Predictors of neck bleeding after eversion carotid endarterectomy

Claudio Baracchini, MD,[a] Mario Gruppo, MD,[b] Franco Mazzalai, MD,[b] Renata Lorenzetti, MD,[b] Giorgio Meneghetti MD,[a] and **Enzo Ballotta, MD,[b]** *Padova, Italy*

Objective: **The aim of this study was to identify predictors for neck bleeding after eversion carotid endarterectomy (eCEA).**
Methods: **A prospectively compiled computerized database of all primary eCEAs performed at a tertiary referral center between September 1998 and December 2009 was analyzed. The end point was any neck bleeding after eCEA. End point predictors were identified by univariate analysis.**
Results: **Of 1458 eCEAs performed by the same surgeon on 1294 patients under general anesthesia with continuous electroencephalographic monitoring and selective shunting, there were five major and three minor perioperative strokes (0.5%), and no deaths. Neck bleeding after eCEA occurred in 120 cases (8.2%), of which 69 (4.7%) needed re-exploration. Univariate analysis (odds ratio [95% confidence interval]) identified preoperative antiplatelet treatment with clopidogrel (1.77 [1.20-2.62], $P = .004$), particularly when continued to the day before CEA (3.84 [2.01-7.33], $P < .001$), and postoperative hypertension (9.44 [6.34-14.06], $P < .001$) as risk factors for neck bleeding in general and for neck bleeding requiring re-exploration (4.50 [1.85-10.89], $P = .001$; 15.27 [2.08-104.43], $P = .006$, and 2.44 [1.12-5.30], $P = .02$, respectively). An increased risk of neck bleeding in general was associated with clopidogrel plus acetylsalicylic acid (12.00 [2.59-56.78], $P = .005$), acetylsalicylic acid alone (4.37 [1.99-9.57], $P < .001$), and ticlopidine (2.49 [1.10-5.63], $P = .02$) only when they were continued to the day before CEA. No neck bleeding was associated with preoperative treatment with dipyridamole or warfarin, or no medication. No further complications occurred in the patients who underwent re-exploration.**
Conclusions: **The results of this single-center university hospital study show that neck bleeding after CEA is relatively common but is not associated with an increased risk of stroke or death. Preoperative treatment with clopidogrel, particularly when it is continued to the day before surgery, and postoperative arterial hypertension seem to be associated with a higher risk of neck bleeding after CEA, requiring re-exploration in most cases. Other antiplatelet agents appear to be associated with an increased risk of postoperative neck bleeding only if they are continued to the day before CEA. Larger studies are warranted to confirm our findings and prevent this feared surgical complication. (J Vasc Surg 2011; 54:699-705.)**

Carotid endarterectomy (CEA) is the current standard care of proven efficacy in reducing the risk of stroke in selected patients with symptomatic and asymptomatic extracranial internal carotid artery (ICA) stenosis.[1-4] Although stroke and death are the most important outcome measures, other far-from-negligible complications contribute to the morbidity of CEA. An uncommon but potentially life-threatening complication of carotid revascularization is postoperative neck bleeding that can cause respiratory failure and requires emergency surgery.

In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), wound bleeding after CEA occurred in 5.5% of patients, making it a more frequent complication than major stroke and death (2.1%) or myocardial infarction (0.9%).[1] No information was available on the outcome of the NASCET patients, but other series have reported that as many as 50% of patients experiencing bleeding required re-exploration.[5] The incidence of neck bleeding after CEA is not easy to ascertain reliably, however, because of substantial differences in its definition and a common tendency to report only bleeding needing surgical evacuation, leading to lower reported rates of hemorrhagic complications.

Preoperative antithrombotic medication (AM) with antiplatelet agents and anticoagulants has often been implicated as a risk factor for wound bleeding.[6-15] Because there are increasingly broad indications in current clinical practice for antiplatelet agents as a primary or secondary prevention of cerebrovascular, peripheral vascular and coronary artery diseases, particularly after percutaneous coronary or peripheral artery procedures,[16] and for anticoagulants for atrial fibrillation, mechanical prosthetic valves, reduced left ventricular systolic function, left ventricular apical thrombus, and prior deep venous thrombosis or pulmonary embolism,[17] most patients requiring CEA are expected to be taking some form of AM. The advisability of AM near the time of CEA is controversial: many surgeons recommend that

From the Department of Neurological Sciences[a] and the Department of Surgical and Gastroenterological Sciences,[b] University of Padua, School of Medicine.

Competition of interest: none.

Correspondence: Enzo Ballotta, MD, Vascular Surgery Section, Geriatric Surgery Clinic, Department of Surgical and Gastroenterological Sciences, University of Padua, School of Medicine, via N. Giustiniani, 35128 Padova, Italy (e-mail: enzo.ballotta@unipd.it).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.

