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Safety and efficacy of intensive versus guideline antiplatelet therapy in high risk patients with recent ischaemic stroke or transient ischaemic attack: a randomised controlled trial

Short title:	Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke.
Acronym:	TARDIS
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SYNOPSIS

Title	Safety and efficacy of intensive versus guideline antiplatelet therapy in high risk patients with recent ischaemic stroke or transient ischaemic attack (TIA): a randomised controlled trial
Acronym	TARDIS
Short title	Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke
Trial Summary	Recurrence is greatest immediately after stroke or TIA; existing prevention strategies (antithrombotic, lipid/blood pressure lowering, carotid endarterectomy) reduce, not abolish, further events. Dual antiplatelet therapy – aspirin & clopidogrel for coronary disease, aspirin & dipyridamole for stroke - is superior to aspirin monotherapy. Triple antiplatelet therapy reduces MI and death in patients with coronary disease. We have shown that it is feasible to give triple antiplatelet therapy (aspirin, clopidogrel, dipyridamole) to patients with ischemic stroke/TIA. We will assess the efficacy, safety, tolerability and feasibility of intensive (combined aspirin, dipyridamole and clopidogrel) versus guideline antiplatelet therapy (combined aspirin and dipyridamole or clopidogrel) given for 1 month in ~1000 patients (over ~4 years) with acute stroke/TIA (i.e. at high risk of recurrence) in the start-up phase of a large randomised controlled trial. This will seamlessly run into the main phase of the trial (total 4100 patients) over the next 5 years providing safety information from the start up phase allows. The primary outcome is ordinal stroke severity at 90 days. Secondary outcomes include safety, serious adverse events, vascular events, death and platelet function.
Chief Investigator	Professor Philip Bath
Primary Objective	The trial will assess ordinal stroke severity: 5-level ordinal stroke and TIA scale with stroke ordered by its severity using the modified Rankin Scale (mRS): fatal stroke / severe non-fatal stroke (mRS 2-5) / mild stroke (mRS 0,1) / TIA / no stroke-TIA, measured at 90 days.
Trial Design	International, collaborative, multicentre, parallel group prospective, randomised, open-label blinded-endpoint, controlled Phase III trial.
Setting	In the start-up phase, patients will be recruited from the UK Stroke Research Network Centres. Further expansion within the UK and overseas will occur in the main phase.
Sample size estimate	The start-up phase is sized to assess safety and will inform the sample size calculation for the main trial phase, which will assess the efficacy of intensive versus guideline therapy. Assuming the distribution in 5 level recurrent stroke/TIA outcome (stroke with mRS 6 =0.1%/ mRS 2-5 = 0.7%/ mRS 0-1 = 1.53%/ TIA = 3.57%), odds ratio of 0.68, alpha 5%, power 90%, losses to follow-up 2%, treatment crossovers 5% the total sample size for the whole study is 4100.

Number of participants	Start up: ~1000; main phase: 3100
Eligibility criteria	Adults at high risk of recurrent ischaemic stroke: 1. Acute high risk TIAs $\leq$48 hours of onset All TIAs must have limb weakness and/or dysphasia lasting at least 10 minutes. 2. Ischaemic, non cardioembolic stroke with limb weakness, dysphasia or hemianopia ≤48 hours of onset with neuroimaging to rule out alternative causes. 3. Meaningful consent, or consent from a relative, carer or legal representative if the patient is unable to give consent (e.g. in cases of dysphasia, confusion, or reduced conscious level).
Description of interventions	Intensive versus guideline antiplatelet therapy will be given for 28 to 30 days along with standard 'best care' (including lifestyle advice, BP and lipid lowering). Randomised patients will receive clopidogrel (loading dose 300 mg, then 75 mg daily), aspirin (loading dose 300 mg, then 75 mg daily), and dipyridamole (modified release 200 mg twice daily), or guideline antiplatelet therapy (aspirin and dipyridamole or clopidogrel, doses as above), .
Duration of study	8 years
Randomisation and blinding	Patients will be randomised through the trial website with stratification and minimisation. Outcome assessments are blinded.
Outcome measures	**Primary:** Ordinal stroke severity at 90 days. **Secondary:** Binary and ordinal outcomes of stroke, TIA, MI, acute coronary syndrome, composite vascular outcome, death. Also safety (ordinal bleeding events), tolerability and feasibility. Additional measures include laboratory measures (FBC and P-Selectin), clinical efficacy (NIHSS), function (mRS, BI), cognition (TICS), quality of life (EuroQoL, EQ-5D), mood (Zung), disposition, days at home and economic activity.
Statistical methods	Ordinal logistic regression on ordered categorical outcomes, binary logistic regression on binary outcomes, analysis of covariance (ANCOVA) on continuous data and Kaplan-Meier and Cox proportional hazards regression on time to event data. Analyses will be adjusted for randomisation/minimisation factors. Subgroup analyses will only be performed in the main trial phase