Eur J Vasc Endovasc Surg **29**, 522–527 (2005)
doi:10.1016/j.ejvs.2005.01.012, available online at http://www.sciencedirect.com on SCIENCE DIRECT®

The Benefits of Combined Anti-platelet Treatment in Carotid Artery Stenting

F.M. McKevitt,[1]* M.S. Randall,[1] T.J. Cleveland,[2] P.A. Gaines,[2] K.T. Tan[2] and G.S. Venables[1]

[1]*Neurology Department, Royal Hallamshire Hospital, and* [2]*Sheffield Vascular Institute, Northern General Hospital, Sheffield Teaching Hospitals NHS Trust, Sheffield, UK*

Objective. *To assess the benefits of a combined anti-platelet regime of aspirin and clopidogrel in carotid artery stenting.*
Methods. *A randomised controlled trial was performed comparing aspirin and 24-h heparin with aspirin and clopidogrel for patients undergoing carotid artery stenting. Outcome measures included 30-day bleeding and neurological complications and 30-day stenosis rates.*
Results. *Bleeding complications (groin haematoma or excessive bleeding at the groin site) occurred in 17% of the heparin and 9% of the clopidogrel group (*$p = 0.35$*; n.s). The neurological complication rate in the 24-h heparin group was 25% compared to 0% in the clopidogrel group (*$p = 0.02$*). The 30-day 50–100% stenosis rates were 26% in the heparin group and 5% in the clopidogrel group (*$p = 0.10$*; n.s).*
Conclusions. *The dual anti-platelet regime has a significant impact on reducing adverse neurological outcomes without an additional increase in bleeding complications. This study was terminated prematurely due to an unacceptable level of complications in the heparin arm of the trial.*

Keywords: Carotid stenosis; Angioplasty and stenting; Anti-platelet drugs.

Introduction

The benefits of combined anti-platelet treatment in coronary artery stenting have been long established.[1] Significant reductions in post procedure myocardial infarction and stent thrombosis have been demonstrated when patients are treated with dual anti-platelet regimens rather than with aspirin alone or aspirin and warfarin.[2] More recently the advantages of dual anti-platelet treatment commencing prior to coronary intervention have also been demonstrated, with a reduction in peri-procedural adverse events.[3] There is as yet, however, no randomised controlled trials to recommend dual anti-platelet regimes in carotid artery stenting.

Before this study commenced patients undergoing carotid endovascular treatment at our centre were treated with aspirin prior to the procedure followed by systemic heparin for anti-coagulation at the time of the procedure and for 24 h afterwards. This was an accepted regime that concurred with specified protocols derived from a randomised controlled trial comparing endovascular treatment with carotid endarterectomy.[4] The emerging evidence from the coronary stenting studies began to make apparent however, the greater role that anti-platelet drugs may have in preventing adverse outcomes, a benefit that may also be applicable to carotid artery stenting. We therefore decided to investigate the benefits of a dual anti-platelet regime in carotid stenting and a prospective, randomised, un-blinded trial comparing aspirin and heparin with aspirin and the thienopyridine anti-platelet agent clopidogrel was performed at our institution. It was intended that this be a pilot for a larger study demonstrating equivalence between the two treatments but the study was terminated prematurely by the investigators due to an unacceptable level of complications in the heparin arm of the trial.

* Corresponding author. Dr Fiona McKevitt, Neurology Department, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK.
E-mail address: fionamckevitt@hotmail.com

1078–5884/000522 + 06 $35.00/0

Materials and Methods

Study design

This was a prospective, randomised, un-blinded trial performed at a single centre between March 2000 and September 2002. Approval was obtained by the local ethics committee and written consent obtained from each patient.

Objectives

The primary objective was to evaluate the safety of clopidogrel and aspirin compared to 24-h heparin and aspirin in patients undergoing carotid artery stenting.

