The Role of Antiplatelet Therapy in Carotid Stenting for Ischemic Stroke Prevention

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Background and Purpose—Carotid angioplasty and stenting (CAS) is a minimally invasive revascularization procedure that has become a popular and acceptable treatment option in the United States for high surgical risk patients with internal carotid artery atherosclerosis. It is effective and has an acceptable risk profile, but ischemic complications caused by distal embolization and underlying atherothrombosis persist.

Summary of Review—Atherothrombosis is the pathological process that is frequently implicated as the underlying cause of stroke, transient ischemic attacks, and most other ischemic vascular disease. Critical steps in the development of occlusive episodes are the disruption of atherosclerotic plaque and subsequent formation of a platelet-rich mural thrombus. Vascular injury as a result of CAS or any other percutaneous intervention triggers platelet adhesion, activation, and aggregation, resulting in the formation of a mural thrombus. This risk, in addition to the potential risk of embolization to distal sites, provides a rationale for early antiplatelet therapy with CAS. The risk of late stent (>30 days after stenting) thrombosis in some patients, particularly those receiving drug-eluting stents, provides a rationale for prolonged antiplatelet prophylaxis as well as for prophylaxis against late atherothrombotic events. Because of the systemic and progressive nature of atherothrombosis, protection against ischemic vascular events in other arterial beds expands the benefits of long-term antiplatelet therapy.

Conclusions—As clinical experience with CAS increases, it is likely that it will be used more frequently for patients with occlusive carotid disease. In addition, adjunct antiplatelet therapy will play a key role in the continued development of CAS. (Stroke. 2006;37:1572-1577.)

Key Words: antiplatelets ■ carotid angioplasty ■ carotid artery stenosis ■ stents

Cerebrovascular disease is a leading cause of morbidity and mortality in most developed countries. In the United States, there are an estimated 700,000 cases of stroke annually (of which ≈88% are ischemic), costing an estimated $56.8 billion in associated treatment and lost productivity.1 Atherothrombotic carotid stenosis is an important cause of ischemic stroke and transient ischemic attacks (TIAs). Population-based studies have shown that the prevalence of carotid stenosis is ≈0.5% in the sixth decade of life and increases to ≈10% in the ninth decade; the majority of cases are asymptomatic.2–4 Asymptomatic carotid stenosis with ≤75% lumen loss carries a stroke risk of 1.3% annually, whereas the combined risk of cardiac ischemia and vascular death is as high as 10%.5 With lumen stenosis >75%, the combined stroke and TIA risk increases to ≈11% annually, with 75% of events ipsilateral to the stenosed artery. Other studies have also shown that the risk of stroke increases with increased severity of stenosis,6–7 with the risk being higher for those who are symptomatic compared with those who are asymptomatic.

Carotid endarterectomy (CE) is currently the accepted standard of treatment for revascularization of extracranial carotid occlusive disease. The surgical procedure has been shown to be superior to medical therapy alone in preventing stroke in patients with symptomatic stenosis of 70% to 99% and to have some benefit in patients with 50% to 69% stenosis.8,9 In addition, there is evidence to suggest that asymptomatic patients with carotid stenosis ≥60% also benefit from elective surgery.10 However, elective surgery for patients with asymptomatic carotid stenosis is controversial because a significant proportion of ipsilateral strokes in these patients are attributable to lacunes or cardioembolism and cannot be prevented by CE.6,7

Recently, carotid angioplasty and stenting (CAS) has emerged as a popular alternative to CE in the United States for the treatment of patients with symptomatic or asymptomatic carotid artery disease. Although it is less invasive than surgery, it is currently considered to be appropriate only for high surgical risk populations, such as those with severe comorbidities or recurrent stenosis after previous CE, for whom CE would be inappropriate. Nevertheless, the available data suggest that the efficacy of CAS is at least comparable to that for CE.11,12 Several ongoing clinical studies are designed to address the issue of whether CAS can be used as an...
alternative to CE in low- to medium-risk patients with symptomatic or asymptomatic carotid stenosis.\textsuperscript{13–16}

**Atherothrombosis**

Atherosclerotic plaque formation, disruption, and subsequent thrombus formation is responsible for most carotid stenoses and subsequent strokes (Figure). It is now well accepted that inflammation plays a fundamental role in atherosclerotic disease, from initiation through progression and thrombotic complications.\textsuperscript{17,18} Both macrophages and smooth muscle cells (SMCs) play a role in the accumulation of extracellular lipid within the developing atheroma. In addition, SMCs are the primary source of collagens and elastic fibers contributing to the formation of a fibrous cover over the accumulation of extracellular lipid that is characteristic of an advanced atherosclerotic lesion.

