The Vulnerable Carotid Artery Plaque
Current Imaging Methods and New Perspectives
Norbert Nighoghossian, MD; Laurent Derex, MD; Philippe Douek, MD

Background and Purpose—Atherosclerosis is a diffuse, chronic inflammatory disorder that involves the vascular, metabolic, and immune systems and leads to plaque vulnerability. The traditional risk assessment relies on clinical, biological, and conventional imaging tools. However, these tools fall short in predicting near-future events in patients with vulnerable carotid artery plaque.

Methods—In current clinical practice, anatomic imaging modalities, such as B-mode ultrasound, spiral computed tomography angiography, and high-resolution MRI, can identify several morphological features characteristic of the vulnerable plaque but give little or no information regarding molecular and cellular mechanisms.

Results—This review is dedicated to factors involved in carotid artery plaque vulnerability and to new imaging methods that target this condition. Our aim is to describe the following: (1) conventional pathologic and imaging markers predictive of plaque vulnerability; (2) the role of relevant biological, genetic, and mechanical factors; (3) the potential of new imaging methods; and (4) current and emerging treatments.

Conclusions—A multimodal assessment of plaque vulnerability involving the combination of systemic markers, new imaging methods that target inflammatory and thrombotic components, and the potential of emerging therapies may lead to a new stratification system for atherothrombotic risk and to a better prevention of atherothrombotic stroke. (Stroke. 2005;36:2764-2772.)

Key Words: carotid plaque vulnerability ■ imaging ■ therapy
This type of superficial plaque injury is called “erosion.” Such erosions may lead to immediate vessel occlusion and hemodynamic compromise, even without rupture of the fibrous plaque cap. What is imaged is not a rupture of the surface but an adherence area where thrombus formation occurs over the plaque surface.

Ulceration, Thrombus, Calcification, and Intraplaque Hemorrhage: Status of Fibrous Cap, Lipidic Core, and Surrounding Inflammation

The radiographic evidence of a carotid plaque surface irregularity in symptomatic arteries is associated with surface irregularity in the contralateral arteries. Ulceration prevalence is comparable for both the ipsilateral symptomatic and contralateral symptomatic patient groups. Thrombus, in contrast, is more common in plaques with both ipsilateral symptoms and ulceration. In addition, cerebral microemboli are more frequent distal to carotid plaques that are subsequently found to have surface thrombus at endarterectomy. Patients with irregular plaques in both arteries were more likely to have a nonstroke vascular death on follow-up. These associations may suggest that other systemic factors are important in the cause of plaque instability.

Extracranial carotid artery calcified plaques are significantly less likely to be symptomatic and, thus, may be more stable than noncalcified plaques. An inverse relationship between the degree of plaque calcification and macrophage infiltration was found in critical carotid stenoses.

Intraplaque hemorrhage (IH) may contribute to plaque destabilization and subsequent clinical symptoms, but conflicting conclusions have been drawn. Several investigators have reported that IH appears to be more common in the plaques of symptomatic patients than in the plaques of asymptomatic patients. Recent studies indicate that IH is equally present in both.

Thickness of Fibrous Cap, Size of the Lipidic Necrotic Core, and Plaque Inflammation

The carotid artery plaque considered responsible for acute ischemic events usually had a thin fibrous cap, a large lipid pool, and macrophage-dense inflammation on or beneath its surface. The responsibility of these factors in plaque vulnerability will be commented on in the imaging section.

Biological Factors and Plaque Vulnerability

Differences in the frequency of thrombosis, cap rupture, cap erosion, and inflammatory infiltrate have been explored in patients with ipsilateral major stroke, TIAs, and those who were asymptomatic. A thrombotically active carotid plaque associated with a high-inflammatory infiltrate was observed in 71 of 96 patients (74%) with ipsilateral major stroke compared with 32 of 91 (35.2%) patients with TIA (P < 0.001) or 12 of 82 patients (14.6%) who were asymptomatic (P < 0.001). Inflammatory processes may involve several biological factors.

Intercellular Adhesion Molecule-1 (ICAM-1)

Elevation of ICAM-1 expression in symptomatic versus asymptomatic plaque suggests that mediators of inflammation are involved in the conversion of carotid plaque to a symptomatic state. However, in a recent study, it was found that symptomatic carotid disease is not associated with increased expression of adhesion molecules.