The secondary objectives were to assess the neurological complications in the first 30 days following the procedure and the 30-day stenosis rates of the treated artery as measured by carotid duplex imaging.

Randomisation

Prior to carotid stenting patients were randomly allocated to a treatment regime. The method used to implement the random allocation sequence was numbered sealed envelopes. An independent statistician prepared the sequence generation, which was blinded to those enrolling patients and to those performing the carotid intervention.

Inclusion and exclusion criteria

Patients with high-grade carotid artery stenosis, confirmed by angiography ($\geq$70% NASCET criteria[5]) with planned treatment by carotid artery stenting, were considered for enrolment. CT or MRI scans were performed on all patients to exclude haemorrhagic stroke or haemorrhagic transformation of an ischaemic stroke.

Other exclusion criteria included pre-existing treatment with clopidogrel; patients unable or unwilling to give informed consent; patients with active bleeding or at high-risk of bleeding, for example, diagnosed peptic ulcer within the last 6 months; patients scheduled for any form of surgery (other than the study procedure) during or for 10 days after the study period; uncontrolled hypertension $>$180/110 mmHg despite optimal medication and contra-indications to study drugs, for example history of clopidogrel sensitivity.

Carotid stent procedure

All procedures were performed by an interventional radiologist (TJC, PAG). The carotid stenting technique has evolved, over the time of this study period, to include the use of a cerebral protection device. The techniques employed have previously been described in detail.[6]

Study drug regimes

Patients prior to the procedure were already on single anti-platelet therapy, aspirin (acetylsalicylic acid) 75 mg. Patients randomised to the heparin group were administered intravenous unfractionated heparin to achieve an activated partial thromboplastin time (APTT) ratio of 1.5–2.5 for 24 h following the procedure ($n=25$). Patients randomised to the clopidogrel group were given a loading dose of clopidogrel 300 mg 6–12 h before the procedure and again as 75 mg 2 h prior to the procedure. This was then continued as 75 mg daily for 28 days following stent placement ($n=25$). All patients were anti-coagulated with a bolus of 5000 units of heparin (1 mg/Kg) during the procedure itself and maintained on aspirin thereafter.

Endpoints

All patients were assessed prior to treatment, at discharge and at 30 days following the procedure by an independent stroke neurologist who was unaware of the treatment allocation.

Primary endpoint

All bleeding complications occurring within the first 30 days of the procedure. These included haemorrhagic stroke, gastro-intestinal bleeding, bleeding from the catheter site resulting in prolonged hospitalisation or the development of a groin haematoma.

Secondary endpoints

Thirty day neurological complication rates. All neurological complication events were documented. Amaurosis fugax was defined as monocular visual loss lasting less than 24 h. Transient ischaemic attack (TIA) was defined as a new neurological deficit lasting less than 24 h. Minor stroke was defined as a new neurological deficit lasting more than 24 h but less than 7 days. Major stroke was defined as a new neurological deficit that persists more than 7 days. It was subdivided at 30 days post-event into non-disabling stroke, if the

Oxford modified handicap score was 0–2 or disabling stroke, if the Oxford modified handicap score was equal or greater than 3.[7]

Thirty day stenosis rates. Carotid Doppler ultrasonography was used to assess stenosis rates at 30 days following treatment. The method used to calculate the stenosis is the in-stent/CCA peak systolic velocity ratio.

Data collection, study power and statistical methods

Information was prospectively recorded for each patient. Demographic, clinical and procedural variables recorded included age, sex, presenting event, vascular risk factors, type of stent, type of cerebral protection device and type of closure device used.

Data from the CAVATAS study suggests that the incidence of death and major stroke within 30 days of the procedure is 10%.[4] To show a benefit of 20% (with power of 80%) in favour of the use of combination anti-platelet therapy would require a sample size in the region of 3000. This was an initial pilot safety study using a sample size of 120 patients to show that patients treated with the combination anti-platelet therapy were not disadvantaged, i.e. there was no major difference between the two groups in terms of embolic events or haemorrhagic complications. Following completion of this study it was planned to expand the study by recruiting other centres.

