A randomised, double blind, placebo-controlled, parallel group Trial of low-dose adjunctive alTeplase during prIMary PCI

(T-TIME)

3 Month Analysis

Statistical Analysis Plan

Study Title:	A randomised, double blind, placebo-controlled, parallel group Trial of low-dose adjunctive alTeplase during prIMary PCI
Short Title:	T-TIME
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Prepared by: Dr Alex McConnachie

Assistant Director of Biostatistics, Robertson Centre for Biostatistics

Approved by: Michele Robertson

Assistant Director Commercial Biostatistics, Robertson Centre for Biostatistics

Prof Ian Ford

Professor of Biostatistics, Robertson Centre for Biostatistics

Professor Colin Berry

Honorary Consultant Physician and Cardiologist, BHF Glasgow CRC, University of Glasgow

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1. INTRODUCTION

1.1. STUDY BACKGROUND

Patients with acute STEMI who present with a blocked coronary artery and/or an artery with a heavy thrombus burden are at increased risk of developing heart failure. This trial aims to enrol patients with a heavy coronary thrombus burden at initial angiography to test the hypothesis that a therapeutic strategy involving reduced dose alteplase given early after coronary reperfusion as a single dose will both prevent and treat distal microvascular thrombosis and microvascular obstruction (MVO). The trial aims to determine the lowest effective dose of alteplase in reducing MVO.

Standard care with primary PCI does not involve alteplase, therefore, the following three arm design is adopted where the alteplase or placebo will be administered at the start of the PCI procedure:

Control Arm:	placebo
Arm A:	alteplase 10mg
Arm B:	alteplase 20mg

The rationale for administering low dose fibrinolytic therapy into the culprit coronary artery at the start of primary PCI (i.e. immediately after coronary reperfusion) is to reduce MVO, infarct size and the future risk of HF.

Since alteplase has a 'deep tissue' half-life of up to 40 minutes, effective local thrombolysis during the procedure with alteplase is intended to treat and reduce persistent MVO at that time.

1.2. STUDY OBJECTIVES

Primary Objective:

To determine the safety and efficacy of reduced doses (10 mg and 20 mg) of intra-coronary alteplase compared with placebo as an adjunct to PCI in reducing MVO and its consequences in high risk patients with STEMI.

Secondary Objectives:

Mechanistic:

To explore mechanisms associated with any beneficial effects of reduced doses of alteplase.

Safety:

To determine the rates of adverse events associated with reduced doses of alteplase administered directly into the coronary artery as an adjunct to PCI.

1.3. STUDY DESIGN

Double-blind, randomised, parallel group, dose-ranging, placebo-controlled clinical trial.

1.4. RANDOMISATION

The study randomisation schedule was stratified by study site, and location of MI (anterior, non-anterior), using the method of randomised permuted blocks of length 6.

1.5. Study Population

Patients with STEMI referred to the participating study centres for primary PCI.

1.5.1. Inclusion Criteria

See section 3.3 of the study protocol.

1.5.2. Exclusion Criteria

See section 3.4 of the study protocol.

1.6. Statistical Analysis Plan (SAP)

1.6.1. SAP Objectives

The objective of this SAP is to describe the statistical analyses to be carried out for the T-TIME Study Final Analysis. This covers primary and secondary outcome data collected up to and including the 3 months assessment. Tertiary outcomes are not covered by this SAP.

1.6.2. General Principles

Efficacy analyses will be carried out according to the intention to treat principle, that is, in relation to randomised treatment allocation, rather than treatment received. Safety analyses will be carried out in relation to treatment received.

Data will be summarised overall and by treatment group. Continuous variables will be summarised as the number of observations, number of missing values, mean, standard deviation, median, quartiles, and range. Categorical variables will be summarised as the number of observations, number of missing values, frequencies, and percentages.

Missing data will not be imputed. No adjustments will be made for multiple comparisons.

1.6.3. Current Protocol

The current study protocol at the time of writing is version 7.0 dated DD/MM/2018. Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary. If no changes are required to this SAP following future amendments to the study protocol, this will be documented as part of the Robertson Centre Change Impact Assessment processes.