The Role of Matrix Metalloproteinases (MMPs) in Carotid Atheroma

MMPs may have a role in determining carotid plaque stability. A recent study has suggested a link between MMP-1 and MMP-12 and carotid plaque instability. In this study, MMP-1 transcript levels were nearly 8-fold higher in thin-cap carotid plaques than in thick-cap plaques, and MMP-12 transcript levels were significantly increased in

**TABLE 1. Conventional Pathologic and Imaging Markers of Plaque Vulnerability**

| Carotid artery intima/media thickness (IMT) |
| Erosion |
| Ulceration |
| Thrombus |
| Intraplaque hemorrhage |
| Calcification |
| Status of fibrous cap |
| Status of lipidic core |
| Degree of plaque inflammation |
| Microembolic signals on transcranial Doppler |

**TABLE 2. Biological and Mechanical Factors Supporting Plaque Vulnerability**

| Systemic factors |
| Leukocyte and monocyte count |
| Fibrinogen level |
| C-reactive protein (conflicting data) |
| Local factors |
| ICAM-1 and cytokines conflicting data |
| MMPs |
| Circulating transforming growth factor-β1 levels |
| Genetic polymorphism of cytokines |
| Plaque neovascularization |
| Shear stress |
ruptured plaques compared with plaques without cap disruption. T cells can induce macrophages to secrete MMPs via stimulation of CD40 and can promote smooth muscle cell apoptosis to through production of interleukin-1. It remains unclear whether raised MMP levels cause rupture of the atherosclerotic plaque or are a result of it. Proof of a causative role might come from the demonstration of the efficacy of pharmacotherapy that targets these collagenases.

**Circulating Transforming Growth Factor-β1 Levels**

Transforming growth factor-β1, generated locally within the atherosclerotic plaque, is involved in the process of plaque stabilization. Cipollone et al.20 have demonstrated that transforming growth factor-β mRNA levels are increased up to 3-fold in asymptomatic compared with symptomatic plaques. On plaque rupture, exposure of the necrotic core to the circulation promotes thrombosis and subsequent plaque progression. Tissue factor (TF) is mainly present in lipid-rich human atherosclerotic plaques, which are the most thrombogenic substrates, and a significant association of TF expression with plaque infiltration by macrophages and T cells was observed, and TF expression was more important in symptomatic plaques.27

**Systemic Markers of Atherosclerotic Inflammatory Processes**

In a trial of clopidogrel versus aspirin in patients at high risk for ischemic events,28 leukocyte counts were assessed during follow-up in 18,558 patients with atherothrombotic events. Patients in the top quartile (>8.2×10⁹/L) had higher risks for ischemic stroke (RR 1.30; P=0.007) after adjustment for other risk factors. Treatment with aspirin or clopidogrel did not influence predictive effects by leukocytes. A large, prospective population-based study29 has analyzed the relationship between monocyte activity and the risk for atherosclerosis in 2,610 subjects, 25 to 82 years of age, who had no plaque in their right carotid artery. After 7 years of follow-up, a new ultrasound screening was performed, and the number of novel plaques was classified as none, 1 plaque, and 2 plaques. For 1 SD (0.17×10⁹) increase in the monocyte count, the risk of being in a higher plaque category increased by 18% [odds ratio (OR), 1.18; 95% CI, 1.08 to 1.29].

The relationship between fibrinogen and the risk of ischemic stroke has been studied in patients with recent TIA or minor ischemic stroke.30 Fibrinogen predicted subsequent ischemic stroke, with a pooled hazard ratio for value above the median of 1.34 (95% CI, 1.13 to 1.6; P=0.001). The risk of plaque rupture was increased in patients who had higher fibrinogen levels.31

The role of C-reactive protein (CRP) as a risk marker for carotid atherosclerosis is conflicting. A recent study showed that the high sensibility-CRP level is associated with a higher risk score for coronary heart disease but not for carotid atherosclerosis. Nevertheless, the removal of atherosclerotic plaques from the carotid arteries markedly decreases the production of high sensibility-CRP and fibrinogen, probably because of the decrease in the inflammatory burden or the removal of the advanced plaques able to produce these proteins. At present, there is not sufficient evidence to recommend measurement of CRP in the routine evaluation of cerebrovascular disease risk in primary prevention.

