Original research

Effect of coronary flow on intracoronary alteplase: a prespecified analysis from a randomised trial

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ABSTRACT

Objectives Persistently impaired culprit artery flow (<TIMI 3) during primary percutaneous coronary intervention is a surrogate for failed myocardial perfusion. We evaluated the effects of intracoronary alteplase according to TIMI flow grade immediately preceding drug administration.

Methods In T-TIME (trial of low-dose adjunctive alteplase during primary PCI), patients ≤6 hours from onset of ST-elevation myocardial infarction (STEMI) were randomised to placebo, alteplase 10 mg or alteplase 20 mg, administered by infusion into the culprit artery, pre-stenting. In this prespecified, secondary analysis, coronary flow was assessed angiographically at the point immediately before drug administration. Microvascular obstruction, myocardial haemorrhage and infarct size were assessed by cardiovascular magnetic resonance (CMR) at 2–7 days and 3 months.

Results TIMI flow was assessed after first treatment (balloon angioplasty/aspiration thrombectomy), immediately pre-drug administration, in 421 participants (mean age 61±10 years, 85% male) and was 3, 2 or 1 in 267, 134 and 19 participants respectively. In patients with TIMI flow ≤2 pre-drug, there was higher incidence of microvascular obstruction with alteplase (alteplase 20 mg (53.1%) and 10 mg (59.5%) combined vs placebo (34.1%); OR=2.47 (95% CI 1.16 to 5.22, p=0.018) interaction p=0.005) and higher incidence of myocardial haemorrhage (alteplase 20 mg (53.1%) and 10 mg (57.9%) combined vs placebo (27.5%); OR=3.26 (95% CI 1.44 to 7.36, p=0.004) interaction p=0.001). These effects were not observed in participants with TIMI 3 flow pre-drug. There were no interactions between TIMI flow pre-drug, alteplase and 3-month CMR findings.

Conclusion In patients with impaired culprit artery flow (<TIMI 3) after initial balloon angioplasty/thrombus aspiration, intra-coronary alteplase was associated with increased presence of microvascular obstruction and myocardial haemorrhage.

Trial registration number NCT02257294.

INTRODUCTION

Despite routinely restoring epicardial coronary patency with primary percutaneous coronary intervention (PCI), microvascular obstruction (MVO) affects about half of patients1 and confers an adverse prognosis.2,3 A key component of MVO is distal embolisation and microvascular thrombosis.4–6

In the T-TIME trial (NCT02257294), we hypothesised that low-dose intracoronary alteplase, administered shortly after balloon angioplasty or aspiration thrombectomy, before stenting, would reduce intracoronary and microvascular thrombosis, and distal embolisation, thereby reducing MVO. However, as assessed by contrast-enhanced cardiovascular magnetic resonance (CMR), MVO did not differ with intracoronary alteplase versus placebo.7 Interestingly, in a T-TIME subgroup analysis, participants presenting ≥4 hours after symptom onset had a dose-dependent increase in mean amount of MVO and myocardial haemorrhage with alteplase versus placebo.7 Invasively measured index of microcirculatory resistance did not differ with intracoronary alteplase versus placebo,9 and there was no difference in clinical outcomes at 1 year between treatment groups.10

Coronary angiography allows a semiquantitative grading of coronary flow, according to the Thrombolysis in Myocardial Infarction (TIMI) flow grades.11 Persistently reduced flow in the culprit coronary artery (TIMI flow <3) after first treatment is termed ‘no-reflow’12 13 TIMI flow <3 is a surrogate for impaired myocardial perfusion14 15 and predicts heart failure,16 larger infarct size14 and mortality16 17 TIMI flow <3 early during the primary PCI procedure (pre-stenting) may be even more closely associated with mortality18–19 and larger infarct size19 than TIMI flow <3 post-stenting. In contrast, recovery of TIMI 3 flow in the culprit artery after first treatment (balloon angioplasty/thrombus aspiration) may help restore microvascular function.15

Persisting impairment of antegrade flow in the culprit artery may influence the effect of intracoronary alteplase. We hypothesised that impaired coronary flow reduces the effective delivery of alteplase
to the microcirculation. The primary aim of this prespecified secondary analysis was to assess the associations between TIMI flow grade, treatment group (placebo, alteplase 10 mg and alteplase 20 mg) and MVO. We also investigated associations between TIMI flow grade, treatment group and the secondary endpoints from the T-TIME trial.10

METHODS

Trial design

T-TIME was a randomised, double-blind, parallel group, phase II clinical trial of low-dose adjunctive intracoronary alteplase during primary PCI.7 10 Patients were enrolled by 11 UK hospitals from March 2016 to December 2017. The methodology has been described previously in detail7 (figure 1).

Consent

Screening and study drug administration occurred during standard care primary PCI. Witnessed verbal assent to participate was obtained in the catheterisation laboratory. Written informed consent was subsequently obtained on the ward.

Eligibility

Patients were eligible to participate if they presented with persistent ST-segment elevation or recent left bundle branch block, ≤6 hours from symptom onset, and with an occluded culprit artery (TIMI 0 flow), TIMI 1 flow (contrast passes beyond the obstruction but fails to opacify the entire distal coronary bed), or reduced coronary flow (TIMI 2 flow, slow but complete filling), in the presence of TIMI thrombus grade ≥2.

Key exclusion criteria (online supplemental methods) included a functional coronary collateral supply (Rentrop grade ≥2) to the culprit artery and cardiogenic shock.

Randomisation and blinding

Participants were randomised using an interactive voice response-based system. The randomisation sequence was computer generated, using the method of randomised permuted blocks of length 6, with stratification by location of myocardial infarction (MI) (anterior vs non-anterior). The allocation sequence was on a 1:1:1 basis, between placebo and the reduced dose of alteplase groups (10 mg and 20 mg), that is, one-tenth or one-fifth, of
standard dose. The participants, staff and researchers were blinded to the treatment group allocation.

