Stroke

Dual Antiplatelet Therapy With Clopidogrel and Aspirin in Symptomatic Carotid Stenosis Evaluated Using Doppler Embolic Signal Detection
The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) Trial

Hugh S. Markus, FRCP; Dirk W. Droste, MD; Manfred Kaps, MD; Vincent Larrue, MD;
Kennedy R. Lees, FRCP; Mario Siebler, MD; E. Bernd Ringelstein, MD

Background—Evidence for efficacy of dual antiplatelet therapy in stroke is limited. Symptomatic carotid stenosis patients are at high risk of early recurrent stroke. In this group, asymptomatic microembolic signals (MES), detected by transcranial Doppler ultrasound (TCD), are markers of future stroke and transient ischemic attack (TIA) risk. They offer a surrogate marker to evaluate antiplatelet therapy, but no multicenter study has evaluated the feasibility of this approach.

Methods and Results—Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) is a randomized, double-blind study in subjects with recently symptomatic $\geq$50% carotid stenosis. Patients were screened with TCD, and if MES were detected, they were randomized to clopidogrel and aspirin or aspirin monotherapy. Repeated TCD recordings were made on days 2 and 7. MES were detected in 110 of 230 patients by online analysis at baseline, of whom 107 were randomized. Intention-to-treat analysis revealed a significant reduction in the primary end point: 43.8% of dual-therapy patients were MES positive on day 7, as compared with 72.7% of monotherapy patients (relative risk reduction 39.8%; 95% CI, 13.8 to 58.0; $P=0.0046$). The secondary end point of MES frequency per hour was reduced (compared with baseline) by 61.4% (95% CI, 31.6 to 78.2; $P=0.0013$) in the dual-therapy group at day 7 and by 61.6% (95% CI, 34.9 to 77.4; $P=0.0005$) on day 2. There were 4 recurrent strokes and 7 TIAs in the monotherapy group versus no stroke and 4 TIAs in the dual-therapy group that were treatment emergent and ipsilateral to the qualifying carotid stenosis; 2 additional ipsilateral TIAs occurred before treatment started. MES frequency was greater in the 17 patients with recurrent ipsilateral events compared with the 90 without (mean$\pm$SD: 24.4$\pm$27.7 versus 8.9$\pm$11.5 per hour; $P=0.0003$).

Conclusions—In patients with recently symptomatic carotid stenosis, combination therapy with clopidogrel and aspirin is more effective than aspirin alone in reducing asymptomatic embolization. Doppler MES detection is a feasible method to evaluate the efficacy of antiplatelet therapy in multicenter studies. (***Circulation***. 2005;111:2233-2240.)

Key Words: trials ■ embolism ■ stroke ■ ultrasonics ■ carotid arteries

Aspirin is the mainstay of antithrombotic medication in the secondary prevention of noncardioembolic stroke and transient ischemic attack (TIA); however, it prevents at best a fifth of recurrent strokes.[1] Combination antiplatelet therapy increasingly is being used in ischemic heart disease, but evidence for its efficacy in preventing stroke is limited. Recent studies suggest that the risk of very early recurrent stroke in patients with minor stroke or TIA has been under-

estimated and may be as high as 8% to 12% at 7 days.[2,3] The risk is particularly high in patients with carotid artery stenosis,[4] suggesting that more aggressive antiplatelet therapy may be indicated in this patient group. Clinical trial evidence for such an approach is still forthcoming.

Trials of antiplatelet agents in stroke prevention are a major undertaking, requiring thousands of patients to demonstrate reductions in clinical end points. There is a large gulf

between preclinical studies evaluating antiplatelet effects and trials with the clinical end point of stroke. Ex vivo assessment of platelet function does not always correlate with clinical efficacy, and animal models may not reflect processes ongoing in the complex atherosclerotic plaque. Therefore, there is a need for an in vivo surrogate marker that can be used to assess antiplatelet efficacy in humans and optimize choice and dosage of agents before evaluation in large clinical trials.

