Process of care for carotid endarterectomy: Perioperative medical management

Michael C. Stoner, MD, and Dorian J. deFreitas, MD, Greenville, NC

Carotid endarterectomy (CEA) has been repeatedly described as a safe and efficacious procedure to provide a stroke-risk reduction benefit in both symptomatic and asymptomatic cases. Contemporary outcomes are acceptable using the large-scale randomized trials as a metric of success. Class I and II data can be applied to improve the care process of patients undergoing CEA. Myocardial infarction remains the most significant nonstroke complication; however, there is no significant benefit to noninvasive stress testing in patients with clinically stable disease. Perioperative β-blockade may offer up to a 10-fold reduction in the rate of perioperative myocardial infarction, but deleterious effects are attributable to high-dose regimens. Angiotensin blockade has been shown to reduce cardiovascular mortality in patients with atherosclerosis by up to 25%, although few studies have examined these agents directly in carotid surgery patients. Statins are beneficial to patients undergoing CEA with trials demonstrating up to a 3% absolute reduction in the incidence of stroke following CEA. Aspirin therapy is associated with an up to 7% absolute reduction in early stroke following CEA; however, the efficacy of combination or high-dose antiplatelet therapy remains ill-defined. A treatment strategy that involves perioperative medical optimization is likely to improve surgical outcomes and long-term cardiovascular risk for patients undergoing CEA. (J Vasc Surg 2010;52:223-31.)

Carotid endarterectomy (CEA) has been well established as the preferred treatment for flow-limiting stenoses of the carotid artery in both symptomatic and asymptomatic patients. The large-scale randomized trials of the early 1990s have established the stroke/death rate metrics that are widely cited today.1-4 Achievement of these outcomes has been replicated outside of clinical trials, and two recent large-scale database studies in fact compare favorably to these data5,6 and are the expectation with CEA across a spectrum of hospitals and surgeons.7 While a perfect surgical operation has long been recognized by vascular surgeons as the sine qua non for minimizing complications, certain care processes, some surgery related and others referable to perioperative medical therapies have been demonstrated to significantly influence at least short-term outcomes of carotid surgery. A recent review of over 20,000 Medicare patients indicated suboptimal rates of major adverse events in asymptomatic patients, presumptively related to the absence of antiplatelet therapy and patch reconstruction.8

Cardiac adverse events represent a significant portion of the nonneurologic complications associated with surgical carotid revascularization. Because CEA represents a risk-reduction procedure, all attempts should be made to improve the safety profile of the procedure. The purpose of this article is to review methods for perioperative care improvement of patients undergoing CEA and to review treatment strategies to reduce both neurologic and non-neurologic adverse events (Table I).

CARDIAC-RELATED EVENTS AFTER CEA

About a decade after the landmark 1954 operation by Eastcott and colleagues,9 DeBakey and other authors described myocardial infarction (MI) as the principle nonneurologic immediate and long-term adverse event associated with CEA.10-12 In addition, longitudinal studies after CEA indicated that associated coronary artery disease was the principle cause of late mortality in patients with or without overt cardiac disease at the time of endarterectomy.13 Subsequently, the association between carotid and coronary disease has been repeatedly demonstrated. Anatomical coronary artery disease has been demonstrated in 73% of patients undergoing carotid revascularization with up to 26% having severe correctable coronary artery disease.14,15

In contemporary practice, the incidence of Q-wave MI following CEA is typically less than 2% but represents almost half of the major adverse events associated with carotid revascularization in asymptomatic patients.4,5,16,17 The incidence of minimal myocardial injury may be higher.
Table I. Summary of pharmacotherapy strategies for patients undergoing carotid endarterectomy

