Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial

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Summary

Background Few randomised clinical trials have investigated the use of antithrombotic drugs for early secondary prevention of stroke or transient ischaemic attack in patients with intracranial atherosclerotic stenosis. Microembolic signals, detected by transcranial doppler, are a surrogate marker of future stroke risk and have been used to show treatment efficacy in patients with extracranial carotid stenosis. We aimed to investigate whether treatment with clopidogrel plus aspirin reduced the number of microembolic signals detected with transcranial doppler ultrasound compared with aspirin alone in patients with recent stroke.

Methods The clopidogrel plus aspirin for infarction reduction in acute stroke or transient ischaemic attack patients with large artery stenosis and microembolic signals (CLAIR) trial was a randomised, open-label, blinded-endpoint trial. Between Oct 28, 2003, and Nov 19, 2008, patients with acute ischaemic stroke or transient ischaemic attack who had symptomatic large artery stenosis in the cerebral or carotid arteries and in whom microembolic signals were present on transcranial doppler were randomly assigned within 7 days of symptom onset to receive clopidogrel (300 mg for the first day, then 75 mg daily) plus aspirin (75–160 mg daily) or aspirin alone (75–160 mg daily) for 7 days. Patients were randomly assigned in blocks of four or six by use of a randomisation website. Monitoring of microembolic signals on transcranial doppler was done on days 2 and 7. The primary endpoint was the proportion of patients who had microembolic signals on day 2. Analysis was by modified intention to treat. All analyses were done by an investigator masked to both patient identity and the day the recording was taken. This trial is registered with the Centre for Clinical Trials, Chinese University of Hong Kong, number CUHK_CCT00164.

Findings 100 patients were randomly assigned to clopidogrel plus aspirin (n=47) or aspirin monotherapy (n=53). 93 of 100 patients had symptomatic intracranial stenosis in either the intracranial internal carotid artery or the middle cerebral artery: 45 of 46 in the dual therapy group and 48 of 52 in the monotherapy group. At day 2, 14 of 45 patients in the dual therapy group and 27 of 50 patients in the monotherapy group for whom data were available had at least one microembolic signal on transcranial doppler (relative risk reduction 42·4%, 95% CI 4·6–65·2; p=0·025). Adverse events were similar in the two groups. No patients had intracranial or severe systemic haemorrhage, but two patients in the dual therapy group had minor haemorrhages.

Interpretation Combination therapy with clopidogrel and aspirin is more effective than aspirin alone in reducing microembolic signals in patients with predominantly intracranial symptomatic stenosis. Clinical trials are now warranted to investigate whether this combination treatment also results in a reduction in stroke incidence.

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Introduction

Atherosclerotic stenosis of cerebral vessels is a common cause of stroke worldwide. In people of European ancestry, stenosis is most common in extracranial carotid arteries. In many other populations, including those in Asia, intracranial stenosis is much more common than extracranial stenosis.[1,2] Despite being one of the most common causes of stroke worldwide,[1,2] there are few effective treatments for prevention of stroke in patients with intracranial stenosis.

The risk of early recurrent stroke in patients with minor stroke or transient ischaemic attack might be as high as 8–12% in the first 7 days.[3] Both extracranial carotid stenosis[4] and vertebral stenosis[5,6] have a high early recurrent stroke risk. Intracranial stenosis also has a high early risk of recurrent stroke, which decreases over time.[7] Extracranial carotid stenosis can be treated with carotid endarterectomy, which is most effective at reducing risk of recurrent stroke if it is done soon after minor stroke or transient ischaemic attack. For patients with intracranial stenosis, for whom endarterectomy is not possible, antiplatelet treatment has been recommended, as it is for any other non-cardioembolic stroke, but evidence for this approach is lacking.

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In acute cardiac ischaemia, combination antiplatelet treatment with clopidogrel and aspirin reduces the risk of recurrent cardiac ischaemia.[8] However, many stroke studies have not separated early secondary prevention from long-term secondary prevention. For example, in the management of atherothrombosis with clopidogrel in high-risk patients (MATCH) study[9] the combination of clopidogrel and aspirin was no more effective than clopidogrel alone in preventing recurrent ischaemic events in patients with stroke, but treatment was not given in the acute setting. Data in the acute setting suggest this combination might be more effective than aspirin alone for the prevention of early recurrent stroke and transient ischaemic attack,[10,11] although more data are needed. In patients with intracranial stenosis, anticoagulation with warfarin or low-molecular-weight heparin was no better than aspirin in reducing risk of recurrent stroke[12] or improving disability,[13] and combination treatment with cilostazol and aspirin did not show any clinical benefit compared with aspirin and placebo.[14]

Trials of antiplatelet drugs in stroke prevention need to include thousands of patients to show reductions in clinical endpoints. Use of in-vivo surrogate markers in trials can help to identify the best choice and dose of drugs for investigation in phase 3 trials. Asymptomatic microembolic signals detected with transcranial doppler ultrasound might be one such marker.[15] Microembolic signals are common in patients with large artery disease and are an independent marker of future stroke risk in patients with extracranial carotid disease[15,16] or intracranial stenosis.[17] In the clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis (CARESS) trial,[10] combination therapy with clopidogrel and aspirin was more effective than aspirin alone in reducing asymptomatic embolisation in patients with recently symptomatic extracranial carotid stenosis, as assessed by detection of microembolic signals on transcranial doppler. In patients with intracranial stenosis, the presence of microembolic signals is associated with risk of early recurrent transient ischaemic attack, stroke,[18] and new silent cerebral infarctions.[19] Although dual antiplatelet treatment is effective in reducing the presence of microembolic signals,[20] no randomised trials have assessed whether antiplatelet drugs reduce the number of microembolic signals in patients with intracranial stenosis.