**TABLE 3. Imaging Markers of Plaque Vulnerability**

<table>
<thead>
<tr>
<th>Imaging Markers of Plaque Vulnerability</th>
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<td>High-resolution MRI identification of a ruptured fibrous cap and size of lipidic-necrotic core, calcification, thrombus, intraplaque hemorrhage, and neovascularization</td>
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<td>MR molecular imaging of macrophage, myeloperoxidase activity, thrombus components, angiogenesis, and cytokines</td>
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<td>Ultrasound and nuclear molecular imaging of cytokines, fibrin, macrophage enzyme activity, LDL metabolism, apoptosis, and glucose metabolism (18F fluorodeoxyglucose positron-emission tomography)</td>
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**Inflammatory Processes and Genetic Profiles**

Proinflammatory genetic profiles are significantly more common in subjects with a history of stroke. One study34 evaluated 237 individuals with a history of ischemic stroke and 223 age-matched and gender-matched controls.

The polymorphisms of CRP, interleukin 6, macrophage migration inhibitory factors, monocyte chemoattractant protein 1, intercellular adhesion molecule 1, E-selectin, and MMP-3 genes were studied. The odds of stroke increased with the number of high-risk genotypes: carrying 1 proinflammatory gene variant conferred a risk of 3.3 (1.6 to 6.9), whereas individuals who carried 2 and 3 gene variants had adjusted odds ratios of 21.0 (7.6 to 57.5) and 50.3 (10.2 to 248.1), respectively. The impact of inflammatory gene polymorphisms and gene-smoking interactions on common carotid artery IMT has also been studied.35 An increasing gene load of inflammatory genotypes was associated with a linear increase in serum interleukin 6 levels and increased carotid artery IMT.

**Arterial Neovascularization and Inflammation in Symptomatic Atherosclerosis**

Pathological neovascularization and inflammation are thought to precipitate plaque rupture or erosion. In a postmortem study,36 the inflammatory infiltrate and microvascular network in the arterial wall of the iliac, carotid, and renal arteries was quantified. Patients with symptomatic atherosclerosis had a more dense network of vasa vasorum than patients with asymptomatic disease.

**Shear Stress and Plaque Unstability**

Chronic exposure of endothelial cells to high levels of shear stress causes them to exhibit an atheroprotective phenotype.37 In subjects considered at low coronary heart disease risk, the presence of carotid atherosclerosis is significantly associated with low shear stress. Low wall shear stress can cause arterial damage and subsequent plaque instability through several factors: increased fluid residence time; increased platelet and macrophage adhesion to the arterial wall; and modulation of platelet-derived growth factor and transforming growth factor-β1.38

**High-Resolution MRI of Vulnerable Carotid Artery Plaque (Table 3)**

Although pathological correlation in studies of carotid plaque imaging cannot be reliably interpreted or compared because of study differences and poorly reported histology methods, there are emerging data that support the potential of high-resolution MRI (Figures 2 and 3). MRI of ex vivo specimens has enabled characterization of the collagenous cap and lipid pool, yielding 2 features that improve our understanding of
plaque vulnerability. MRI identification of a ruptured fibrous cap is highly associated with a recent history of TIA or stroke. This rupture occurred more likely in plaque with a thin fibrous cap and large lipidic necrotic core.

Plaque composition can be determined in vivo using a combination of pulse sequences that produce bright-blood and dark-blood images. Several plaque components have a characteristic appearance and can be assessed qualitatively according to established high-resolution MRI classification. MRI-based tissue quantification was demonstrated to be accurate and reproducible. Thirty-one subjects scheduled for carotid endarterectomy were imaged with a 1.5 T scanner using time-of-flight-, T1-, proton density-, and T2-weighted images. A total of 214 MRI locations were matched to corresponding histology sections. MRI measurements of plaque composition were statistically equivalent to those of histology for the lipid-rich/necrotic core (23.7% versus 20.3%; P=0.1), loose matrix (5.1% versus 6.3%; P=0.1), and dense (fibrous) tissue (66.3% versus 64%; P=0.4). Calcification differed significantly when measured as a percentage of wall area (9.4% versus 5%; P<0.001). Furthermore, multicontast MRI was used to identify fibrous cap rupture, allowing a plaque stratification according to complicated and noncomplicated subtypes.