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Key points</th>
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<tbody>
<tr>
<td>β-blockade</td>
<td>• Reduces myocardial injury rates following surgery in appropriately selected patients</td>
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<tr>
<td></td>
<td>• Low-risk patients likely do not derive a benefit if not already on a β-blocker</td>
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<td></td>
<td>• May be associated with adverse events at higher doses or if used indiscriminately</td>
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<tr>
<td>ACE inhibitor/</td>
<td>• Associated with improved long-term survival in patients with peripheral vascular disease</td>
</tr>
<tr>
<td>ARB</td>
<td>• Stabilizes carotid plaque and improve vessel wall biology</td>
</tr>
<tr>
<td></td>
<td>• Appropriate long-term agent for patients without contraindications</td>
</tr>
<tr>
<td>Statin</td>
<td>• Reduces acute and long-term stroke risk, reduces cardiovascular event rate, associated with long-term survival</td>
</tr>
<tr>
<td></td>
<td>• Multiple mechanisms of action including lipid profile and plaque stabilization</td>
</tr>
<tr>
<td></td>
<td>• Reasonable agent for all patient undergoing vascular surgery</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>• Reduces acute and long-term stroke risk, reduction in cardiovascular event rate</td>
</tr>
<tr>
<td></td>
<td>• Low-dose aspirin efficacious</td>
</tr>
<tr>
<td></td>
<td>• No clear benefit to dual therapy or high-dose therapy in patients undergoing CEA</td>
</tr>
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ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CEA, carotid endarterectomy.

When utilizing a selective biomarker, myocardial injury was noted to be 6.7% in the surgical arm of the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, although this study stands as an outlier with respect to preoperative cardiac events when compared to the bulk of the literature. While the clinical significance of this finding to the individual patient is nebulous, these data demonstrates the significant atherosclerotic disease burden in patients undergoing CEA.

CARDIAC RISK STRATIFICATION

Much of the prodigious literature on cardiac risk stratification was developed in vascular surgery patients. The ground-breaking work looking into noninvasive physiologic testing (nuclear stress test) to predict cardiac events was reported in a series of vascular surgery patients.

Decades ago, it was realized that postoperative MI risk following CEA was directly associated with a history of angina symptoms. However, despite a prevalence of anatomical coronary disease as high as 75%, the past literature did not support coronary revascularization in patients with either stable angina or occult disease. More recent reviews have demonstrated that prophylactic myocardial revascularization has only an anecdotal benefit and has not been demonstrated to be of benefit in any randomized trial. The randomized CARP trial failed to demonstrate a benefit to prophylactic coronary revascularization in patients undergoing elective vascular surgery. With these considerations in mind, specific coronary workup is not routinely recommended in patients undergoing CEA. Conversely, there is little evidence patients undergoing coronary artery bypass grafting (CABG) should be routinely screened for carotid disease preoperatively unless they fall into a high-risk group (age greater than 65, carotid bruit or history of cerebrovascular disease). There is evidence that patients who have symptomatic carotid disease undergoing CABG benefit from CEA. There are limited high-quality data to support the use of CEA in asymptomatic patients undergoing coronary revascularization.

The current American College of Cardiology/American Heart Association guidelines consider CEA as an intermediate-risk surgical procedure. The ACC/AHA guidelines provide class I (Table II) data to support noninvasive stress testing in patients with active cardiac conditions: unstable coronary syndrome, decompenated heart failure, significant arrhythmias or severe valvular disease.

Other indications for noninvasive testing may be appropriate in select patients but are not supported with class I data. The DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo)-II study showed that if patients were appropriately β-blocked, the perioperative cardiac event rate was reduced regardless of preoperative noninvasive testing. The cardiac death and MI rate at 30 days in patients with no testing was 1.8% vs 2.3%; odds ratio (OR) 0.78, 95% confidence interval (CI) 0.28-2.1. Cardiac testing delayed surgery for more than 3 weeks. Based on the lack of data to support coronary revascularization to reduce myocardial injury risk, there are likely few cases which will benefit from expanded indications. Medical optimization of myocardial risk remains the cornerstone of treatment for patients undergoing carotid endarterectomy.

β-BLOCKADE

β-adrenergic receptor antagonists (β-blockers, β-blockers) were originally brought to clinical fruition in the 1960s and have been used for a variety of approved indications including angina pectoris, hypertensive control, cardiac arrhythmia management, postcoronary revasculariza-
The cautiously raised a cautionary flag with respect to the ubiqu-
and warns against overly aggressive 
porate metoprolol used in this study may have caused some adverse events in the metoprolol group. The relatively higher doses of metopro-
clinically significant hypotension and bradycardia was higher in the group (3.1% vs 2.3%; 0.95, 0.53-1.66). Metoprolol did not decrease cardiovascular events 32% when compared with placebo 34%; 0.95, 0.53-1.66.