Interventions
The trial protocol encouraged achieving TIMI flow grade ≥2, using balloon angioplasty/aspiration thrombectomy, prior to randomisation. After randomisation, the allocated intervention was prepared, during which TIMI flow grade deteriorated in a minority of patients prior to study drug administration, before stent deployment. The 20 mL volume of study drug was manually infused into the culprit artery, over 5–10 min, proximal to the culprit lesion, using either an intracoronary catheter or the guiding catheter if selectively engaged.

Cardiovascular magnetic resonance
CMR (1.5 Tesla) was analysed by an investigator who was blind to the angiographic findings and treatment allocation. A second read was undertaken by a cardiologist with level 3 CMR certification. MVO presence and extent (% left ventricular (LV) mass) was revealed by late gadolinium enhancement (LGE), 10–15 min after administration of gadolinium-based contrast media. MVO was defined as a dark zone on early gadolinium enhanced imaging 1, 3, 5 and 7 min post-contrast injection that persisted within an area of LGE at 15 min. The myocardial mass of the dark zone was quantified by manual delineation and expressed as % of LV mass.

Myocardial haemorrhage presence and extent (% LV mass) was revealed by T2* mapping. A region of reduced signal intensity within the infarcted area, with a T2* value <20 ms was considered to confirm the presence of myocardial haemorrhage. This area was manually delineated and expressed as % LV mass.

The presence of acute infarction was established based on abnormalities in cine wall motion, rest first-pass myocardial perfusion and LGE imaging in two imaging planes. The myocardial mass of late gadolinium was quantified using a 5 standard deviation (SD) semiautomated method and expressed as % of total LV mass. Myocardial salvage was calculated by subtraction of percent infarct size from percent area at risk (as reflected by the extent of oedema), and the myocardial salvage index was calculated by dividing the myocardial salvage area by the initial area at risk.

MVO and myocardial haemorrhage were reported on CMR scans acquired 2–7 days post-STEMI. The other CMR parameters were reported from the 2–7 day and 3-month scans (online supplemental file 1).

Angiography, ECGs and troponin
The ECGs and angiographic parameters were determined by blinded core laboratory analysis (blinded to CMR data and treatment allocation).

The angiograms were analysed prospectively by one researcher, and then a second read was undertaken by an experienced interventional cardiologist. Discrepancies were resolved by consensus agreement. The following were assessed in the culprit artery: TIMI flow grade, TIMI frame count, myocardial perfusion grade, TIMI thrombus grade and plaque characteristics (online supplemental file 1).

The angiogram acquisition protocol required stored fluoroscopy of study drug administration to enable verification by the core laboratory that the guide catheter was selectively engaged in the culprit artery during drug delivery. This also enabled core laboratory evaluation of TIMI flow grade immediately before study drug administration, which was submitted to the data coordination centre prior to database lock. Participants were grouped according to TIMI flow grade (≤2 vs 3) in the culprit artery immediately preceding study drug administration.

The absolute percentage ST-segment resolution on ECGs obtained 60 min after reperfusion (ie, after initial restoration of flow in the culprit artery), compared with pre-reperfusion, was calculated. Troponin T area under the curve was measured in blood samples obtained immediately pre-reperfusion (0 hours), then at 2-hour and 24-hour post-reperfusion.

Coagulation
Coagulation and haemostasis parameters were measured in peripheral blood samples taken pre-reperfusion, then 2-hour and 24-hour post-reperfusion. The parameters included fibrinogen and plasminogen (both measures of systemic fibrinolysis), fibrin D-dimer (a measure of fibrin lysis), tissue plasminogen activator (a measure of endogenous fibrinolytic system activation and circulating alteplase) and prothrombin fragment F1+2 (a measure of thrombin generation).

Statistical analysis
This study was a prespecified secondary analysis in the T-TIME trial population. The analyses were performed according to treatment received (alteplase 20 mg, 10 mg or placebo). The trial endpoints were assessed using linear regression (continuous variables), or logistic regression (binary variables), to make treatment effect estimates. In regression models, logarithmic or square root transformations were used where necessary to improve model residual distributions. As MVO extent was not normally distributed, we adopted square root transformation for MVO extent, in keeping with the analysis plan for the main T-TIME trial. However, as 56% of patients had zero values for MVO extent, we also performed a sensitivity analysis using bootstrapping CIs to model this endpoint. Regression models were used to assess treatment effects through interactions, with treatment as three-level and two-level categorical variables. The regression analyses were adjusted for the location of MI (anterior vs non-anterior). All tests were two tailed and assessed at the 5% significance level. There was no imputation for missing values, and there were no adjustments for multiple statistical comparisons. Given the high proportion of participants with a 0 value for MVO extent and myocardial haemorrhage extent, the median values for MVO and myocardial haemorrhage were 0 for all groups; therefore, the mean (SD) values were reported, despite not being ideal summaries for these data. Data were analysed using R (V3.6.1, R Development Core Team, Auckland, New Zealand) and SPSS (V25.0).

RESULTS
Population
Four hundred and forty participants were randomised to placebo, alteplase 10 mg or alteplase 20 mg. Nineteen patients were excluded from the analysis (figure 2): in seven patients, TIMI flow grade was unevaluable immediately before study drug administration; in five participants, study drug was not given; in three participants, study drug was administered post-stent implantation; and in four participants, study drug was administered distal to the lesion.

