Acute stroke or transient ischaemic attack (TIA): triple antiplatelet therapy no more effective and higher bleeding risk than clopidogrel monotherapy or combined aspirin and dipyridamole

A large, prospective, randomised trial (TARDIS) compared intensive triple antiplatelet therapy (aspirin, dipyridamole and clopidogrel) with clopidogrel monotherapy or combined aspirin and dipyridamole, after acute ischaemic stroke or TIA. Triple therapy was no more effective than either comparator for preventing recurrent stroke or TIA and was associated with more bleeding and bleeding of greater severity (including fatal bleeding). The trial was stopped early on the advice of the data monitoring committee. The study does not provide a reason to depart from current national guidance on antiplatelet treatment in the immediate period after ischaemic stroke or TIA, or recommended longer-term secondary prophylaxis.

Overview and current advice

The risk of recurrence after ischaemic stroke and transient ischaemic attack (TIA) is highest immediately after the event and declines over the following weeks (Rothwell et al. 2007). Antiplatelet treatment is one of the most important interventions for reducing the risk of recurrent vascular events including stroke (National clinical guideline for stroke, Royal College of Physicians [RCP] 2016).

Antiplatelet therapy can be divided into the immediate treatment period (within 24 hours of the stroke or TIA and for up to 2 weeks afterwards in the case of stroke, or until diagnosis of TIA is confirmed) and long-term prophylaxis. Triple antiplatelet therapy is not currently recommended in any NICE guidance on stroke or TIA.

The NICE clinical guideline on stroke and transient ischaemic attack (which was published in 2008 and is being updated) gives recommendations on antiplatelet treatment in the immediate treatment period. For people with acute stroke in whom primary intracerebral haemorrhage has been excluded, the guideline recommends aspirin 300 mg started as soon as possible, but certainly within 24 hours, and continued for 2 weeks. Long-term antithrombotic treatment should be started after this (or sooner, if the person is discharged earlier than 2 weeks after their stroke). People with a history of dyspepsia associated with aspirin should be given a proton pump inhibitor in addition to aspirin. People who are allergic to or have a genuine intolerance to aspirin should use an alternative antiplatelet agent.
People who have had a TIA should have aspirin 300 mg daily started immediately, followed by specialist assessment: investigation and measures for secondary prevention should be introduced as soon as the diagnosis is confirmed.

Recommended options for longer-term prophylaxis after ischaemic stroke or TIA are given in NICE technology appraisal guidance 210: Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events.

For people who have had an ischaemic stroke:

- Clopidogrel is recommended as the most cost-effective treatment option.
- For people who have a contraindication or intolerance to clopidogrel, modified-release dipyridamole plus aspirin is recommended as a treatment option.
- For people who have a contraindication or intolerance to both clopidogrel and aspirin, modified-release dipyridamole alone is recommended as a treatment option.

For people who have had a transient ischaemic attack:

- Modified-release dipyridamole plus aspirin is recommended as a treatment option.
- For people who have a contraindication or intolerance to aspirin, modified-release dipyridamole alone is recommended as a treatment option.

The technology appraisal guidance does not recommend clopidogrel as an option for longer-term prophylaxis after TIA because this is outside its marketing authorisation. NICE has produced an evidence summary: unlicensed or off-label medicine (ESUOM) on clopidogrel monotherapy for transient ischaemic attack. This found no relevant randomised controlled trials or high quality observational data on the efficacy of clopidogrel monotherapy as secondary prophylaxis after TIA.

The recommendations for antiplatelet therapy in the more recent, NICE-accredited, National clinical guideline for stroke (RCP 2016) are in line with the practice recommendations in the NICE clinical guideline and the options for treatment recommended in the NICE technology appraisal. The only exception is that clopidogrel is recommended as first-choice longer-term prophylaxis after TIA ahead of modified-release dipyridamole plus aspirin. The guideline states that this was because the guideline Working Party considered that a unified approach to the treatment of TIA and ischaemic stroke was more appropriate.

Note that there are different recommendations for long-term prophylaxis of stroke in people who have non-valvular atrial fibrillation: see the NICE guideline on atrial fibrillation.

The NICE Pathway: stroke brings together all related NICE guidance and associated products on this topic in a set of interactive flow charts.