Mangano27 Atenolol (99) Placebo (101) Improved mortality with atenolol 10% vs placebo 21%, P = .019 at 3 years
Poldermans28 Bisoprolol (59) Placebo (53) Death from cardiac causes of nonfatal MI was improved with bisoprolol 3.4% vs 34% P = .001.
DIPOM77 Metoprolol (462) Placebo (459) Perioperative mortality and cardiac morbidity was not significantly affected by metoprolol 21% vs 20%, 1.06, 0.8-1.41, in diabetic patients.
MaVS Study77 Metoprolol (246) Placebo (250) No benefit in reducing cardiac events at 30 days and 6 months with an increased rate of hypotension and bradycardia.
POBBLE78 Metoprolol (55) Placebo (48) Metoprolol did not decrease cardiovascular events 32% when compared with placebo 34%; 0.95, 0.53-1.66.
POISE28 Metoprolol (4174) Placebo (4177) Metoprolol decreased rate of cardiovascular death, myocardial infarction, and nonfatal cardiac arrest; 5.8% vs 6.9% P = .04 but at the cost of higher overall death and stroke rate.

Table III. Selected trials of β-blockers compared to placebo in patients undergoing noncardiac vascular surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>β-blocker (n)</th>
<th>Comparison (n)</th>
<th>Findings</th>
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β-blockers have been universally reproduced. The POISE trial looked at one, with a resultant negative inotropic and chronotropic effect. β-blockade also leads to a decreased production of renin, which provides an antihypertensive effect. Furthermore, a reduction of sympathetic nervous system activity has been described for agents that cross the blood-brain barrier.

Perioperative β-blockade has become standard therapy in the prevention of MI in patients undergoing vascular surgery. This enthusiasm arose after two landmark publications showed a significant improvement in cardiovascular complications and mortality in patients undergoing noncardiac vascular surgery. Mangano et al randomized 200 patients to receive atenolol or placebo in the perioperative period. It was surmised that the prevention of cardiac deaths in the first 6 to 8 months led to a survival advantage at 2 years.29 Poldermans’ study randomized patients to bisoprolol or standard of care in patients undergoing vascular surgery. This study showed a 10-fold reduction in the perioperative cardiovascular event rate among the patients who received bisoprolol.27

A number of follow-up studies have been performed comparing β-blockers with placebo in noncardiac vascular surgery with mixed results (Table III). Unfortunately, the dramatic benefits seen in the studies cited above have not been universally reproduced. The POISE trial looked at 8351 patients who received a single preoperative dose of 100 mg of extended-release metoprolol followed by 200 mg daily for 30 days.30 There were 4174 patients in the treatment arm and 4177 patients in the placebo group. The rate of MI was lower in the treatment group vs the placebo group (4.2% vs 5.7%, P = .0017). However, there were more deaths in the metoprolol group than in the placebo group (3.1% vs 2.3%, P = .0317). It is important to note that clinically significant hypotension and bradycardia was higher in the metoprolol group. The relatively higher doses of metoprolol used in this study may have caused some adverse events and warns against overly aggressive β-blockade.

A recent meta-analysis of 33 randomized controlled trials has raised a cautionary flag with respect to the ubiquitous application of perioperative β-blockers.31 In this study, β-blockers were not associated with any significant reduction in the risk of all-cause mortality, cardiovascular mortality, or heart failure but did reduce the incidence of nonfatal MI (odds ratio [OR] 0.65, 95% CI, 0.54-0.79) and myocardial ischemia (OR 0.36, 0.26-0.50) at the expense of an increase in nonfatal strokes (OR 2.01, 1.27-3.68).31 The POISE trial was a major component in this meta-analysis and therefore caution must be used when interpreting this data, again because of the relatively high dose β-blockade.30

Heart rate control remains a contentious issue in perioperative β-blocker management. Trials that allowed for an increased dose have had overall worse outcomes than those that did not. The optimal heart rate has not been confirmed as of yet. Rate control of less than 75 beats per minute was not significant for efficacy outcomes other than nonfatal MI.34 These data that do not refute the potential protective benefits of β-blockers do, however, urge caution in their unfettered use because of potential consequences and an ill-defined therapeutic window.

Finally, this issue is looming on the horizon as a performance measure despite the unanswered questions about β-blockade including optimal target heart rate, duration, timing of administration, and efficacy.