1.6.4. Deviations from Protocol

No deviation from the analyses specified in the Protocol are planned.

1.6.5. Additional Analyses

No analyses additional to those specified in the Protocol are planned.

1.6.6. Software

All statistical analyses will be carried out with SAS v9.3 or R v3.2.3 [R Development Core Team 2015] or higher versions of these programs.

2. ANALYSIS

2.1. STUDY POPULATIONS

The Screened Population (SP) will consist of all patients screened for inclusion in the study, as recorded on the study screening logs.

The Full Analysis Set (FAS) will consist of all patients who were randomised. Analyses within the FAS will compare treatment groups as randomised, regardless of which (if any) treatment was received.

The Safety Set (SS) will consist of all patients who were randomised and received treatment. Analyses within the SS will compare treatment groups according to the treatment received.

The numbers of patients included in the SP and FAS will be reported as a whole, and study site, by age, and by sex. Reasons for exclusion from the FAS will be summarised as a whole, by study site, by age, and by sex.

The numbers of patients included in the FAS and SS will be reported as a whole and by treatment group. The numbers of patients in the FAS who did not receive treatment, or received a different treatment to that allocated at randomisation, will be reported.

2.2. BASELINE CHARACTERISTICS

Baseline characteristics will be summarised in the FAS as a whole and by treatment group. The following baseline characteristics will be reported:

- demographics:
    - age (continuous);
    - sex (male, female);
    - SIMD (quintiles);
    - race (white, Asian (Bangladeshi), Asian (Indian), Asian (Pakistani), Asian (other), black (African), black (Carribean), black (other), Chinese, mixed (white and Asian), mixed (white and black African), mixed (white and black Carribean), other);

- mode of admission (one of the following):
    - ambulance direct to PPCI centre;
    - self referral to PPCI centre;
    - ambulance transfer to A&E in another hospital and ambulance transfer to PPCI centre;
    - self referral to A&E in another hospital and ambulance transfer to PPCI centre;
    - ambulance transfer from ward in another hospital;

- treatment times (continuous):
    - time from symptom onset to arrival in PPCI centre;
    - time from symptom onset to first treatment for reperfusion;
    - time from call for help to first treatment for reperfusion;
    - time from arrival in PPCI centre to first treatment for reperfusion;

- vital signs and measurrements (continuous, unless stated otherwise):
    - heart rate;
    - heart rhythm (sinus, not sinus, other);
    - systolic blood pressure, diastolic blood pressure;
    - activated clotting time;
    - height, weight, BMI;
    - infarct location (anterior, inferior, lateral, posterior, other);
    - serum creatinine;
    - eGFR;

- medical history (yes/no, unless stated otherwise):
    - cardiac arrhythmia (none, AF/flutter, sinus arrhythmia);
    - treated hypercholesterolaemia;
    - hypertension;
    - renal impairment (none, stage 1/2, 3A/3B, 4/5);
    - family history of CAD;
    - diabetes (none, type I, type II);
    - smoking (never, former, current – some days, current – every day);
    - previous PCI;
    - previous CABG;
    - previous MI;
    - CCS angina class (no angina, I, II, III, IV);
    - NYHA functional class (no known heart disease, I, II, III, IV);
    - congestive heart failure;
    - COPD;
    - peripheral vascular disease;
    - stroke/TIA;
    - malignancy;

- physical examination (yes/no, unless stated otherwise):
    - presence of heart failure;
    - Killip class (No heart failure, I, II, III, IV);

- medications (yes/no, unless stated otherwise):
    - Aspirin;
    - Anti-platelet medication (none, clopidogrel, ticagrelor, prasugrel, other);
    - Statin;
    - Other lipid lowering drug;
    - Beta blocker;
    - ACE inhibitor;
    - Angiotensin receptor blocker;
    - ACE inhibitor or angiotensin receptor blocker
    - Aldosterone receptor antagonist;
    - Calcium channel blocker;
    - Long acting nitrate;
    - Nicorandil;
    - Alpha blocker;
    - Diuretic;
    - Other cardiac medication;