0741-5214/$36.00

doi:10.1016/j.jvs.2011.03.262

AM administration be continued to help prevent thrombotic events, whereas others prefer to discontinue AM to minimize the risk of perioperative bleeding.[11,13,15]

The aim of this study was to identify predictors of neck bleeding after eversion CEA (eCEA) to prevent this surgical complication.

METHODS

This study was approved by the Institutional Review Board of the University of Padua.

Patients. Demographic and clinical data were prospectively entered into a computerized vascular surgery registry for all patients who underwent CEA for symptomatic and asymptomatic ICA disease, based on the recommendations of the NASCET[1] and the Asymptomatic Carotid Atherosclerosis Study (ACAS),[3] at our institution. The registry was queried to identify patients who had neck bleeding after CEA that did or did not require surgical re-exploration, from September 1998 to December 2009. The analysis excluded patients scheduled for CEA and concomitant coronary artery bypass grafting or with associated supra-aortic trunk lesions requiring concurrent surgery and patients who required procedures for recurrent disease.

The patients' demographic and clinical data were recorded on a standardized form, including potential atherosclerotic risk factors, anatomic and clinical variables, preoperative medication, including antiplatelet agents or anticoagulants, whether they were discontinued before surgery, antihypertensive drugs, details of surgery, hospital stay, and perioperative (30-day) outcomes.

Medication protocol. Our preoperative protocol for symptomatic and asymptomatic patients includes the discontinuation of any type of preoperative antiplatelet agents, including clopidogrel (75 mg/d); acetylsalicylic acid (ASA; 100 mg/d); dipyridamole (400 mg/d), ticlopidine (500 mg/d), or clopidogrel plus ASA, at least 8 days before surgery. All patients who take oral anticoagulants discontinue their warfarin medication 7 days before CEA to allow the international normalized ratio to normalize. These patients are transitioned to low-molecular-weight heparin, which is stopped the night before CEA. In many cases, this practice is only in part observed (patient's omission, family doctor's suggestion, early admission), so AM is stopped between days 2 and 8 before CEA, whereas in other cases (patient's omission, family doctor's fear, transfer from neurological wards) it is continued to the day before surgery.

The day after surgery, all patients restart their original AM, and those who preoperatively were not taking AM start with ASA (325 mg on the first day, followed by 100 mg daily). In this analysis, patients were arbitrarily stratified according to whether or not they continued their AM to the day before surgery.

Surgical procedures. All surgical procedures were eCEAs performed by the same surgeon, with patients under deep general anesthesia and with routine intraoperative electroencephalographic (EEG) monitoring for a selective use of intraluminal shunting. The technical details of the eCEA have been described elsewhere.[18,19] Shunting depended exclusively on EEG changes consistent with cerebral ischemia occurring during carotid cross-clamping, unrelated to any bradycardia or arterial hypotension.[20] Patients were administered intravenous unfractionated heparin (5000 U) before ICA clamping, and heparinization was never reversed with protamine.

Surgicel Fibrillar, an oxidized regenerated cellulose (Ethicon, Somerville, NJ) was routinely used on the suture line after the ICA was reimplanted in the common carotid artery. No completion angioscopy or imaging studies were performed. A single 14F suction drain was placed during wound closure in all cases.

All patients were extubated immediately at the end of the procedure and were monitored in the recovery room for 3 hours, where their neurologic status was routinely assessed by a neurologist. Patients were transferred to the general ward only if they remained neurologically and hemodynamically stable. All patients had invasive blood pressure monitoring throughout the operation and while in the surgical recovery unit. Antihypertensive medication was given in the recovery room if blood pressure rose >20% above the mean preoperative values or the systolic blood pressure was >180 mm Hg.

Study end points. The study end points were any clinical signs of neck bleeding after CEA, warranting or not warranting surgical re-exploration, including (1) expanding wound hematoma, defined as postoperative neck swelling with respiratory distress or airway obstruction requiring tracheal reintubation or wound re-exploration; (2) sudden or excessive bleeding into the surgical drain with minimal signs of hematoma formation, which required re-exploration; and (3) nonoperative hematoma, defined as neck swelling not expanding and stable in size on serial examination, and not causing airway or swallowing compromise, with no need for re-exploration. Patients always underwent re-exploration under general anesthesia, and they were all transferred to intensive care, where the endotracheal tube was left in place for at least 12 hours afterward.