The analysis therefore included 421 participants (mean age 61±10 years, 85% male). Out of the 421 participants who were included, one participant who was randomised to 10 mg of alteplase received 20 mg and one participant randomised to placebo received 20 mg of alteplase because of handling errors.
Coronary artery disease

The baseline and procedural characteristics for participants with TIMI flow ≤2 (n=154) or TIMI 3 flow (n=267) pre-study drug were broadly similar (tables 1 and 2 and online supplemental table 1).

The distribution of TIMI flow grades immediately before study drug administration was as follows: TIMI grade 0 in one participant (0.2%), who received alteplase 10 mg; TIMI grade 1 in 19 participants (4.5%), of whom eight received placebo, four received alteplase 10 mg and seven received alteplase 20 mg; TIMI grade 2 in 134 participants (31.8%), of whom 42 received placebo, 44 received alteplase 10 mg and 48 received alteplase 20 mg; and TIMI grade 3 in 267 participants (63.4%), of whom 92 received placebo, 88 received alteplase 10 mg and 87 received alteplase 20 mg.

Figure 2  Study flow diagram. CMR follow-up is reported according to treatment received. CMR, cardiovascular magnetic resonance; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.
Table 1  Baseline characteristics, by subgroups of TIMI flow grade (≤2 vs 3) immediately before study drug administration

|                          | Impaired coronary flow (TIMI flow ≤2) | Normal coronary flow (TIMI 3 flow) |
|--------------------------|--------------------------------------|-------------------------------------|
|                          | All (n=154)                          | Placebo (n=50)                      |
|                          | Alteplase 10 mg (n=49)               | Alteplase 20 mg (n=55)              |
| Age 59.5±10.7            | 59.5±11.3                            | 58.7±11.3                           |
| Male                     | 134 (87)                             | 44 (88)                             |
| White                    | 143 (93)                             | 46 (92)                             |
| Asian                    | 9 (6)                                | 3 (6)                               |
| Body mass index (kg/m²)  | 28.4±4.8                             | 29.1±5.6                            |
| Heart rate at presentation, beats/min | 73.7±17.2                           | 72.1±16.2                           |
| Systolic blood pressure at presentation, mm Hg | 132.4±22.9                           | 134.8±23.8                           |
| Diastolic blood pressure at presentation, mm Hg | 81.1±14.7                            | 81.1±14.3                           |
| Infarct location:        | 81 (53)                              | 26 (52)                             |
|                          | 73 (47)                              | 24 (48)                             |
|                          | 53 (34)                              | 18 (36)                             |
|                          | 2 (1)                                | 1 (2)                               |
|                          | 1 (1)                                | 1 (2)                               |
|                          | 40 (26)                              | 15 (30)                             |
|                          | 20 (13)                              | 5 (10)                              |
| Smoking:                 |                                       |                                     |
| Current                  | 75 (49)                              | 29 (53)                             |
| Former (stopped >3 months) | 32 (21)                             | 23 (47)                             |
| Never                    | 47 (31)                              | 33 (33)                             |
| Previous PCI             | 4 (3)                                | 4 (2)                               |
| Angina                   | 2 (1)                                | 1 (2)                               |
| Previous myocardial infarction | 2 (1)                              | 2 (4)                               |
| Stroke/transient ischaemic attack | 0                                   | 0                                   |
| Peripheral vascular disease | 3 (2)                              | 2 (4)                               |
| Pre-existing maintenance medication: |                                       |                                     |
| Aspirin                  | 16 (10)                              | 5 (10)                              |
| clopidogrel              | 1 (1)                                | 1 (2)                               |
| Ticagrelor or prasugrel  | 4 (3)                                | 3 (8)                               |
| Statin                   | 31 (20)                              | 9 (16)                              |
| Beta blocker             | 14 (9)                               | 4 (7)                               |
| ACE inhibitor or ARB     | 30 (20)                              | 10 (20)                             |
| Mineralocorticoid receptor antagonist | 2 (1)                              | 0                                   |
| Symptom onset to arrival at primary PCI centre, median (IQR), hours | 2.2 (1.6–3.4)                        | 2.1 (1.5–3.8)                        |
| Arrival at primary PCI centre to reperfusion, median (IQR), hours | 0.4 (0.3–0.6)                        | 0.4 (0.3–0.6)                        |
| Symptom onset to reperfusion, median (IQR), hours | 2.7 (2.1–3.8)                        | 2.9 (2.1–3.8)                        |
| Initial blood results on admission: |                                       |                                     |
| Haemoglobin, g/dL        | 147.3±13.2                           | 144.9±15.1                          |
|                          | 145.7±11.0                           | 151.0±12.5                          |
|                          | 144.6±13.3                           | 145.9±13.6                          |
|                          | 143.8±12.8                           | 143.8±12.8                          |

Continued
In multivariable logistic regression analysis, only anterior MI was associated with TIMI flow ≤2 pre-study drug (OR 1.61 (95% CI 1.07 to 2.43), p=0.023). Ischaemic time (symptom onset to reperfusion time) was not associated with TIMI flow ≤2 immediately pre-study drug (OR 1.05 (95% CI 0.91 to 1.22), p=0.499).

**CMR parameters**

CMR was performed in 387 participants (92%) at 2–7 days (table 3 and online supplemental table 2) and in 358 participants (85%) at 3 months post-STEMI (table 4 and online supplemental table 2). The CMR results (2–7 days) stratified by location of MI are shown in online supplemental table 3. Baseline/procedure characteristics were similar for patients who had MVO data available (n=383) versus those with missing MVO data (n=38) (online supplemental tables 4 and 5). This suggests that data were missing at random, and the impact of missing data should be affecting each treatment group in a similar way.