Increasing evidence suggests that asymptomatic microembolic signals (MES), detected by transcranial Doppler ultrasound (TCD), offer such a marker. TCD is a painless noninvasive technique that allows prolonged monitoring for periods of an hour or longer. Validation studies demonstrated that it is highly specific and sensitive in detecting platelet and thrombus emboli.[5,6] MES have been recorded in patients with a wide variety of embolic sources; their clinical significance varies according to their source.[7] Considerable data suggest that they are useful markers of risk in patients with carotid stenosis. During a single hour's recording from the ipsilateral middle cerebral artery, asymptomatic embolization has been reported in ≈40% of patients with symptomatic carotid stenosis.[8–12] MES are more common in patient groups known to be at higher risk of recurrent stroke, including those with more recent symptoms,[10,13] plaque ulceration,[10,14–15] tighter stenosis,[10] and symptomatic versus asymptomatic status.[8] In carotid stenosis, MES are an independent predictor of TIA and stroke risk.[10,16–19] In a small acute study, their frequency was reduced, but not abolished, by intravenous aspirin.[20] Small single-center studies suggest that dual antiplatelet therapy, with aspirin in combination with the nitric oxide donor *S*-nitrosothiol[21] or the glycoprotein IIb/IIIa inhibitor tirofiban,[22] is more effective than aspirin alone. Still, no multicenter study has yet used MES detection to evaluate antiplatelet efficacy.

The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial was designed to evaluate the efficacy of dual antiplatelet therapy with clopidogrel and aspirin, compared with aspirin alone, on asymptomatic embolization in patients with recently symptomatic carotid stenosis. Clopidogrel is an ADP-receptor antagonist that has synergistic effects when given in addition to aspirin on both ex vivo platelet aggregation and thrombus formation in animal models.[23] In the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial,[24] the ischemic stroke patients receiving clopidogrel monotherapy showed a reduction in recurrent cardiovascular events compared with those on aspirin alone. Moreover, in patients with unstable angina[25] and after coronary stenting,[26] combination therapy with clopidogrel and aspirin is more effective than aspirin alone. On the other hand, recent data from the MATCH trial have shown that the combination is no better than clopidogrel alone in long-term secondary prevention of ischemic stroke.[27]

Methods

CARESS is a randomized, double-blind, multicenter, prospective study performed in 11 centers in France, Germany, Switzerland, and the United Kingdom. It was designed to evaluate whether clopidogrel in combination with aspirin is superior to aspirin alone in reducing the incidence of MES detected by TCD in patients with recently symptomatic carotid stenosis. Patients were screened with TCD to identify those in whom MES could be detected, and only those in whom MES were detected were randomized to treatment. All patients gave signed informed consent, and local ethics committees for all participating centers approved the study.

Inclusion Criteria

Patients were eligible for inclusion if they were aged >18 years, had ≥50% carotid stenosis, and had experienced ipsilateral carotid territory TIA (including amaurosis fugax) or stroke within the last 3 months. Carotid stenosis ≥50% was established by color-coded carotid duplex ultrasound with the use of published criteria,[28] including peak flow velocity ≥120 cm/s. Eligible patients were then screened with TCD (see below).

Exclusion Criteria

Patients were excluded from enrollment if any of the following criteria were met: clinical and/or brain CT findings compatible with hemorrhagic transformation; recent strokes with focal hypodensity in >33% of corresponding middle cerebral artery territory on initial CT scan or National Institutes of Health Stroke Scale score >22[29]; carotid endarterectomy scheduled within the next 2 weeks; acoustic window that did not allow TCD recordings; atrial fibrillation or other major cardiac source of embolism; thrombolysis within the last 2 weeks; anticoagulation within the last 3 days; administration of antiplatelet agents other than aspirin within the last 3 weeks (3 days for dipyridamole extended release); history of clinically significant or persistent thrombocytopenia or of bleeding diathesis or coagulopathy; history of clinically significant or persistent neutropenia; history of drug allergy to thienopyridine derivatives and/or aspirin; inability to provide written informed consent; and women of childbearing potential who were not on an effective method of contraception or who were breast feeding.