Acute rupture of the atherosclerotic plaque is usually the trigger leading to manifest ischemic disease. Both immunological and mechanical forces are thought to contribute, in part, to plaque vulnerability to rupture.\textsuperscript{19} Rupture of the atherosclerotic plaque exposes collagen within the plaque or in the subendothelium, which allows platelets to adhere to the arterial wall or ruptured plaque, where they become activated. In turn, activated platelets secrete products such as adenosine diphosphate (ADP), serotonin, and thromboxane A\(_2\) that are themselves promoters of platelet activation, vasoconstriction, and neointimal proliferation, thereby contributing to further disease progression.\textsuperscript{20} Other inflammatory modulators produced by activated platelets include platelet-derived growth factor, platelet factor 4, CD40 ligand, regulated-on-activation normal T cell expressed and secreted (RANTES), thrombospondin, transforming growth factor, and NO. The final steps in platelet aggregation involve activation of the platelet glycoprotein Ib/IIa (GPIIb/IIIa) receptor, which binds to fibrinogen and, in turn, to other platelets, leading to the formation of a platelet-rich mural thrombus with or without peripheral embolization and subsequent manifestation of stroke or TIA.

**Platelet Activation and Complications of Carotid Stenting**

Intimal injury of the arterial vessel during percutaneous interventions releases procoagulant tissue factor and exposes collagen and other platelet-adhesive proteins in the subendothelium, thereby triggering formation of a platelet-rich thrombus that seals the site of injury. The extent of platelet deposition and thrombus formation is dependent on the degree of vessel wall injury and local shear forces; in some cases, such as certain types of ischemic stroke, the thrombus may expand to occlude the vessel. In addition, the presence of distal microemboli after carotid artery intervention is indicative of increased platelet reactivity to ADP and increased systemic inflammation.\textsuperscript{21,22} The subsequent healing processes involve intense cellular (monocyte/macrophage) infiltration of the thrombus along with SMC migration to and proliferation at the site of injury site, resulting in gradual resorption of the thrombus and replacement with neointimal tissue. An excessive healing process, neointimal hyperplasia, leading to in-stent restenosis, is an important late
(typically >30 days after stent placement) sequela of stenting. Moreover, the extent of vascular inflammatory response after carotid stent implantation determined by acute-phase reactants measurement was shown to be associated with 6-month patency. Although a significant (P<0.001) increase in C-reactive protein and serum amyloid levels within 48 hours was found in both patients who did or did not develop restenosis, patients with 6-month restenosis had significantly higher postintervention serum levels of acute-phase reactants compared with patients without restenosis. Indeed, multiple logistic regression analysis demonstrated that 48-hour postintervention C-reactive protein levels were independent clinical predictors of postangioplasty outcome.

Long term, restenosis that occurs 3 to 10 years after CE is usually atherosclerotic in nature, and this phenomenon may also be of concern after stent placement. Almost all of our information on stent thrombosis is from the coronary circulation. The definition of coronary stent thrombosis in studies varies from angiographically documented stent occlusion to the occurrence of major adverse occlusive events, including death. Both definitions have their limitations; angiographic determination may miss cases if the angiogram is not performed at the time of the event, whereas clinical definitions may potentially overestimate the incidence of stent thrombosis. In addition, the observation period for stent thrombosis varies between studies (within 1 week or 1 month and including or excluding the first 24 hours), making comparisons of thrombosis rates difficult. Nevertheless, the incidence of angiographically documented thrombosis after coronary stent placement in the modern era of dual antiplatelet therapy is low, varying between 0.4% and 2.8%.25