Mean MVO extent was higher in patients who had TIMI flow ≤2 (3.7%±6.0%) vs TIMI 3 flow (2.3%±4.2%) immediately pre-drug (coefficient: 0.33 (95% CI 0.05 to 0.60), p=0.022 (derived from linear regression, using square root transformed MVO)).

In participants with TIMI 3 flow pre-study drug, there were no associations between alteplase and infarct characteristics, apart from an increase in LV end-diastolic volume with alteplase 10 mg versus placebo (tables 3 and 4 and online supplemental table 2).

**Microvascular obstruction**

Participants with TIMI flow ≤2 pre-study drug had MVO present more often with alteplase (placebo: 34.1% (n=15/44); alteplase 10 mg: 59.5% (n=25/42); alteplase 20 mg: 53.1% (n=26/49); OR for alteplase 10 mg and 20 mg combined versus placebo 2.47 (95% CI 1.16 to 5.22), p=0.018 (table 3 and figure 3A). Interactions were observed for association with MVO presence, between TIMI flow pre-drug, and treatment analysed as three-level, or two-level categorical variables (p=0.013 and p=0.005, respectively) (table 3). When the 19 patients with TIMI 1 flow and the one patient with TIMI 0 flow immediately pre-drug were excluded, significant interactions remained between alteplase, TIMI flow pre-drug (2 vs 3) and the presence of MVO (p=0.022) (online supplemental table 6).

Participants with TIMI flow ≤2 pre-drug had increased extent of MVO (% LV mass) with alteplase (placebo 2.6%±5.7%, alteplase 10 mg 2.7%±3.9%, alteplase 20 mg 5.4%±7.4%, estimated mean difference (for MVO analysed on a square root scale) alteplase 20 mg and 10 mg combined versus placebo 0.53 (95% CI 0.06 to 1.00), p=0.027 (table 3). There was an interaction between MVO extent (% LV mass), TIMI flow pre-drug and treatment when alteplase 10 mg and 20 mg were combined versus placebo (p=0.041) but not for treatment as a three-level categorical variable (p=0.070) (table 3). On bootstrap linear regression analysis, 20 mg alteplase was associated with MVO extent when compared with placebo in patients with TIMI flow ≤2 pre-drug (mean difference: 3.37 (95% CI 0.77 to 6.89), p=0.016) but not in patients with TIMI three flow pre-drug (mean difference: 1.91 (95% CI –0.74 to 3.01), p=0.287) (online supplemental table 7).
Table 2  Procedure characteristics by subgroups of TIMI flow grade (≤2 vs 3) immediately before study drug administration