We aimed to assess whether combination therapy with clopidogrel and aspirin is more effective than aspirin monotherapy in patients from Asia who had symptomatic cerebral or carotid artery stenosis.

Methods

Patients

The CLAIR study was an investigator-initiated, multicentre, randomised trial with blinded outcome assessment, with patients recruited at sites in Hong Kong, Singapore, China, Thailand, and Malaysia.

Patients from Asia aged at least 18 years with a clinical diagnosis of acute ischaemic stroke or transient ischaemic attack according to WHO criteria who had microembolic signals at baseline were eligible. Inclusion criteria were symptom onset within 7 days before receiving the first dose of trial drug; exclusion of intracerebral haemorrhage, brain tumour, or both on CT; and presence in the symptomatic area of substantial (≥50%) extracranial or intracranial internal carotid artery or middle cerebral artery stenosis confirmed with carotid duplex, transcranial doppler, or magnetic resonance angiography. Exclusion criteria were a National Institutes of Health stroke scale (NIHSS) score greater than 8; no large artery occlusive disease on neurovascular assessment; history of intracerebral haemorrhage; known contraindication to clopidogrel or aspirin; anticoagulation therapy before onset of stroke or definite indication for anticoagulation; sustained hypertension (systolic blood pressure >220 mm Hg or diastolic blood pressure >120 mm Hg) before randomisation; coexisting severe systemic diseases, such as terminal carcinoma, renal failure (creatinine >200 μmol/L), cirrhosis, severe dementia, or psychosis; known atrial fibrillation on electrocardiogram (past or present); rheumatic heart disease or metallic heart valve; thrombocytopenia (platelet count <100 000 per mm^3); being pregnant, breastfeeding, planning pregnancy during the course of the trial, or having a positive urine pregnancy test before randomisation; and participation in another clinical trial. Written informed consent was obtained before randomisation from each patient or a legally acceptable representative. The study was approved by local trial ethics committees.

Randomisation and masking

Randomisation was done via the Singapore Clinical Research Institute randomisation website. Patients were randomly allocated (1:1) in blocks of four or six (stratified by centre) to receive either dual therapy of clopidogrel 300 mg for the first day and then 75 mg daily plus 75–160 mg aspirin daily for 7 days, or monotherapy (75–160 mg aspirin once daily for 7 days). The password-protected randomisation list was prepared by the trial statistician and locked by the head of the statistics department after uploading to the randomisation program. Authorised site coordinators randomly assigned patients through the website.

All transcranial doppler recordings were done by an investigator masked to both patient identity and the day the recording was taken (baseline, day 2, or day 7). MRI films and images were reviewed centrally by a radiologist (W Lam) who interpreted scans masked to clinical and transcranial doppler data.

Procedures

At baseline, the intracranial arteries of each patient were examined by transcranial doppler and the extracranial carotid arteries by duplex ultrasound, and the percentage

of lumen stenosis was calculated by use of previously described criteria.[18] 30-min recordings were taken from each patient at baseline from the ipsilateral middle cerebral artery distal to any symptomatic middle cerebral artery or carotid artery stenosis. The local investigator reviewed the recording in real time to identify any microembolic signals.[21] The doppler signal was also recorded on digital audiotape for central review. If at least one microembolic signal was detected during real-time review the patient was included in random allocation of treatment. The use of microembolic signals also allows assessment of efficacy over a short time period. Intravenous drugs reduce microembolic signals within hours[22] or significantly reduce the number of microembolic signals at 24 h.[10] Therefore, we did the same transcranial doppler recordings on days 2 and 7. Study investigators had training and assessment for microembolic signal interpretation during investigator meetings and during preparation of the site before inclusion in the study.

All transcranial doppler recordings were centrally reviewed by a core laboratory (St George's, University of London, London, UK). The doppler recording was played back through a standard transcranial doppler system (Pioneer, EME/Nicolet, Madison, USA, or DWL, Singen, Germany) with a 2 MHz transducer and analysed by fast Fourier transform, and the presence of microembolic signals was assessed by use of international consensus criteria[21] based on both the visual and acoustic characteristics of microembolic signals. We used an intensity threshold of 7 dB for detection of microembolic signals because this results in high specificity.[23]

All data sheets were then sent from each clinical site to the Singapore Clinical Research Institute. The primary analysis was by modified intention to treat and was based on data from the masked central review of microembolic signals. An additional prespecified per-protocol analysis was done on microembolic signals and diffusion-weighted MRI data for patients who adhered to the trial protocol.