The Role of Antiplatelet Therapy in Carotid Stenting

The occurrence of rapid thrombus formation immediately after arterial injury and stenting, and potential embolization of the thrombus to distal sites, provides the rationale for early antiplatelet therapy. To this end, there is clinical evidence supporting the use of antiplatelet therapy after percutaneous coronary intervention. Furthermore, because of the highly diffuse nature of the atherosclerotic disease process, patients undergoing CAS are also at risk of ischemic atherothrombotic events in other vascular beds, expanding the benefits of antiplatelet therapy. For example, an estimated 25% to 60% of patients with carotid disease, but without clinical manifestation of coronary heart disease, have abnormal provocative test results for myocardial ischemia or angiographic evidence of severe coronary heart disease. As such, stroke or TIA is not only risk factors for recurrent cerebral events but also for ischemic cardiac events. Although the risk of a recurrent ischemic cerebral event after a stroke is greater during the first year (16%), subsequently declining to ~4% per year, cardiovascular disease increasingly becomes a major cause of mortality after a stroke. In one study, large variations in the 90-day risk of recurrence after incident ischemic stroke (5% to 23%) were reported because of considerable variation in the definitions used for recurrent stroke. Nonetheless, over a 10-year period after a first ischemic stroke, patients are twice as likely to die from a cardiovascular event than from recurrent stroke. As the risk of atherosclerosis persists long term, therapy should also involve the lifelong management of risk factors via lifestyle modifications such as smoking cessation, healthy diet, exercise, and weight reduction, and measures to control blood pressure, cholesterol levels, underlying diabetes, and atrial fibrillation.

Aspirin is an effective antiplatelet agent and remains the mainstay of antithrombotic therapy. However, the platelet response to aspirin shows marked interpatient variability, and some patients appear to be aspirin resistant. ADP receptor antagonists such as clopidogrel and ticlopidine inhibit platelets via a pathway separate from the effects of aspirin on thromboxane. Several studies have established the benefits of ticlopidine plus aspirin over aspirin alone or in combination with an anticoagulant in coronary stenting. A meta-analysis of 3 randomized controlled studies and 7 single-center registries involving 13,955 patients after coronary stent placement showed that clopidogrel plus aspirin was at least as effective as ticlopidine plus aspirin in reducing the 30-day incidence of major adverse cardiac events, but with a better tolerability profile.

The Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) trial assessed combination clopidogrel plus aspirin versus clopidogrel alone over 18 months of treatment in high-risk patients (n=7,599) with recent TIA or ischemic stroke. In the MATCH trial, high-risk patients included those who had ≥1 additional vascular risk factor within the previous 3 years, such as previous ischemic event, previous myocardial infarction, history of angina pectoris, symptomatic peripheral arterial disease, or diabetes. The MATCH study showed that in a patient population with a high incidence of hypertension and diabetes and mostly lacunar infarcts, treatment with clopidogrel plus aspirin provided no significant clinical benefit over clopidogrel alone. However, combination therapy resulted in significantly more bleeding complications than clopidogrel alone, and the incidence of life-threatening bleedings was higher in the combination group (2.6% versus 1.3%; P<0.001). Major and minor bleedings were also increased in the combination group. Consequently, any benefit of clopidogrel plus aspirin is negated by the high bleeding risk. Nevertheless, the results of MATCH, obtained in high-risk patients with inherent increased risk of bleeding and other complications, may not be generalizable to the whole ischemic stroke population.

In contrast, dual antiplatelet therapy with clopidogrel and aspirin was shown to be more effective than aspirin monotherapy in reducing the incidence of silent microemboli, an independent predictor of subsequent cerebrovascular events in patients with recent symptomatic carotid stenosis. The Clopidogrel and Aspirin for the Reduction of Emboli in Symptomatic carotid Stenosis (CARESS) study, conducted in 108 patients who had recently experienced a stroke or TIA, found that treatment with clopidogrel (300-mg loading dose on day 1, 75 mg daily thereafter) and aspirin (75 mg daily) reduced the incidence of silent cerebral microemboli present on Doppler ultrasonography by 25% after 1 day and by 37% after 7 days of treatment compared with aspirin alone. Furthermore, dual antiplatelet therapy did not result in any reports of life-threatening, intracranial, or major bleeding.
Moreover, a randomized controlled trial in 47 patients with high-grade carotid artery stenosis (>70% North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria) demonstrated that dual antiplatelet therapy with clopidogrel and aspirin significantly reduced the 30-day incidence of adverse neurological outcomes after carotid stenting compared with aspirin plus heparin (0% versus 25%; P = 0.02), without an additional increase in bleeding complications.38 Interestingly, the 30-day 50% to 100% stenosis rates were lower in the dual antiplatelet group compared with the aspirin plus heparin group (5% versus 26%; P = 0.1). Moreover, an overall unacceptable level of complications in the aspirin plus heparin group resulted in the premature termination of the study in favor of clopidogrel plus aspirin.