- standard care blood count (continuous):
    - haemoglobin;
    - platelet count;
    - white cell count;

- standard care blood chemistry (continuous):
    - creatinine;
    - glucose;
    - CRP;
    - troponin;

- coagulation measures:
    - fibrinogen;
    - D-dimer;
    - prothrombin F1+2;
    - tissue plasminogen activator;

- procedure details (yes/no, unless stated otherwise):
    - French size of coronary catheter (5, 6, 7);
    - whether catheter size changed;
    - catheter used for study drug administration (perfusion catheter, thrombectomy catheter, guide catheter, other);

- acute STEMI pathway medications (yes/no, unless stated otherwise):
    - total dose of unfractionated heparin (continuous);
    - minimum ACT, maximum ACT (continuous);
    - morphine;
    - heparin;
    - aspirin;
    - aspirin loading dose (300mg, 600mg, 1200mg);
    - anti-platelet medication (none, clopidogrel, ticagrelor, prasugrel, other);
    - anti-platelet medication dose (continuous – medication specific)
    - bivalirudin;
    - bivalirudin used as bail out;
    - bivalirudin continued in CCU (no, 1 hour, 2 hours, 3 hours, 4 hours, >4 hours);
    - glycoprotein IIb/IIIa antagonist;
    - glycoprotein IIb/IIIa antagonist used as bail out;
    - IV amiodarone;
    - IV amiodarone dose (continuous);
    - low molecular weight heparin;
    - low molecular weight heparin dose (continuous);
    - IV or IC adenosine;
    - IV or IC adenosine dose (continuous);
    - IV or IC metoprolol;
    - IV or IC metoprolol dose (continuous);
    - IV or IC nicorandil;
    - IV or IC nicorandil dose (continuous);
    - IV or IC sodium nitroprusside;
    - IV or IC sodium nitroprusside dose (continuous);
    - IV or IC nitrate;
    - IV or IC nitrate dose (continuous);
    - IV or IC verapamil;
    - IV or IC verapamil dose (continuous);

- non-study coronary treatment (yes/no, unless stated otherwise):
    - type of first non-coronary treatment (aspiration thrombectomy, balloon, primary stent);
    - balloon angioplasy;

- PCI procedure (patient-level data):
    - whether PCI performed (yes, no);
    - TIMI Coronary Flow Grade at initial angiography;
    - TIMI Thrombus Grade at initial angiography;
    - AHA lesion score post-reperfusion;
    - TIMI Coronary Flow Grade pre study drug;
    - Stent thrombosis in infarct-related artery
    - whether pre-stent inflation performed (yes, no);
    - number of arteries treated;
    - left main artery treated (yes, no);
    - left anterior descending artery treated (yes, no);
    - circumflex artery treated (yes, no);
    - right coronary artery treated (yes, no);
    - number of stents deployed;
    - total length of stents deployed;
    - whether post-stent inflation performed (yes, no);

- PCI procedure (treated artery-level data):
    - artery (left main, left anterior descending, circumflex, right coronary)
    - stent type (bare metal, drug eluting, bioresorbable);
    - stent length;
    - stent diameter;
    - total inflation time;
    - maximum pressure;

- study drug administration (yes/no, unless stated otherwise):
    - drug administered;
    - drug administered according to protocol;
    - total drug administration time (continuous).

2.3. EFFICACY OUTCOMES

2.3.1. PRIMARY OUTCOME

The primary outcome will be the extent (% of left ventricular (LV) mass) of microvascular obstruction (MVO) revealed by late (10-15 minutes after contrast administration) gadolinium contrast-enhanced MRI, 2-7 days post-MI.

The primary outcome will be summarised in the FAS as a whole and by treatment group. Treatment groups will be compared with a van Elteren (stratified Wilcoxon-Mann-Whitney) test, stratified by the location of the MI. First, the Alteplase 20mg group will be compared with the placebo group, then the Alteplase 10mg group will be compared with placebo. If the first analysis is not significant at the 5% level, then the low-dose vs. placebo comparison will be considered a secondary analysis.

