Eur J Vasc Endovasc Surg (2009) **38**, 402–407

Variations in the Pharmacological Management of Patients Treated with Carotid Endarterectomy: A Survey of European Vascular Surgeons

M. Hamish, M.S. Gohel, A. Shepherd, N.J. Howes, A.H. Davies*

Imperial Vascular Unit, Charing Cross Hospital, London W6 8RF, UK

Submitted 19 December 2008; accepted 5 July 2009
Available online 3 August 2009

KEYWORDS
Carotid endarterectomy;
Antiplatelet;
Heparin;
Statin

Abstract *Objectives:* The peri-operative use of antiplatelet, anticoagulant and other drugs for patients undergoing carotid endarterectomy (CEA) is unclear and consensus is lacking. This study aimed to assess the current peri-operative practice of European vascular surgeons with respect to antiplatelet and other medications for patients undergoing CEA.
Design: Online questionnaire study.
Methods: Members of the Vascular Society of Great Britain & Ireland and European Society for Vascular Surgery were invited to complete an online survey in March 2008. Surgeons were asked about their preferences for the peri-operative administration of antiplatelet, statin and other medications for patients undergoing carotid endarterectomy.
Results: Partial or complete responses were received from 399/650 (61.4%) surgeons with a collective annual throughput of >11500 CEA procedures. For symptomatic and asymptomatic patients, 20/392 (5%) and 47/392 (12%) of surgeons would stop aspirin before surgery and 170/392 (43%) and 217/392 (55%) of surgeons would stop Clopidogrel prior to CEA. Of surgeons who would stop Clopidogrel, 84/170 (49%) and 124/217 (57%) would do so >7 days before surgery for symptomatic and asymptomatic patients respectively. 12/393 (3%) surgeons would prescribe one 75 mg dose of Clopidogrel on the evening before surgery. Intra-operative Dextran was used selectively by 40/395 (10%). Only 78/393 (20%) would delay surgery to commence a statin. Intra-operatively, 348/394 (88%) used intravenous heparin, which was reversed routinely by 47/348 (13%) and selectively by 60/348 (17%).
Conclusions: There appears to be broad consensus between vascular surgeons in the pharmacological management of patients undergoing carotid endarterectomy, although some variations do exist. Further clinical studies may help clarify the optimum management strategy in this patient group.

Introduction

Numerous large randomized studies including the North American Symptomatic Carotid Endarterectomy Trial

* Corresponding author. Tel.: +44 2088467320; fax: +44 2088467362.
E-mail address: a.h.davies@imperial.ac.uk (A.H. Davies).

1078-5884/$36
doi:10.1016/j.ejvs.2009.07.001

(NASCET),[1] the European Carotid Surgery Trial (ECST)[2] and the Asymptomatic Carotid Surgery Trial (ACST)[3] have evaluated the effectiveness of carotid endarterectomy in patients with significant internal carotid artery stenosis. These have demonstrated a significant reduction in the risk of death or disabling strokes for patients randomized to surgery in comparison to those in the non-surgical arms. However, consensus is lacking on the peri-operative prescription of antiplatelet, cholesterol lowering or other medications for patients requiring carotid endarterectomy (CEA). A recent meta-analysis reported that aspirin was protective in most patients at increased risk of occlusive vascular events.[4] Furthermore, large randomized clinical studies have demonstrated reductions in stroke and death rates in patients treated with aspirin after stroke.[5] These findings suggest that a period of pre-operative administration followed by post-operative administration of aspirin may have a protective effect in patients undergoing CEA.

In order to maintain low complication rates following CEA, multiple components of the pre, intra and post-operative care must be carefully managed. Tsurgical technique and appropriate use hese factors include patient selection, assessment of cardiac risk factors, precise blood pressure control, meticulous of antiplatelet, anti-coagulation and other medications. The aim of this study was to evaluate the use of peri-operative antiplatelet, anticoagulant and other medications amongst European Vascular Surgeons.