Statistical analysis. All values are expressed as mean ± standard deviation. Continuous data were compared with the Student *t* test (two-tailed) and categoric variables with Pearson χ^2 test (two-tailed) or the Fisher exact test, as appropriate, calculating the odds ratio (OR) with 95% confidence intervals (CIs). Statistical significance was inferred for $P < .05$. Univariate analysis was used to determine the factors that might predict bleeding complications. Several data items were analyzed by surgical procedures rather than by patients because each perioperative outcome was correlated with the surgical procedure and because patients who underwent bilateral CEAs were exposed to twice the risk of stroke, death, neck hemorrhage, or other complications.

RESULTS

A total of 1458 eCEA procedures were performed in 1294 patients, of whom 164 had staged bilateral CEAs. None of the CEAs were aborted or incomplete because of

Table I. Patients demographics and clinical details

Variables	*No. (%), Mean (range), or Mean ± SD*
Patients, total	1294
Eversion CEA procedures	1458
Age, years	75.1 (39-96)
Male	885 (68.4)
Risk factors	
Hypertension	787 (60.8)
Smoking	869 (67.1)
Diabetes	416 (32.1)
Hyperlipidemia	569 (43.9)
Cardiac disease	558 (43.1)
Chronic kidney disease	106 (8.2)
Pulmonary disease	207 (16.0)
Symptoms	953 (65.4)
Stroke	301 (20.6)
Transient ischemic attack	466 (32.0)
Amaurosis fugax	186 (12.8)
No symptoms	505 (34.6)
Antithrombotic medication	
Clopidogrel	363 (24.9)
Continued to the day before CEA	110 (7.5)
Stopped before CEA	253 (17.4)
Clopidogrel plus ASA	86 (5.9)
Continued to the day before CEA	10 (0.7)
Stopped before CEA	76 (5.2)
ASA	387 (26.5)
Continued to the day before CEA	95 (6.5)
Stopped before CEA	292 (20.0)
Ticlopidine	273 (18.7)
Continued to the day before CEA	88 (6.0)
Stopped before CEA	185 (12.7)
Dipyridamole	81 (5.6)
Continued to the day before CEA	9 (0.6)
Stopped before CEA	72 (5.0)
Warfarin	102 (7.0)
No antithrombotic medication	166 (11.4)
Statin medication, n (%)	709 (48.6)
Intraoperative variables	
Left side of operation	837 (57.4)
Contralateral carotid occlusion	203 (15.7)
Shunt placement	219 (15.0)
Blood loss, mL	60 ± 25
Duration of CEA, minutes	74 ± 6.9
Clamping time, minutes	22 ± 8.8

ASA, Acetylsalicylic acid; *CEA,* carotid endarterectomy; *SD,* standard deviation.

technical issues arising during surgery. Preoperative demographic data, risk factors, clinical signs, type of AM, whether or not AM was discontinued before CEA, statin medication, and other intraoperative variables, including the side of the revascularized ICA, contralateral carotid occlusion, incidence of shunting, perioperative blood loss, carotid cross-clamping, and CEA procedure times are summarized in Table I. Patients undergoing staged CEA procedures had the same AM for both procedures. Almost half of eCEAs (48.6%) were performed with patients taking statin medication. No ischemic or hemorrhagic cerebral accidents or deaths occurred in the 8 days before CEA among those patients who had discontinued their AM.

Table II. Perioperative (30-day) outcomes

Outcomes	*No. (%) or Mean ± SD*
Patients	1294
CEA procedures	1458
Neck bleeding/hematoma	120 (8.2)
Re-exploration	69 (4.7)
Post-op hypertension in recovery	198 (13.6)
Death	0
Stroke	8 (0.5)
Major	5 (0.3)
Ipsilateral	4
Contralateral	1
Minor	3 (0.2)
Ipsilateral	1
Contralateral	2
Transient ischemic attack	38 (2.6)
Ipsilateral	23 (1.6)
Contralateral	15 (1.0)
Cerebral hemorrhage	0
Hyperperfusion syndrome	0
Myocardial infarction	1 (0.06)
Nerve injury	59 (4.0)
Hospital stay, days	4.6 ± 2.8

CEA, Carotid endarterectomy; *SD,* standard deviation.

Perioperative (30-day) outcomes. Overall, 120 (8.2%) neck hemorrhages occurred after CEA, and 69 (4.7%) needed re-exploration (Table II). The surgeon's report indicated the causes of the hematoma were bleeding arising from the wound edges in 47 patients, venous oozing from the superficial layers of the cervicotomy in 10, and an excessive bleeding into the surgical drain in the remaining 12. All neck bleeding occurred within 1 to 8 hours after the procedure and was promptly treated surgically. No further complications occurred in the patients who required re-exploration. Fifty-one cases of bleeding were conservatively managed: 43 neck swellings proved stable in size on serial examination and 8 large ecchymotic suffusions, extending from the neck to the upper third of the anterior thoracic wall, reabsorbed within 10 to 15 days after CEA. Overall, postoperative hypertension needing medication in the recovery room was recorded in 198 CEA procedures (13.6%), of which 62 (31.3%) involved neck bleeding after CEA and 44 (22.2%) required re-exploration.