The use of gadolinium contrast agent may additionally enhance differentiation between plaque components, such as the fibrous cap and necrotic core (Figure 1). Moreover, detection of other plaque characteristics, such as increased neovascularization, was possible using a gadolinium contrast agent.

Differentiation between complex atherosclerotic plaques and mural thrombosis remains difficult because of the components (eg, platelets, fibrin, and red blood cells) of thrombus and the resultant complex magnetic resonance (MR) signal characteristics on T1-, T2-, and proton density-weighted images of arterial thrombi.

Thrombus MRI showed time-dependent changes on T2W and T1W images in an animal model of carotid artery thrombus. These changes reflected the thrombus organization as shown by histologic analysis.

Viereck et al showed that MRI is able to identify complicated plaques by directly visualizing the thrombus inside the carotid artery. Specifically, MR direct thrombus imaging has the ability to discriminate between the different stages of thrombus and hemorrhage formation. In the acute/subacute phase, formation of methemoglobin results in the shortening of T1, producing an increase in signal on a T1-weighted sequence. The prevalence of complicated carotid artery plaques was studied in 120 patients with carotid endarterectomy and compared with 14 control subjects. Direct MRI thrombus imaging was also performed in 14 control subjects. None of the control arteries demonstrated the “high-signal” characteristic of a complicated plaque. In contrast, such signals were found in 60% of the patients’ arteries ipsilateral to the symptoms. On the contralateral, asymptomatic side, the prevalence of high signal dropped to 36% (P<0.001).

Murphy et al and Takaya et al tested the hypothesis that hemorrhage into carotid atheroma stimulates plaque progression. Twenty-nine subjects (14 cases with IH and 15 controls with comparably sized plaques without IH at baseline) underwent serial carotid MRI examination with a multicontrast weighted protocol (T1, T2, proton density, and 3D time of flight) over a period of 18 months. The percentage of change in wall volume (6.8% versus −0.15%; P=0.009) and lipid-rich necrotic core volume (28.4% versus −5.2%; P=0.001) was significantly higher in the hemorrhage group than in the controls.

The ability of multicontrast-weighted MRI to additionally characterize the location of hemorrhage (intraplaque versus juxtaluminal) in advanced atherosclerotic lesions has also been established. IH without fibrous cap rupture is not associated with clinical symptoms, whereas juxtaluminal hemorrhage/thrombus indicates an erosion, ulceration, or rupture, each of which is recognized as a marker of vulnerable plaque.

Ultrasound Imaging
Measurement of carotid wall thickness, as well as qualitative and quantitative analysis of plaques, can be determined by surface ultrasound. The echogenicity of the plaque is determined by its composition: hypoechoic heterogeneous plaque is associated with both IH and lipids, whereas hyperechoic homogeneous plaque is mostly fibrous. Using 8-MHz transducers, B-mode ultrasonography can be used for measuring carotid IMT. Because of the physical principles of diagnostic ultrasonography, the measurement is reliable only at the far arterial wall and does not indicate whether the thickening is attributed to intima or media infiltration and/or hypertrophy. Intravascular ultrasound (IVUS) is an invasive technique and requires a transluminal catheter. Similar to MRI, IVUS provides direct imaging of the arterial wall. The safety and utility of IVUS in carotid artery stenting was recently demonstrated; IVUS imaging provides a more accurate assessment of stent dimensions, expansion, and apposition than angiography and may allow the detection of severe calcification, which may increase the risk of stroke.

However, both current IVUS and MRI methods are significantly hampered by limited spatial resolution and are really only applicable to atherosclerotic disease in a relatively advanced stage. In addition, these techniques do not detect specific molecular or biological activity. To detect earlier events in atherosclerosis, it is necessary to adopt other strategies.

MR Molecular Imaging
Conventional imaging technologies are based on anatomical, physiological, or metabolic heterogeneity to provide image

Figure 2. In vivo normal carotid artery: transverse image obtained with ECG-gated T1-weighted fast spin echo sequence.
contrast. Conversely, the emerging field of molecular imaging uses targeted and “activatable” imaging agents to exploit specific molecular targets, pathways, or cellular processes to generate image contrast. The primary advantage of MRI as a molecular imaging system is its ability to provide soft tissue and functional information by exploring proton density, perfusion, diffusion, and biochemical contrasts. This feature allows coregistration of molecular information with anatomical information within a single imaging mode.

