2] MD, Margaret McEntegart[2] PhD, J. Paul Rocchiccioli[2] MD, Aadil Shaukat[2] MBBS, Richard Good[2] MD, Stuart Watkins[2] MD, Keith Robertson[2] PhD, Christopher Malkin[4] MD, Lynn Martin[2] BN, Lynsey Gillespie[11] PhD, Robin A. Weir[12] MD, Thomas J. Ford[1] MBChB, Mark C. Petrie[1,2] MBChB, Aengus Murphy[13] MD, Colin J. Petrie[13] PhD, Nitish Ramparsad[14] BSc, Kirsty Wetherall[14] BSc, Keith A. Fox[15] MB ChB, Ian Ford[14] PhD, Alex McConnachie[14] PhD, Colin Berry[1,2] PhD for the T-TIME group.

Institutions: [1]British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, U.K; [2] West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Glasgow, U.K; [3]Leeds University and Leeds Teaching Hospitals NHS Trust, Leeds, U.K; [4]James Cook University Hospital NHS Trust, Middlesbrough, U.K; [5]Manchester University NHS Foundation Trust, Manchester, U.K; [6]Leicester University Hospitals NHS Trust, Leicester, U.K; [7]Liverpool Heart and Chest Hospital NHS Foundation Trust, Liverpool, U.K; [8]Wolverhampton University Hospital NHS Trust, Wolverhampton, U.K; [9]Barts and The London Hospital, London, U.K; [10]University Hospital Southampton Foundation Trust, & School of Medicine, University of Southampton, Southampton, U.K; [11]Greater Glasgow and Clyde Health Board, Glasgow, U.K; [12]University Hospital Hairmyres,

East Kilbride, U.K; [13]University Hospital Monklands, NHS Lanarkshire, UK; [14]Robertson Centre for Biostatistics, Institute of Health and Wellbeing, University of Glasgow, U.K; [15] Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, U.K.

Correspondence: Professor Colin Berry, British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, 126 University Place, University of Glasgow, Glasgow, G12 8TA, Scotland, UK. Telephone: +44 (0) 141 330 1671 or +44 (0) 141 951 5180. Fax +44 (0) 141 330 6794. Email: colin.berry@glasgow.ac.uk

Clinical Trial Registration: ClinicalTrials.gov Identifier NCT02257294

Word count: 799

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.

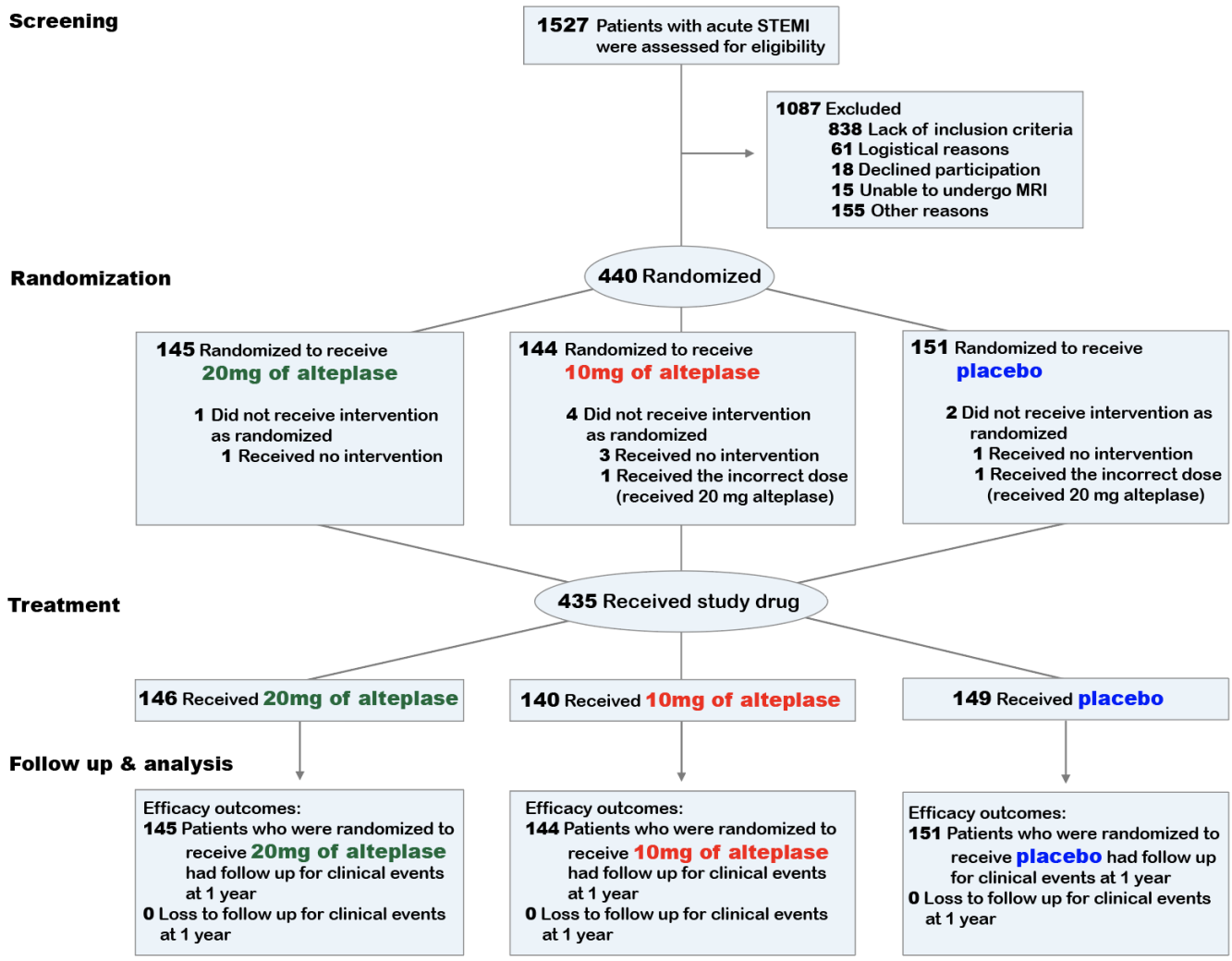
Current trials of adjunctive intracoronary fibrinolysis during primary PCI include RESTORE-MI [NCT03998319], STRIVE [NCT0335839], and OPTIMAL [NCT02894138]. Further research should build on the new knowledge arising from T-TIME, to elucidate which patient groups might benefit.