Other perioperative outcomes and the mean hospital stay are reported in Table II. Five major and three minor perioperative strokes (0.5%) occurred in patients with no neck bleeding after CEA. Two major strokes occurred in patients who had discontinued their AM (ASA in both cases) 5 and 6 days before surgery, three strokes occurred in patients not taking AM, and three perioperative minor strokes occurred in patients who had not discontinued their AM (clopidogrel in 2, and clopidogrel plus ASA in 1). Patients taking clopidogrel had a 1.8-fold and 2.6-fold risk of neck hemorrhage compared with those taking ASA (OR, 1.79; 95% CI, 1.08-2.95: $P = .02$) or warfarin (OR, 2.60; 95% CI, 1.03-6.55: $P = .04$), respectively, whereas the risk was comparable with all other types of AM (Table III).

Table III. Risk of neck bleeding in general and neck bleeding requiring re-exploration related to preoperative antithrombotic medication (*AM*)

	Neck bleeding			
	General		*Requiring re-exploration*	
Variable	*OR (95% CI)*	P	*OR (95% CI)*	P
Clopidogrel vs				
Clopidogrel plus ASA	1.31 (0.60-2.84)	.50	1.42 (0.59-3.40)	.44
ASA	1.79 (1.08-2.95)	.02	2.47 (1.35-4.51)	.003
Ticlopidine	1.33 (0.79-2.23)	.27	2.54 (1.28-5.03)	.007
Dipyridamole	2.58 (0.93-7.11)	.07	8.53 (1.45-49.86)	.01
Warfarin	2.60 (1.03-6.55)	.04	. . .[a]	
No AM	2.65 (1.23-5.68)	.01		. . .[a]
Clopidogrel plus ASA vs				
ASA	1.36 (0.61-3.07)	.45	1.70 (0.68-4.45)	.25
Ticlopidine	1.01 (0.45-2.30)	.96	1.78 (0.66-4.81)	.26
Dipyridamole	1.97 (0.60-6.41)	.37	6.00 (0.91-38.60)	.12
Warfarin	2.01 (0.66-6.07)	.22	. . .[a]	
No AM	2.02 (0.75-5.41)	.16		. . .[a]
ASA vs				
Ticlopidine	1.27 (0.77-2.09)	.35	1.02 (0.47-2.21)	.94
Dipyridamole	1.44 (0.51-4.05)	.62	3.45 (0.57-20.61)	.32
Warfarin	1.45 (0.56-3.74)	.45	. . .[a]	
No AM	1.48 (0.67-3.26)	.34		. . .[a]
Ticlopidine vs				
Dipyridamole	1.94 (0.68-5.49)	.25	3.35 (0.54-20.46)	.31
Warfarin	1.95 (0.75-5.07)	.17	. . .[a]	
No AM	1.99 (0.89-4.43)	.09		. . .[a]
Dipyridamole vs				
Warfarin	0.99 (0.25-3.82)	.99	. . .[a]	
No AM	1.02 (0.31-3-31)	.96		. . .[a]
Warfarin vs no AM	1.01 (0.34-3.05)	.97		. . .[a]

ASA, Acetylsalicylic acid; *CEA,* carotid endarterectomy; *CI,* confidence interval; *OR,* odds ratio.
[a]Patients taking warfarin and not taking antithrombotic medications never needed re-exploration.

Patients taking clopidogrel also had a 2.4-fold (OR, 2.47; 95% CI, 1.35-4.51; $P = .003$), 2.5-fold (OR, 2.54; 95% CI, 1.28-5.03; $P = .007$), and 8.5-fold (OR, 8.53; 95% CI, 1.45-49.86; $P = .01$) need for re-exploration compared with patients taking ASA, ticlopidine, or dipyridamole, respectively. Patients taking warfarin and those taking no AM never needed re-exploration (Table III).