All data were analysed using the SPSS® software package. Only patients undergoing the carotid stenting procedure were analysed. Comparisons between groups were made using either Chi-square test or Fisher's exact test if the assumptions were not fulfilled. A p value of <0.05 was considered significant.

Results

It was initially planned to randomise 120 patients into this study but following an interim analysis it was decided to stop the trial earlier than planned. During this period 50 patients had been randomised to intravenous unfractionated heparin ($n=25$) or clopidogrel ($n=25$). Three patients did not undergo carotid artery stenting (heparin=1, clopidogrel=2) since, they were found to have carotid artery occlusions ($n=2$) or a non-significant stenosis ($n=1$) prior to treatment and were, therefore, excluded from further analysis. Patient baseline characteristics are detailed in Table 1. All complications are listed in Table 2.

Table 1. Baseline characteristics

	Heparin ($n=24$)	Clopidogrel ($n=23$)
Age		
Mean (±SD)	66 (±8)	67 (±10)
Range	53–83	53–81
Male sex	13 (54%)	14 (61%)
Cerebral protection device	15 (63%)	17 (74%)
Stent device		
Wallstent	23 (96%)	100 (100%)
SMART	1 (4%)	0 (0%)
Closure device used	23 (96%)	21 (91%)
Symptomatic disease	20 (83%)	18 (78%)
Degree of stenosis		
Median	80	85
Range	70–98	70–99
Medical history		
Hypertension	16 (67%)	16 (70%)
Peripheral vascular disease	7 (29%)	5 (22%)
Diabetes	5 (21%)	3 (13%)
Smoker (current or previous)	18 (75%)	16 (70%)
Ischaemic heart disease	11 (46%)	8 (35%)
Atrial fibrillation	0 (0%)	0 (0%)
Hypercholesterolaemia*	23 (96%)	21 (91%)

* Total cholesterol >5.0 mmol/l.

Bleeding complications

There were no gastro-intestinal bleeding complications or haemorrhagic strokes. Groin complications occurred in 17% ($n=4$) of the heparin group and in 9% ($n=2$) of the clopidogrel group. These differences were not statistically different ($p=0.35$ 95% CI −11 to 27%). In the heparin group, the complications comprised three small groin haematomas that did not delay discharge (in one there was failure to deploy the closure device and manual compression alone was performed) and one groin haematoma that did delay discharge by 24 h. In this later case, the APPT ratio was greater than 10.

In the clopidogrel group, the groin complications consisted of one small groin haematoma that did not

Table 2. Thirty day complications

	Heparin ($n=24$)	Clopidogrel ($n=23$)
Amaurosis fugax	1 (4%)	0 (0%)
TIA	2 (8%)	0 (0%)
Minor stroke	0 (0%)	0 (0%)
Major non-disabling stroke	1 (4%)	0 (0%)
Major disabling stroke	2 (8%)	0 (0%)
Death	0 (0%)	1* (4%)
Groin complications	4 (17%)	2 (9%)
30 day stenosis rates		
0–49%	17/23 (74%)	20/21 (95%)
40–69%	2/23 (9%)	0/21 (0%)
70–99%	0/23 (0%)	1/21 (5%)
100%	4/23 (17%)	0/21 (0%)

TIA, transient ischaemic attack.
* Non-neurological related.

cause delay of discharge and one groin haematoma that resulted in a prolonged discharge (by 4 days). In this case, a closure device was not used and manual compression alone was performed.