Materials and Methods

An email invitation to complete an online 16-part questionnaire was sent to all listed members of the European Society of Vascular Surgery (ESVS) and the Vascular Society of Great Britain and Ireland (VSGBI). The societies were not involved in the design of the study. Questions relating to the pre, peri and post-operative pharmacological management of patients undergoing CEA were devised by the study authors (Appendix 1). Questions related to pre-operative antiplatelet, anticoagulant and statin use; intra-operative heparin, dextran, protamine and dexamethasone use and post-operative antiplatelet use. The initial invitation email was sent in March 2008 and a reminder email was sent in June 2008. The questionnaire responses were anonymized and only one response per email address was allowed by the online academic survey software (Bristol Online Surveys). All complete and partially completed responses were included in the analysis and the number of completed responses received for each question is presented as the denominator. Statistical analysis was performed using the Chi Square test (SPSS v16.0, Chic, IL, USA).

Results

Partial or completed questionnaires were received from 399 of the 650 (61.4%) Vascular Surgeons invited to participate. Published email addresses were inaccurate for 98/650 (15.1%) and 153/650 (23.5%) did not respond. A total of 284 responses were received after the initial invitation email and a further 115 responses were received after the reminder email. The combined throughput of those who completed the survey was >11,500 CEA procedures per annum. Of the 361 respondents that answered the specific question, 239 (66.2%) performed >20 CEA procedures per annum. Procedures were routinely performed using general anaesthesia by 178/362 (49.1%) whereas 151/362 (41.7 %) used local anaesthesia and 33/362 (9.1%) used both techniques.

Pre-operative management

The vast majority of vascular surgeons surveyed would not stop aspirin prior to carotid endarterectomy for symptomatic or asymptomatic patients (372/392 [94.8%] and 345/392 [88.0%] respectively) (Table 1). Of the 47 respondents that would discontinue aspirin (including 20 who would do so for patients with symptomatic and asymptomatic carotid stenosis), 33/47 (70.2%) would do so 1–7 days before surgery and 14/47 (29.8%) would stop aspirin for at least 7 days. When asked about pre-operative Clopidogrel use, 170/392 (43.3%) and 217/392 (55.3%) of surgeons would stop Clopidogrel before surgery for symptomatic and asymptomatic patients respectively. Of surgeons who would stop Clopidogrel, 84/170 (49.4%) and 124/217 (57.1%) would do so >7 days before surgery for symptomatic and asymptomatic patients respectively. For both aspirin and Clopidogrel, surgeons were more likely to stop antiplatelet medications prior to surgery for asymptomatic rather that symptomatic carotid stenosis ($p = 0.001$, $p = 0.001$ respectively, Chi Squared test) (Table 1).

A high proportion of respondents stated that they would continue Dipyridamole prior to surgery for symptomatic or asymptomatic disease; 247/250 (98.8%) and, 211/250 (84.4%) respectively. A total of 285/392 (72.7%) and 389/392 (99.2%) of respondents would stop Warfarin prior to CEA (Table 1). Interestingly, 12/393 (3.0%) of surgeons would prescribe a pre-operative 75 mg dose of Clopidogrel, the day before surgery. CEA would be delayed by surgeons to give statin medication by 18/393 (4.9%) for symptomatic patients and 60/393 (15.2%) for asymptomatic patients.

Intra-operative management

Only 13/394 (3.2%) surgeons would give intra-operative pooled platelets if the patient was on dual antiplatelet

Table 1 Numbers of respondents who would stop antiplatelet and anticoagulant medications prior to CEA

Patient category	Aspirin	Clopidogrel	Dipyridamole	Warfarin
Symptomatic	20/392(5.1%)	170/392(43.3%)	83/394(21.0%)	285/392(72.7%)
Asymptomatic	47/392(11.9%)	217/392(55.3%)	93/394(23.6%)	389/392(99.2%)
	$p = 0.001$*	$p = 0.001$*	$p = 0.441$*	$p = 0.001$*

* Chi-square test.

therapy (aspirin and Clopidogrel or Dipyridamole). The majority of surgeons would routinely give heparin prior to arterial clamping (348/394 [88.3%]), but only 47/348 (13.5%) would routinely reverse the heparin and 60/348 (17.2%) would reverse it selectively. Regarding blood pressure management during surgery, 245/394 (62.1%) would aim to maintain normotension during CEA, although 97/394 (24.6%) would aim to keep patients hypertensive. Dextran was routinely prescribed by 40/397 (10.0%) of respondents and selectively (based on transcranial Doppler readings) by a further 27/397 (6.8%). Dexamethasone was used routinely or selectively by a minority of respondents; 14/363 (3.8 %) and 35/363 (9.6%) respectively.