Univariate analysis identified clopidogrel (OR, 1.77; 95% CI, 1.20-2.62, $P = .004$), particularly when continued until the day before CEA (OR, 3.84; 95% CI, 2.01-7.33, $P < .001$), and postoperative hypertension (OR, 9.44; 95% CI, 6.34-14.06; $P < .001$) as predictors of neck hemorrhage in general and neck bleeding requiring re-exploration (OR, 4.50; 95% CI, 1.85-10.89, $P = .001$; OR, 15.27; 95% CI, 2.08-104.43, $P = .006$; and OR, 2.44; 95% CI, 1.12-5.30; $P = .02$, respectively). Clopidogrel plus ASA (OR, 12.00; 95% CI, 2.29-56.78; $P = .005$), ASA (OR, 4.37, CI 95% 1.99-9.57; $P < .001$), and ticlopidine (OR, 2.49, CI 95% 1.10-5.63; $P = .02$) were associated with an increased risk of neck hemorrhage in general only when they were continued to the day before CEA. Preoperative dipyridamole or warfarin treatment or no AM were not associated with neck bleeding. None of the other variables considered, including sex, baseline risk factors, presenting symptoms, statin medication, and anatomic and intraoperative details, were of predictive value for the risk of postoperative bleeding (Table IV).

DISCUSSION

In this study of 1294 patients undergoing 1458 eCEAs, the overall incidence of postoperative neck bleeding was 8.2%, with a 4.7% rate of cases warranting surgical re-exploration. Although a comparison with other series is challenging and should be drawn with caution because of the substantial differences in the definition of neck hematoma and the tendency of most authors to focus mainly on hemorrhagic complications requiring prompt re-exploration, our neck bleeding rates compared favorably with those reported in previous investigations, ranging between 1.5% and 12%,[6,7,9,10,21-27] and rising to 25% for radiographically defined neck bleeding after CEA.[8]

The results of this study show that the risk of neck bleeding after CEA, requiring re-exploration in most cases, was significantly higher in patients taking clopidogrel, particularly if continued up to the day before CEA and in patients with postoperative hypertension requiring medication in the recovery room. Patients taking clopidogrel plus ASA, ASA, or ticlopidine were more prone to hemorrhagic complications in general only when they continued their

Table IV. Univariate analysis of all considered variables and neck bleeding after carotid endarterectomy (*CEA*)

Covariate	*Univariate analysis*	
	OR (95% CI)	P
Male	0.84 (0.57-1.25)	.40
Hypertension	1.21 (0.82-1.80)	.32
Smoking	1.1 (0.73-1.65)	.62
Diabetes mellitus	1.19 (0.81-1.77)	.36
Hyperlipidemia	1.08 (0.74-1.58)	.66
Cardiac disease	0.97 (0.66-1.41)	.88
Chronic kidney disease	0.78 (0.37-1.63)	.52
Pulmonary disease	1.2 (0.74-1.94)	.46
Symptoms	1.2 (0.80-1.80)	.41
Stroke	1.18 (0.76-1.84)	.44
Transient ischemic attack	1.35 (0.92-1.99)	.11
Amaurosis fugax	0.53 (0.26-1.05)	.07
No symptoms	0.82 (0.55-1.23)	.41
Antithrombotic medication		
Clopidogrel	1.77 (1.20-2.62)	.004
Continued to the day before CEA	3.84 (2.01-7.33)	<.001
Bleeding with re-exploration	4.5 (1.85-10.89)	.001
Continued to the day before CEA	15.27 (2.08-104.43)	.006
Clopidogrel plus ASA	1.15 (0.55-2.41)	.70
Continued to the day before CEA	12 (2.59-56.78)	.005
Bleeding with re-exploration	1.95 (0.42-8.83)	.70
Continued to the day before CEA	NA (0.60-NA)	.42
ASA	0.78 (0.50-1.22)	.29
Continued to the day before CEA	4.37 (1.99-9.57)	<.001
Bleeding with re-exploration	0.87 (0.36-2.09)	.82
Continued to the day before CEA	2 (0.43-9.14)	.45
Ticlopidine	1.15 (0.73-1.82)	.53
Continued to the day before CEA	2.49 (1.10-5.63)	.02
Bleeding with re-exploration	0.39 (0.16-0.95)	.04
Continued to the day before CEA	4.8 (0.90-25.06)	.11
Dipyridamole	0.56 (0.21-1.51)	.40
Continued to the day before CEA	2.87 (0.37-23.56)	.38
Bleeding with re-exploration	0.19 (0.02-1.43)	.15
Continued to the day before CEA	0 (0.00-1.20)	.25
Warfarin	0.55 (0.22-1.35)	.20
No antithrombotic medication	0.53 (0.25-1.09)	.09
Statin medication	0.85 (0.58-1.24)	.40
Left side operation	1.31 (0.89-1.92)	.17
Contralateral carotid occlusion	0.74 (0.43-1.30)	.31
Shunt placement	1.3 (0.80-2.10)	.28
Postoperative arterial hypertension	9.44 (6.34-14.06)	<.001
Bleeding with re-exploration	2.44 (1.12-5.30)	.02

ASA, Acetylsalicylic acid; *CI,* confidence interval; *NA,* not available; *OR,* odds ratio.