MRI was done on day 1 (within 24 h of transcranial doppler microembolic signal monitoring) and on day 7. The MRI protocol included standard brain axial T2-weighted MRI, axial diffusion-weighted MRI at B0, B500, and B1000, and an apparent diffusion coefficient map. The films or images were recorded on a CD and sent to the Chinese University of Hong Kong for central review.

At baseline, all patients had their clinical history taken and had general and neurological examinations. The NIHSS, Barthel index, modified Rankin scale, and mini-mental state examination were done at baseline and on day 7 (±1 day). If a patient was discharged from the trial site before 7 days, then these assessments were done before discharge. Adverse events, including any recurrent vascular event and haemorrhage, were documented during the 7-day study period. Any events were reviewed by the endpoint committee, which was masked to treatment allocation.

The primary outcome was the proportion of patients with at least one microembolic signal on transcranial doppler on day 2. Secondary outcomes were number of microembolic signals on days 2 and 7; proportion of patients with at least one microembolic signal on day 7; number of new acute infarctions, defined by recent infarctions visible on diffusion-weighted MRI on day 7 but not on day 1; number of acute infarctions on diffusion-weighted MRI; NIHSS score at day 7; difference in NIHSS score between baseline and day 7; modified Rankin scale score at day 7; mortality at day 7; thromboembolic events during the study period; and occurrence of recurrent stroke, coronary syndrome, deep vein thrombosis, or pulmonary embolus. Safety endpoints were haemorrhagic episodes occurring between day 1 and day 7, defined as the presence of any of the following: symptomatic haemorrhagic transformation of the cerebral infarction; symptomatic intracerebral haemorrhage not associated with cerebral infarction; serious extracranial haemorrhage (eg, gastrointestinal bleeding, haematoma, or haematuria); death of any

	Dual therapy (n=46)	Monotherapy (n=52)
Age (years)	59·2 (12·5)	56·4 (12·8)
Men	36 (78%)	40 (77%)
Systolic blood pressure (mm Hg)	139·4 (22·2)	148·6 (23·1)
Diastolic blood pressure (mm Hg)	80·1 (11·6)	83·9 (11·6)
Time from onset of stroke to randomisation (days)	2·5 (1·6)	3·2 (1·8)
Site of arterial stenosis		
Intracranial	45 (98%)	48 (92%)
Extracranial	12 (26%)	16 (31%)
Both	11 (24%)	12 (23%)
Previous myocardial infarction	3 (7%)	3 (6%)
Previous angina	5 (11%)	4 (8%)
Hypertension	27* (60%)	35† (69%)
Diabetes mellitus	21 (46%)	16 (31%)
Hyperlipidaemia	23‡ (50%)	16§ (33%)
Peripheral vascular disease	4 (9%)	2 (4%)
Never smoked	25 (54%)	22 (42%)
Previous or ongoing drug treatments		
β blockers	12 (26%)	10 (19%)
Drugs acting on the renin–angiotensin system	10 (22%)	10 (19%)
Calcium-channel blockers	9 (20%)	9 (17%)
Other antihypertensive drugs	3 (7%)	5 (10%)
Hypoglycaemic drugs	17 (37%)	14 (27%)
Statins	21 (46%)	16 (31%)

Data are mean (SD) or number (%). Data were unavailable for hypertension or hyperlipidaemia in some patients. *Out of 45 patients. †Out of 51 patients. ‡Out of 45 patients. §Out of 49 patients.

Table 1: **Demographics and baseline characteristics**

cause; and death related to haemorrhagic complications. Serious haemorrhage was defined as any symptomatic intracranial haemorrhage or any haemorrhage requiring blood transfusion or prolonged stay in hospital.

Statistical analysis

A sample size of 100 patients (50 patients per study group) was calculated to detect about a 40% relative reduction in the percentage of patients with microembolic signals on day 2, assuming 70–80% of patients would have microembolic signals in the monotherapy group at this timepoint, and assuming a type 1 error of 0·05 and power of 80%.

All statistical analyses were done with SAS version 9.1. Proportions between groups were analysed with the χ^2 or Fisher's exact tests. The mean or median difference between the treatment groups was assessed by a two-sample *t* test or Mann-Whitney *U* test, depending on the result of the Kolmogorov-Smirnov normality test. We also did multiple log-binomial or Poisson regression, adjusting for relevant covariates.

Meta-analysis of the results of the CARESS and the present study was done with Review Manager 5.0 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration).

The trial is registered with the Centre for Clinical Trials, Chinese University of Hong Kong, CUHK_CCT00164.

Role of the funding source

The sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the study data and shared responsibility for the final decision to submit for publication.

Results

Between Oct 28, 2003, and Nov 19, 2008, 100 patients were randomly assigned to treatment. 47 patients were assigned to the dual therapy group and 53 to the monotherapy group. The imbalance in the number of patients in the two groups was because of the block randomisation design. 45 of 46 patients in the dual therapy group and 48 of 52 in the monotherapy group had symptomatic intracranial stenosis (table 1). 11 of 46 patients in the dual therapy group and 12 of 52 in the monotherapy group had both extracranial and intracranial stenosis.