New evidence

The TARDIS trial (Bath et al. 2018) compared the safety and efficacy of triple antiplatelet therapy with clopidogrel monotherapy or aspirin plus dipyridamole in people with acute, non-cardioembolic ischaemic stroke or TIA.

TARDIS was a large, pragmatic, prospective, randomised, open-label, blinded-endpoint (PROBE) trial completed in the UK, Denmark, Georgia and New Zealand: 95% of participants were recruited in the UK. It included 3096 adults (mean age 69 years; 63% male). Investigations after randomisation judged the qualifying event to be ischaemic stroke in 72%, TIA in 27% and neither ischaemic stroke nor TIA in 1%.

Participants were randomised 1:1 using a secure web-based system to receive open-label:
intensive therapy: 300 mg aspirin as a loading dose then 50 to 150 mg aspirin daily (typically 75 mg), 300 mg clopidogrel as a loading dose then 75 mg daily and dipyridamole modified release 200 mg twice daily or 100 mg 3 or 4 times daily.

comparator therapy: combined aspirin and dipyridamole, or clopidogrel monotherapy, using the same loading and maintenance doses as the intervention group.

Allocation to treatment was concealed. The choice of which comparator therapy to use was made in advance by each site individually and was chosen separately for ischaemic stroke and TIA. Sites could choose to use only aspirin and dipyridamole as comparator, or only clopidogrel, or randomise participants 1:1 to either regimen. This choice could be changed at any time during the trial with 48 hours’ notice. The authors describe the comparator treatments as ‘standard guideline therapy’; however, as described in the overview section above, treatment with aspirin and dipyridamole is not recommended in NICE or RCP guidance as antiplatelet therapy in the immediate period after an ischaemic stroke.

Participants had to be randomly assigned within 48 hours of symptom onset (median time to randomisation 29 hours). Aspirin could be given to any patient before randomisation, but clopidogrel could be given only if the person would receive it after randomisation (either as part of the intensive treatment or because the local choice of comparator treatment was clopidogrel monotherapy only). Similarly, aspirin plus dipyridamole could be used only if the local choice of comparator treatment was aspirin plus dipyridamole only. Those who received thrombolysis could be randomised as long as 24 hours had elapsed since that treatment had stopped, and secondary cerebral bleeding had been excluded. Study drugs were given for 30 days after which participants were treated according to local guidelines, typically with combined aspirin and dipyridamole or clopidogrel monotherapy.

The primary efficacy outcome was the incidence and severity of recurrent stroke and TIA at 90 days. Severity of stroke was measured on a 4-point scale from mild to fatal. The primary safety outcome was haemorrhage, again measured on a 4-point scale from mild to fatal. Analysis was on intention to treat.

Recruitment was halted early on the advice of the independent monitoring committee, after 76% of the planned number of participants had been recruited. After observing that intensive antiplatelet therapy was associated with an increase in major (including fatal) bleeding, that it was not associated with a significant reduction in the primary outcome, and that the trial was highly unlikely to demonstrate a significant difference between the groups in the primary outcome if it were to continue, the data monitoring committee advised that the trial should be terminated early on the basis of futility.

At this point in the study, there was no statistically significant difference in the incidence or severity of stroke (the primary outcome) between the 2 groups (6% in the intensive antiplatelet group compared with 7% in the comparator group, adjusted common odds ratio [cOR] 0.90; 95% confidence interval [CI] 0.67 to 1.20; g=0.47). There was also no statistically significant difference between the groups in rates of fatal stroke or secondary outcomes including disability, mood, cognition or quality of life.

However, there was more bleeding and bleeding of greater severity in participants in the intensive therapy group than in the comparator group (all bleeding 20% compared with 9% respectively, adjusted cOR 2.54; 95% CI 2.05 to 3.16; p<0.0001). A total of 17 participants (1%) in the guideline therapy group had severe (major or fatal) bleeding by day 90 compared with 39 (3%) in the intensive therapy group (adjusted hazard ratio [HR] 2.23; 95% CI 1.25 to 3.96; p=0.0063). The composite endpoints of any stroke, fatal haemorrhage, or major haemorrhage; and death, stroke, myocardial infarction, fatal haemorrhage, or major haemorrhage, did not differ between the groups.
The authors state that the study had many strengths including its large size, generalisability to practice because of wide inclusion criteria, prospective assessment of multiple outcomes, and very high follow-up (99% for the primary outcome). The stated limitations included the broad population which might have meant that some people were more likely to respond or to experience a major bleed, the open-label nature of the study which might have driven reporting of bleeding events in the intensive therapy group, the comparator group including different antiplatelet agents, and the duration of assigned treatments of 30 days which might have been too long in view of the identified bleeding risk.