TCD Recordings

At each time point, TCD recordings were made from the middle cerebral artery ipsilateral to the symptomatic carotid stenosis. All recordings were made with the use of either EME/Nicolet Pioneer or Companion or DWL Multidop equipment with a 2-MHz transducer. Standard recording settings were used, as recommended in International Consensus Criteria,[30] with a sample volume of 4 to 5 mm and a sweep speed of 4 to 5 seconds. No intensity (dB) threshold was used. The raw Doppler audio signal was recorded onto digital audiotape for subsequent central analysis. In addition, for each recording the local investigator monitored recordings online to identify MES. Central blinded offline analysis was used for primary end point evaluation, but online analysis of the baseline recording was used to identify whether the patient had MES and therefore was eligible for recruitment. Before study commencement, standard tapes were distributed among centers for blinded evaluation, training was given where necessary, and a high level of intercenter reproducibility in identification of MES was obtained. The central reading center (Muenster, Germany) was validated against a second experienced center (St George's, London, United Kingdom) on a subset of 11 randomly selected 1-hour recordings, one from each study site, containing a total of 203 MES found by either center. The proportion of specific agreement[31] between the 2 centers was 0.802, meaning that 80.2% of the signals found by one center were also found by the other.

Treatment Protocol

A 1-hour TCD recording was performed on eligible patients. If ≥1 MES were identified, the patient was then randomized to receive either a 300-mg loading dose of clopidogrel on day 1, followed by 75 mg once daily until day 7, or matching placebo. Patients were randomized by center in balanced blocks of size 4. Both arms also received aspirin 75 mg once daily for the duration of the study (Figure 1). All study drugs were administered orally. Repeated TCD recordings were made for 1 hour on days 2 and 7. All TCD recordings were performed at the same time of day for individual
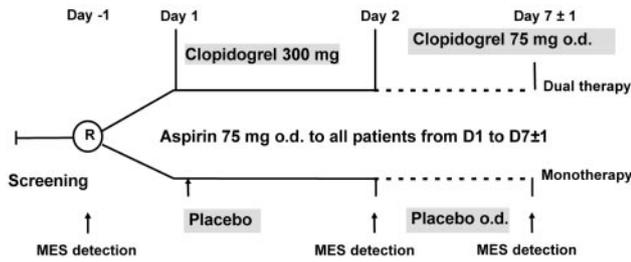
Figure 1. Summary of study design. o.d. indicates once daily.

patients (±2 hours). Concomitant use of the following treatments was restricted: anticoagulants, thrombolytic agents, additional anti-platelet agents, and all analgesics except paracetamol and opioids.

End Points

The prespecified primary end point was the proportion of patients who were MES positive, as detected by analysis by the central reading center, on the 1-hour recording performed on day 7. Prespecified secondary end points were the proportion of patients who were MES positive on day 2, the rate of embolization (number of MES per hour) on both days 2 and 7, and their percent change from baseline. Specified safety end points were the presence of any adverse events and cerebrovascular events (TIA, ischemic stroke, and cerebral hemorrhage). The protocol required that if a cerebro-vascular event occurred, it was reported as a serious adverse event, and brain imaging with CT or MRI was performed to exclude hemorrhage. The final diagnosis of TIA or stroke relied on the investigator's judgment. An event was considered treatment emer-gent if its onset time was after the first study drug administration and before the study completion of the patient. Bleeding events were divided into the categories "life threatening," "major," and "minor."

Central Data Analysis

All TCD tapes were coded, randomized, and then analyzed blinded to patients' identity by a single observer in the Central Reading Station. International Consensus Criteria[30] were used to identify MES according to their characteristic spectral and acoustic appear-ance. Analysis was performed with a 128-point fast Fourier trans-form and a time window overlap of >50%.

Platelet Studies

In addition to TCD recordings, collagen-induced platelet aggregation tests on platelet-rich plasma were performed locally at baseline and at day 7 with the use of the turbidimetry method of Born and Cross.[32] The test was standardized across participating centers that were provided with the same batch of collagen reagent and a dilutional protocol intended to achieve a concentration of 2.5 μg/mL. All aggregation tracing recordings were centrally validated by a blinded observer, and those considered of good quality were analyzed according to internationally established standards.[33] Results were expressed as aggregation intensity, corresponding to the percentage of light transmission obtained with platelet-rich plasma in compar-ison to the baseline obtained with platelet-poor plasma.