The American College of Cardiology and American Heart Association (ACC/AHA) currently recommend β-blockers for noncardiac surgery (inclusive of CEA) in a number of clinical situations:26

1. Patients already on therapy or who are having vascular surgery and have ischemia on preoperative testing or are taking a β-blocker for a defined indication ie, hypertension, arrhythmia or angina, or other ACC/AHA class I indication (class I)
2. Patients that are undergoing vascular surgery and have congestive heart failure or more than one clinical risk factor for cardiac disease recognized on preoperative evaluation (class II)
3. Patients undergoing vascular surgery with one or more clinical risk factors for cardiac disease (class IIb)
A complete understanding of the safety and efficacy of β-blockers in patients undergoing CEA may require robust registry data or larger-scale randomized trials, especially in light of the confounding trials cited.

ANGIOTENSIN BLOCKADE

Several trials have demonstrated a protective benefit attributable to agents that block the renin-angiotensin system. Angiotensin-converting enzyme was discovered in 1956 by Skeggs and colleagues.32 Throughout the 1960s and 1970s, the biochemical pathways associated with angiotensin were elucidated and lead to the approval of captopril, the first angiotensin-converting enzyme (ACE) inhibitor, in 1981.

ACE inhibitors impart cardiovascular protection through a variety of mechanisms, including hypertensive control, inhibition of platelet aggregation, reduced oxidative stress, nitric oxide stimulation, and enhancing endogenous fibrinolysis.33,34 Furthermore, ACE inhibitors are hypothesized to stabilize vascular plaques, which has a direct implication on the management of carotid surgery patients.35 The role of ACE in the pathogenesis of inflammation and rupture of atherosclerotic plaque has led to a myriad of studies that demonstrated ACE-inhibitor-related carotid plaque stabilization and improved vessel wall histopathology.36 Evolving data indicate that a similar protective benefit can be attributed to angiotensin receptor antagonist, although the volume of evidence is not as compelling. Furthermore, there is biologic evidence that angiotensin blockade coupled with antiplatelet (aspirin) therapy, may have a synergistic effect on plaque inflammatory markers, adding a scientific background to the role of multiagent medical therapy for patients with atherosclerosis.37

The risk reduction attributed to ACE inhibition is significant. The 2004 HOPE trial was a large-scale trial designed to examine the effects of ramipril on cardiovascular events in patients with peripheral arterial occlusive disease.38 Enrolling over 8000 patients, the study demonstrated a 25% mortality rate reduction, regardless of hypertensive status.

The ACC/AHA guidelines recommend treating all patients with atherosclerotic disease with an ACE inhibitor, unless there is a contraindication.39 This recommendation is based on the myocardial risk reduction attributed to these agents and patients with both coronary and noncoronary vascular disease. There are no data to date that demonstrate a stroke-risk reduction in patients undergoing carotid surgery.

The aforementioned HOPE trial, which enrolled patients who are at high risk for renal artery stenosis, reported a 0.12% rate of renal dysfunction following the initiation of ACE inhibitor therapy, and only 0.5% of patients were removed from ACE inhibitor therapy long-term because of renal function deterioration.38 These data contradict the classical concern that renal artery stenosis is a contraindication to angiotensin blockade.

HMG COA REDUCTASE INHIBITORS (STATINS)

Statins are competitive inhibitors of 3-hydroxy 3-methylglutaryl coenzyme A (HMG CoA) reductase, the rate-limiting step in cholesterol biosynthesis. This enzyme converts HMG-CoA into mevalonic acid, which is a cholesterol precursor. Statin therapy inhibits this pathway within several cell types, resulting in several therapeutic benefits in a patient’s lipid profile.40-43 The end result is a 25% to 50% reduction in the level of circulating low-density lipoprotein (LDL) cholesterol as well as a reduction in the total cholesterol and triglyceride levels and an elevation in high-density lipoprotein level (HDL). Rosuvastatin is the most potent at lowering LDL and triglyceride levels and raising HDL levels.44

The ability of statins to affect perioperative outcomes appears to be related to effects other than simply lowering cholesterol and is referred to as pleiotropic effects. One of the most important effects in the prevention of perioperative events is its ability to stabilize atheromatous plaque that is at risk of rupture resulting in thrombosis or embolism and acute ischemic events. Patients on statins were also less likely to have spontaneous cerebral embolization detected by Doppler during carotid endarterectomy.45 Other nonlipid profile effects include reduction in levels of C-reactive protein, inhibition of thrombosis and platelet aggregation, and nitric oxide-mediated vasodilation.46,47 The expanding list of lipid profile-independent effects strongly supports the use of statins in patients with peripheral vascular disease and certainly expands their indication to include all patients undergoing CEA.