Neurological complications

The neurological complication rate including all amaurosis fugax, TIA and all stroke in the heparin group was 25% ($n=6/24$). The complications comprised amaurosis fugax ($n=1/24$), TIA ($n=2/24$), major non-disabling stroke ($n=1/24$) and major disabling stroke ($n=2/24$). All these neurological events were ipsilateral to the treated artery. These events occurred within 24 h ($n=4$), within 48 h ($n=1$) and at 8 days ($n=1$). In the clopidogrel group, the all neurological complication rate was 0% ($n=0/23$). This difference was statistically different ($p=0.02$, 95%CI 8–42%). There was one death (clopidogrel treated group) that was related to the insertion of a pacemaker and not stroke related.

Thirty-day stenosis rates

In the heparin arm the 50–69% stenosis rate was 9% ($n=2/23$), 0% ($n=0/23$) had a 70–99% stenosis and 17% ($n=4/23$) had a 100% occlusion. Three of these total occlusions were associated with adverse neurological events. In the clopidogrel group, the 50–69% stenosis rate was 0% ($n=0/20$), 5% ($n=1/20$) had a 70–99% stenosis and 0% ($n=0/20$) had a 100% occlusion. The difference between the two groups was not statistically significant ($p=0.10$).

Loss of data

The reasons for loss of duplex data at 30 days included death (one), stroke (one), and non-attendance (two).

Discussion

This study demonstrates that a dual anti-platelet regime instigated prior to carotid artery stenting has a significant impact on reducing adverse neurological outcomes without an additional increase in bleeding complications. This was an un-blinded randomised controlled trial with patients reviewed at discharge and at 30 days by an independent stroke neurologist who had no access to the treatment allocation at the time of review. It is the first randomised trial to assess the benefits of a dual anti-platelet regime in carotid artery stenting, however it was terminated early following a review of the first 50 enrolled patients. Though the numbers were relatively small (the results therefore at risk of a type II error) there was a marked difference in outcome measures between the two groups. This finding in addition to data emerging from coronary stenting trials, demonstrating the significant advantage of dual anti-platelet therapy on preventing adverse events,[8–10] lead to the decision by the investigators to terminate the study prematurely. It is noted that this difference is less marked if the outcome measure, death and all stroke (as usually used in carotid intervention studies) is employed. However, anti-platelet agents and heparin are administrated during carotid artery stenting to protect against possible thrombo-embolic complications. As this includes transient ischaemic attack, as well stroke, all ischaemic neurological complications were included.

At the beginning of this trial there was no consensus for peri-procedural anti-platelet or anti-thrombotic regimes. Some centres were already using dual anti-platelet regimes,[11] some were using aspirin with procedural heparin and heparin for 24 h following the procedure,[4] some were using both a dual anti-platelet regime and procedural heparin plus heparin for 24 h following the stenting procedure[12] and some were withholding all peri-procedural anti-platelets until 3 days after the procedure.[13] Strong evidence from percutaneous coronary intervention studies was beginning to make clear however, that dual anti-platelet regimes may be beneficial.

Early coronary angioplasty studies first demonstrated the benefits of aspirin in place of unfractionated heparin with a 76% relatively risk reduction of post procedure myocardial infarction seen in the anti-platelet group.[14] As coronary artery stenting replaced primary angioplasty the benefits of using a thienopyridine based dual anti-platelet regimen in place of aspirin alone, or an aspirin and warfarin combination, were soon confirmed by several randomised controlled trials.[1,2,15,16]

These initial trials were performed using the thienopyridine ticlopidine, and despite ticlopidine having several known unwanted side effects, including causing severe neutropenia in 1% of patients, and potentially fatal thrombotic thrombocytopenic purpura (TTP) in 0.2% of patients, benefit for its use was shown. At the inception of our trial clopidogrel had recently been developed as an alternative agent with fewer side effects and with probable equal efficacy. The benefits of aspirin and clopidogrel following coronary stenting have since been demonstrated in several large randomised trials assessing this combination with

aspirin and ticlopidine.[8–10,17] Though dual anti-platelet therapy have been shown to be efficacious following coronary interventions it does not automatically follow however, that the same benefit will be derived following carotid procedures. Glycoprotein IIb/IIIa inhibitors have been shown to reduce ischaemic events following coronary interventions,[18] but has not reduced neurological complications following carotid interventions.[19] In addition, there is concern that it is also associated with increased rates of intracerebral haemorrhage.[20] The use of glycoprotein IIb/IIIa inhibitors during carotid artery stenting therefore, has actively been discouraged.