Sample Size Calculations

A sample size of 100 (50 patients in each study group) was selected. The assumption was made that 70% to 80% of the monotherapy group (70% of patients with prior aspirin therapy for <1 week and 80% for patients with prior aspirin therapy for ≥1 week) would remain MES positive; these figures were derived from review by the steering committee of original data from a number of studies (References 8, 10, and 12 and H.S. Markus, FRCP, unpublished data, 1994–2001) in which recordings had been repeated in patients with carotid stenosis on aspirin. The detectable risk reduction compatible with 80% power and significance of 0.05 was 35% to 41%. This reduction was within the range of the reduction in MES reported in previous small single-center studies comparing aspirin to dual

antiplatelet therapy[21,22] and in unpublished data on the combination of clopidogrel and aspirin (V. Larrue, MD, unpublished data, 1999–2001).

Statistical Methods

The primary analysis was performed with the use of offline central analysis of MES recordings. The primary end point was compared between the treatment groups with the Fisher exact test. Analyses were performed on both an intention-to-treat (ITT) basis and on the per protocol population. For ITT analyses, data were included from all randomized subjects whose relevant offline analysis recordings were of sufficient quality. A treated subject who dropped out before day 7 because of TIA or ischemic stroke was considered MES positive. The per protocol population was defined as those treated patients who were confirmed as MES positive at baseline (by offline analysis) and who completed the study with MES assessment by offline analysis on day 7 or who dropped out before day 7 because of TIA or ischemic stroke without major violation of protocol. This analysis was planned because the definitive recording determining whether a subject was MES positive was considered the central blinded offline analysis, which was considered more consistent and reliable than the baseline online analysis performed by different investigators in each center. Homogeneity of the treatment difference among centers was determined for MES positivity by testing for and excluding (P>0.05) center-by-treatment interaction with the use of a likelihood ratio test in a log-linear model. For analysis of frequency of embolization, rates of 0 MES per hour (ie, MES negative) were replaced by 0.3 MES per hour to facilitate a log transformation performed to reduce skewness and the number of outliers. The values for log of the percentage of baseline rate were compared by t tests. Center-by-treatment interaction was tested by 2-way ANOVA. The embolization rate reductions with 95% CIs are presented after an anti–log transformation of the results. The Cochran-Armitage trend test was used to analyze the correlation of recurrent events and MES rates without adjustment for treatment to most easily allow for events that occurred after baseline and before treatment. These analyses used the online MES rates in place of unavailable offline MES rates to be able to use the entire ITT safety population and all recurrent events. Baseline characteristics were compared with the 2-sample t test for continuous data and the Fisher exact test for categorical data.

Results

Study Population

A total of 230 patients were screened with TCD. MES were detected in 110 (47.8%) during initial screening online analysis. Of these 110 eligible patients, 107 were randomized, of whom the number recruited from each center were as follows: Toulouse 5, Chemnitz 7, Düsseldorf 14, Giessen 4, Magdeburg 5, Münster 16, Bern 7, Glasgow 11, Leicester 4, London 24, Manchester 10.

The numbers available for each of the ITT analyses are shown in Table 1. Two withdrew consent after screening recordings, and one was discovered to already be taking clopidogrel. Fifty-one were randomized to dual therapy and 56 to monotherapy. During offline analysis of 6 baseline tapes (3 dual therapy, 3 monotherapy), MES were not identified. Five further baseline tapes (3 dual therapy, 2 monotherapy) were of insufficient quality for offline analysis. One additional patient (dual therapy) withdrew because of myocardial infarction. Therefore, 44 dual-therapy and 51 monotherapy patients were included in the per protocol analysis.

Table 2 summarizes demographic and other baseline data in the 2 groups. The qualifying event was TIA in 61.7% and stroke in 38.3%. Forty percent of patients had experienced

TABLE 1. Number of Subjects Available for ITT Analysis of Each End Point

ITT Analysis	Dual Therapy		Monotherapy	
	Day 2	Day 7	Day 2	Day 7
Primary analysis (MES positivity or withdrawal for TIA/stroke)	50	48	54	55
Secondary analysis (MES frequency as a percentage of baseline)	48	47	53	53
Platelet aggregation	. . .	31	. . .	40
Safety	. . .	51	. . .	56
Safety related to a day 2 TCD	50	. . .	56	. . .