AM to the day before CEA. No other complications occurred in the patients who had neck bleeding.

Our finding that taking clopidogrel before CEA correlates significantly with neck bleeding is not new, although the introduction of this medication for patients with established vascular disease is relatively recent. The relationship between clopidogrel and neck bleeding has been documented in recently published reports (Table V). All of the observational studies summarized in Table V considered a relatively small number of patients taking AM, however, so their lack of statistical power prevents any definite conclusion from being drawn on the relationship between bleeding complications and AM. Similarly, no relationship emerged between AM and neck bleeding in two randomized studies in which low-dose clopidogrel[23] and clopidogrel plus ASA and dipyridamole[29] were used to prevent embolization after CEA (a marker of thromboembolic stroke). Neither study was numerically powerful enough to assess bleeding complications, however.

The present study also showed that patients who continued their AM (clopidogrel plus ASA, ASA, or ticlopidine) until the day before CEA had an increased risk of neck bleeding compared with all other patients who discontinued their AM or were not taking AM preoperatively; also of note is that no preoperative or perioperative adverse ischemic cerebral events developed in patients who were not taking AM preoperatively.

Some surgeons prefer to discontinue AM before surgery, fearing a risk of perioperative bleeding, whereas others perform CEA in patients taking AM to prevent perioperative neurologic events, despite the higher incidence of hemorrhagic complications.[11,13,15] Data to support either approach are limited and relate mainly to the literature on cardiothoracic procedures (in favor of discontinuing treatment),[14] or orthopedic and ocular surgery (favoring continued treatment).[30-32]

A 2007 audit on the United Kingdom community of vascular surgeons investigated clopidogrel use at the time of CEA and established that 52% of surgeons discontinue it preoperatively, and 51% of them administer no alternative, whereas 49% replace it with ASA.[13] No data were available on how many days before CEA the treatment was stopped.

A 2009 survey on the perioperative practices of European vascular surgeons found different attitudes, depending on the type of AM.[15] Of the surgeons surveyed, 88% would not discontinue ASA for symptomatic or asymptomatic patients, whereas 12% would stop the treatment 1 to 7 days before surgery.[15] About half the surgeons would not stop clopidogrel for symptomatic and asymptomatic patients, but the other half would, at least a week before surgery; surgeons were more likely to stop clopidogrel for asymptomatic than for symptomatic patients.[15] However, in a report on a small sample, there were no episodes of neck bleeding, stroke, or death among 29 patients taking no AM preoperatively.[10] Because on the strength of available data, it is still impossible to state the best way to manage AM around the time of elective carotid surgery, it is quite obvious that the only way to answer this question is to pool prospective data so that sufficiently powerful results can be achieved in a field where the number of events is very small.

The close relationship found in our analysis between postoperative arterial hypertension and neck bleeding con-

Table V. Studies examining the association between antiplatelet/antithrombotic medication (*AM*) and neck bleeding after carotid endarterectomy (*CEA*)

First author	*Year*	*Medication, patients*	*Neck bleeding*
Rosembaum[10]	2010	Clopidogrel: 50; ASA: 171	More wound hematomas requiring re-exploration in the clopidogrel group than in the ASA group (16% vs 1.7%, $P = .0004$)
Wait[25]	2010	Clopidogrel up to 5 days pre-CEA: 42	Small but significant increase in nonoperative neck swelling
		Clopidogrel up to 8 days pre-CEA: 58	Statistically insignificant trend toward more nonoperative neck swelling
Payne[26]	2010	AM in most of the patients: 448	No association with any preoperative AM among 27 patients with postoperative neck bleeding requiring re-exploration
Di Fiore[25]	2009	Clopidogrel; ASA	Trend toward a higher risk of bleeding in the clopidogrel group than in the ASA group (OR, 1.84; $P = .09$).
Fleming[28]	2009	Clopidogrel: 19; no clopidogrel: 81	Only one neck bleeding not requiring re-exploration in the non-clopidogrel group
Self [21]	1999	ASA, ticlopidine, heparin, Coumadin: 249	At univariate analysis, preoperative ASA was identified as predictive factor (OR, 3.4; 95% CI, 1.0-11.4; $P = .04$) in 29 cases of post-CEA neck hematoma

ASA, Acetylsalicylic acid; *CI,* confidence interval; *OR,* odds ratio.

firms previous reports.[6,7,26] Although patients requiring reoperation for neck hematoma were reportedly hypertensive before CEA and remained so after surgery,[7,26] we found that many of our patients with neck bleeding did not have overt arterial hypertension before CEA. Hypertensive swings and coughing at the time of extubation may also be responsible for bleeding at the surgical site not seen at the time of wound closure.