Post-operative management

Among the surgeons who would discontinue antiplatelet drugs, 18/20 (90.0%) would restart aspirin and 131/189 (69.3%) would restart Clopidogrel on first day post-operatively (Table 2).

Discussion

This survey demonstrated that the majority of European Vascular Surgeons who responded would continue aspirin, but most would stop other antiplatelet and anticoagulant medications prior to carotid endarterectomy. Moreover, most respondents would use heparin intra-operatively, aim to maintain normal blood pressure during surgery and restart antiplatelet medications on the first post-operative day. Although a broad consensus was seen, it is worth noting that some variation in the clinical practice of European Vascular Surgeons was demonstrated in this study, highlighting the scarcity of level 1 evidence or clinical guidelines in this area.

The decision to continue to stop antiplatelet and anticoagulant drugs requires the clinician to evaluate the risks and benefits for each individual patient and balance the risks of bleeding and thrombosis. In a study that investigated the use of 75 mg of Clopidogrel in addition to 150 mg of aspirin, a significant reduction in peri-operative emboli was seen without any increase in bleeding complications or blood transfusion.[6] A recent systematic review found that the risk of peri-operative stroke among those receiving antiplatelet agents was significantly reduced in comparison with the risk for those not receiving antiplatelet therapy, but that the risks of peri-operative death in the two groups were not significantly different.[7] Another study suggested that a single 75-mg dose of Clopidogrel, taken the evening before carotid endarterectomy, may reduce post-operative embolisation, a marker of thrombo-embolic stroke.[8] Moreover, a recent meta-analysis suggested that the use of Dipyridamole in combination with aspirin may be the best choice for secondary prevention of vascular events after stroke or TIA.[9] Despite these studies, 5—12% of surveyed surgeons would stop aspirin and more than half would stop Clopidogrel pre-operatively. Clearly, further clinical studies demonstrating clear benefits are needed before dual antiplatelet therapy is widely adopted by surgeons performing CEA.

Interestingly, a small proportion of surgeons would delay carotid endarterectomy for a week or more in order to give statins. The use of statins has been suggested as a potential method of plaque stabilization prior to CEA, a hypothesis supported by histological studies.[10] Clinical studies have also shown lower rates of adverse events in patients taking statins prior to CEA.[8] Interestingly, large studies have suggested that this benefit is greatest in symptomatic rather than asymptomatic patients.[11,12] In a retrospective study, McGirt et al. suggested that peri-operative statin use (at least for one week before surgery and one month after) may reduce the incidence of cerebrovascular events and mortality among patients undergoing CEA.[13] A further study demonstrated that 4 weeks of treatment with atorvastatin resulted in significant local and systemic reductions in inflammatory mediators in patients undergoing carotid endarterectomy. These findings suggest that statins may reduce atherosclerotic plaque inflammation and potentially delay or prevent plaque rupture.[14] These observations are intriguing, but more definitive studies are needed before broad recommendations can be agreed. A strategy of delaying CEA for the administration of statins may seem logical in asymptomatic patients, but may be detrimental in symptomatic patients. The increasingly widespread use of statins in high-risk populations is likely to mean that the vast majority of patients requiring CEA will already be on cholesterol lowering medication.

The maintenance of hypertension (around 20% above pre-operative systolic pressure) during CEA may be justified by fears of 'watershed' stroke during carotid cross-clamping[15] and evidence from patients undergoing awake CEA where neurological deficits may be reversed by elevation of arterial pressure.[16] However, most clinicians would agree that absolute values or targets should be viewed as guidelines only and adapted to individual patients,[17] particularly as augmentation of arterial pressure may be associated with increased risks, including a higher incidence of myocardial infarction[18] and intracerebral haemorrhage.[19] Dextran is thought to prevent platelet adherence to the endarterectomy site, although its role in CEA remains unclear. There is evidence to suggest that dextran 40 may reduce the incidence of post-operative emboli and stroke (assessed using transcranial Doppler).[20] Corticosteroids (dexamethasone 24—40 mg/day in divided doses) may reduce vasogenic cerebral oedema, but their routine use in treatment of ischaemic strokes is doubtful.[21] Studies evaluating peri-operative corticosteroids in patients treated with CEA are scarce, although a recent