As a secondary analysis, the primary outcome will be analysed using the same methods as for the secondary outcomes (see section 2.3.2), namely using linear regression.

2.3.2. SECONDARY OUTCOMES

Secondary outcomes will be summarised in the FAS as a whole and by treatment group. Continuous outcomes will be analysed using linear regression, with transformation if necessary to satisfy distributional assumptions, adjusted for the location of the MI. Treatment will be included as a three-level categorical variable, and treatment effects reported for each active treatment group vs. placebo. In addition, the two active treatment groups combined will be compared to the placebo group, using the same methods, though with treatment included as a binary variable. Treatment effect estimates will be reported with 95% confidence intervals (CIs), and p-values. Where no suitable transformation can be found, each active treatment group will be compared to placebo using van Elteren tests, stratified by the location of the MI. Ordinal outcomes will be compared between groups using proportional odds logistic regression models, adjusted for the location of the MI. Binary outcomes will be compared between groups using logistic regression models, adjusted for the location of the MI. Logistic regression model results will be reported as odds ratios for each active treatment group vs. placebo, with 95% CIs and p-values. For those outcomes measured at both 2-7 days and at 3 months, changes between the two time points will be summarised, and regression models of 3 month outcomes will be extended to include an adjustment for the day 2-7 measurement.

The secondary outcomes will be:

Acute

Angiogram

TIMI Coronary Flow Grade at end of PCI — Ordinal

TIMI Myocardial Perfusion Grade at end of PCI	Ordinal
TIMI Frame Count at end of PCI	Continuous
TIMI Thrombus Grade at end of PCI	Ordinal
ECG	
% ST segment resolution on the 12- lead ECG (pre- vs. 60 min post-reperfusion with primary PCI).	Continuous
Day 2 -7	
MRI	
Late MVO (presence / absence) 10-15 minutes after contrast administration	Binary
Infarct size (% of LV)	Continuous
Area at Risk	Continuous
Myocardial salvage index (1-[infarct size/area-at-risk])	Continuous
LV end-diastolic volume (LVEDV)	Continuous
LV end-systolic volume (LVESV)	Continuous
LV ejection fraction (LVEF)	Continuous
Myocardial haemorrhage (presence/absence)	Binary
Myocardial haemorrhage extent (% of LV)	Continuous
Biochemistry	
Troponin T (Area Under Curve at 0, 2, 24 hours)	Continuous
NT-proBNP	Continuous
Quality of life	
EQ5D-5L	Continuous
3 month follow-up	
MRI	
Infarct size	Continuous
Myocardial salvage index (1-[final infarct size/initial area-at-risk])	Continuous
LV end-diastolic volume (LVEDV)	Continuous
LV end-systolic volume (LVESV)	Continuous
LV ejection fraction (LVEF)	Continuous
ECG	
ECG for final infarct size	Continuous
Biochemistry	
NT-proBNP	Continuous
Quality of life	
EQ5D-5L	Continuous

2.3.3. Tertiary Outcomes

The tertiary outcomes are listed in the study protocol, section 2.3. This SAP does not cover the analysis of tertiary outcomes.

2.4. Safety Outcomes

2.4.1. Premature Withdrawal

The number of patients who withdraw from the study prior to the 3 month assessment visit will be summarised for the FAS and SS as a whole and by treatment group. Kaplan-Meier curves will be presented for time to withdrawal by treatment group, and compared with a log rank test.

2.4.2. SERIOUS ADVERSE EVENTS

The characteristics of serious adverse events (SAEs) that occur on or before the date of the 3 month assessment will be summarised as for the SS as a whole and by treatment group. For subjects who withdraw prior to the 3 month assessment, SAEs up to the point of withdrawal will be included. For subjects who did not have a 3 month assessment, but remained in the study, SAEs up to 98 days (14 weeks) from randomisation will be included.

Characteristics of SAEs to be reported are:

- days since randomisation;
- duration (in days);
- severity;
- relationship to study drug;
- whether classified as a SUSAR;
- outcome;
- whether emergency unblinding was required.