| Procedure characteristics | Impaired coronary flow (TIMI flow ≤2) | Normal coronary flow (TIMI 3 flow) |
|---------------------------|---------------------------------------|-----------------------------------|
|                           | All (n=154)                           | Placebo (n=50)                    | Alteplase 10 mg (n=49) | Alteplase 20 mg (n=55) | All (n=267) | Placebo (n=92) | Alteplase 10 mg (n=87) | Alteplase 20 mg (n=88) |
| Culprit artery*:*         |                                       |                                   |                        |                         |             |                 |                            |                            |
| left anterior descending   | 82 (53)                               | 26 (52)                           | 27 (55)                | 29 (53)                 | 109 (41)    | 40 (44)          | 35 (40)                      | 34 (39)                      |
| Circumflex                | 12 (8)                                | 3 (6)                             | 3 (6)                  | 6 (11)                  | 41 (15)     | 16 (17)          | 14 (16)                      | 11 (13)                      |
| Right coronary artery      | 60 (39)                               | 21 (42)                           | 19 (39)                | 20 (36)                 | 117 (44)    | 36 (39)          | 38 (44)                      | 43 (49)                      |
| Multivessel disease*:*    |                                       |                                   |                        |                         |             |                 |                            |                            |
| 1                         | 112 (73)                              | 34 (68)                           | 34 (69)                | 44 (80)                 | 165 (62)    | 62 (67)          | 52 (60)                      | 51 (58)                      |
| 2                         | 37 (24)                               | 13 (26)                           | 14 (29)                | 19 (38)                 | 80 (30)     | 25 (27)          | 27 (31)                      | 28 (32)                      |
| 3                         | 5 (3)                                 | 3 (6)                             | 1 (2)                  | 1 (2)                   | 22 (8)      | 5 (5)            | 8 (9)                        | 9 (10)                       |
| Initial TIMI coronary flow grade*†: |                                       |                                   |                        |                         |             |                 |                            |                            |
| 0 (no flow)               | 112 (77)                              | 41 (82)                           | 38 (78)                | 40 (73)                 | 216 (81)    | 81 (88)          | 67 (77)                      | 68 (77)                      |
| 1 (minimal flow)          | 9 (6)                                 | 2 (4)                             | 2 (4)                  | 5 (9)                   | 23 (9)      | 1 (1)            | 12 (14)                      | 10 (11)                      |
| 2 (slow but complete flow) | 25 (16)                              | 7 (14)                            | 8 (16)                 | 10 (18)                 | 23 (9)      | 8 (9)            | 6 (7)                        | 9 (10)                       |
| 3 (normal flow)           | 1 (1)                                 | 0                                 | 1 (2)                  | 0                       | 5 (5)       | 2 (2)            | 2 (2)                        | 1 (1)                        |
| Initial TIMI thrombus grade*‡: |                                       |                                   |                        |                         |             |                 |                            |                            |
| 0–2                       | 0                                     | 0                                 | 0                      | 0                       | 0          | 0               | 0                            | 0                            |
| 3                         | 3 (2)                                 | 1 (2)                             | 1 (2)                  | 1 (2)                   | 8 (3)       | 2 (2)            | 1 (1)                        | 5 (6)                        |
| 4                         | 32 (21)                               | 9 (18)                            | 9 (18)                 | 14 (26)                 | 43 (16)     | 9 (18)           | 19 (22)                      | 15 (17)                      |
| 5                         | 119 (77)                              | 40 (80)                           | 39 (80)                | 40 (73)                 | 216 (81)    | 81 (88)          | 67 (77)                      | 68 (77)                      |
| Mode of reperfusion:      |                                       |                                   |                        |                         |             |                 |                            |                            |
| Aspiration thrombectomy   | 45 (29)                               | 12 (24)                           | 14 (29)                | 19 (35)                 | 74 (28)     | 23 (25)          | 28 (32)                      | 23 (26)                      |
| Balloon angioplasty       | 109 (71)                              | 38 (76)                           | 35 (71)                | 36 (66)                 | 192 (72)    | 69 (75)          | 59 (68)                      | 64 (73)                      |
| Primary stent             | 0                                     | 0                                 | 0                      | 0                       | 1 (0.4)     | 0               | 0                            | 1 (1)                        |
| Balloon angioplasty pre-stent | 144 (94)                          | 48 (96)                           | 46 (94)                | 50 (91)                 | 244 (91)    | 83 (90)          | 82 (94)                      | 79 (90)                      |
| Method of study drug delivery: |                                       |                                   |                        |                         |             |                 |                            |                            |
| Thrombectomy catheter     | 112 (73)                              | 38 (76)                           | 36 (74)                | 38 (69)                 | 188 (70)    | 65 (71)          | 58 (67)                      | 65 (74)                      |
| Guide catheter            | 35 (23)                               | 10 (20)                           | 9 (18)                 | 16 (29)                 | 65 (24)     | 21 (23)          | 26 (30)                      | 18 (21)                      |
| Other                     | 7 (5)                                 | 2 (4)                             | 4 (8)                  | 1 (2)                   | 14 (5)      | 6 (7)            | 3 (3)                        | 5 (6)                        |
| PCI with stent implantation | 152 (99)                          | 50 (100)                          | 48 (96)                | 54 (98)                 | 266 (100)   | 91 (99)          | 87 (100)                     | 88 (100)                     |
| Post-stent dilatation     | 133 (86)                              | 48 (96)                           | 42 (86)                | 43 (78)                 | 233 (87)    | 76 (83)          | 76 (87)                      | 81 (92)                      |
| Total length of stents deployed from QCA (mm) * | 32.7±14.4                            | 32.9±13.8                         | 35.2±16.2              | 30.2±13.1              | 34.5±14.4   | 34.9±13.3        | 34.8±14.2                    | 33.9±14.7                    |
| QCA reference vessel diameter post-stent (mm) * | 3.3±0.5                              | 3.2±0.5                           | 3.3±0.6                | 3.2±0.4                | 3.1±0.4     | 3.2±0.5          | 3.2±0.4                      | 3.2±0.4                      |
| Loading with aspirin at first medical contact | 135 (88)                          | 44 (88)                           | 43 (88)                | 48 (87)                 | 230 (86)    | 78 (85)          | 77 (89)                      | 75 (85)                      |
| Aspirin loading dose, mg, no./total (%): |                                       |                                   |                        |                         |             |                 |                            |                            |
| 300                       | 133/135 (99)                          | 44/44 (100)                       | 42/43 (98)             | 47/48 (98)             | 220/230 (96) | 73/78 (94)       | 74/77 (96)                    | 73/75 (97)                    |
| >300                      | 2/135 (2)                             | 0                                | 1/43 (2)               | 1/48 (2)               | 10/230 (4.3) | 5/78 (8)         | 3/77 (4)                      | 2/75 (3)                      |
### Table 2  Continued

|                     | Impaired coronary flow (TIMI flow ≤2) | Normal coronary flow (TIMI 3 flow) |
|---------------------|--------------------------------------|-----------------------------------|
|                     | All (n=154)                          | Placebo (n=50) | Alteplase 10 mg (n=49) | Alteplase 20 mg (n=55) | All (n=267) | Placebo (n=92) | Alteplase 10 mg (n=87) | Alteplase 20 mg (n=88) |
| Additional antiplatelet medication at first medical contact |                                      |                     |                       |                     |                  |                              |                              |                           |
| None                | 18 (12)                              | 5 (10)             | 5 (10)                | 8 (15)               | 30 (11)           | 12 (13)          | 8 (9)                  | 10 (11)                  |
| Clopidogrel         | 55 (36)                              | 20 (40)            | 20 (41)               | 15 (27)              | 90 (34)           | 26 (28)          | 29 (33)               | 35 (40)                  |
| Ticagrelor          | 75 (49)                              | 24 (48)            | 22 (45)               | 29 (53)              | 142 (53)          | 53 (58)          | 49 (56)               | 40 (46)                  |
| Prasugrel           | 6 (4)                                | 1 (2)              | 2 (4)                 | 3 (6)                | 5 (2)             | 1 (1)            | 1 (1)                 | 3 (3)                    |
| Unfractionated heparin, median (IQR), U            | 10 0000 (8000.0–13 000.0) | 10 0000 (8000.0–15 000.0) | 10 0000 (8000.0–12 000.0) | 10 0000 (7000.0–12 000.0) | 10 0000 (7000.0–13 000.0) | 10 0000 (5000.0–13 000.0) | 10 0000 (7000.0–13 000.0) |
| Activated clotting time (s)                          | 276.3±89.8                          | 264.3±89.8         | 303.4±97.6           | 263.0±78.3         | 284.0±87.4       | 280.8±88.5       | 294.9±88.5           | 276.1±85.2              |
| Intravenous morphine                                    | 114 (74)                            | 37 (74)            | 38 (78)              | 39 (71)             | 197 (74)         | 62 (67)          | 64 (74)               | 71 (81)                  |
| Inhaled oxygen, no./total (%)                          | 28/151 (19)                         | 8/49 (16)          | 14/48 (29)           | 6/54 (11)          | 32/259 (12)      | 1490 (15)        | 10/85 (12)            | 8/84 (10)               |
| Glycoprotein IIb/IIIa antagonist, no./total (%)        | 28/151 (19)                         | 6/49 (12)          | 11/48 (23)           | 11/54 (20)         | 38/259 (15)      | 8/90 (9)         | 17/85 (20)            | 13/84 (16)              |
| Duration of study drug infusion (min)                  | 6.6±2.0                             | 6.9±2.1            | 6.5±2.0              | 6.5±1.9             | 6.4±1.9          | 6.2±1.9          | 6.4±1.9               | 6.7±2.0                  |
| Days from PCI to 2–7 days CMR, median (IQR)            | 4.0 (3.0–6.0)                       | 4.0 (3.0–6.0)      | 4.0 (3.0-6.0)        | 4.0 (2.8–6.0)      | 4.0 (3.0–6.0)    | 4.0 (2.8–5.0)    | 5.0 (3.0–6.0)         | 4.0 (4.0–6.0)            |
| Days from PCI to 3-month CMR, median (IQR)             | 91.0 (85.0–98.8)                    | 91.0 (85.0–97.0)   | 92.0 (86.0–99.5)     | 90.0 (85.0–99.0)   | 90.0 (86.0–95.3) | 90.0 (85.8–94.0)  | 90.0 (86.0–96.0)       | 91.0 (86.0–97.0)         |