Table 2 Time to restarting antiplatelet and anticoagulant medications

Patient category	Aspirin	Clopidogrel	Dipyridamole	Warfarin
Day 1	18/20(90.0%)	131/189(69.3%)	78/110(70.9%)	84/184(45.6%)
Day 2—6	1/20(5.0%)	52/189(27.5%)	30/110(27.2%)	88/184(47.8%)
Day 7	1/20(5.0%)	6/189(3.1%)	2/110(1.8%)	12/184(6.4%)

randomized trial did suggest that dexamethasone may be effective in reducing the incidence of temporary cranial nerve injuries during CEA.[22]

We recognize that survey studies are often limited by poor response rates. The response rate in this study was only 61%, although this compares favourably with other similar studies.[23] Moreover, it is likely that a large number of surgeons (not members of ESVS or VSGBI) were not included and heterogeneity in clinical practice across Europe may limit the generalisability of this study. Another limitation of this study was the lack of questions on the management of patients taking dual antiplatelet medications, which is an increasingly common clinical scenario. In conclusion, there appears to be broad consensus between vascular surgeons in the use of antiplatelet and statins for patients undergoing carotid endarterectomy, although some variations do exist. Only by establishing evidence-based guidelines can we achieve greater consistency of treatment for this patient group.

Conflict of Interest/Funding

None.

Appendix 1
Survey questionnaire.

No.	Question	Choice of responses
1—4	Please indicate if you would routinely stop the following medications prior to CEA: • Aspirin • Clopidogrel • Dipyridamole • Warfarin	a. Do not stop prior to surgery b. Stop > 7 days pre-op c. Stop 2—7 days pre-op d. Stop 48 h pre-op e. Stop <48 h pre-op f. Other (specify) g. *No Answer*
5	Do you use an additional antiplatelet medication pre-operatively?	a. no b. Yes, if yes please specify below c. Clopidogrel one dose pre-operatively only d. Clopidogrel 48 h pre-operatively e. Clopidogrel 7 days pre-operatively f. Other g. *No Answer*
6	If a patient is not taking a statin would you delay endarterectomy in order to start one?	a. No b. Yes 7 days c. Yes 1—6 weeks d. Yes More than 6 weeks e. Other f. *No Answer*
7	If you do not routinely stop antiplatelet medication, would you routinely give patients additional platelets?	a. No b. Yes if the patient is on aspirin c. Yes but only if the patient is on Clopidogrel d. Yes but only if the patient is taking aspirin and Clopidogrel e. Yes if the patient is taking aspirin and Dipyridamole f. *No Answer*
8	Intra operatively do you routinely give heparin before clamping the arteries?	a. Yes b. No c. Selectively d. Other e. *No Answer*
9	If you do give heparin before clamping the arteries, do you reverse it?	a. Yes b. No c. Selectively d. Other e. *No Answer*
10	Intra operatively, how best describes the patients' systolic blood pressure before clamping the arteries?	a. Normotensive b. Hypertensive c. Hypotensive d. Other e. *No Answer*

(*continued on next page*)

Appendix (*continued*)

No.	Question	Choice of responses
11	Peri-operatively, do you give dextran?	a. Yes b. No c. Selectively based on TCD d. Selectively based on clinical assessment e. *No Answer*
12	Peri-operatively do you give dexamethasone?	a. Yes b. No c. Selectively based on TCD d. Selectively based on clinical assessment e. *No Answer*
13	If you usually stop antiplatelet medication prior to surgery, when do you restart it?	a. Aspirin Day1 Day 2—6 After day 7 b. Clopidogrel c. Dipyridamole d. Warfarin e. *No Answer*
14	On average how many carotid endarterectomy procedures do you perform in one year?	a. Less than 10 b. 11—20 c. 21—30 d. 31—50 e. Over 50 f. *No Answer*
15	What type of anaesthesia do you use for the majority of your carotid endarterectomy procedures?	a. General anaesthesia b. Local anaesthesia c. Equal numbers of each d. *No Answer*
16	Which antiplatelet medications do you routinely prescribe for patients requiring carotid endarterectomy? (please select all that)	a. Aspirin b. Clopidogrel c. Dipyridamole d. other f. *No Answer*

References

1 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—53.