Commentary

Commentary provided by NICE

Previous meta-analyses of trials of antiplatelets for recurrent stroke prevention after acute stroke or TIA have suggested that dual therapy with antiplatelets is more effective than monotherapy for the prevention of recurrent vascular events after stroke or TIA (Geeganage et al. 2012; Wong et al. 2013). The CHANCE study (Wang et al. 2013) compared combination aspirin and clopidogrel with aspirin monotherapy in Chinese people with minor stroke or high-risk TIA. Treatment was commenced within 24 hours of the event and continued for 3 weeks. The trial showed greater efficacy of the dual antiplatelet regimen and no difference in the rate of moderate or severe bleeding or haemorrhagic stroke between the two groups.

The TARDIS trial investigators theorised that if 2 antiplatelets are better than 1, 3 might be more effective still. However, the trial found that intensive triple antiplatelet therapy was no more effective than antiplatelet therapy consisting of clopidogrel monotherapy, or combination aspirin and dipyridamole. Furthermore the risk and severity of bleeding was significantly increased in the intensive therapy group. Triple antiplatelet therapy is not currently recommended in any NICE guidance on stroke or TIA.

The most obvious limitation of the study when assessing its application to practice is that one of the comparators (aspirin plus dipyridamole) is not recommended in NICE or RCP guidance on management of acute stroke (it is an option for long-term prophylaxis after stroke, but only if clopidogrel cannot be used). The other comparator, clopidogrel, is recommended as an alternative to aspirin in the initial period after a stroke if aspirin cannot be used.

NICE technology appraisals are health technology assessments of specific drugs and other technologies, and recommend treatments as options based on clinical and cost-effectiveness evidence (‘what could be done’). They have a different function and purpose from NICE guidelines, which set out the care and services suitable for most people with a specific condition or need, and people in particular circumstances or settings (‘what should [usually] be done’). NICE technology appraisal guidance 210 was a health technology assessment of clopidogrel and modified-release dipyridamole, within their licensed indications, for the prevention of occlusive vascular events in people with established peripheral arterial disease or with a history of myocardial infarction, ischaemic stroke or TIA (TA210 scope). Most participants in the studies of these drugs after stroke or TIA did not have acute stroke. For example, the ESPRIT study (ESPRIT study group 2006) compared aspirin with aspirin plus dipyridamole started up to 6 months after a TIA or minor ischaemic stroke; the PRoFESS study (Sacco et al. 2008) compared aspirin and dipyridamole with clopidogrel started within 90 days of an ischaemic stroke: median time from the qualifying stroke to randomisation was 15 days.

An editorial accompanying the TARDIS publication (Amarenco 2017) suggests several other limitations of the study. It notes that people who had experienced a severe stroke and those who had undergone thrombolysis could be recruited to the trial. The author states that such people have increased risk of bleeding complications, particularly intracerebral haemorrhage or haemorrhagic transformation, and people with severe stroke are unlikely to benefit, because little or no remaining cerebral tissue in the hemisphere of the brain infarction can be preserved from a potential recurrent
stroke. The RCP guideline states that the findings in the CHANCE study were probably due to the exclusion of moderate and severe stroke and the relatively short period of dual therapy. It also states that the epidemiology of stroke in the Chinese population differs from that of Western European populations and people in CHANCE were highly selected. Other limitations suggested by the editorialist include the high proportion of TIAs among the recurrent events, which could have been misdiagnosed.

The findings of TARDIS do not provide a reason to depart from current recommendations on antiplatelet treatment in the immediate period after ischaemic stroke or TIA, or recommended longer-term secondary prophylaxis.

**Study sponsorship**

This study was funded by the National Institutes of Health Research Technology Assessment Programme and the British Heart Foundation.

**References**


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