None of the participants received intravenous or intracoronary treatment with bivalirudin, metoprolol, nicorandil, or sodium nitroprusside.

Missing: body mass index (calculated as weight in kg divided by height in meters squared): 2; creatinine: 68; eGFR: 68; haemoglobin: 16; platelets: 30.

Data are reported according to treatment received (n=421). Data are mean±SD or n (%) unless otherwise stated.

*The angiographic parameters are based on central laboratory assessments.*

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

‡TIMI thrombus grade allows the classification of thrombus burden (greatest dimension) revealed during coronary angiography. TIMI thrombus grade: 0: no thrombus; 1: possible thrombus, with reduced contrast density, haziness, irregular lesion contour; 2: definite thrombus less than half the vessel diameter; 3: definite thrombus greater than half, but less than 2 vessel diameters; 4: definite thrombus greater than or equal to 2 vessel diameters; 5: total occlusion.

CMR, cardiovascular magnetic resonance; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; TIMI, Thrombolysis in Myocardial Infarction.
Myocardial haemorrhage

Myocardial haemorrhage presence/absence was evaluable in 366 participants at 2–7 days, and myocardial haemorrhage extent was evaluable in 348 participants.

In participants with TIMI flow ≤2 pre-study drug, myocardial haemorrhage occurred more often with alteplase than placebo (alteplase 20 mg: 53.1% (26/49), alteplase 10 mg: 57.9% (n=22/38) vs placebo: 27.5% (n=11/40); OR for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs placebo: 3.26 (95% CI 1.44 to 7.36), p=0.004) (figure 3A). Interactions for alteplase 10 mg and 20 mg combined vs place
TABLE 4  Analysis of CMR parameters 3 months after primary PCI, by subgroups of TIMI flow grade (≤2 versus 3) immediately before study drug administration (adjusted for MI location (anterior vs non-anterior))

| Treatment group | Treatment effect | Interaction p value (treatment as a three-level categorical variable) | Treatment effect (treatment as a two-level categorical variable) |
|-----------------|------------------|----------------------------------------------------------|----------------------------------------------------------|
|                 | Placebo (n=142)† | Alteplase 10 mg versus placebo | Alteplase 20 mg versus placebo | Alteplase 10 mg versus placebo | Alteplase 20 mg versus placebo | Alteplase 10 mg versus placebo | Alteplase 20 mg versus placebo |
| Infarct size (% LV mass)* | TIMI flow ≤2 | 21.3±14.7 | 22.1±11.3 | 23.9±13.0 | 1.11 (−3.61 to 5.83) | 0.645 (p=0.242) | 2.73 (−1.84 to 7.3) | 0.488 (p=0.675) |
| | TIMI 3 flow | 17.5±11.2 | 16.3±10.3 | 16.2±10.3 | −1.09 (−4.57 to 2.39) | 0.539 (p=0.675) | −0.74 (−4.17 to 2.7) | 0.675 (p=0.552) |

Myocardial salvage index*  
TIMI flow ≤2 | 0.5±0.3 | 0.5±0.2 | 0.5±0.2 | 0.0 (−0.09 to 0.10) | 0.929 (p=0.437) | −0.04 (−0.13 to 0.06) | 0.844 (p=0.675) | −0.02 (−0.10 to 0.07) | 0.623 (p=0.671) |
TIMI 3 flow | 0.6±0.2 | 0.6±0.2 | 0.6±0.2 | 0.02 (−0.05 to 0.09) | 0.596 (p=0.940) | 0.0 (−0.07 to 0.07) | 0.01 (−0.05 to 0.07) | 0.801 (p=0.800) |

LV ejection fraction (%)  
TIMI flow ≤2 | 47.4±11.9 | 47.3±8.7 | 46.8±9.2 | −0.26 (−3.83 to 3.32) | 0.889 (p=0.696) | −0.69 (−4.15 to 2.77) | 0.805 (p=0.754) | −0.49 (−3.55 to 2.57) | 0.632 (p=0.632) |
TIMI 3 flow | 50.8±6.8 | 49.1±7.3 | 49.9±7.9 | −1.7 (−4.31 to 0.90) | 0.201 (p=0.389) | −1.13 (−3.71 to 1.44) | 0.389 (p=0.216) | −1.41 (−3.65 to 0.82) | 0.216 (p=0.164) |

The p values and 95% CI have not been adjusted for multiplicity; therefore, these analyses should be interpreted as exploratory and not definitive.