Of the 47 patients in the dual therapy group, one was recruited more than 7 days after symptom onset and was withdrawn by the local investigator before baseline assessments. Thus, 46 patients on dual therapy were

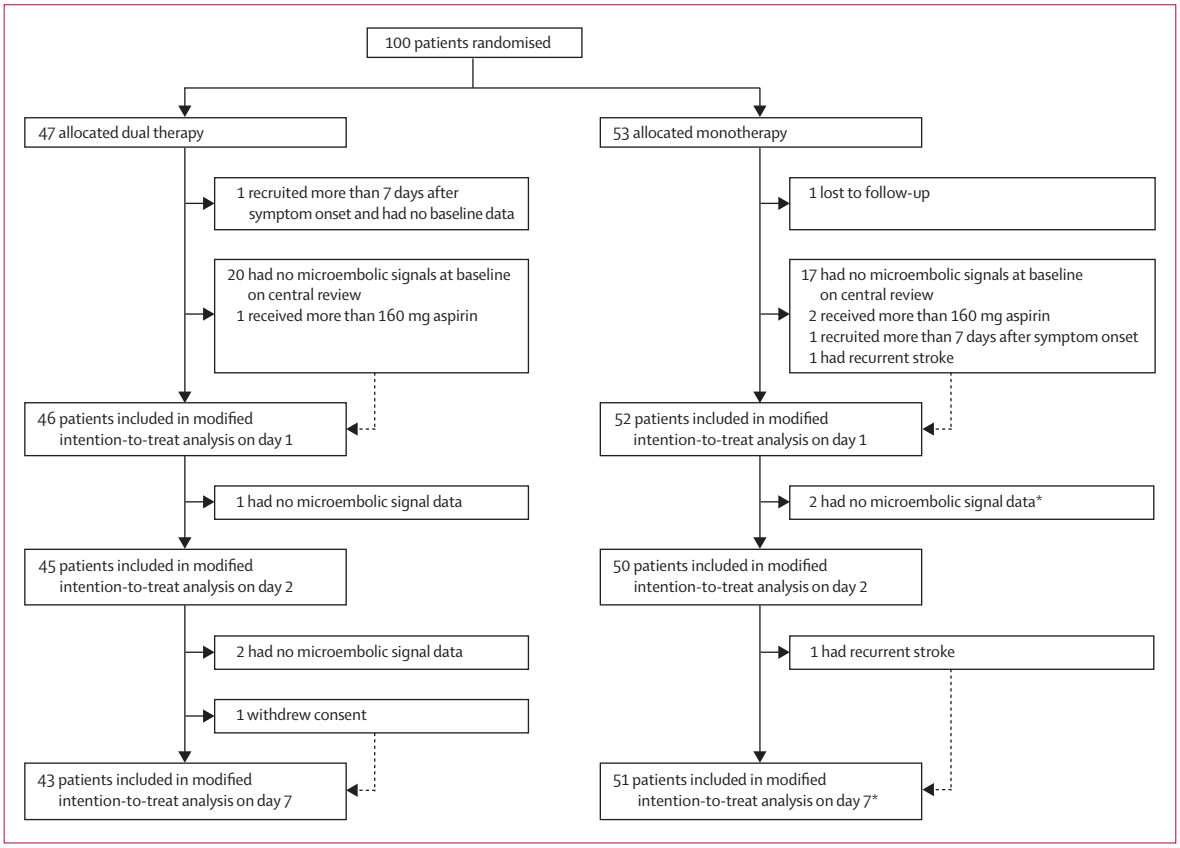

Figure 1: **Flow diagram of patient data available for analysis at different timepoints**
*One patient had no microembolic signal data at day 2 but did have data at day 7.

available for the modified intention-to-treat analysis (figure 1). One patient received more than 160 mg aspirin and 20 patients had no microembolic signals at baseline on central review, either because the recordings were not of sufficient technical quality to be analysed or because no microembolic signals could be detected. Therefore, 25 patients on dual therapy were included in the per-protocol analysis.

Of the 53 patients in the monotherapy group, one patient was lost to follow-up soon after randomisation and had no baseline or post-baseline assessments (figure 1). Therefore, 52 patients in the monotherapy group were included in the modified intention-to-treat analysis. 17 patients had no microembolic signals at baseline on central review, one had symptom onset more than 7 days before randomisation, one had recurrent stroke, and two received more than 160 mg aspirin. Therefore, 31 patients in the monotherapy group were included in the per-protocol analysis.

A few patients did not have microembolic signal monitoring during the study period (eg, because they refused to have transcranial doppler done or they needed to undergo other investigation or treatments). Thus, the numbers of patients included in the modified intention-to-treat and per-protocol analyses were different at days 2 and 7 from day 1 (tables 2 and 3).

