

# Triple versus guideline antiplatelet therapy to prevent recurrence after acute ischaemic stroke or transient ischaemic attack: the TARDIS RCT

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## Scientific summary

### The TARDIS RCT

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# Scientific summary

## Background

Stroke is devastating to patients, carers and society through high mortality, morbidity and cost. Both stroke incidence and prevalence will increase as the UK population ages. Following stroke or transient ischaemic attack (TIA), the risk of recurrence is high, especially immediately after the event after which it falls. Typically, recurrent strokes are more severe than earlier events.

The archetypal antiplatelet, aspirin, reduces recurrence by 17% in patients with prior stroke or TIA. Clopidogrel is slightly more efficacious than aspirin, especially in high-risk patients. Dipyridamole reduces recurrence with comparable efficacy to aspirin. The combination of aspirin and dipyridamole is more effective than either drug alone.

In acute cerebral ischaemia, aspirin is effective, but two agents may be superior, as shown in a large Chinese trial of combined aspirin and clopidogrel (Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, *et al.* Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013;**369**:11–19), and a meta-analysis of this and other smaller trials involving this combination, and aspirin and dipyridamole (Wong KS, Wang Y, Leng X, Mao C, Tang J, Bath PM, *et al.* Early dual versus mono antiplatelet therapy for acute non-cardioembolic ischemic stroke or transient ischemic attack: an updated systematic review and meta-analysis. *Circulation* 2013;**128**:1656–66).

The Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS) trial was designed to extend this observation by investigating the safety and efficacy of intensive antiplatelet treatment with three drugs as compared with guideline therapy.

## Objectives

The main objective was to compare the safety and efficacy of intensive versus guideline antiplatelet therapy for participants with acute ischaemic stroke and TIA. A second objective was to test and demonstrate the use of ordinal trial outcomes, including recurrent stroke and TIA, bleeding, and adverse events.

## Methods

The TARDIS trial was an international prospective randomised open-label blinded end-point superiority clinical trial.

## Setting

The trial enrolled patients from 106 hospitals in the UK, Denmark, Georgia and New Zealand.

## Participants

Participants were > 50 years of age with acute non-cardioembolic ischaemic stroke or TIA within 48 hours of ictus (or 24–48 hours if they had received thrombolysis). Participants with a TIA had to score  $\geq 4$  on the ABCD2 scale [which takes account of age (A), blood pressure (B), clinical symptomology (C), duration of symptoms (D), and presence of diabetes (D)], already be on two antiplatelet agents, or have a crescendo TIA. Those with an ischaemic stroke had to have one or more of limb weakness, dysphasia or hemianopia. Patients were excluded if they had isolated sensory or vertiginous symptoms (or only facial weakness), intracranial haemorrhage or presumed cardioembolic cerebral ischaemia.

### Randomisation

Participants were allocated at random to 1 month of antiplatelet agents comparing intensive (combined aspirin, clopidogrel and dipyridamole) versus guideline therapy.

### Interventions

Originally, the guideline therapy comprised the combination of aspirin and dipyridamole, but clopidogrel alone was added following a change in National Institute for Health and Care Excellence (NICE) guidance in 2010 [NICE. *Clopidogrel and Modified Release Dipyridamole for the Prevention of Occlusive Vascular Events. Technology Appraisal Guidance (TA210)*. London: NICE; 2010]. Aspirin and clopidogrel were each given as a loading dose (300 mg) followed by maintenance doses (75 mg daily). Modified-release dipyridamole was recommended (200 mg twice daily). Gastroprotection was recommended.