Targeted MRI agents have largely been based on either superparamagnetic iron oxide nanoparticles or gadolinium chelates. Superparamagnetic iron oxide nanoparticles exert strong and reversible relaxation effects on their surrounding environment. Several forms of such iron oxides are in use, with some preparations under clinical investigation. Gadolinium has also been used in the development of targeted MRI contrast agents, but its lower intrinsic relaxivity often necessitates larger-sized nanoparticle constructs, such as polymerized liposomes, dendrimers, or perfluorocarbon nanoparticles. Nonetheless, these agents have been successfully used to specifically image angiogenesis, progenitor cells, and thrombosis in vivo. “Activatable” smart agents have recently been developed for MRI and are generally based on 1 of 2 chemical principles: (1) enzymatic conversion of paramagnetic compounds; or (2) assembly-disassembly of paramagnetic substrates or nanoparticles. In the first approach, investigators developed a contrast agent that is nearly magnetically silent at baseline. Suppression of the baseline MR signal occurs when cleavable high-affinity chelators are attached and block the access of water molecules to gadolinium, inhibiting its relaxation effects. An exhaustive description of molecular imaging markers is beyond the scope of this review; however, some challenging applications and recent clinical data suggest a growing interest in the future assessment of vulnerable plaque with these methods.

**Human Atherosclerotic Macrophage Imaging**

In 2 studies of carotid endarterectomy patients, baseline carotid MRI scans were obtained, and nanoparticles were then administered. Within 24 to 48 hours, areas of inflammation within the atherosclerotic plaques became enhanced compared with the baseline images. Histopathological correlation demonstrated a focal iron signal in areas of MRI plaque signal loss.

**Molecular Imaging of Myeloperoxidase (MPO) Activity**

“Activatable” paramagnetic MRI agents can be used to directly image MPO activity in humans. Jaffer and Weissleder have demonstrated the MPO activity in enzyme solutions and in a model tissue-like system. Winter et al have recently shown that MPO activity may be predictive of myocardial infarction in patients with chest pain.

**Molecular Imaging of Thrombus**

Molecular imaging of microthrombus within the fissures of vulnerable atherosclerotic plaques has been demonstrated with fibrin-targeted nanoparticles. This molecular imaging approach might assess the responsiveness of individual patients to antithrombotic therapies.
Molecular Imaging of Angiogenesis

Angiogenesis might also play a key role in both the initiation and later rupture of plaque. In a model of induced atherosclerosis, α(v)β3-integrin-targeted, paramagnetic nanoparticles were injected IV and provided specific detection of the neovascularature within 2 hours by MRI. Histology and immunohistochemistry confirmed marked proliferation of angiogenic vessels among cholesterol-fed, atherosclerotic rabbits.

Other Molecular Imaging Modalities: Ultrasound, Optical, and Nuclear

Ultrasonic contrast agent have been introduced to improve image resolution and specificity, for example, acoustic liposomes conjugated with monoclonal antibodies or gas-filled phospholipid microbubbles. Using this approach, it has been possible to image a range of targets similar to those described for MRI. Specifically, ICAM-1, vascular cell adhesion molecule 1, P-selectin, fibrin, and integrins have all been imaged with targeted ultrasound probes. Optical techniques offer an interesting approach to functional imaging. Fluorescent probes can be introduced in a quiescent or “quenched” state pending activation (eg, by enzymatic cleavage), at which point fluorescence can increase many hundred-fold. Optical techniques offer excellent spatial and temporal resolution but at the expense of tissue penetration compared, for example, with MRI or positron-emission tomography. In spite of these difficulties, it is possible to image small structures in 3D using multiphoton microscopy. Multiple probes can form part of the same experiment. For example, thrombus formation has been imaged in real time, in vivo using fluorescently labeled antibodies to fibrin, TF, and CD41 (platelet specific). Imaging using near-infrared fluorescent agents has been adapted to probe imaging. After site-specific cleavage by proteolytic enzymes, the probe becomes brightly fluorescent. This technique identified the activity of the macrophage-associated protease cathepsin B in the atherosclerotic plaques of apolipoprotein-E-deficient mice.