26 of 46 patients in the dual therapy group and 35 of 52 in the monotherapy group had microembolic signals at baseline (p=0·272; table 2). On day 2, 14 of 45 patients in the dual therapy group and 27 of 50 in the monotherapy group had microembolic signals (p=0·025). At day 7, ten of 43 patients in the dual therapy group and 26 of 51 in the monotherapy group had microembolic signals (p=0·006).

In the per-protocol analysis on day 2, microembolic signals were detected in ten of 25 patients in the dual therapy group and in 22 of 30 in the monotherapy group (p=0·013). On day 7, microembolic signals were detected in eight of 24 patients in the dual therapy group and 20 of 31 in the monotherapy group (p=0·022).

We did multiple regression analysis to adjust for the imbalance in the proportion of patients with microembolic signals at baseline. This confirmed that treatment allocation remained an independent factor, with dual therapy being associated with a lower proportion of patients having microembolic signals at both days 2 and 7 (table 4).

At baseline, the median number of microembolic signals was 1·5 (range 0–31) in the dual therapy group and 2 (0–29) in the monotherapy group (table 3). In the modified intention-to-treat analysis, the median number of microembolic signals at day 2 was 0 (0–8) in the dual therapy group and 1 (0–18) in the monotherapy group, and the median number of microembolic signals on day 7 was 0 (0–3) in the dual therapy group and 1 (0–11) in the monotherapy group. The findings were much the same in the per-protocol analysis.

32 of 44 patients in the dual therapy group and 41 of 52 in the monotherapy group had acute infarctions on baseline diffusion-weighted MRI. The median number of acute infarctions on diffusion-weighted MRI on day 7 was 1 (range 0–13) in the dual therapy group and 1 (0–12) in the monotherapy group (p=0·58; table 5). The median number of new acute infarctions between baseline and day 7 was 0 (0–4) in the dual therapy group and 0 (0–1) in the monotherapy group (p=0·26; table 5). Results from the per-protocol analysis were much the same (data not shown). There were no significant differences between the two groups on NIHSS, modified Rankin scale, or mini-mental state examination (table 5).

During the 7-day study period no patients in the dual therapy group and two patients in the monotherapy

	Dual therapy	Monotherapy	Relative risk reduction, % (95% CI)	p
Modified intention to treat	n=46	n=52		
Baseline	26/46 (57%)	35/52 (67%)	16·0% (–15·2 to 38·8)	0·272
Day 2	14/45 (31%)	27/50 (54%)	42·4% (4·6 to 65·2)	0·025
Day 7	10/43 (23%)	26/51 (51%)	54·4% (16·4 to 75·1)	0·006
Per protocol	n=25	n=31		
Baseline	25/25 (100%)	31/31 (100%)	..	..
Day 2	10/25 (40%)	22/30 (73%)	45·5% (7·7 to 67·8)	0·013
Day 7	8/24 (33%)	20/31 (65%)	48·3% (3·7 to 72·3)	0·022

Table 2: **Number of patients with at least one microembolic signal on transcranial doppler**

	Dual therapy	Monotherapy	Difference (95% CI)*	p
Modified intention to treat				
Baseline	n=46	n=52		
Mean (SD)	3·2 (5·7)	4·1 (6·1)	..	..
Median (range)	1·5 (0–31)	2 (0–29)	0 (–1 to 0)	0·292
Day 2	n=45	n=50		
Mean (SD)	0·5 (1·3)	2·2 (3·6)	..	..
Adjusted mean (SD)†	0·5 (0·1)	1·8 (0·2)	–1·3 (–1·7 to –0·9)	0·0001
Median (range)	0 (0–8)	1 (0–18)	0 (–1 to 0)	0·004
Day 7	n=43	n=51		
Mean (SD)	0·3 (0·7)	1·8 (2·7)	..	..
Adjusted mean (SD)†	0·3 (0·1)	1·6 (0·3)	–1·2 (–1·6 to –0·9)	0·0004
Median (range)	0 (0–3)	1 (0–11)	0 (–1 to 0)	0·002
Per protocol				
Baseline	n=25	n=31		
Mean (SD)	5·8 (6·7)	6·1 (6·7)	..	..
Median (range)	3 (1–31)	4 (1–29)	0 (–2 to 1)	0·815
Day 2	n=25	n=30		
Mean (SD)	0·8 (1·6)	3·2 (4·2)	..	..
Median (range)	0 (0–8)	1·5 (0–18)	–1 (–2 to 0)	0·002
Day 7	n=24	n=31		
Mean (SD)	0·5 (0·9)	2·2 (3·1)	..	..
Median (range)	0 (0–3)	1 (0–11)	–1 (–1 to 0)	0·014

The numbers of patients included differed between analyses and timepoints because some patients did not have imaging at either day 2 or day 7. *Dual therapy minus monotherapy. †Adjusted least square means of microembolic signals were estimated using Poisson regression with mean number of microembolic signals at baseline.

