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What is the best treatment after stroke?

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Registration date 30/05/2008	**Overall study status** Completed	
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Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

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ClinicalTrials.gov number

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TSA 2005/05; 05.0105; Current Protocol 1.2. 04Sept2007

Study information

Scientific Title

Dual antiplatelet therapy in the acute phase following stroke and transient ischaemic attack (TIA): which is the best regimen?

Acronym
AMBDAP (AMBulatory Dual Anti-Platelet)

Study objectives
The early risk of stroke after minor stroke or transient ischaemic attack (TIA) is high, but we do not know the best drug regimen for early secondary prevention. The CARESS trial recently showed that aspirin and clopidogrel was better at preventing embolisation, detected using transcranial doppler ultrasound, than aspirin alone. Using a novel ambulatory transcranial doppler (TCD) system that allows us to perform prolonged recordings, we will determine whether clopidogrel or dipyridamole is better at preventing embolisation in patients with recent large artery stroke who are already taking aspirin.

Recent studies have shown that the early risk of stroke after TIA or minor stroke is considerable and much higher than previously appreciated, being about 10% in the first week. A recent meta-analysis has shown much of this risk is accounted for by patients with large artery atherosclerotic disease. There is therefore a great opportunity to intervene early and prevent these recurrent strokes, particularly in large artery disease. Implementing such an approach will depend on both developing clinical services which allow patients to be identified very soon after the event and also developing better treatment approaches to prevent recurrent stroke after the patients present.

Few studies have looked at optimal treatment regimes to prevent early recurrent stroke. One proven treatment strategy is early carotid endarterectomy. However, more effective medical treatments are also required for a number of reasons. Firstly much of the risk of stroke occurs within the first day or two after TIA or stroke; investigating and operating on patients within this time window is extremely difficult. Secondly in patients with lesser degrees of carotid stenosis endarterectomy is not indicated. Thirdly many patents with large artery disease are not amenable to endarterectomy (e.g. vertebral artery stenosis and intracranial disease). Therefore we need much more effective drug regimes to reduce this early recurrent stroke risk.

We have very little information as to which anti-thrombotic regime is optimal in this group of patients. Aspirin has been shown to reduce the long-term risk of recurrent stroke; additionally the International Stroke Trial found that it reduced early recurrence by 0.7% in acute ischaemic stroke. Dual anti-platelet therapy with dipyridamole slow release and aspirin was shown to be more effective than aspirin alone in the long term secondary prevention of stroke in the ESPS 2 trial, a finding substantiated by our recent individual patient data meta-analysis of trials in patients with prior ischaemic stroke or TIA. In contrast, therapy with clopidogrel and aspirin was no more effective than clopidogrel alone in the long-term secondary prevention of stroke in the MATCH trial, although this interpretation has been challenged.

However, these dual therapy trials have looked at long-term secondary prevention and the situation in the acute setting might be quite different. This is certainly the case in cardiology where different therapeutic regimes have been identified for the acute treatment of myocardial ischaemia, and its long term secondary prevention. The recent CARESS trial demonstrated that the combination of clopidogrel and aspirin was more effective than aspirin alone at reducing embolisation in patients with acutely symptomatic large vessel disease. This was the first multi-centre trial to use the surrogate endpoint of asymptomatic embolisation to evaluate anti-platelet therapy. Using transcranial doppler ultrasound (TCD) it is possible to detect

asymptomatic emboli as they pass through the cerebral circulation, because they reflect and backscatter more ultrasound than surrounding red blood cells. Such embolic signals are markers of stroke risk in carotid artery stenosis; their presence independently predicts recurrent stroke and TIA risk in prospective studies, including a study of 200 patients from our unit.

In CARESS, the clopidogrel and aspirin combination led to a 37% reduction in the proportion of patients embolising. This was over a short time period of seven days, although treatment effects were present at 24 hours. There was also a highly significant reduction in the frequency of embolic signals per hour in the dual therapy group. Again this effect was present at 24 hours. Furthermore, although the trial was not powered to look at clinical events, there was a trend towards fewer recurrent events in the dual therapy group (0 strokes versus 4 strokes in the aspirin only group). Importantly if this technique is to be used as a surrogate endpoint, there was a highly significant relationship between recurrent events and embolic signals.

