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

Polly Scutt,[1] Jason P Appleton,[1] Mark Dixon,[1] Lisa J Woodhouse,[1] Nikola Sprigg,[1] Joanna M Wardlaw,[2] Alan A Montgomery,[3] Stuart Pocock,[4] Philip M Bath,[1] on behalf of the RIGHT-2 Trialists

[1] Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, Nottingham, UK
[2] Neuroimaging Sciences, University of Edinburgh, Edinburgh, UK
[3] Clinical Trials Unit, University of Nottingham, Nottingham, UK
[4] Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK

Correspondence: Professor Philip M Bath
Stroke Trials Unit
Division of Clinical Neuroscience
University of Nottingham
City Hospital campus
Nottingham NG5 1PB UK

Email: philip.bath@nottingham.ac.uk
Twitter: @right2trial
Url: http://right-2.ac.uk

Keywords
Acute stroke, antihypertensive therapy, glyceryl trinitrate, nitroglycerin, randomised controlled trial, cerebrovascular disorders, statistical analysis plan

Word count: 2,058

Conflict of Interest: None declared

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 strokeTrial-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).

References

1. Wardlaw JM, Murray V, Berge E, del Zoppo G. Thrombolysis for acute ischaemic stroke. Cochrane Database of Systematic Reviews 2014;7(CD000213).
2. Emberson J, Lees K, Lyden P, et al. Effect of treatment delay, age and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. The Lancet 2014;384(9958):1929-35.
3. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;397(10029):1723-31.
4. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med 2013;368(25):2355-65.
5. Hemphill J, Greenberg S, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage. Stroke 2015;46(7):2032-60.
6. Steiner T, Al-Shahi Salman R, Beer R, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. International Journal of Stroke 2014;9(7):840-55.
7. Saver JL, Kidwell C, Eckstein M, Starkman S, for the FAST-MAG Pilot Trial Investigators. Prehospital neuroprotective therapy for acute stroke. Results of the field administration of stroke therapy-magnesium (FAST-~MAG) pilot trial. Stroke 2004;35:106-8.
8. Kostopoulos P, Walter S, Haass A, et al. Mobile stroke unit for diagnosis-based triage of persons with suspected stroke. Neurology 2012;78(23):1849-52.
9. Walter S, Kostopoulos P, Haass A, et al. Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: a randomised controlled trial. The Lancet Neurology 2012;11(5):397-404.
10. Nurmi J, Lindsberg PJ, Happola O, Klemetti E, Westerbacka J, Castren M. Strict glucose control after acute stroke can be provided in the prehospital setting. Acad Emerg Med 2011;18(4):436-9.

11. Hougaard K, Hjort N, Zeidler D, et al. Remote ischemic perconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial. Stroke 2013;45:159-67.
12. Shaw L, Price L, McLure S, et al. Paramedic Initiated Lisinopril For Acute Stroke Treatment (PIL-FAST): results from the pilot randomised controlled trial. Emergency Medicine Journals 2013;31(12):994-9.
13. Ankolekar S, Sare G, Geeganage C, et al. Determining the Feasibility of Ambulance-Based Randomised Controlled Trials in Patients with Ultra-Acute Stroke: Study Protocol for the "Rapid Intervention with GTN in Hypertensive Stroke Trial" (RIGHT, ISRCTN66434824). Stroke Res Treat 2012;2012:385753.
14. Ankolekar S, Fuller M, Cross I, et al. Feasibility of an ambulance-based stroke trial, and safety of glyceryl trinitrate in ultra-acute stroke: the rapid intervention with glyceryl trinitrate in Hypertensive Stroke Trial (RIGHT, ISRCTN66434824). Stroke 2013;44(11):3120-8.
15. Shaw L, Price C, McLure S, Howel D, McColl E, Ford G. Paramedic Initiated Lisinopril For Acute Stroke Treatment (PIL-FAST): study protocol fo a pilot randomised controlled trial. Trials 2011;12(152).
16. Kunz A, Ebinger M, Geisler F, et al. Functional outcomes of pre-hospital thrombolysis in a mobile stroke treatment unit compared with conventional care: an observational registry study. Lancet Neurol 2016;15(10):1035-43.
17. Saver J, Starkman S, Eckstein M, et al. Prehospital use of magnesium sulfate as neuroprotection in acute stroke. The New England Journal of Medicine 2015;372(6):528-36.
18. Willmot MR, Bath PMW. The potential of nitric oxide therapeutics in stroke. Expert Opinion Investigational Drugs 2003;12(3):455-70.
19. Srivastava K, Bath PM, Bayraktutan U. Current therapeutic strategies to mitigate the eNOS dysfunction in ischaemic stroke. Cellular and molecular neurobiology 2012;32(3):319-36.
20. Rashid PA, Whitehurst A, Lawson N, Bath PMW. Plasma nitric oxide (nitrate/nitrite) levels in acute stroke and their relationship with severity and outcome. JStroke CerebrovascDis 2003;12(2):82-7.
21. Willmot M, Gray L, Gibson C, Murphy S, Bath PMW. A systematic review of nitric oxide donors and L-arginine in experimental stroke; effects on infarct size and cerebral blood flow. Nitric Oxide 2005;12:141-9.
22. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA. Blood pressure and clinical outcomes in the International Stroke Trial. Stroke 2002;33(5):1315-20.

23. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. Hypertension 2004;43(1):18-24.
24. Sprigg N, Gray LJ, Bath PM, et al. Relationship between outcome and baseline blood pressure and other haemodynamic measures in acute ischaemic stroke: data from the TAIST trial. J Hypertens 2006;24(7):1413-7.
25. Bath PMW, Pathansali R, Iddenden R, Bath FJ. The effect of transdermal glyceryl trinitrate, a nitric oxide donor, on blood pressure and platelet function in acute stroke. Cerebrovascular diseases (Basel, Switzerland) 2001;11:265-72.
26. Rashid P, Weaver C, Leonardi-Bee JA, Fletcher S, Bath FJ, Bath PMW. The effects of transdermal glyceryl trinitrate, a nitric oxide donor on blood pressure, cerebral and cardiac haemodynamics and plasma nitric oxide levels in acute stroke. J Stroke Cerebrovasc Dis 2003;13:143-51.
27. Willmot M, Ghadami A, Whysall B, Clarke W, Wardlaw J, Bath PMW. Transdermal Glyceryl Trinitrate Lowers Blood Pressure and Maintains Cerebral Blood Flow in Recent Stroke. Hypertension 2006;47:1209-15.
28. Bath P, Woodhouse L, Scutt P, et al. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. The Lancet 2015;385(9968):617-28.
29. Woodhouse L, Scutt P, Krishnan K, et al. Effect of hyperacute administration (within 6 hours) of transdermal glyceryl trinitrate, a nitric oxide donor, on outcome after stroke: subgroup analysis of the Efficacy of Nitric Oxide in Stroke (ENOS) trial. Stroke 2015;46:3194-201.
30. Bath P, Woodhouse L, Krishnan K, et al. Effect of treatment delay, stroke type, and thrombolysis on the effect of glyceryl trinitrate, a nitric oxide donor, on outcome after acute stroke: a systematic review and meta-analysis of individual patient from randomised trials. Stroke Research and Treatment 2016;2016:9706720.
31. Appleton JP, Scutt P, Dixon M, et al. Ambulance-delivered transdermal glyceryl trinitrate versus sham for ultra-acute stroke: Rationale, design and protocol for the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2) trial (ISRCTN26986053). Int J Stroke 2017:1747493017724627.
32. Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. Lancet 2001;357(9253):373-80.
33. Bath PM, Houlton A, Woodhouse L, et al. Statistical analysis plan for the 'Efficacy of Nitric Oxide in Stroke' (ENOS) trial. International Journal of Stroke 2014;9(3):372-4.

34. Bath PM, Krishnan K, Appleton JP. Nitric oxide donors (nitrates), L-arginine, or nitric oxide synthase inhibitors for acute stroke. Cochrane Database Syst Rev 2017;4:CD000398.
35. Blood pressure in Acute Stroke Collaboration (BASC), Bath FJ, Iddenden RG, Bath PMW. How should blood pressure be managed in acute stroke? A systematic review of individual patient data from randomised controlled trials. Cerebrovascular Diseases 1999;9 (suppl 1):103 (abstract).
36. Bath PM, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database of Systematic Reviews 2014;(10): CD000039.pub3.doi: 10.1002/14651858.CD000039.
37. Ali M, Bath PMB, Davis SM, et al. The virtual international stroke trials archive (VISTA). Stroke 2007;38:1905-10.
38. Sandercock PA, Niewada M, Czlonkowska A. The International Stroke Trial database. Trials 2011;12(1):101.
39. Wardlaw J, Bath P, Sandercock P, et al. The NeuroGrid stroke examplar clinical trial protocol. International Journal of Stroke 2007;2:63-9.