Table 3: **Number of microembolic signals per person on transcranial doppler**

	Estimated coefficient (SE)	Adjusted relative risk reduction, % (95% CI)	p
Day 2			
Treatment (dual *vs* monotherapy)	−0·528 (0·235)	41·0% (6·5 to 62·8)	0·025
Presence of microembolic signals at day 1	1·211 (0·383)	−235·6% (−610·9 to −58·5)	0·002
Day 7			
Treatment (dual *vs* monotherapy)	−0·696 (0·293)	50·2% (11·5 to 72·0)	0·018
Presence of microembolic signals at day 1	1·190 (0·427)	−228·6% (−685·1 to −42·4)	0·005

Multiple regression analysis is based on the modified intention-to-treat population; numerical imbalance between baseline characteristics were all statistically insignificant, and hence these characteristics have been removed from the model.

Table 4: **Predictors of microembolic signal positivity by log-binomial regression analysis**

	Dual therapy	Monotherapy	Difference (95% CI)*	p
MRI analysis				
Numbers of acute infarctions on diffusion-weighted MRI				
Baseline	n=44	n=52		
Mean (SD)	3·5 (3·7)	2·6 (3·8)	..	..
Median (range)	2 (0 to 13)	1 (0 to 20)	0·5 (0·0 to 2·0)	0·25
Day 7	n=41	n=52		
Mean (SD)	2·3 (3·2)	1·8 (2·6)	..	..
Median (range)	1 (0 to 13)	1 (0 to 12)	0·0 (0·0 to 1·0)	0·58
Number of new acute infarctions on day 7 but not visible on day 1	n=41	n=52		
Mean (SD)	0·2 (0·7)	0·1 (0·3)	..	..
Median (range)	0 (0 to 4)	0 (0 to 1)	0·0 (0·0 to 0·0)	0·26
NIHSS				
NIHSS at day 7	n=44	n=52		
Median (range)	1 (0 to 6)	1 (0 to 5)	0·0 (0·0 to 1·0)	0·81
Score 0–3	36 (81·8%)	45 (86·5%)	−4·7% (−20·1 to 9·9)	0·53
NIHSS at day 7 minus NIHSS at day 1	n=44	n=52		
Mean (SD)	−0·9 (1·8)	−0·8 (1·5)	..	..
Median (range)	0 (−6 to 2)	−0·5 (−5 to 3)	0·0 (−1·0 to 1·0)	0·98
MMSE				
MMSE at day 7	n=44	n=47		
Mean (SD)	27·1 (3·7)	27·5 (3·0)	..	..
Median (range)	28 (15 to 30)	28 (18 to 31)	0·0 (−1·0 to 1·0)	0·74
Modified Rankin scale at day 7 (n, %)				
0–2	38 (90·5%)	46 (93·9%)	−3·4% (−16·6 to 8·5)	0·70
0–1	32 (76·2%)	38 (77·6%)	−1·4% (−18·8 to 15·6)	0·70

All analyses are modified intention to treat. *Dual therapy minus monotherapy. NIHSS=National Institutes of Health stroke scale. MMSE=mini-mental state examination.

Table 5: **Other outcome measures**

group had ischaemic stroke; two patients in the dual therapy group and one patient in the monotherapy group had transient ischaemic attacks. All recurrent events were in the same arterial territory as the presenting event. Therefore, the diffusion-weighted MRI lesions on day 7 in the two patients with recurrent stroke were categorised as extension of infarction rather than new infarction by the reading radiologist.

	Dual therapy (n=46)	Monotherapy (n=52)
Intracranial haemorrhage or haemorrhagic transformation of infarction	0	0
Other serious haemorrhage	0	0
Minor bleeding	2	0
Death of any cause	0	0
Any adverse events		
Mild	4	6
Moderate	1	2
Severe	0	1

Table 6: **Adverse events**

The number of adverse events was similar between the two groups (table 6). No participants had intracranial or severe systemic haemorrhage. However, two patients in the dual therapy group had minor haemorrhages: one mucosal and one subcutaneous.

Discussion

In patients from Asia with transient ischaemic attack or stroke, most of whom had intracranial stenosis, dual therapy with clopidogrel and aspirin was more effective than aspirin alone in reducing asymptomatic embolisation detected by transcranial doppler. In the modified intention-to-treat analysis, treatment effects were found on both the primary endpoint of the presence of microembolic signals and a secondary endpoint of the mean number of microembolic signals per patient. Effects were also consistent in the per-protocol analyses.

Two patients in the monotherapy group had a new ischaemic stroke compared with none in the combination therapy group during the 7-day trial, suggesting that dual therapy might reduce the number of patients who have recurrent stroke. This finding now needs confirmation in a large randomised trial with clinical outcomes.

Our results are consistent with those from the CARESS study,[10] the only previous study on the effect of dual antiplatelet therapy on embolisation for patients with stroke who have large artery occlusive disease. That study used the same dual antiplatelet drugs as the CLAIR trial for 7 days and assessed microembolic signals on transcranial doppler at days 2 and 7, but included only patients with extracranial carotid stenosis.[16] In CARESS,[10] combination therapy was associated with a 37% reduction in the number of patients who had microembolic signals at day 7 compared with monotherapy. There was a higher rate of early recurrent stroke and transient ischaemic attack than in the CLAIR trial, and the CARESS study was of sufficient power to show a significant association between the presence of microembolic signals and recurrent clinical events, both at baseline and after 24 h of treatment. There were also fewer strokes in the dual therapy group than in the monotherapy group.