The need for higher levels of platelet inhibition with stents may in part be explained by the higher and prolonged degree of platelet activation seen in stented vessels as opposed to angioplasty alone.[21,22] Previous studies on heparin use in coronary stenting have demonstrated a significant increase in platelet activation but in addition the initial adhesion of platelets to the stent surface is not prevented by heparin. Platelet aggregation is allowed to occur and this may furthermore explain the higher re-stenosis and complication rates demonstrated in patients treated with anti-coagulants.[23] In this study acute total thrombosis of the treated carotid artery and all neurological complications were seen in the heparin group only and were ipsilateral to the stented carotid artery.

One potential confounding factor in this study is the concomitant use of cerebral protection devices. These devices reduce thrombo-embolic complications at the time of the carotid stenting procedure and have been shown to reduce neurological complication rates.[24] Cerebral protection was utilised in 63% of the heparin group and 74% of the clopidogrel group. All neurological events occurred in the heparin group and so a separate review of this group was performed to assess if the use of cerebral protection devices had an impact on adverse events. Though the difference was not statistically significant ($p=0.35$) the trend seen was surprising. There was an 11% ($n=1/9$) neurological complication rate for procedures performed without a cerebral protection device compared to 33% ($n=5/15$) for procedures performed with a cerebral protection device. It is unlikely therefore, that the use of cerebral protection devices accounts for the difference seen between the two groups.

Stent endothelialisation is a slow process and is known to take between 28 and 96 days to complete.[25] During this time the exposed metallic stent continues to act as a source of platelet activation. The prolonged use of clopidogrel after the procedure in comparison to a limited period of heparin use may partly explain the difference in outcomes between the two groups, in particular the complications that occurred after 24 h.

This study adds to the limited literature on the use of dual anti-platelet therapy in carotid artery stenting and supports evidence from other forms of endovascular stenting that platelet activation plays a key role in the pathogenesis of stent occlusion and embolic complications. We recommend dual anti-platelet treatment with aspirin and clopidogrel for all patients undergoing carotid stenting particularly when a cerebral protection device is employed. If stents take at least 96 days to endothelialise however, further work needs to be considered to investigate the optimum length of time needed to give dual anti-platelet therapy.

Acknowledgements

Costs incurred in this study were met by an unrestricted grant from Sanofi Ltd.

References

1 Schomig A, Neumann FJ, Kastrati A, Schuhlen H, Blasini R, Hadamitzky M *et al*. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996;**334**:1084–1089.
2 Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK *et al*. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent anticoagulation restenosis study investigators. *N Engl J Med* 1998;**339**:1665–1671.
3 Steinhubl SR, Ellis SG, Wolski K, Lincoff AM, Topol EJ. Ticlopidine pretreatment before coronary stenting is associated with sustained decrease in adverse cardiac events: data from the evaluation of platelet iib/iiia inhibitor for stenting (EPISTENT) trial. *Circulation* 2001;**103**:1403–1409.
4 CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the carotid and vertebral artery transluminal angioplasty study (CAVATAS): a randomised trial. *Lancet* 2001;**357**:1729–1737.
5 North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;**325**:445–453.
6 McKevitt FM, Macdonald S, Venables GS, Cleveland TJ, Gaines PA. Complications following carotid angioplasty and carotid stenting in patients with symptomatic carotid artery disease. *Cerebrovasc Dis* 2004;**17**:28–34.
7 Bamford JM, Sandercock PA, Warlow CP, Slattery J. Inter-observer agreement for the assessment of handicap in stroke patients. *Stroke* 1989;**20**:828.
8 Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, Investigators FT. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation* 2000;**102**:624–629.
9 Berger PB. Results of the ticlid or plavix post-stents (TOPPS) trial: do they justify the switch from ticlopidine to clopidogrel after coronary stent placement? *Curr Control Trials Cardiovasc Med* 2000;**1**:83–87.