This data suggests that we should perhaps be using dual anti-platelet therapy in the acute setting in patients with stroke and TIA. This hypothesis will need to be tested in large clinical trials with the endpoint of recurrent stroke. However, before any clinical trials are performed in this area we need to know which is the optimal anti-platelet regime. The only dual antiplatelet regime currently recognised by the National Institute for Clinical Excellence (NICE) is dipyridamole and aspirin, but we have no information about its efficacy in the acute setting. Therefore it is important that the combination of clopidogrel and aspirin is compared with that of dipyridamole and aspirin. We plan to do this in a further study using Doppler embolic signal monitoring as a surrogate endpoint.

One problem with assessing the effects of dipyridamole is that its mechanisms of action as an antiplatelet agent are mediated as agonists of inhibitory systems, e.g. dipyridamole prevents red cell uptake of adenosine, an endogenous antiplatelet agent. Hence, conventional platelet function testing is not very sensitive to its effects. Thus, it is better to use a clinical surrogate endpoint such as embolic signals which will be more directly related to clinical efficacy.

In the CARESS study doppler embolic signal recordings were performed for one hour. We can now record using ambulatory TCD for eight hours. This allows much more information to be obtained on the rate of embolisation, markedly reducing inter-subject variability, and therefore treatment effects can be studied in smaller groups of patients. In this study we plan to use ambulatory TCD to allow us to test efficacy in a smaller sample size than used in CARESS.

In a further study with ambulatory TCD we have performed 24 eight-hour recordings in symptomatic carotid stenosis. Patients on dipyridamole and aspirin had embolic signal counts not significantly different from those on aspirin alone, but those on clopidogrel and aspirin had significantly lower counts. This was not a randomised trial, and therefore we must be cautious in interpretation, but it has provided useful additional data to plan sample size calculations and suggests there may be differences in efficacy between the regimens.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval received from the Wandsworth Local Research Ethics Committee on the 28th June 2005 (ref: 05/Q0803/124).

Study design

A randomised double-blinded single-centre controlled phase IV study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Symptomatic (stroke/TIA/amaurosis fugax) carotid artery stenosis

Interventions
1. Aspirin (75 mg orally [po] once daily [od]) and dipyridamole SR (200 mg po twice daily [bd])
2. Aspirin (75 mg po od) and clopidogrel (300 mg po loading dose following by 75 mg po od)

Patients randomised to aspirin and dipyridamole will continue with this treatment long-term as this is the standard treatment regimen. Patients randomised to aspirin and clopidogrel will continue will this treatment for one month, and then will revert to the aspirin and dipyridamole combination long-term. Patients will be followed up for recurrent strokes and TIA up until one month, or until carotid endarterectomy or stenting is performed.

This is a pragmatic study to compare two anti-platelet regimes used in clinical practice. The loading dose of clopidogrel of 300 mg followed by 75 mg a day has been shown to have a rapid efficacy with maximal effect on the rate of embolisation within 24 hours. Dipyridamole SR has been shown to demonstrate maximal platelet concentrations within two hours and a loading dose is therefore unnecessary.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Aspirin, dipyridamole SR, clopidogrel

Primary outcome measure
The number of embolic signals (using international consensus criteria) detected during transcranial doppler recording from ipsilateral middle cerebral artery at 48 hours after study entry.

Secondary outcome measures
No secondary outcome measures

Overall study start date
26/08/2005

Completion date
30/11/2008

Eligibility

Key inclusion criteria
1. Women or men aged greater than 18 years
2. Patients with greater than or equal to 50% carotid artery stenosis
3. Symptoms of TIA or stroke within the last month
4. Baseline magnetic resonance imaging (MRI) or computed tomography (CT) imaging has been performed
5. Consented to take part in the study

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
60

Key exclusion criteria
1. Currently taking antiplatelet/antithrombotic medication other than aspirin (although low does prophylactic subcutaneous heparin for deep vein thrombosis [DVT] prophylaxis will be allowed)
2. Patients with prosthetic heart valves who have gaseous embolic signals
3. Where clopidogrel or dipyridamole is contra-indicated
4. Carotid endarterectomy planned within the next month
5. Pregnant and lactating women

Date of first enrolment
26/08/2005

Date of final enrolment
30/11/2008

Locations

Countries of recruitment
England

United Kingdom

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Sponsor type
Hospital/treatment centre

Website
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ROR
https://ror.org/039zedc16

Funder(s)

Funder type
Charity

Funder Name

The Stroke Association (UK) - research project grant (ref: TSA/2005/05)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/03/2011		Yes	No