Treatment effect estimates and interaction with treatment received are shown (see footnotes). Data are mean±SD or median (IQR) unless otherwise stated.
* Treatment effect estimates reported as mean differences between groups.
† Data analysed on a logarithmic scale. Treatment effect estimates reported as relative difference between groups.
‡ Missing data: infarct size (n=66); myocardial salvage index (n=72); LV ejection fraction (n=63).
CMR, cardiovascular magnetic resonance; LV, left ventricular; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

or two-level categorical variables (p=0.004 and p=0.001, respectively) (table 3). When the 19 patients with TIMI 1 flow and the one patient with TIMI 0 flow immediately pre-drug were excluded, significant interactions remained between alteplase, TIMI flow pre-drug (2 vs 3) and the presence of myocardial haemorrhage (p=0.009) (online supplemental table 6).

Infarct size, myocardial salvage index, LV ejection fraction and LV volumes at 2–7 days and 3 months
An interaction was observed for association with infarct size (2–7 days), between TIMI flow and treatment analysed as a two-level categorical variable (p=0.026). Similar findings were observed for myocardial salvage index at 2–7 days post-STEMI (table 3).

In participants with TIMI flow ≤2 pre-study drug, alteplase was not associated with LV ejection fraction or LV volumes 2–7 days post-STEMI (table 3, online supplemental table 2) or at 3 months (table 4, online supplemental table 2).

Angiographic and ECG parameters
The interobserver reliability for TIMI flow grade pre-study drug, assessed in 65 consecutive participants, was excellent (kappa=0.94). Occlusion of the culprit coronary artery after study drug administration occurred in 44 out of 334 patients (13%). There were no interactions between TIMI flow pre-drug, alteplase and angiographic or ECG surrogates of failed microvascular reperfusion (online supplemental table 8).

Blood chemistry
There were no interactions between TIMI flow pre-drug, alteplase and troponin T measured in 306 participants (online supplemental table 8).

Coagulation
Regarding coagulation data (table 5, online supplemental table 9), there was an increase in fibrin D-dimers (a product of fibrin lysis) and decrease in plasminogen and fibrinogen, 2-hours post-primary PCI relative to baseline, with alteplase versus placebo, regardless of TIMI flow grade pre-drug. This is consistent with what is expected following intra-arterial fibrinolysis. There was an increase in prothrombin fragment F 1+2 (a measure of lysis) and decrease in plasminogen and fibrinogen, 2- hours post-PCI relative to baseline, with alteplase vs placebo, regardless of TIMI flow grade pre-drug (table 5).

DISCUSSION
Low-dose adjunctive intracoronary alteplase administered early during primary PCI was associated with increased MVO and myocardial haemorrhage in participants who had TIMI flow ≤2 pre-drug administration (figure 3A). These effects were not observed in participants with normalised TIMI 3 flow.

Our findings contrast with a previous study (n=95), which reported smaller infarct size at 6 months in patients given intracoronary streptokinase immediately post-primary PCI. Differences between the previous study and ours include the fact, increased fibrin D-dimer and lower plasminogen concentrations were observed with alteplase in patients with TIMI flow ≤2 pre-drug (table 5, and online supplemental table 9),
Figure 3  Summary of main findings and potential mechanisms. (A) Forest plots showing increased MVO and myocardial haemorrhage presence associated with alteplase versus placebo in participants with TIMI flow ≤2 at the time of study drug administration. (B) In participants with reduced antegrade flow in the culprit artery (TIMI flow ≤2), there may have been increased microvascular exposure to higher local concentrations of alteplase for longer. TIMI coronary flow ≤2 may indicate ongoing impaired myocardial reperfusion due to extensive microvascular damage. In these circumstances, intracoronary fibrinolysis appears to worsen MVO and extravasation of erythrocytes, resulting in myocardial haemorrhage in the infarct core and potentially promotes microvascular thrombosis. An increase in extravasation of blood into the interstitial space results in external compression of capillaries with an associated increase in microvascular resistance. This leads to a further reduction in myocardial blood flow and exacerbates myocardial necrosis and capillary destruction, which promotes further myocardial haemorrhage. CMR, cardiovascular magnetic resonance; MVO, microvascular obstruction; TIMI, Thrombolysis in Myocardial Infarction.
Table 5  Analysis of coagulation variables at 2 hours compared with baseline by subgroups of TIMI flow grade (≤2 vs 3) immediately before study drug administration (adjusted for MI location (anterior vs non-anterior))