For analysis of the primary end point, all subjects were included. The secondary analysis of MES frequency as a percentage of baseline could only be performed in subjects in whom MES were confirmed on central analysis of baseline recordings. Data from the dual-therapy subject who withdrew because of myocardial infarction was available on day 2 but not on day 7.

symptoms within the last week, and 77.1% had experienced symptoms within the last month. Baseline rates of embolization were similar ($P=0.86$) in the 2 groups: mean±SD (median [range]) values were 9.5±13.5 (4.5 [0.0 to 59.0]) in the dual-therapy group and 11.6±17.8 (6.0 [0.0 to 96.0]) in the monotherapy group. Results for both ITT and per protocol analyses are summarized in Table 3.

Primary End Point
On ITT analysis there was a significant reduction in the primary end point: 43.8% of dual-therapy patients were MES positive on day 7 compared with 72.7% of monotherapy patients (relative risk reduction 39.8%; 95% CI, 13.8 to 58.0; $P=0.0046$). On the per protocol analysis there was a similar

reduction: 45.5% of dual-therapy patients were MES positive on day 7 compared with 72.5% of monotherapy patients (relative risk reduction 37.3%; 95% CI, 9.7 to 56.5; $P=0.011$). Center-by-treatment interaction was not significant.

Secondary End Points
On ITT analysis, MES frequency per hour was reduced by 61.4% (95% CI, 31.6 to 78.2; $P=0.0013$) in the dual-therapy group at day 7 and by 61.6% (95% CI, 34.9 to 77.4; $P=0.0005$) at day 2. The results are shown in Figure 2. The proportion of MES-positive patients at 24 hours was nonsignificantly reduced (dual-therapy group 56.0% versus monotherapy group 74.1%; relative risk reduction 24.4%; 95% CI,

TABLE 2. Baseline Demographic Data for the 2 Treatment Groups

Characteristic	Treatment Group		P
	Dual Therapy (n=51)	Monotherapy (n=56)	
Age, mean±SD, y	66.4±8.1	62.8±10.7	0.053
Male gender	35 (68.6)	39 (69.6)	0.910
Degree of carotid stenosis, mean±SD, %	84.3±11.1	80.2±12.8	0.082
TIA as qualifying event	32 (62.7)	34 (60.7)	0.845
Qualifying event within 7 days	19 (37.3)	23 (42.6)	0.686
Stroke history before index event	3 (5.9)	4 (7.1)	1.000
Hypertension	38 (74.5)	31 (55.4)	0.045
Diabetes	16 (31.4)	18 (32.1)	1.000
Hypercholesterolemia	28 (54.9)	32 (57.1)	0.847
Angina	11 (21.6)	13 (23.2)	1.000
Prior myocardial infarction	6 (11.8)	10 (17.9)	0.426
Prior coronary bypass	4 (7.8)	4 (7.1)	1.000
Prior coronary stenting/angioplasty	1 (2.0)	2 (3.6)	1.000
Peripheral artery disease	11 (21.6)	6 (10.7)	0.185
On aspirin before enrollment	46 (90.2)	52 (92.9)	0.734
Statin therapy	34 (66.7)	33 (58.9)	0.430
Drugs acting on the renin–angiotensin system	22 (43.1)	20 (35.7)	0.552
β-Blocking agents	21 (41.2)	16 (28.65)	0.222
Calcium channel blockers	10 (19.6)	13 (23.2)	0.814
PPAR-γ agonists	0	0	. . .

PPAR-γ indicates peroxisome proliferator-activated receptor-γ. Values are n (%) unless otherwise indicated.