We did a meta-analysis of the CARESS[10] and CLAIR trials (figures 2 and 3). The forest plot of microembolic

signals combining the CLAIR and CARESS studies suggests a beneficial effect of dual therapy compared with monotherapy at both days 2 and 7. Neither CARESS nor CLAIR showed a beneficial effect of dual therapy in reducing the risk of recurrent stroke, but when both studies were combined there was a reduction in risk of 6% (95% CI 1–11) with use of dual therapy compared with monotherapy (figure 3).

Consistent with the results of CLAIR and our meta-analysis, the fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER)[11] phase 2 trial reported reduced risk of early recurrent stroke in patients with acute stroke or transient ischaemic attack who were treated with aspirin and clopidogrel compared with those treated with aspirin alone. However, this trial included patients with all stroke subtypes, and because it was based in North America most patients had extracranial stenosis.

In the MATCH study,[9] significantly more patients had a haemorrhage in the clopidogrel and aspirin group than in the clopidogrel monotherapy group. However, patients were treated for 18 months, and about half of patients had small vessel disease, which is associated with an increased risk of intracerebral haemorrhage. In the CLAIR study, there were no major haemorrhages in either group, consistent with the low risk of recurrent stroke in the dual therapy group in the CARESS study,[10] in which treatment was given for 7 days. Therefore, the combination of clopidogrel and aspirin for 7 days seems to have a low bleeding risk when given over short periods of time in the acute setting, particularly when compared with the high recurrent stroke risk shortly after minor stroke and transient ischaemic attack.

Detection of microembolic signals on transcranial doppler can be used to show the therapeutic efficacy of drugs in single-centre studies,[22,24–26] as well as in the CARESS[10] and CLAIR trials. Microembolic signal detection on transcranial doppler is an attractive surrogate marker for risk of stroke for two main reasons. First, microembolic signals are much more common than recurrent stroke and thus efficacy can be assessed in a smaller number of patients. To show efficacy of treatment with recurrent stroke as the endpoint would require inclusion of hundreds or thousands of patients. For example, to show a 40% reduction in recurrent stroke risk from 10% to 6% with a power of 0·9 and a

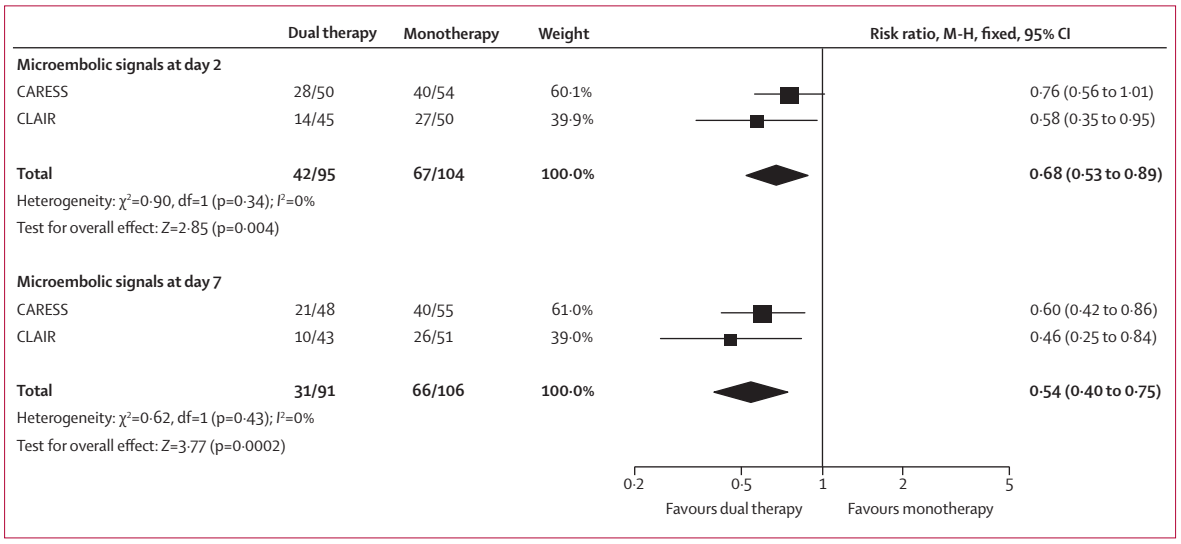

Figure 2: **Meta-analysis of number of patients with at least one microembolic signal in CARESS and CLAIR**
M-H=Mantel-Haenszel.