There is a growing body of literature that demonstrates that statins reduce baseline and perioperative mortality, MI, and stroke rates in vascular patients.48,49 One of the largest studies to evaluate the benefit of statins in patients with CAD or peripheral vascular disease was the heart protection study. All-cause mortality was significantly reduced over a 5-year period, regardless of the initial cholesterol level, with 1328 (12.9%) deaths among 10,269 allocated placebo; 1507 (14.7%) deaths among 10,267 allocated simvastatin; and 1328 (12.9%) deaths among 10,269 allocated placebo; P = .0003. This protective effect was attributed to a highly significant 18% relative reduction in the coronary death rate (5.7% vs 6.9%, P = .0005), a marginally significant reduction in other vascular deaths (1.9% vs 2.2%, P = .07), and a nonsignificant reduction in nonvascular deaths (5.3% vs 5.6%, P = .4).50

The StaRRS study looked at patients undergoing major vascular surgery including carotid endarterectomy, aortic surgery, and lower extremity revascularization with the primary outcome measure being death, MI, ischemia, congestive heart failure, and ventricular tachyarrhythmias occurring during the index hospitalization. These data showed significantly fewer patients reached the primary endpoint who were taking statins vs patients who were not on a statin (9.9% vs 16.5%, P = .001). The benefit arose primarily from a reduction in the rate of MI and congestive heart failure. With a risk-adjusted model, statins still provided a protective effect (OR 0.52, CI 0.35-0.76).51 In a
study published by Durazzo, 100 patients were randomized to atorvastatin or placebo for 45 days in the perioperative period. There was a threefold reduction in cardiac events including death due to a cardiac cause, MI, unstable angina, and stroke for the patients on atorvastatin (8% vs 26%).52 The recent SPARCL study has also demonstrated a benefit to statin therapy in terms of both primary and secondary stroke prevention, in addition to protection from major cardiac events.53 In a subgroup analysis, high-dose atorvastatin imparted a protective, albeit nonsignificant, benefit on patients with large or small vessel disease-related stroke and those with transient ischemic attacks.54

Statins have the ability to cause a significant regression in the carotid intima-media thickness (IMT) as well as IMT progression rates. IMT is considered a marker of cardiovascular risk, and therefore, one may be able to derive treatment efficacy from this data point. A recent meta-analysis including over 90,000 patients showed a strong correlation between LDL lowering and carotid IMT reduction (r = 0.55, P = .04).55 Meta-analyses have shown that statins are beneficial in the primary and secondary prevention of strokes. A large-scale study published in 2008 by O’Regan and colleagues involved an analysis of over 120,000 patients who were placed in randomized trials to evaluate statin therapy.56 Statin therapy was found to be protective for all stroke prevention (OR 0.84, CI 0.79-0.91), with a protective benefit also seen in all-cause mortality, cardiovascular-related death, and nonhemorrhagic stroke. These data are backed up by a previous meta-analysis that showed that for each 10% reduction in LDL cholesterol, there was an estimated 15.6% reduction in the risk of stroke.55

Current recommendations by the AHA/ACC for perioperative statin use for noncardiac vascular surgery are as follows:56

1. Patients who are on statins preoperatively should have them continued (class I) and
2. Patients undergoing vascular surgery with or without clinical risk factors, statin use is reasonable (class II).