Detection of apoptotic cells in atherosclerotic lesions may represent another molecular imaging strategy to identify high-risk lesions. Apoptotic cells are able to bind a number of proteins, such as annexin V. Using radiolabeled annexin A5, investigators have imaged apoptosis in patients with acute myocardial infarction. More recently, radiolabeled annexin A5 was administered to 4 patients with carotid atherosclerosis. In 2 of these patients with recent TIAs, an elevated annexin A5 nuclear signal was detected in the ipsilateral carotid lesion. These 2 patients had histologically confirmed vulnerable plaques.

However, nuclear techniques are of limited use for in vivo situations in which labeled particles are cleared slowly from circulating blood and, therefore, contribute a low target:background scintigraphic ratio. The relatively poor spatial resolution of nuclear techniques and the paucity of anatomical information they generate about plaques can be counteracted to a degree by coregistration of scintigraphic images with computed tomography or MRI.

Positron Emission Tomography and single-photon-emission computed tomography benefit from imaging agents that can be detected at extremely low concentrations and provide an excellent sensitivity in molecular imaging applications but with lower spatial resolution than other technologies. 18F fluoro-2-deoxyglucose is a glucose analogue that marks active glycolysis. Rudd et al demonstrated that 18F fluoro-2-deoxyglucose accumulated in the plaques of patients with symptomatic carotid atherosclerosis after IV injection. These findings were confirmed by autoradiography after carotid endarterectomy.

Current Therapy Targeted at Plaque Instability

Antiplatelet Therapy

In patients with TIA or ischemic stroke of noncardiac origin, antiplatelet drugs are able to decrease the risk of stroke by 11% to 15% and decrease the risk of myocardial infarction (and vascular death by 15% to 22%.

Adding aspirin to clopidogrel in high-risk patients with recent ischemic stroke or TIA is associated with a significant difference in reducing major vascular events. However, the threat of major bleeding is increased by the addition of aspirin.

The Clopidogrel and Aspirin Regimen for the Reduction of Embolism in Symptomatic Carotid Stenosis (CARESS) trial was designed to evaluate the efficacy of dual antiplatelet therapy with clopidogrel and aspirin, compared with aspirin alone, on asymptomatic embolization in patients with recently symptomatic stenosis. Patients were screened with transcranial Doppler and if microembolic signals (MES) were detected, they were randomized to clopidogrel and aspirin or aspirin alone. MES were detected in 110 of 230 patients at baseline, of whom 107 were randomized. An intention-to-treat analysis revealed a significant reduction in the primary end point: 43.8% of dual therapy patients were MES positive on day 7, compared with 72.7% of patients in the aspirin-alone group (relative risk reduction, 39.8%; 95% CI, 13.8 to 58; P=0.0046). During the 1-week follow-up, there was a high rate of recurrent ipsilateral events in the monotherapy group, with a 7.1% risk of stroke and a 12.5% risk of recurrent TIA. Even in the dual therapy arm, 44% of subjects still had MES on day 7. Accordingly, additional approaches to target other parts of the process, such as inflammation and monocyte aggregates, which could also contribute to MES formation, may also be beneficial.

Anticoagulant Therapy

Warfarin is commonly used in preference to aspirin for atherosclerotic intracranial arterial stenosis, and these therapies have been compared in a randomized trial. Patients with symptoms caused by angiographically verified 50% to 99% stenosis (intracranial arterial stenosis) were randomly assigned to receive warfarin (target international normalized ratio, 2 to 3) or aspirin (1300 mg per day). After 569 patients had undergone randomization, the study was stopped because of concerns about the safety of the patients who had been assigned to receive warfarin. During a mean follow-up period of 1.8 years, the rate of death from vascular causes was 3.2% in the aspirin group and 5.9% in the warfarin group (P=0.16).

In this trial, warfarin was associated with a higher rate of adverse events and provided no benefit over aspirin.
**Statins**

A relationship between low-density lipoprotein-cholesterol (LDL-C) reduction by statins and carotid artery IMT has been demonstrated. A recent meta-analysis of randomized trials that tested statins showed a strong correlation between LDL-C reduction and carotid IMT reduction \( r = 0.65; \ P = 0.004 \). Each 10% reduction in LDL-C was estimated to reduce the carotid IMT by 0.73% per year (95% CI, 0.27 to 1.19).

