6030

Effects of adjunctive treatment with low-dose alteplase during primary percutaneous coronary intervention according to ischaemic time

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Background: Microvascular obstruction affects half of patients with acute ST-segment elevation myocardial infarction and confers an adverse prognosis.

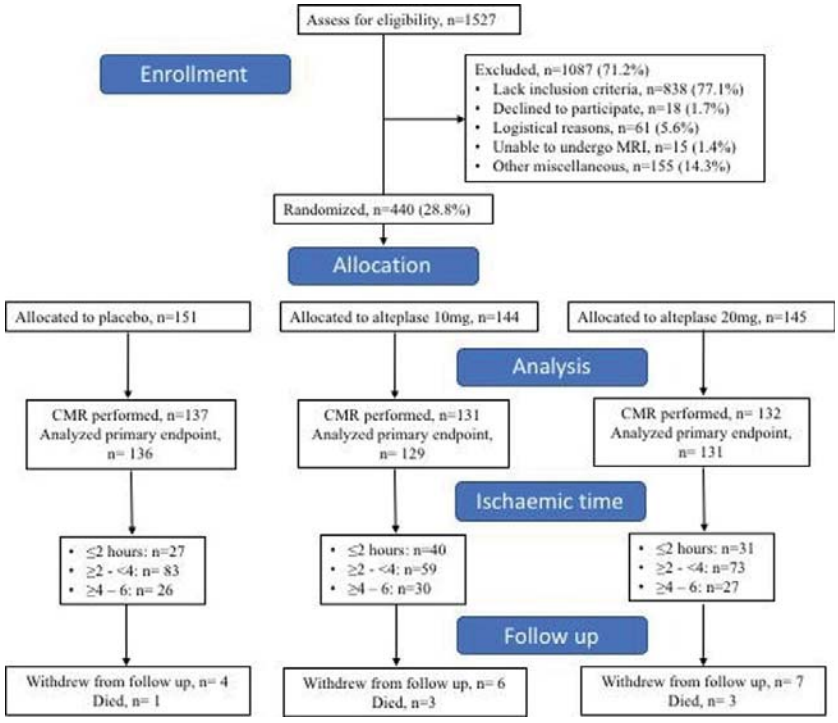
Purpose: We aimed to determine whether the efficacy and safety of a therapeutic strategy involving low-dose intra-coronary alteplase infused early after coronary reperfusion associates with ischaemic time.

Methods: We conducted a prospective, multicentre, parallel group, 1:1:1 randomised, dose-ranging trial in patients undergoing primary percutaneous coronary intervention. Ischaemic time, defined as the time from symptom onset to coronary reperfusion, was a pre-specified sub-group of interest. Between March 17, 2016, and December 21, 2017, 440 patients presenting at 11 hospitals in the UK were enrolled with follow up to 3 months. Patients with acute myocardial infarction due to occlusion of a major coronary artery presenting ≤6 hours from symptom onset were randomly assigned to treatment with placebo, alteplase 10mg or alteplase 20mg. The primary outcome was the amount of microvascular obstruction disclosed by cardiac magnetic resonance imaging at 2–7 days. Secondary outcomes included infarct size, myocardial haemorrhage, left ventricular ejection fraction, and troponin T area-under-the curve.

Results: 440 patients were randomized (figure), the primary endpoint was achieved in 396 (90%), seventeen (3.9%) withdrew and all other patients were followed up to 3 months. In the primary analysis, the amount of microvascular obstruction did not differ between the groups. Their ischaemic times were: ≤2 hours, n=98; ≥2–<4 hours, n=215; and ≥4–6 hours, n=83. In patients with an ischaemic time ≥4 hours, treatment with alteplase (10 mg, n=26; 20 mg, n=30) was associated with a dose dependent increase in the amount (mean) of microvascular obstruction (% left ventricular mass) compared to placebo (n=27) 1.14 vs. 3.11 vs. 5.20; mean difference on square root scale 0.81 (95% CI 0.21, 1.42), p=0.009. The interaction test between ischaemic time and treatment (active vs. placebo) was not statistically significant p=0.06, however when the interaction was assessed for a trend across treatment groups this did reach statistical significance, p=0.018.

Furthermore, a higher proportion of patients presenting ≥4–6 hours treated with 20 mg of alteplase had myocardial haemorrhage (59.3%) compared to the placebo group (28.0%), odds ratio 3.81 (95% CI 1.19, 12.25), p=0.025. The amount of haemorrhage was also greater; estimated mean difference 3.49 (95% CI 1.22, 5.75), p=0.0026. No between-treatment group differences for myocardial haemorrhage were observed in patients presenting with shorter ischaemic times.

Conclusions: In patients presenting with an ischaemic time ≥4 hours, adjunctive treatment with low-dose intra-coronary alteplase during primary PCI was associated with increases in microvascular obstruction and myocardial haemorrhage. The mechanism may involve haemorrhagic transformation within the infarct core.



Study flow diagram