TABLE 3.   Summary of Primary and Secondary End Point Results for Both the ITT and Per Protocol Analyses

| End Point | Treatment Group | | Relative Risk Reduction or Embolization Rate Reduction, % (95% CI) | P |
	Dual Thgerapy	Monotherapy		
ITT analysis	n=51	n=56		
MES present at day 7, n (%)	21 (43.8)	40 (72.7)	39.8 (13.8, 58.0)	0.005
MES present at day 2, n (%)	28 (56.0)	40 (74.1)	24.4 (−1.2, 43.5)	0.065
MES frequency day 7, mean±SD	1.8±3.9	5.9±9.3	61.4 (31.6, 78.2)	0.001
MES frequency day 2, mean±SD	3.3±6.4	9.5±14.6	61.6 (34.9, 77.4)	<0.001
Per protocol analysis	n=44	n=51		
MES present at day 7, n (%)	20 (45.5)	37 (72.5)	37.3 (9.7, 56.5)	0.011
MES present at day 2, n (%)	25 (56.8)	38 (76.0)	25.2 (−1.0, 44.7)	0.078
MES frequency day 7, mean±SD	1.9±4.0	6.3±9.6	61.2 (31.7, 78.0)	0.001
MES frequency day 2, mean±SD	3.7±6.7	10.1±15.0	62.7 (37.6, 77.7)	<0.001

−1.2 to 43.5; $P=0.065$). There were similar reductions in the per protocol population. MES frequency per hour in the dual-therapy group compared with the monotherapy group was reduced by 61.2% (95% CI, 31.7 to 78.0; $P=0.0013$) at day 7 and by 62.7% (95% CI, 37.6 to 77.7; $P=0.0003$) at day 2. The proportion of MES-positive patients at 24 hours was nonsignificantly reduced (dual-therapy group 56.8%, monotherapy group 76.0%; relative risk reduction 25.2%; 95% CI, −1.0 to 44.7; $P=0.078$). Center-by-treatment interaction was not significant for any secondary end point.

During the 1-week follow-up, 4 monotherapy patients suffered recurrent ipsilateral ischemic stroke compared with none in the dual-therapy group. Seven monotherapy patients experienced recurrent ipsilateral treatment emergent TIA compared with 4 dual-therapy patients. Additionally, 2 dual-therapy patients experienced recurrent ipsilateral TIA only before treatment began. Brain imaging confirmed absence of hemorrhage in all cases. The presence and frequency of MES at both baseline and day 2 were correlated with the presence of recurrent ipsilateral TIA and stroke. The 17 subjects who had further ipsilateral TIA or stroke during the 7-day follow-up had higher baseline MES frequency than the 90 without recurrent ipsilateral events (mean±SD: 24.4±27.7

Figure 2. Effect of dual therapy on MES frequency shown by a box plot of frequency of MES at baseline, day 2, and day 7 on ITT analysis. *Box plots display median, quartiles, nonextreme values, and extreme values. Rates of 0.0 MES per hour were replaced by 0.3 MES per hour before percentages were calculated.

versus 8.9±11.5 per hour; $P=0.0003$). The 14 subjects who had further ipsilateral TIA or stroke after the day 2 visit had higher day 2 MES frequency than the 92 without (1 patient withdrew before the second TCD) (mean±SD: 16.1±21.4 versus 6.0±10.7 per hour; $P=0.0063$).

Platelet Studies

A total of 71 (31 dual-therapy and 40 monotherapy) patients had both baseline and day 7 tracings available and validated. Mean maximum intensity of platelet aggregation at day 7 was 106.7% of baseline in the monotherapy group and 70.9% in the dual-therapy arm (relative risk reduction 36.0%; 95% CI, 20.5 to 48.5; $P=0.0001$). Center-by-treatment interaction was not significant.
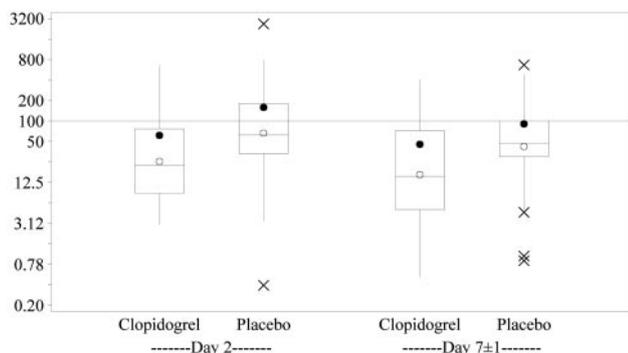
Side Effects

