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Statistical analysis plan for the 'Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2' (RIGHT-2)

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INTRODUCTION

Most effective interventions for acute stroke are time limited so that treatment has to be commenced within 4.5 hours (intravenous alteplase) or 6 hours (mechanical thrombectomy) of ictus (1-3). Within these time windows, efficacy is time-dependent with the greatest benefit occurring when treatment starts very early after stroke onset (2, 3). These interventions are only appropriate for ischaemic stroke and require prior brain scanning to exclude intracerebral haemorrhage. Further, they are both expensive. There are no definitive treatments for patients with spontaneous intracerebral haemorrhage (ICH) although intensive blood pressure (BP) lowering in the hyperacute period may be effective, as is recommended in guidelines (4-6). One approach to accelerating the onset of treatment is to deliver interventions before hospital admission with recruitment at the emergency scene or in the ambulance. Several pilot trials have assessed a variety of interventions including magnesium, insulin, remote ischaemic conditioning, and BP lowering (7-15). A common feature of these treatments is that prior brain imaging is not required, although successful studies of mounting a CT scanner and point of care laboratory in an ambulance have also been performed in patients with suspected stroke (16). Recently, the FAST-Mag trial showed that it was feasible to deliver a large phase III trial in the pre-hospital arena, at least in the US emergency care system and with medical support and consent via telephone (17).

Nitric oxide donors

In view of their multi-modal effects, nitric oxide (NO) donors are candidate treatments for acute stroke (18, 19). NO is a mixed arterial and venous vasodilator, modulates vascular and neuronal function, and inhibits apoptosis. As such, it is a key neurovascular modulator and yet circulating levels are low in acute stroke (20). Preclinical stroke studies have shown that supplementation of NO with donors reduce stroke lesion size if given very early in a variety of stroke models, and improves regional cerebral blood flow in permanent models of stroke (21). Four small clinical studies of glyceryl trinitrate (GTN), a NO donor that can be administered transdermally, in patients with recent stroke found that it reduced blood pressure (an independent risk factor for a poor outcome (22-24)) and pulse pressure; had no effects on middle cerebral artery blood flow velocity, cerebral blood flow, or intracranial pressure; did not alter platelet activity (so GTN can be given in ICH);

improved vascular compliance; and had no apparent safety concerns (14, 25-27). In the last of these pilot studies (Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial (RIGHT)), GTN was administered by paramedics in the ambulance within 4 hours of stroke onset and significantly improved functional outcome (14). The large Efficacy of Nitric Oxide in Stroke (ENOS) trial (4,011 patients recruited from 173 sites in 23 countries) found that GTN was safe to administer but did not modify outcome if given within 48 hours of stroke onset (28); however, functional outcome was improved in those patients recruited within 6 hours (a pre-specified subgroup) (28, 29), this result mirroring that seen in RIGHT (30).

Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2) trial

On the basis of pre-clinical data for NO donors, and clinical data showing feasibility, tolerability and safety of GTN, and the potential for efficacy if given very early after stroke, the RIGHT-2 trial is assessing the safety and efficacy of GTN when administered by paramedics in the pre-hospital environment to 850 patients from across the UK, as detailed in the trial's published protocol (31). The primary outcome and analysis is a comparison of the modified Rankin Scale between treatment groups assessed using ordinal logistic regression. The present paper details the statistical analysis plan (SAP), as given in the accompanying supplement. This information is presented blinded to treatment assignment and prior to locking of the trial database so that analyses are not data-driven or selectively reported (32). Following on from the ENOS trial and its protocol (33), this SAP includes not just information on the primary publication (GTN vs no GTN) but also describes information on additional planned publications, including baseline characteristics, and a series of secondary publications.

Data sharing

Once completed, data from RIGHT-2 will be added to summary and individual patient data (IPD) meta-analyses in acute stroke, first those focusing on nitric oxide donors (30, 34), and then of blood pressure lowering (through the 'Blood pressure in Acute Stroke Collaboration', BASC) (35, 36). IPD will be made available to the 'Virtual International Stroke Trials Archive' (VISTA) (37), and subsequently over the web, as with the International Stroke Trial (38). Similarly, anonymised baseline and on-treatment neuroimaging data will be published (39).

Supporting information

Additional supporting information may be found in the online version of this article with the accompanying Supplement (RIGHT-2 SAP Supplement).

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