10 Muller C, Buttner HJ, Petersen J, Roskamm H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. *Circulation* 2000;**101**:590–593.
11 Roubin GS, New G, Iyer SS, Vitek JJ, Al-Mubarak N, Liu MW *et al*. Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis: a 5-year prospective analysis. *Circulation* 2001; **103**:532–537.
12 Henry M, Amor M, Klonaris C, Henry I, Masson I, Chati Z *et al*. Angioplasty and stenting of the extracranial carotid arteries. *Tex Heart Inst J* 2000;**27**:150–158.
13 Guimaraens L, Sola MT, Matali A, Arbelaez A, Delgado M, Soler L *et al*. Carotid angioplasty with cerebral protection and stenting: report of 164 patients (194 carotid percutaneous transluminal angioplasties). *Cerebrovasc Dis* 2002;**13**:114–119.
14 Schwartz L, Bourassa MG, Lesperance J, Aldridge HE, Kazim F, Salvatori VA *et al*. Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. *N Engl J Med* 1988;**318**:1714–1719.
15 Hall P, Nakamura S, Maiello L, Itoh A, Blengino S, Martini G *et al*. A randomized comparison of combined ticlopidine and aspirin therapy versus aspirin therapy alone after successful intravascular ultrasound-guided stent implantation. *Circulation* 1996;**93**:215–222.
16 Bertrand ME, Legrand V, Boland J, Fleck E, Bonnier J, Emmanuelson H *et al*. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The full anticoagulation versus aspirin and ticlopidine (FANTASTIC) study. *Circulation* 1998;**98**:1597–1603.
17 Moussa I, Oetgen M, Roubin G, Colombo A, Wang X, Iyer S *et al*. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. *Circulation* 1999;**99**:2364–2366.
18 The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997;**336**:1689–1696.
19 Wholey MH, Eles G, Toursakissian B, Bailey S, Jarmolowski C, Tan WA. Evaluation of glycoprotein IIb/IIIa inhibitors in carotid angioplasty and stenting. *J Endovasc Ther* 2003;**10**:33–41.
20 Arab D, Yahia AM, Qureshi AI. Use of intravenous abciximab as adjunctive therapy for carotid angioplasty and stent placement. *Int J Cardiovasc Intervent* 2003;**5**:61–66.
21 Gawaz M, Neumann FJ, Ott I, May A, Rudiger S, Schomig A. Changes in membrane glycoproteins of circulating platelets after coronary stent implantation. *Heart* 1996;**76**:166–172.
22 Parsson H, Cwikiel W, Johansson K, Swartbol P, Norgren L. Deposition of platelets and neutrophils in porcine iliac arteries after angioplasty and wallstent placement compared with angioplasty alone. *Cardiovasc Intervent Radiol* 1994;**17**:190–196.
23 Knight CJ, Panesar M, Wilson DJ, Patrineli A, Chronos N, Wright C *et al*. Increased platelet responsiveness following coronary stenting. Heparin as a possible aetiological factor in stent thrombosis. *Eur Heart J* 1998;**19**:1239–1248.
24 Kastrup A, Groschel K, Krapf H, Brehm BR, Dichgans J, Schulz JB. Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. *Stroke* 2003;**34**:813–819.
25 Grewe PH, Deneke T, Machraoui A, Barmeyer J, Muller KM. Acute and chronic tissue response to coronary stent implantation: pathologic findings in human specimen. *J Am Coll Cardiol* 2000;**35**:157–163.

Accepted 17 January 2005
Available online 17 February 2005