For patients undergoing CE, aspirin in a dose of 81 to 325 mg is recommended on the basis of the Aspirin and Carotid Endarterectomy (ACE) trial.39 A recent study suggested the potential value of combination antiplatelet therapy in the preoperative phase. Payne et al randomized 100 patients on routine aspirin to concomitant clopidogrel (n = 46) or placebo (n = 54) before CE.40 After surgery, platelet response to ADP was assessed in whole blood, and the number of emboli was determined by transcranial Doppler ultrasonography. Clopidogrel and aspirin reduced the platelet response to ADP by 8.8% while conferring a 10-fold reduction in the relative risk of those patients having >20 emboli in the postoperative period. This reduction in thrombogenic potential occurred without an increase in the risk of bleeding complications.

Dual antiplatelet therapy was also shown to be associated with a low rate of ischemic events in a single-center carotid stent registry study, which included 162 patients with severe symptomatic (>70% stenosis) or asymptomatic (>80% stenosis) carotid artery stenosis who were not appropriate candidates for CE.41 The overall 30-day rate of ischemic events (death, stroke, TIA, myocardial infarction) was 5.6% in patients who received an ADP receptor antagonist (clopidogrel or ticlopidine) and aspirin; a significant number of patients also received concomitant treatment with a GPIIb/IIIa inhibitor. No case of stent thrombosis was reported in patients who received clopidogrel/ticlopidine and aspirin, but 1 of 5 patients who did not receive an ADP antagonist did develop in-stent thrombosis. Furthermore, the 30-day rate of ischemic events was much higher in patients who received ticlopidine than those who received clopidogrel (13% versus 4.3%; odds ratio, 5.77; 95% CI, 1.45 to 22.91). Dual antiplatelet therapy did not appear to increase the incidence of intracranial hemorrhage. Other case reports have also documented fatal strokes in carotid stent patients who did not receive dual antiplatelet therapy.42

The use of platelet GPIIb/IIIa inhibitors along with aspirin and an ADP receptor antagonist was shown to be associated with a low risk for ischemic complications during carotid stenting and with a negligible risk of stent thrombosis during follow-up.43 Kapadia et al recruited 151 patients deemed to be at high surgical risk, of whom 128 received the GPIIb/IIIa inhibitor abciximab 12 hours before stenting. All patients subsequently received aspirin and either clopidogrel or ticlopidine after the stenting procedure. The procedural event rate (all events occurring up to hospital discharge) was lower in the abciximab-treated group (1.6%; 1 minor stroke and 1 retinal infarction) compared with the control group (8%; 1 major stroke and 1 neurological death). Furthermore, the number of new periprocedural events occurring in the first 30 days after hospital discharge was lower in the abciximab-treated group than the control group (8% versus 4.5%). However, other studies have described cases of intracranial hemorrhage in carotid stent patients who received a GPIIb/IIIa inhibitor.44,45

Adjunct abciximab has been shown to limit thrombus propagation and thrombus stabilization after carotid stenting by reducing platelet-induced monocyte activation and associated reduction in monocyte tissue factor production and decreased sCD40L-mediated cross-linking of platelets.46 Kopp et al randomized patients with cerebrovascular disease to either standard antithrombotic therapy (n = 30) comprising clopidogrel, aspirin, and heparin, or adjunct bolus and 12-hour infusion of abciximab (n = 20) before CAS. A third cohort of patients was stented with filter protection (n = 30). Adjunct abciximab did not significantly reduce the incidence of peri-interventional ischemic events (10% versus 23%; P = 0.2) and the number of de novo ischemic lesions detected by diffusion-weighted MRI (30% versus 47%; P = 0.17) compared with standard antithrombotic therapy. However, these were significantly reduced with filter protection (P = 0.023) compared with standard antithrombotic therapy. Nevertheless, TIs occurred less frequently with adjunct abciximab (P = 0.05) compared with standard antithrombotic therapy. Clinical improvement with adjunct abciximab compared with standard antithrombotic therapy was paralleled by a reduction in the postinterventional percentage of activated monocyte-platelet aggregates (CD62P+/CD14+; P = 0.018) and the number of tissue factor–positive monocytes (TF+/CD14+; P = 0.005) between the 2 groups. Moreover, both adjunct abciximab and filter protection suppressed prothrombin fragment F1.2 generation and significantly reduced sCD40L compared with standard antithrombotic therapy.