Because all CEA procedures in our series were eCEAs, the relatively high 13.6% incidence of postoperative arterial hypertension may relate to the possible interruption of fibers in the carotid sinus nerve, despite every effort being made to preserve the sinus nerves by transecting the ICA at the carotid bulb just laterally to the carotid body. A significantly higher hypertension rate of 24% was documented after eCEA in a retrospective analysis of 82 eCEAs compared with 6% in 137 standard CEAs,[33] consistent with reports by other investigators who suggest that destroying the baroceptor apparatus may result in postoperative hypertension.[34,35]

Study limitation. This study has several limitations. First, although data were prospectively collected, the analysis is retrospective in nature, limiting its strength. Second, any study that only considers the results achieved by one surgeon can hardly be used to draw any generalized conclusions, although the involvement of only one surgical procedure (the eversion technique), one type of anesthesia (general vs local), and one surgeon may help to reduce the number of potential variables associated with hemorrhagic complications after CEA. The surgeon's reluctance to use protamine for heparin reversal stems from its possible association with perioperative stroke,[36] although recent studies have reported that it reduces bleeding complications associated with CEA without increasing the stroke risk.[27]

CONCLUSIONS

The results of our study have shown that neck bleeding after CEA is relatively common but is not associated with an increased risk of stroke or death. Preoperative antiplatelet treatment with clopidogrel, particularly when continued to the day before surgery, and postoperative hypertension seem to be predictors of a higher risk of neck bleeding after CEA, which requires re-exploration in most cases. Other antiplatelet agents appear to be associated with an increased risk of postoperative neck bleeding in general only when they are continued up to the day before CEA. Larger studies are warranted to confirm our findings and prevent this feared surgical complication.

AUTHOR CONTRIBUTIONS

Conception and design: CB, GM, EB
Analysis and interpretation: CB, GM, EB
Data collection: FM, RL
Writing the article: CB, GM, EB
Critical revision of the article: CB, GM, EB
Final approval of the article: CB, MG, FM, RL, GM, EB
Statistical analysis: MG
Obtained funding: Not applicable
Overall responsibility: CB, GM, EB

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. European Carotid Surgery Trialists Collaborative Group. MRC European Carotid Surgery Trial. Interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 1991;337:1235-43.
3. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995;273:1421-28.
4. MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomized controlled trial. Lancet 2004;363:1491-502.
5. Cikrit DF, Larson DM, Sawchuk AP, Lalka SG, Shafique S, Dalsing MC, et al. Short-stay carotid endarterectomy in a tertiary-care Veterans Administration hospital. Am J Surg 2004;188:544-8.