Statins have the potential to “stabilize” the carotid atherosclerotic plaque against disruption by reducing the lipid content, as well as the inflammatory process. Statins inhibit the expression of specific cell surface receptors on monocytes, adhesion molecules, and integrin-dependent leukocyte adhesions. The effect of 3 months of the pravastatin on the composition of human carotid plaques removed during carotid endarterectomy for symptomatic severe stenosis has been evaluated. Pravastatin decreased lipids, lipid oxidation, inflammation, MMP-2, and cell death and increased the tissue inhibitors of metalloproteinase 1 and collagen content in human carotid plaques. This study provided the first evidence that statin therapy is associated with changes in human carotid plaque composition that favor plaque stability.

**Endovascular Treatment of Carotid Artery Stenosis**

Large randomized trials have convincingly shown that carotid endarterectomy significantly reduces the long-term risk of subsequent stroke from severe carotid artery stenosis. Endovascular treatment of atherosclerotic carotid artery stenosis may be an alternative to surgical endarterectomy. Five trials involving 1269 patients have recently been analyzed through the Cochrane Stroke Group trials register. Analysis of 30-day safety data found no significant difference in the odds of treatment-related death or any stroke, death, or disabling stroke (OR, 1.22; 95% CI, 0.61 to 2.41) or death, any stroke, or myocardial infarction (OR, 1.04; 95% CI, 0.06 to 0.25). No significant difference in the major risks of treatment was found, but the wide CIs indicate that it is not possible to exclude a difference in favor of 1 treatment. There is currently insufficient evidence to support a widespread change in clinical practice away from recommending carotid endarterectomy as the treatment of choice for suitable carotid artery stenosis. Patients suitable for carotid endarterectomy should only be offered stenting within the ongoing randomized trials of stenting versus surgery.

**Potential of Emergent Therapy in Plaque Stabilization**

**Cilostazol**

Cilostazol, a phosphodiesterase 3 inhibitor, has both an antiplatelet function and vasodilating effects. Recently, 135 patients with acute symptomatic stenosis in the M1 segment of the middle cerebral artery or the basilar artery were randomized either to cilostazol, 200 mg per day, or placebo for 6 months. Aspirin was also given to all of the patients each day. The primary outcome was the progression of symptomatic intra-arterial stenosis (IAS) on MRA. Outcomes included clinical events and progression on transcranial Doppler. In the cilostazol group, 3 of 45 symptomatic IAS (6.7%) progressed, and 11 (24.4%) regressed. In the placebo group, 15 symptomatic IAS (28.8%) progressed, and 8 (15.4%) regressed. Progression of symptomatic IAS in the cilostazol group was significantly lower than in the placebo group \( P = 0.008 \).

**Peroxisome Proliferator-Activated Receptor**

Peroxisome Proliferator-Activated Receptor (PPAR) signaling pathways have been reported to exert anti-inflammatory effects and attenuate atherosclerosis formation. Several recent studies have demonstrated that PPAR agonists improve atherosclerosis by ameliorating systemic metabolic risk factors for atherogenesis and inflammatory events that occur within the arterial wall. The PPAR\( \gamma \) agonist rosiglitazone exerted a significant vascular protective effect in hypercholesteremic rabbits, most likely by attenuation of oxidative and nitrative stresses. The endothelial protective effects of PPAR\( \gamma \) agonists may reduce leukocyte accumulation in vascular walls and contribute to the antiatherosclerotic effect.

**MMP Inhibitors**

Inhibitors aimed at blocking the proteolytic activity of MMPs have been used in patients with advanced solid cancer and may contribute to the prevention of matrix collagen degradation. However, there is concern that the use of these agents might be associated with rash and frequent musculoskeletal side effects, as observed in a recent study assessing the effectiveness of MMZ270 (an oral direct inhibitor of MMP-2, MMP-8, and MMP-9).

**Conclusion**

Atherosclerosis is a diffuse and multisystem, chronic inflammatory disorder involving the vascular, metabolic, and immune systems. The traditional risk assessment relies on clinical, biological, and conventional imaging tools. However, these tools fall short in predicting near-future events, particularly in individual clinical practice. At the beginning of the third millennium, it is essential to reconsider the assessment of vulnerable carotid artery plaques in light of new imaging tools in order to optimize therapeutic management. Accordingly, a new stratification for atherothrombotic risk may involve, in the future, the combination of systemic markers, high-resolution MRI, and molecular MRI that targets the inflammatory and thrombotic components of atherosclerotic plaque.

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