Adverse events in the 2 groups are shown in Table 4. There was no significant difference in bleeding between the 2 groups, with no episodes of life-threatening, major, or intracerebral hemorrhage in either group. There were 3 minor bleeding events: 2 on dual therapy (1 epistaxis, 1 mild

TABLE 4.   Bleeding and Recurrent Cardiovascular Adverse Effects

| Characteristic | Treatment Group | |
	Dual Therapy (n=51)	Monotherapy (n=56)
Any bleeding	2 (3.9)	1 (1.8)
Life-threatening bleeding	0	0
Major bleeding including intracranial bleeding	0	0
Minor bleeding	2 (3.9)	1 (1.8)
Any recurrent vascular event		
TIA/ischemic stroke	5 (9.8)	12 (21.4)
TIA/ischemic stroke ipsilateral to the qualifying stenosis	4 (7.8)	11 (19.6)
Ischemic stroke alone	0	4 (7.1)
Myocardial infarction	1 (2.0)	0

Values are shown as n (%). $P>0.05$ for all comparisons.

hemorrhage not otherwise specified) and 1 on monotherapy (epistaxis).

Discussion

These results demonstrate that, in actively embolizing patients with recently symptomatic carotid stenosis, combination therapy with clopidogrel and aspirin is more effective than aspirin alone in reducing asymptomatic embolization. There was a 40% relative reduction in the proportion of patients embolizing at 1 week and a more marked reduction in the frequency of MES. A rapid treatment response was found, with a similar magnitude of effect on rate of embolization at day 2. Similar results were found with the use of both ITT analysis and our prespecified per protocol analysis. The TCD results are consistent with those from the platelet aggregation studies, with the addition of clopidogrel resulting in a significant reduction in platelet aggregation.

There has been limited evidence for dual antiplatelet therapy in the secondary prevention of stroke. The European Stroke Prevention Study 2 (ESPS2) demonstrated an additive effect of dipyridamole with aspirin,[34] but the combination appeared less effective in other smaller studies.[1] The recent MATCH trial found no additional benefit of aspirin and clopidogrel over clopidogrel alone in the secondary prevention of stroke over an 18-month follow-up.[27] This study population differed from CARESS in a number of important aspects. All types of ischemic stroke were included, with an overrepresentation of patients with small-vessel disease, a group in whom the underlying process is not embolism from atherosclerotic plaque and who have a lower risk of early recurrent stroke.[35] Furthermore, MATCH recruited most patients several weeks after the acute phase, when the risk of recurrent events is highest.[35] The results of CARESS suggest that dual antiplatelet therapy with clopidogrel and aspirin is likely to be more effective in patients with large-vessel atherosclerotic stroke in the acute phase. The differences from MATCH emphasize the heterogeneity of stroke and therefore the need for examining the effect of therapies on different stroke subtypes. They also emphasize the need for examining efficacy during the acute phase, as well as for long-term secondary prevention.[35] It is possible that acute atherosclerotic stroke behaves in a fashion similar to that of acute myocardial ischemia; for example, in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study, in which the combination of clopidogrel and aspirin was more effective than aspirin alone in acute coronary syndrome, patients were only entered within 24 hours of symptom onset.[25]

The CARESS results demonstrate the feasibility of using TCD detection of MES as a surrogate end point for evaluating antiplatelet therapy. Previous small single-center studies[20–22] have used this technique, and a recent large single-center study in patients undergoing carotid endarterectomy in the immediate postoperative period also demonstrated that the combination of clopidogrel and aspirin was more effective than aspirin alone in reducing MES.[36] However, CARESS is the first multicenter trial to use this method. The results demonstrate the power of this technique to detect treatment effects in relatively small groups of patients, far less than those required with the use of a clinical end point such as stroke. We also found that the relative reduction in our TCD end point was of a magnitude similar to the 36% relative reduction in our platelet aggregation studies.