A retrospective review of 550 patients who underwent carotid artery angioplasty and stent placement demonstrated that combination therapy with GPIIb/IIIa inhibitors and heparin significantly increased the 30-day incidence of the composite end point of all stroke and neurological death compared with heparin alone (6.6% versus 2.4%; P = 0.04).47 In addition, there were a number of intracranial and extracranial hemorrhage events in the GPIIb/IIIa inhibitors plus heparin group, but none were reported in heparin alone group. Consequently, the authors of the retrospective review suggested that the use of GPIIb/IIIa inhibitors and heparin in carotid stenting should be discouraged.

Most centers currently administer dual antiplatelet therapy for up to 4 weeks after carotid stent insertion to protect against subacute thrombosis. However, there have been a number of case reports of late stent thrombosis (typically >30 days after the procedure) after discontinuation of antiplatelet therapy with drug-eluting coronary stents with serious consequences.48,49 Until recently, late stent thrombosis was almost entirely limited to patients receiving coronary brachytherapy and was thought to be related to the delayed endothelialization caused by the administered radiation. De-
layed endothelialization results in prolonged exposure of potentially thrombogenic stent surfaces to circulating blood, and this can result in late thrombotic occlusion. In a study of 2229 consecutive patients who received drug-eluting coronary stents, premature discontinuation of antiplatelet therapy (hazard ratio, 89.8; \( P<0.001 \)) was associated with development of stent thrombosis in the 9-month period after the procedure.\(^{50}\) There is evidence to suggest that prolonged treatment with dual antiplatelet therapy with clopidogrel plus aspirin is effective in reducing overall major cardiac events, repeat revascularization rates, and the incidence of late thrombosis in patients undergoing coronary brachytherapy.\(^{51}\) Thus, prolonged antiplatelet therapy beyond the periprocedural period would also be beneficial in preventing late stent thrombosis in patients receiving drug-eluting stents. Drug-eluting stents are not routinely used in the carotid circulation, and therefore additional studies are needed to define the optimal duration of dual antiplatelet therapy for carotid stent patients.

In the coronary circulation, the prolonged use of clopidogrel and aspirin has been associated with a decrease in major vascular events.\(^{26,52}\) The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, which enrolled 12,562 patients with unstable angina or non–ST-segment elevation myocardial infarction, demonstrated that treatment with clopidogrel plus aspirin up to 12 months reduced the relative risk of the composite of cardiovascular death, stroke, or myocardial infarction by 20% and the absolute risk by 2.1% compared with aspirin alone (\( P<0.001 \)). In addition, the Clopidogrel for the Reduction of Events During Observation (CREDO) study, which enrolled 2116 patients after a percutaneous coronary intervention, found that there was a 26.9% relative reduction in the combined risk of death, myocardial infarction, or stroke (absolute reduction 3%) with dual antiplatelet therapy for 1 year compared with aspirin alone (\( P=0.02 \)).\(^{26}\) Prolonged dual antiplatelet therapy may also reduce major ischemic events in patients after carotid stenting. The recent demonstration that high-risk subgroups such as diabetics and patients with previous cardiac surgery show magnified benefit with clopidogrel compared with aspirin raises the possibility that these subgroups in particular may derive benefit from extended dual antiplatelet therapy.\(^{53}\) Other prescription antiplatelet agents such as aspirin plus extended release dipyridamole may also be useful in decreasing the long-term stroke rate in patients beyond the 30-day stenting period.

Conclusions
Atherothrombosis is a diffuse pathological process and frequently the underlying cause of TIAs, strokes, and ischemic cardiovascular events. CE is currently the gold standard for revascularization in extracranial symptomatic carotid occlusive disease. Recently, CAS has gained increasing acceptance as a treatment option for patients with high-grade symptomatic or asymptomatic carotid artery disease for whom CE would be inappropriate. Intimal injury of the arterial vessel during CAS triggers platelet activation and aggregation, as well as the inflammatory cascade and subsequent smooth muscle proliferation. Thrombus formation immediately after CAS and embolization to distal sites can cause serious postprocedural complications. Antiplatelet therapy is effective at reducing stent thrombosis in patients undergoing CAS and reduces the risk of vascular events in other arterial beds, expanding the benefits of antiplatelet therapy and providing a rationale for long-term use. CAS is minimally invasive, and as clinical experience with the procedure increases, in conjunction with advances in stent, delivery system, and protection device technology, it is likely that CAS may become the treatment of choice for patients with occlusive carotid disease.

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