The number and percentage of patients with at least one SAE on or before the date of the 3 month assessment will be reported for the SS as a whole and by treatment group, for any SAE and by MedDRA system organ class and preferred term. These summaries will be repeated for fatal SAEs and SUSARs.

2.4.3. ADJUDICATED ENDPOINTS

Health outcomes are included in the 12 month follow-up of study particiants. These will be determined by independent, blinded adjudication of SAEs, and will be analysed as part of the 12 month analysis. For the 3 month analysis, the number and percentage of participants in the SS who experience at least one adjudicated event on or before the date of the 3 month assessment will be reported as a whole and by treatment group.

The following adjudicated events will be reported:

- Major Adverse Cardiovascular and Cardiac Events (MACCE): cardiovascular death, non-fatal MI, unplanned hospitalisation for TIA or stroke;
- Major Adverse Cardiac Events (MACE): cardiac death, non-fatal MI, unplanned hospitalisation for heart failure;
- Spontaneous MACE: MACE, excluding MI associated with revascularisation procedures (Type 4 or 5 MI);
- MI associated with revascularisation procedures (Type 4 or 5 MI);
- All cause mortality or unplanned hospitalisation for heart failure;
- All cause mortality;
- Unplanned hospitalisation for heart failure;
- BARC Type 3, Type 4, and Type 5 bleeding events.

2.4.4. OTHER SAFETY OUTCOMES

Summmaries will be provided for the SS as a whole and by treatment group for the following specific safety outcomes:

- Acute (day of procedure):
    - TIMI Coronary Flow Grade post study drug;
    - no-reflow/slow-reflow/normal flow in main vessel;
    - no-/slow-reflow with TIMI Myocardial Perfusion Grade ≤1;
    - no-/slow-reflow with TIMI Myocardial Perfusion Grade ≤2;
    - intraprocedural thrombotic events (IPTE);
    - cerebral stroke;

- non-serious GI bleeding;
- non-serious peripheral bleeding;
- serious (BARC 3-5) bleeding event;
- coagulation measures at 2 hours, and change from baseline (fibrinogen, D-dimer, prothrombin F1+2, tissue plasminogen activator);
- activated clotting time;

- 24 hours:
  - haemoglobin at 24 hours, and change from baseline;
  - coagulation measures at 24 hours, and change from baseline (fibrinogen, D-dimer, prothrombin F1+2, tissue plasminogen activator)

- Early (Day 2-7):
  - cerebral stroke
  - non-serious GI bleeding;
  - non-serious peripheral bleeding;
  - serious (BARC 3-5) bleeding event.

2.5. Subgroup Analyses

The primary outcome will be summarised in subgroups of the FAS as a whole and by treatment group. For each subgrouping variable, the linear regression model used in the analysis of the primary outcome will be extended to include a main effect for the subgrouping variable, and an interaction between the subgrouping variable and treatment. A likelihood ratio test will be applied to test whether treatment effects vary between subgroups, and subgroup-specific treatment effect estimates will be reported with 95% CIs. Treatment will be modelled as a 3-level categorical variable, and as a binary variable of active treatment vs. placebo.

The following subgrouping variables will be considered:

- age;
- sex;
- location of MI;
- smoking status;
- symptom onset to reperfusion time;
- TIMI Coronary Flow Grade at initial angiography;
- pre-existing anti-platelet therapy.

Continuous variables will be categorised into approximate tertiles for analysis.

3. Document History

This is v1_0 of the Statistical Analysis Plan for T-TIME Final Analysis, dated dd/mm/yyyy. This is the original version of this document.

4. Tables

All statistical tables within the final statistical report will be produced using dummy treatment codes and the content and layout approved prior to database lock.

5. FIGURES

All figures within the final statistical report will be produced using dummy treatment codes and the content and layout approved prior to database lock.

6. LISTINGS

No formal data listings will be produced as part of the final statistical report. All data (raw data and derived analysis datasets) will be made available to the study investigators as Excel files.