We chose the dichotomous end point of the presence or absence of MES rather than their frequency. This is because previous natural history studies have used this cutoff when determining associations between MES and stroke and TIA risk.[10,15–19] However, our results demonstrate that by using the frequency of embolic signals rather than their presence or absence, a more significant treatment effect was demonstrated. The use of this end point may therefore allow treatment effects to be demonstrated with a smaller sample size in future studies.

In this study MES were detected in 47.8% of patients at screening during a single hour's recording. This is very similar to previously published results[8–12] and emphasizes how frequently asymptomatic embolization occurs in this patient group. During the 1-week follow-up, there was a high rate of recurrent ipsilateral ischemic events in the monotherapy group, with a 7.1% risk of stroke and 12.5% risk of recurrent TIA. Therefore, the presence of asymptomatic embolization identified a high-risk group. Furthermore, the MES rate at both baseline and day 2 was significantly higher in patients who suffered recurrent stroke and TIA during the 7-day and day 2 to 7 follow-up period, respectively. This is consistent with a number of prospective studies showing that the presence of MES is associated with a markedly increased risk of recurrent stroke and TIA.[10,15–20] It is also consistent with recent epidemiological data demonstrating a high risk of early recurrent stroke after TIA or minor stroke, of ≈8% to 12% at 7 days and 17% to 18.5% at 1 month.[2,3] Patients with carotid stenosis appear to have a particularly high recurrent stroke risk.[4] The 1-week risk identified in these studies is very similar to the 7.1% risk in subjects treated only with aspirin. These converging lines of evidence suggest that patients with carotid artery stenosis, identified either by very recent events or the presence of MES, are a very high-risk group who should be considered for dual or perhaps even triple antiplatelet therapy. Data from the European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET) demonstrated that endarterectomy reduces recurrent stroke risk in patients with ≥70% stenosis.[37,38] These results emphasize the importance of operating urgently in patients whenever possible. However, many surgeons recommend waiting for a few weeks to operate in patients with completed stroke, and in many countries endarterectomy is delayed because of logistics or a resource shortage. To ensure that no delay occurred by enrolling patients in CARESS, we performed a prospective audit of a subset of 28 enrolled and 57 excluded consecutive patients considered for study entry; average time to carotid surgery or stenting was 34 (SD 20) days in patients randomized into CARESS, 44 days[27] in patients entered but who were not randomized because of no MES at baseline, and 47 days[33] in patients not entered. Therefore, there was no delay in patients entering the study. More importantly, although the delays partly reflect reluctance to operate on patients early after stroke because of concerns about early operative risk, they

emphasize that in the "real world" patients are waiting too long for surgery. Therefore, even when patients are waiting for planned carotid endarterectomy, combination antiplatelet therapy appears an attractive option.

A rapid onset of action is important in the acute phase, and therefore we used a 300-mg loading dose of clopidogrel, which has been used in the acute coronary setting.[25] The use of a loading dose has been shown to result in more rapid inhibition of platelet aggregation with an antithrombotic effect apparent within 90 minutes and maximal within 6 hours.[39] We found a rapid onset of action and no excess of bleeding complications when it was administered over a short time period of 7 days. This is in contrast to the MATCH study, in which the long-term administration of the combination resulted in significantly more bleeding complications than clopidogrel alone.[27]

Even in the dual-therapy arm, 44% of subjects still had MES on day 7. This suggests that even more effective therapy may reduce MES and recurrent stroke to a greater extent. A small study with the novel antiplatelet agent *S*-nitrosoglutathione found a greater reduction in MES frequency,[21] suggesting even more potent antiplatelet regimens may have benefit if they are not associated with excessive bleeding. Alternatively, additional approaches targeting other parts of the process, such as inflammation and monocyte aggregates, which could also contribute to MES formation, may be beneficial.

In conclusion, CARESS has demonstrated that dual antiplatelet therapy with clopidogrel and aspirin results in a rapid reduction in asymptomatic embolization compared with aspirin alone. It has also demonstrated the feasibility of using TCD MES detection as a surrogate marker to evaluate the relative efficacy of different combinations of antiplatelet therapy before much larger trials with clinical end points.

Acknowledgments

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