2 Rothwell PM, Gutnikov SA, Warlow CPfor the European Carotid Surgery Trialists' Collaboration. Reanalysis of the final results of the European Carotid Surgery Trial. *Stroke* 2003;**34**:514—23.

3 Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et alMRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;**363**:1491—502.

4 Antithrombotic Trialists' Collaboration Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high-risk patients. *BMJ* 2002;**324**:71—86.

5 CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. *Lancet* 1997;**349**:1641—9.

6 Payne DA, Jones CI, Hayes PD. Beneficial effects of Clopidogrel combined with aspirin in reducing cerebral emboli in patients undergoing carotid endarterectomy. *Circulation* 2004;**109**: 1476—81.

7 Engelter S, Lyrer P. Antiplatelet therapy for preventing stroke and other vascular events after carotid endarterectomy. *Cochrane Database Syst Rev* 2003;(Issue 3). doi:10.1002/14651858. Art. No.: CD001458.

8 Payne DA, Jones CI, Hayes PD, Naylor AR, Goodal AHI. Therapeutic benefit of low-dose Clopidogrel in patients undergoing carotid surgery is linked to variability in the platelet adenosine diphosphate response and patients' weight. *Stroke* 2007;**38**: 2464—9.

9 Verro P, Gorelick PB, Nguyen D. Aspirin plus dipyridamole versus aspirin for prevention of vascular events after stroke or TIA: a meta-analysis. *Stroke* 2008;**39**:1358—63.

10 Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, Zhu J, Nilsson J. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization. *Circulation* 2001;**103**:926—33.

11 Kennedy J, Quan H, Buchan AH. Statins are associated with better outcomes after carotid endarterectomy in symptomatic patients. *Stroke* 2005;**36**:2072—6.

12 Poldermans D, Bax JJ, Kertai MD, Krenning B, Westerhout CM, Schinkel AFL, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. *Circulation* 2003;**107**: 1848—51.

13 McGirt M, Perler B, Brooke B, Woodworth G, Coon A, Jain S, et al. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors reduce the risk of perioperative stroke and mortality after carotid endarterectomy. *J Vasc Surg* 2005;**42**:829—36.

14 Martin-Ventura JL, Blanco-Colio LM, Gomez-Hernandez A, Munoz- Garcia B, Vega M, Serrano J, et al. Intensive treatment with atorvastatin reduces inflammation in mononuclear cells and human atherosclerotic lesions in one month. *Stroke* 2005; **36**:1796—800.

15 Krul JM, van Gijn J, Ackerstaff RG, Eikelboom BC, Theodorides T, Vermeulen FE. Site and pathogenesis of infarcts associated with carotid endarterectomy. *Stroke* 1989;**20**:324—8.
16 Stoneham MD, Warner O. Blood pressure manipulation during awake carotid surgery to reverse neurological deficit after carotid cross-clamping. *Br J Anaesth* 2001;**87**:641—4.
17 Stoneham MD, Thompson JP. Arterial pressure management and carotid endarterectomy. *Br J Anaesth* 2009;**102**(4):442—52.
18 Riles TS, Kopelman I, Imparato AM. Myocardial infarction following carotid endarterectomy: a review of 683 operations. *Surgery* 1979;**85**:249—52.
19 Russell DA, Gough MJ. Intracerebral haemorrhage following carotid endarterectomy. *Eur J Vasc Endovasc Surg* 2004;**28**:115—23.
20 Lennard N, Smith JL, Dumville J, Abbott R, Evans DH, London NJ, et al. Prevention of post-operative thrombotic stroke after carotid endarterectomy: the role of transcranial Doppler ultrasound. *J Vasc Surg* 1997;**26**:579—84.
21 Norris JW, Hachinski V. High doses steroid treatment in cerebral infarction. *BMJ* 1986;**292**:22—3.
22 Regina G, Angiletta D, Impedovo G, De Robertis G, Fiorella M, Carratu' MR. Dexamethasone minimizes the risk of cranial nerve injury during CEA. *J Vasc Surg* 2009 Jan;**49**:99—102.
23 Girn H, Dellagrammaticas D, Laughlan K, Gough M. Carotid endarterectomy: technical practices of surgeons participating in the GALA trial. *Eur J Vasc Endovasc Surg* 2008;**36**(4): 385—9.