| Treatment group | Treatment effect | Interaction p value | Interaction p value |
|-----------------|-------------------|--------------------|--------------------|
| Placebo (n=142) |                   |                    |                    |
| Placebo (n=142) |                   |                    |                    |
| Alteplase 10 mg (n=136) | | | |
| Alteplase 20 mg (n=143) | | | |
| Alteplase 10 mg versus placebo | | | |
| Alteplase 20 mg versus placebo | | | |
| Ratio of fibrinogen at 2 hours relative to baseline * | | | |
| TIMI flow ≤2 | 1.00 (1.00–1.14) | 1.03 (0.90–1.17) | 0.97 (0.90–1.05) |
| TIMI 3 flow | 1.00 (0.90–1.11) | 1.00 (0.90–1.10) | 1.00 (0.90–1.14) |
| Change in plasminogen (U/dL) at 2 hours relative to baseline † | | | |
| TIMI flow ≤2 | 1.0 (−2.0 to 3.0) | −3.0 (−9.5 to 4.5) | −10.0 (−15.0 to −6.0) |
| TIMI 3 flow | 1.0 (−3.3 to 5.0) | −5.0 (−11.0 to −0.8) | −9.5 (−16.0 to −4.0) |
| Ratio of fibrin D-dimer at 2 hours relative to baseline * | | | |
| TIMI flow ≤2 | 1.1 (1.0–1.3) | 3.2 (2.2–6.3) | 3.8 (2.0–6.2) |
| TIMI 3 flow | 1.1 (0.9–1.5) | 3.4 (2.2–4.6) | 4.9 (3.2–7.4) |
| Ratio of prothrombin fragment F1+2 at 2 hours relative to baseline * | | | |
| TIMI flow ≤2 | 1.1 (0.9–1.3) | 1.3 (1.1–1.6) | 1.2 (1.0–1.6) |
| TIMI 3 flow | 1.1 (0.9–1.4) | 1.2 (0.9–1.5) | 1.3 (1.1–1.6) |
| Ratio of tissue plasminogen activator at 2 hours relative to baseline * | | | |
| TIMI flow ≤2 | 1.1 (0.0–3.0) | 1.4 (1.2–1.7) | 1.5 (1.2–2.0) |
| TIMI 3 flow | 1.1 (−0.3 to 2.0) | 1.3 (1.1–1.7) | 1.3 (1.1–1.7) |

The p values and 95% CI have not been adjusted for multiplicity; therefore, these analyses should be interpreted as exploratory and not definitive. Significant p values are highlighted in bold.

Treatment effect estimates and interaction with treatment received are shown (see footnotes). Data are median [IQR], unless otherwise stated.

*Data analysed on a logarithmic scale. Treatment effect estimates reported as relative difference between groups.
†Missing data: change in coagulation parameters at 2 hours relative to baseline (n=80).
which indicates that fibrinolysis did indeed occur in this group of participants.

Our findings may be related to the undesired procoagulant effects of fibrinolytic therapy (figure 3B). In circumstances of slow microvascular flow, intracoronary alteplase potentially promotes the procoagulant effects of alteplase, thereby promoting microvascular thrombosis and worsening MVO. Indeed, increased prothrombin fragment F$_{1+2}$ concentrations were observed with intracoronary alteplase (table 5), despite therapeutic anticoagulation with heparin, indicating thrombin generation and increased risk of thrombosis.

Our findings may suggest that in circumstances of reduced antegrade flow, myocardial perfusion is reduced leading to prolonged, higher local concentrations of alteplase due to reduced washout of alteplase from the microcirculation. TIMI 3 flow is not synonymous with normal myocardial perfusion; for example, in our population 42% of patients with TIMI 3 flow pre-study drug administration had MVO present. However, participants with TIMI flow ≤2 immediately pre-study drug had more extensive microvascular injury, evidenced by these patients having significantly more MVO than the patients with TIMI 3 flow pre-drug. Myocardium with extensive microvascular damage from coronary occlusion is characterised by loss of capillary integrity. In these circumstances, intracoronary fibrinolysis appears to worsen extravasation of erythrocytes, resulting in myocardial haemorrhage in the infarct core (an irreversible manifestation of persistent MVO). An increase in extravasation of blood into the interstitial space of the infarct core results in external compression of capillaries, which worsens MVO (figure 3B).

Insights from previous studies of glycoprotein IIb/IIIa inhibitors are consistent with our findings. An animal study demonstrated an increased incidence of myocardial haemorrhage with the addition of intracoronary glycoprotein IIb/IIIa inhibitors, and in humans, periprocedural glycoprotein IIb/IIIa inhibitors have also been associated with myocardial haemorrhage.

Our findings are relevant to clinicians when considering bail-out lytic therapy in acute STEMI patients with massive thrombus and angiographic ‘no reflow’. Our findings are also relevant to ongoing clinical trials. Notably, the RESTORE-MI trial (NCT03998319) is randomising patients with STEMI (n=800) to adjunctive intracoronary tenecteplase or placebo, in a double-blind design, during primary PCI. For the RESTORE-MI trial, a key inclusion criteria is a post-stent index of microcirculatory resistance >32 in the culprit artery, which signifies incomplete microvascular reperfusion and microvascular dysfunction. Our analyses raise the possibility that low-dose intracoronary lytic therapy in patients with STEMI, who have incomplete reperfusion at the end of PCI, may not reduce infarct pathology and, indeed, may be harmful. Nonetheless, there are important differences in the design of T-TIME as compared with RESTORE-MI, such as the timing of study drug administration (before or after stent implantation, respectively) and the lytic agent (alteplase vs tenecteplase).

**Strengths and limitations**

Strengths of our study include the double-blind design, high follow-up rates with CMR, core-lab analyses and the fact that TIMI flow grade immediately pre-study drug administration was prospectively analysed and was submitted to the data coordination centre prior to database lock. However, due to the potential for type 1 statistical error, the findings should be interpreted as exploratory/hypothesis generating.
Coronary artery disease

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Contributors AMM wrote the manuscript. AMM and CB conceived the idea for the manuscript. AMM, CB and MM performed the angiogram analyses. AMM, PD and AM performed the statistical analyses. PMcC and CB analysed the magnetic resonance images. PMac analysed the ECGs. RCT analysed the coagulation data. JG, KGO, MM, CB, DM, SC, AHG, CA, HE, JC, AW and NC contributed to data acquisition. KAAF, RCT and NC contributed to interpreting the data and revising the work critically for intellectual content. All authors made the decision to submit. CB is guarantor.

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