6. Kunkel JM, Gomez ER, Spebar MJ, Delgado RJ, Jarstfer BS, Collins GJ Jr, et al. Wound hematomas after carotid endarterectomy. Am J Surg 1984;148:844-7.
7. Welling RE, Ramadas HS, Gansmuller KJ. Cervical wound hematoma after carotid endarterectomy. Ann Vasc Surg 1989;3:229-31.
8. Carmichael FJ, McGuire GP, Wong DT, Crofts S, Sharma S, Montanera W, et al. Computed tomographic analysis of airway dimensions after carotid endarterectomy. Anesth Analg 1996;83:12-7.
9. Greenstein AJ, Chassin MR, Wang J, Rockman CB, Riles TS, Tuhrim S, et al. Association between minor and major surgical complications after carotid endarterectomy: results of the New York Carotid Artery Surgery study. J Vasc Surg 2007;46:1138-46.
10. Rosenbaum A, Rizvi AZ, Alden PB, Tretinyak AS, Graber JN, Goldman JA, et al. Outcomes related to antiplatelet or anticoagulation use in patients undergoing carotid endarterectomy. Ann Vasc Surg 2011;25: 25-31.
11. Smout J, Stansby G. Current practice in the use of antiplatelet agents in the peri-operative period by UK vascular surgeons. Ann R Coll Surg Engl 2003;85:97-101.
12. Burger W, Chemnitius JM, Kneissl GD, Rücker G. Low-dose aspirin for secondary cardiovascular prevention – cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation – review and meta-analysis. J Intern Med 2005;257:399-414.
13. Jackson AJ, Teenan RP, Orr DJ. The use of clopidogrel in carotid endarterectomy: an audit of current practice. Eur J Vasc Endovasc Surg 2007;34:312-3.
14. Pickard AS, Becker RC, Schumock GT, Frye CB. Clopidogrel-associated bleeding and related complications in patients undergoing coronary artery bypass grafting. Pharmacotherapy 2008;28:376-92.
15. Hamish M, Gohel MS, Shepherd A, Howes NJ, Davies AH. Variations in the pharmacological management of patients treated with carotid endarterectomy: a survey of European vascular surgeons. Eur J Vasc Endovasc Surg 2009;38:402-07.
16. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706-17.
17. Crowther MA, Warkentin TE. Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. Blood 2008;111:4871-79.
18. Ballotta E, Da Giau G, Saladini M, Abbruzzese E, Renon L, Toniato A, et al. Carotid endarterectomy with patch closure versus eversion carotid endarterectomy and reimplantation: a prospective randomized study. Surgery 1999;125:271-9.
19. Ballotta E, Da Giau G. Selective shunting with eversion carotid endarterectomy. J Vasc Surg 2003;38:1045-50.
20. Ballotta E, Saladini M, Gruppo M, Mazzalai F, Da Giau G, Baracchini C, et al. Predictors of electroencephalographic changes needing shunting during carotid endarterectomy. Ann Vasc Surg 2010;24:1045-52.
21. Self DD, Bryson GL, Sullivan PJ. Risk factors for post-carotid endarterectomy hematoma formation. Can J Anaesth 1999;46:635-40.
22. Beard JD, Mountney J, Wilkinson JM, Payne A, Dicks J, Mitton D, et al. Prevention of postoperative wound haematomas and hyperperfusion following carotid endarterectomy. Eur J Vasc Endovasc Surg 2001;21:490-3.
23. Payne DA, Jones CI, Hayes PD, Thompson MM, London NJ, Bell PR, et al. Beneficial effects of clopidogrel combined with aspirin in reducing cerebral emboli in patients undergoing carotid endarterectomy. Circulation 2004;109:1476-81.
24. Di Fiore R, Martinez J, Tzilinis A, Wojnarowski D, LaPorte F, Comerota AJ. Cervical hematoma following carotid endarterectomy is morbid and preventable: a 12-year case-controlled review [abstract]. Stroke 2009;40:e109.
25. Wait SD, Abla AA, Killory BD, Starke RM, Spetzler RF, Nakaji P, et al. Safety of carotid endarterectomy while on clopidogrel (Plavix). Clinical article. J Neurosurg 2010;113:908-12.
26. Payne DA, Twigg MW, Hayes PD, Naylor AR. Antiplatelet agents and risk factors for bleeding postcarotid endarterectomy. Ann Vasc Surg 2010;24:900-7.
27. Stone DH, Nolan BW, Schanzer A, Goodney PP, Cambria RA, Likosky DS, et al for the Vascular Study Group of Northern New England. Protamine reduces bleeding complications associated with carotid endarterectomy without increasing the risk of stroke. J Vasc Surg 2010;51: 559-64.
28. Fleming MD, Stone WM, Scott P, Chapital AB, Fowl RJ, Money SR, et al. Safety of carotid endarterectomy in patients concurrently on clopidogrel. Ann Vasc Surg 2009;23:612-15.
29. de borst GJ, Hilgevoord AA, de Vries JP, van der Mee M, Moll FL, van de Pavoordt HD, et al. Influence of antiplatelet therapy on cerebral micro-emboli after carotid endarterectomy using postoperative transcranial Doppler monitoring. Eur J Vasc Endovasc Surg 2007;34:135-42.
30. Smit A, Hooper G. Elective hand surgery in patients taking warfarin. J Hand Surg Br 2004;29:206-7.
31. Rhodes DA, Severson EP, Hodrick JT, Dunn HK, Hofmann AA. Discontinuation of warfarin is unnecessary in total knee arthroplasty. Clin Orthop Relat Res 2009;468:120-6.
32. Hall DL, Steen WH, Jr, Drummond JW, Byrd WA. Anticoagulants and cataract surgery. Ophthal Surg 1988;19:221-2.
33. Mehta M, Rahmani O, Dietzek AM, Mecenas J, Scher LA, Friedman SG, et al. Eversion technique increases the risk for post-carotid endarterectomy hypertension. J Vasc Surg 2001;34:839-45.
34. Bove EL, Fry WJ, Gross WS, Stanley JC. Hypotension and hypertension as consequences of baroreceptor dysfunction following carotid endarterectomy. Surgery 1979;85:633-7.
35. Raithel D, Kasprzak PM. The eversion endarterectomy – a new technique. In: Greenhalgh RM, Hollier LJ (editors). Surgery for stroke. London: WB Saunders; 1993, p. 189-93.
36. Fearn SJ, Parry AD, Picton AJ, Mortimer AJ, McCollum CN. Should heparin be reversed after carotid endarterectomy. A randomized prospective trial. Eur J Vasc Endovasc Surg 1997;13:394-7.

Submitted Jan 10, 2011; accepted Mar 15, 2011.