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

1. van Kranenburg M, Magro M, Thiele H, de Waha S, Eitel I, Cochet A, Cottin Y, Atar D, Buser P, Wu E et al. Prognostic value of microvascular obstruction and infarct size, as measured by CMR in STEMI patients. JACC Cardiovasc Imaging 2014;**7**(9):930-9.
2. McCartney PJ, Eteiba H, Maznyczka AM, McEntegart M, Greenwood JP, Muir DF, Chowdhary S, Gershlick AH, Appleby C, Cotton JM et al. Effect of Low-Dose Intracoronary Alteplase During Primary Percutaneous Coronary Intervention on Microvascular Obstruction in Patients With Acute Myocardial Infarction: A Randomized Clinical Trial. JAMA 2019;**321**(1):56-68.
3. 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):569-78.
4. Ellis SG, Tendera M, de Belder MA, van Boven AJ, Widimsky P, Janssens L, Andersen HR, Betriu A, Savonitto S, Adamus J et al. Facilitated PCI in patients with ST-elevation myocardial infarction. N Eng J Med 2008;**358**(21):2205-17.
5. Zalewski J, Bogaerts K, Desmet W, Sinnaeve P, Berger P, Grines C, Danays T, Armstrong P, Van de Werf F. 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):1867-73.

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



MRI = magnetic resonance imaging; STEMI = ST-segment elevation myocardial infarction

Funding Sources

This work was supported by an NIHR EME Grant (12/170/45) and Boehringer Ingelheim provided the study drugs. AMM was funded by a Fellowship from the British Heart Foundation (BHF, reference FS/16/74/32573). CB and MCP are supported by BHF RE/18/6/34217. The research was part-supported by the National Institute for Health Research (NIHR) infrastructure at Leeds. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the department of health.

Role of Funder Statement

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

The University of Glasgow and Greater Glasgow and Clyde Health Board were independent co-sponsors of the trial. The co-sponsors 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.

Conflict of Interest Disclosures

Annette M. Maznyczka – Fellowship from the British Heart Foundation (reference FS/16/74/32573)
Peter J. McCartney – none
Hany Eteiba – none
Robin A. Weir – none
Aengus Murphy – none
Colin J. Petrie - none
John P. Greenwood – none
Douglas F. Muir – none
Saqib Chowdhary – none
Anthony H. Gershlick – none
Clare Appleby – none
James M. Cotton – none
Andrew Wragg – none
Nick Curzen – has received an unrestricted research grant and fees for lectures and consultancy from Abbott Vascular and Boston Scientific.
Keith G. Oldroyd – none
Mitchell Lindsay – none
Margaret McEntegart – none
Paul Rocchiccioli – none
Aadil Shaukat – none
Richard Good – none
Stuart Watkins – none
Keith Robertson – none
Christopher Malkin – none
Lynn Martin – none
Lynsey Gillespie – none
Nitesh Ramparsad – none
Kirsty Wetherall - none
Thomas J. Ford – none
Mark C. Petrie – none
Keith A. Fox – has received grants and personal fees from Bayer/Janssen, grants from AstraZeneca, personal fees from Sanofi/Regeneron and Verseon.
Ian Ford – none
Alex McConnachie – has received grants from Medical Research Council / NIHR-EME program during the conduct of the study
Colin Berry – based on contracts with the University of Glasgow, Professor Berry has held research and/or consultancy agreements with Abbott Vascular, AstraZeneca, Boehringer Ingelheim, HeartFlow, GSK, Novartis, Philips and Siemens Healthcare. He has held grants from NIHR-EME (reference 12/170/45) and the British Heart Foundation (reference FS/16/74/32573; RE/18/6/34217) in support of the current study.
None of the other investigators or committee members have any relevant potential conflict of interest to declare.

Acknowledgements

Responsible individual at Data Coordinating Centre: Alex McConnachie

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

Author contributions:

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.

Lynn Martin supported screening and enrolment, data collection, and event reporting.

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.

Colin Berry is Chief Investigator and Saqib Chowdhary, Ian Ford, John P. Greenwood, Douglas Muir, and Keith G. Oldroyd were co-applicants on the grant from the National Institute for Health Research – Efficacy and Mechanism Evaluation (NIHR EME) programme (reference: 12/170/45).

We acknowledge the clinical staff and the patients who participated in this project.