### Outcomes

The primary efficacy outcome was the incidence and severity of any recurrent stroke [ischaemic, haemorrhagic; severity determined using the modified Rankin Scale (mRS)] or TIA at 90 days, and assessed using a six-level ordered categorical scale: fatal stroke, severe stroke (mRS score of 4–5), moderate stroke (mRS score of 2–3), mild stroke (mRS score of 0–1), TIA or no cerebral ischaemic event. Analysis used ordinal logistic regression and was by intention to treat. Secondary efficacy outcomes included disability, cognition, health-related quality of life, mood and discharge disposition. The main safety outcome was bleeding comprising a five-level ordered categorical scale: fatal, major, moderate, minor and no bleeding. Additional safety outcomes included all-cause and cause-specific case fatality, early neurological deterioration and serious adverse events. The net balance between efficacy and hazard was assessed as the composite end points of any stroke or major (including fatal) bleeding and death, stroke, myocardial infarction (MI) or major bleeding.

### Sample size

Using an ordinal rather than binary outcome, and including TIA along with stroke, meant that the sample size could be reduced from > 8000 participants to 4100, assuming an overall type I error rate of 5% with two-sided significance test, power 90%, odds ratio of 0.68, treatment crossovers 5%, losses to follow-up 2% and a reduction of 20% for baseline covariate adjustment.

## Results

The trial was stopped early on the recommendation of the Data Monitoring Committee after recruitment of 3096 participants (intensive,  $n = 1556$ ; guideline,  $n = 1540$ ) from 106 hospitals in four countries between April 2009 and March 2016. The advice to stop was based on three observations: (1) the presence of a significant increase in major bleeding in participants randomised to intensive antiplatelet therapy, (2) the absence of a significant reduction in the primary outcome and (3) a conditional power analysis suggested that the trial was highly unlikely to demonstrate a significant difference in the primary outcome. Baseline characteristics were well balanced between the two treatment groups.

### Primary outcome

The incidence and severity of recurrent stroke or TIA did not differ between intensive and guideline therapy [adjusted common odds ratio (acOR) 0.90, 95% confidence interval (CI) 0.67 to 1.20;  $p = 0.47$ ].

### Safety outcomes

Major (encompassing fatal) bleeding increased with intensive as compared with guideline therapy (adjusted hazard ratio (aHR) 2.23, 95% CI 1.25 to 3.96;  $p = 0.006$ ) and the difference only developed during the active treatment phase. Headache, by day 35, was more common in participants receiving intensive antiplatelets (aHR 4.13, 95% CI 2.09 to 8.15;  $p < 0.001$ ).

### Secondary outcomes

Length of stay in hospital, discharge disposition, dependency, disability, cognition, quality of life and mood did not differ between the treatment groups.

### Net benefit: risk

There were no differences between treatment groups in all-cause mortality (aHR 0.89, 95% CI 0.51 to 1.55;  $p = 0.69$ ), number and severity of adverse events (acOR 1.02, 95% CI 0.86 to 1.22;  $p = 0.80$ ), combined stroke and major/fatal bleeding (aHR 1.24, 95% CI 0.90 to 1.70;  $p = 0.19$ ) or the composite of death, stroke, MI and major bleeding (aHR 1.02, 95% CI 0.77 to 1.35;  $p = 0.88$ ).

### Meta-analysis of antiplatelet intensity trials

In a meta-analysis, heterogeneity was present between the group of trials of dual antiplatelet therapy and the TARDIS trial when compared with guideline therapy in respect of preventing stroke. No heterogeneity was present for major bleeding.

## Conclusions

### Implications for health care

- The TARDIS trial found that there was no significant reduction in the recurrence of stroke or TIA, or their severity, with intensive antiplatelet therapy based on three agents as compared with guideline therapy. However, triple antiplatelet therapy was associated with increased major bleeding. Overall, there was no effect on the net balance between harm and benefit confirming the overall neutral finding of the trial.
- In the context of the patients studied in the TARDIS trial, there is no evidence to support the use of intensive treatment based on three standard antiplatelets (aspirin, clopidogrel, dipyridamole).

### Future research implications

- There is no obvious reason to further study the use of intensive antiplatelet therapy with three agents in patients with acute stroke or TIA.
- Future trials examining potent antiplatelet agents should consider whether it would be safe to use them with existing antiplatelets in patients with acute cerebral ischaemia.

## Trial registration

This trial is registered as ISRCTN47823388.

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