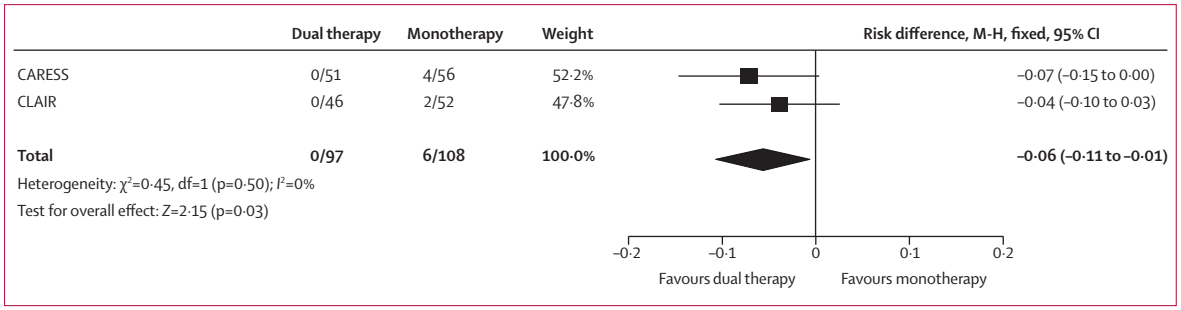

Figure 3: **Meta-analysis of number of patients with recurrent stroke in CARESS and CLAIR**
M-H=Mantel-Haenszel.

significance level of 0·05 would require a sample size of 1922. Second, microembolic signals are clinically relevant. Microembolic signals were independent predictors of recurrent stroke risk in prospective studies in patients with cerebral large artery disease, including intracranial stenosis,[15–17] and are rapidly reduced in frequency by antiplatelet therapies.[22,24,25] Many clinical studies have used microembolic signals to assess the therapeutic effect of antithrombotic drugs.[27] Secondary analyses from the CARESS study[10] showed microembolic signals were a more useful surrogate marker than platelet aggregation: although microembolic signal counts at both baseline and 24 h after starting therapy predicted risk of future stroke or transient ischaemic attack, there was no association between platelet aggregation at baseline or at 24 h with future events.[16]

The presence of new infarctions detected by diffusion-weighted MRI has also been suggested as a surrogate marker for use in trials of new antiplatelet drugs. New infarctions might be more common than clinical recurrent events and could allow a treatment to be studied with small sample sizes. The CLAIR trial combined both detection of microembolic signals on transcranial doppler and assessment of new infarctions on diffusion-weighted MRI. By contrast with the significant treatment effect we showed with transcranial doppler, we were unable to identify any treatment effect by use of diffusion-weighted MRI. This was partly because of the small number of new infarctions seen in both groups. Our data suggest that detection of microembolic signals with transcranial doppler is a more useful surrogate marker of treatment efficacy than is diffusion-weighted MRI.

A few patients who had been identified as having microembolic signals by local centres did not have the presence of microembolic signals confirmed on central review. Several factors might account for this difference. First, for technical reasons, a number of recordings were of insufficient quality to be analysed by the core laboratory. These were classified as microembolic signal negative even though microembolic signals had been detected by the recruiting centre. Second, recruiting centres had to analyse transcranial doppler recordings in real time. Analysis in the clinical setting, with the complications of surrounding noise and interference, leads to less accurate microembolic signal detection.[28] Third, central analysis used an intensity threshold of 7 dB, which led to classification of some patients with smaller embolic signals as microembolic signal negative. Microembolic signals from the intracranial artery have lower intensity than do those from the extracranial artery.[29] Despite these considerations, there was no difference between the proportion of patients with microembolic signals in either group on both modified intention-to-treat and per-protocol analyses. Furthermore, a regression analysis controlling for the proportion of patients who had microembolic signals produced similar results.

The per-protocol analysis was underpowered. However, even with 28 patients in each group, our study would still have had 71% power to detect the reported difference in the per-protocol analysis if 73% of patients in the monotherapy group had microembolic signals at day 2 (as was noted in this study) and using the larger relative reduction of 45% rather than the expected 40%. The results of the primary analysis were statistically significant, confirming that the trial had enough power to detect the actual difference in the studied population.

Another limitation was the use of asymptomatic microembolic signals as a surrogate marker. Microembolic signal monitoring itself is technically demanding and might not be available in many general hospitals. In addition, the prevalence of microembolic signals has been declining recently, probably because of better medical therapy.[30]

In conclusion, this study shows that combination therapy with clopidogrel and aspirin is more effective than aspirin alone in reducing the proportion of patients with at least one microembolic signal in a population of patients who have cerebral or carotid artery stenosis, most of whom had stenosis of the intracranial carotid artery.

Contributors

PCC and AK collected the case record forms and managed the database. YZ did the data analysis. All other authors contributed to the design of the protocol, recruited patients, and wrote the draft of the manuscript. All authors approved the final version of the manuscript.

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Conflicts of interest

KSLW received research grants, honoraria, and travel support to meetings from Boehringer Ingelheim, Otsuka, Sanofi-Aventis, and Servier for other research studies not connected to the CLAIR study. NCS received research grants, honoraria, and travel support to meetings not connected to the CLAIR study from Otsuka, Sanofi-Aventis, Pfizer, Takeda, and AstraZeneca. HSM received research grants and travel expenses from the Chinese University of Hong Kong. All other authors have no conflicts of interest.

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