There are a number of retrospective studies looking at statin use and endarterectomy. One of the largest studies comes from a Canadian administrative database reviewing carotid endarterectomy in 3360 patients. In patients treated for symptomatic disease, there was a protective effect of statin use and perioperative death (OR = 0.25, 95% CI 0.07-0.90), perioperative stroke and death (OR = 0.55, 95% CI 0.32-0.95) but not to cardiovascular outcomes (OR = 0.87, 95% CI 0.49-1.54). These protective effects were largely driven by the symptomatic CEA cases, with no statistically significant benefit seen in asymptomatic cases.57

A 10-year review from the Johns Hopkins University Hospital demonstrated a stroke-risk reduction benefit and improved periprocedural outcomes.58 Forty-two percent of the patients were on statin therapy at the time of operation. Statin use was associated with a significant reduction in perioperative strokes (1.2% vs 4.5%, P < .01). When other confounders were adjusted for, perioperative statin use was found to reduce the odds of stroke (OR = 0.35, 95% CI 0.15-0.85) and death (OR = 0.20, 95% CI 0.04-0.99). There was an insignificant trend toward a lower rate of perioperative MI.

A second 10-year retrospective study from LaMuraglia demonstrated an association between statin therapy and restenosis after CEA.59 The authors examined 2127 carotid endarterectomy cases and conducted a multivariate analysis for correlates of both early and late anatomical failure. Female gender, renal insufficiency, and elevated cholesterol were all found to be correlates of restenosis. Lipid-lowering pharmacotherapy was protective for both early and late recurrent carotid disease. The fact that drug therapy modulates restenosis at both time points, suggests that statin therapy has a beneficial effect to both intimal hyperplasia remodeling and recurrent atherosclerosis after CEA. In a subsequent study, the same group demonstrated a long-term survival benefit attributed to drug therapy for hyperlipidemia, in a cohort of patients undergoing reoperative carotid surgery.60

Despite all the benefits of statin therapy, longer-term compliance after carotid endarterectomy still remains low at 38%.61 Widespread use of statins drugs in this patient population has the potential to improve both neurologic and nonneurologic adverse events associated with CEA and the long-term vascular health of this patient population. The long-term adoption of statin therapy has obvious advantages, especially when evaluated within the context of a stroke-risk reduction operation.

ANTIPLATELET THERAPY

The causes of stroke after carotid endarterectomy are multifactorial. Intraoperative stroke tends to follow inadvertent technical error such as intraoperative embolization, carotid dissection, or creation of an intimal flap. Postoperative stroke can be the result of hyperperfusion or hemorrhage. Thromboembolic events are the most common cause of postoperative stroke.62 Transcranial Doppler (TCD) is a validated method to evaluate patients undergoing carotid endarterectomy. It has been noted that approximately 50% of patients with a sustained high rate of embolization will progress toward thrombotic stroke.63,64 Patients who thrombose after carotid reconstruction may have a 1- to 2-hour period of increasing cerebral embolization that precedes the onset of symptoms, that has been detected with TCD.63

Antithrombotic therapy is an intuitive adjuvant for patients undergoing carotid endarterectomy. Immediately following CEA, the endarterectomy bed represents a thrombogenic nidus. In fact, tagged platelet studies have demonstrated a decreased platelet adherence to the carotid endarterectomy site in patients treated with antplatelet therapy.65 TCD has been used to demonstrate that incremental doses of Dextran can significantly reduce the rate of postoperative embolization after CEA.66 Furthermore, the therapeutic benefit to antplatelet therapy logically extends to the coronary vascular bed.
Several trials have demonstrated a cardiovascular benefit to antiplatelet therapy in patients with coronary and noncoronary vascular disease. The antithrombotic trialist’s collaboration looked at randomized controlled trials of patients on antiplatelet therapy vs control of patients at high risk for cardiovascular events. They reviewed 287 trials looking at the endpoints of nonfatal MI, nonfatal stroke, and death. Antiplatelet therapy reduced combined vascular events by one-quarter, nonfatal MI by one-third, nonfatal stroke was reduced by one-quarter, and vascular mortality by one-sixth. The absolute benefits outweighed the risks of bleeding.

The CAPRIE study compared aspirin (325 mg once daily) vs clopidogrel (75 mg once daily) in reducing the risks of a composite outcome of stroke, MI, or vascular death. The patients studied had an atherosclerotic disease manifested by recent stroke, recent MI or symptomatic peripheral arterial disease. Over a mean follow-up of almost 2 years, patients taking clopidogrel had an annual 5.32% risk of stroke, MI, or vascular death vs 5.83%. While a relative risk reduction of 8.7% was realized, the longitudinal use of a relatively expensive drug may not justify the cost efficacy vis a vis a modest absolute risk reduction of less than 1%.

The MATCH study, a randomized, double-blind, placebo-controlled trial compared aspirin (75 mg once daily) with placebo in 7599 high-risk patients with recent ischemic stroke or transient ischemic attack and at least one additional vascular risk factor who were already receiving clopidogrel 75 mg once per day. Duration of treatment and follow-up was 18 months. The primary endpoint was a composite of ischemic stroke, MI, vascular death, or rehospitalization for an acute ischemic event. The absolute risk reduction was 1% over that time period. The risk of life-threatening bleeding was higher in the aspirin and clopidogrel group (2.6%) vs clopidogrel (1.3%).

The aforementioned studies demonstrate a benefit to antiplatelet therapy in the general high-risk vascular population, which can be extrapolated to the subset of patients undergoing CEA. Several studies have also been undertaken in patients undergoing CEA. Lindblad et al randomized 232 patients undergoing CEA to aspirin 75 mg once daily, starting preoperatively (n = 117) to placebo (n = 115). Stroke rates were significantly reduced in those taking aspirin (2%) vs placebo (9%, P = .01) at 6 months. A further study looking at low-dose aspirin vs placebo started postoperatively showed a trend toward reduced vascular events at 2 years. A 1999 study randomized over 2700 patients to varying doses of aspirin (81-1300 mg daily) and examined stroke, MI, and death at 30 and 90 days after carotid revascularization. Using a composite endpoint, aspirin doses of 325 mg or less were associated with improved outcomes at both the 30-day (5.4% vs 7.0%) and 90-day (6.2% vs 8.4%) time points, compared with the higher dose regimen. Cervical hematoma rate and systemic bleed complications did not differ between treatment groups. While caution must be exercised when concluding that higher-dose regimens are deleterious, these data demonstrate the noninferiority of lower-dose regimens.

To date, there has not been a randomized trial comparing antiplatelet agents and neurologic outcomes in CEA. A study from Payne and colleagues demonstrated a potential benefit to combination (aspirin and clopidogrel) antiplatelet therapy. Patients on combined therapy had a longer operative time, presumptively because of hemostatic issues. This did not translate into clinically significant hematoma formation or estimated blood loss. Preoperative clopidogrel in addition to aspirin significantly reduces the rate of microembolization, conferring a 10-fold reduction in the relative risk of those patients having >20 emboli in the postoperative period (OR = 10.23, 95% CI, 1.3 - 83.3, P = .01). The clinical relevance of this finding in the larger population is unknown, but presumptively, these data suggest a mechanism to prevent cognitive decline sometimes seen after CEA.

A recent publication from the Cochrane Collaboration reviewed randomized trials looking at the use of antiplatelet medication after CEA. Six trials fit the criteria for entry into this meta-analysis. Antiplatelet therapy was found to be significantly protective for the occurrence of stroke (OR = 0.58, CI 0.34-0.98). This study estimated that three out of 100 patients treated with antiplatelet therapy could be saved from stroke within the follow-up period.

Recent work by the Vascular Study Group of Northern New England have definitively shown that preoperative antiplatelet therapy protected against stroke and death (OR, 0.4; 95% CI, 0.2-0.9; P = .02) in patients undergoing CEA. These data were reaffirmed in a multistate Medicare database proving that antiplatelet therapy is essential to performing safe carotid surgery and should be considered as evidence-based practice measures.

Based on the rationale that antiplatelet therapy reduces procedural stroke rate, MI rate, and provides a long-term cardiovascular event risk reduction, the American College of Chest Physicians recommends perioperative low-dose aspirin and lifelong therapy for patients undergoing CEA. The role of other agents and multiagent therapy is unclear, and thus far, only a theoretical advantage has been proposed. Despite the recommendations, up to one-third of patients undergoing CEA are not placed on antiplatelet therapy preoperatively.

CONCLUSION

CEA remains the gold standard for stroke-risk reduction in patients with hemodynamically significant carotid bifurcation disease. With the adoption of evidence-based medical therapy, there exists an avenue to optimize the care of patients with carotid disease, to both improve the stroke-risk reduction benefit of CEA and the short- and long-term cardiovascular event rate of this at-risk patient population.

AUTHOR CONTRIBUTIONS

Conception and design: MS, DD
Analysis and interpretation: MS, DD
Data collection: MS, DD
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