Research Progress on the Risk Factors and Outcomes of Human Carotid Atherosclerotic Plaques

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Objective: Atherosclerosis is an inflammatory process that results in complex lesions or plaques that protrude into the arterial lumen. Carotid atherosclerotic plaque rupture, with distal atheromatous debris embolization, causes cerebrovascular events. This review aimed to explore research progress on the risk factors and outcomes of human carotid atherosclerotic plaques, and the molecular and cellular mechanisms of human carotid atherosclerotic plaque vulnerability for therapeutic intervention.

Data Sources: We searched the PubMed database for recently published research articles up to June 2016, with the key words of “risk factors”, “outcomes”, “blood components”, “molecular mechanisms”, “cellular mechanisms”, and “human carotid atherosclerotic plaques”.

Study Selection: The articles, regarding the latest developments related to the risk factors and outcomes, atherosclerotic plaque composition, blood components, and consequences of human carotid atherosclerotic plaques, and the molecular and cellular mechanisms of human carotid atherosclerotic plaque vulnerability for therapeutic intervention, were selected.

Results: This review described the latest researches regarding the interactive effects of both traditional and novel risk factors for human carotid atherosclerotic plaques, novel insights into human carotid atherosclerotic plaque composition and blood components, and consequences of human carotid atherosclerotic plaque.

Conclusion: Carotid plaque biology and serologic biomarkers of vulnerability can be used to predict the risk of cerebrovascular events. Furthermore, plaque composition, rather than lesion burden, seems to most predict rupture and subsequent thrombosis.

Key words: Human Carotid Atherosclerosis; Outcomes; Plaques; Progress; Risk Factors

Interactive Effects of Traditional and Novel Risk Factors on Human Carotid Atherosclerotic Plaques

Traditional risk factors for human carotid atherosclerotic plaques include age and history of diabetes mellitus, coronary artery disease, hypertension, stable angina pectoris, and high cholesterol levels. These factors can lead to the formation of plaques that may rupture and cause cerebrovascular events. The identification and management of these risk factors are crucial in preventing plaque rupture and reducing the risk of cerebrovascular events.

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and chronic kidney disease. Novel risk factors for human carotid atherosclerotic plaques include shear stress, carotid atherosclerotic plaque morphologic risk factors, biochemical risk factors in carotid atherosclerotic plaques and blood, and infection risk factors (such as *Chlamydia pneumoniae*). The morphologic risk factors for carotid atherosclerotic plaque include plaque surface ulceration, thrombosis, luminal surface irregularity, intraplaque hemorrhage, nonhyperechoic plaque, hypoechoic or predominantly hypoechoic plaque, echoluent plaque, complex plaque, stenoses grade ≥ 70%, early- and end-stage calcifications, gray-scale median score in imaging of plaque echogenicity, plaque lipid core presence, lipid-rich plaque, intima-media thickness (IMT), and plaque score. The biochemical risk factors in carotid atherosclerotic plaques and blood include C-reactive protein (CRP), total bilirubin, neopterin, fibrinogen, high-sensitivity CRP (hsCRP), parathyroid hormone, fetuin-A, monocyte chemoattractant protein-1, cyclooxygenase-2, Type 1 prostaglandin E (PGE) synthase, PGE2 receptor 4, matrix metalloproteinase (MMP) (-1, -2, -3, -7, -8, -9, -12, and -14), tissue inhibitor of MMP (TIMP) (-1 and -3), interleukin (IL-1β, -6, -8, -17A, -18, -21, and -23), CD (36, 146), soluble CD40 (sCD40) ligand, leukocyte count, monocyte count, osteopontin, osteoprotegerin, tumor necrosis factor-α (TNF-α), soluble urokinase-type plasminogen activator receptor (suPAR), enzyme chitin (YKL)-40, S100A12, interferon-γ, plaque macrophage, M1 macrophage, plaque T-cells accumulation, vascular cell adhesion molecule-1, erythrocyte sedimentation rate, glucose, homocysteine, lipid, total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein B, oxidized low-density lipoprotein, lipoprotein-associated phospholipase A2, pregnancy-associated protein A, hematocrit, 1267 heat shock protein 70-2 gene, cyclooxygenase-2 gene, BRCA-1-associated protein (BRAP) gene, osteoprotegerin gene, IL-1 receptor antagonist gene, MMP-3 genotype, and MMP-14 genotype.

Scientists have found interactive effects between traditional risk factors and novel risk factors for human carotid atherosclerotic plaques. For example, the frequency of carotid nonhyperechoic plaque was significantly increased in elderly type 2 diabetes mellitus patients with carotid stenosis and heart shock protein 70-2 gene B' allele (at position 1267), compared with the frequency in elderly type 2 diabetes mellitus patients with carotid stenosis and heat shock protein 70-2 gene B’ allele (at position 1267). In patients with hypoechoic carotid plaques on ultrasound and asymptomatic patients with carotid plaque progression, history of coronary disease was significantly related to the increased MMP activity. Intraplaque active MMP-9 levels were significantly increased in patients with hypertension compared with normotensive patients. The rates of carotid plaque formation were significantly decreased in patients with essential hypertension and mild hyperlipidemia receiving lipid-lowering agent and antihypertensive treatment for 24 months, compared with those in the control group.

Blood pressure levels were significantly increased in patients with a recently diagnosed internal carotid artery (ICA) stenosis >50%, compared with healthy controls. Serum CRP was significantly increased and total bilirubin was significantly decreased in hypertensive patients with carotid atherosclerosis, compared to hypertensive patients without carotid atherosclerosis. Plasma neopterin levels were significantly increased in patients with stable angina pectoris and complex carotid plaques, compared to patients with stable angina pectoris and noncomplex carotid plaques, or patients with stable angina pectoris without carotid plaques. Immunohistochemical staining revealed abundant neopterin-positive macrophages in complex carotid lesions. The early- and end-stage calcifications in unstable and ruptured lesions were significantly increased in patients with chronic kidney disease, compared to those in patients without chronic kidney disease. Finally, serum fibrinogen, hsCRP, parathyroid hormone, fetuin-A, and MMP-7 levels were significantly increased in patients with advanced carotid stenosis >70% and chronic kidney disease, compared to those in patients with advanced carotid stenosis >70% but without chronic kidney disease.

**Novel Insights into Human Carotid Atherosclerotic Plaque Composition and Blood Components**

**Plaque morphologic risk factors**

On histologic examination, there was recent hemorrhage and remote hemorrhage on plaque sections in most carotid bifurcation plaques. These included high-grade stenoses removed through carotid endarterectomy (CEA) and nonstenotic plaques recovered at autopsy. The incidence of ulceration, thrombosis, and lumen surface irregularity was significantly increased in high-grade stenotic plaques compared to asymptomatic nonstenotic plaques. There were prominent lesional features in 80% of the stenotic bifurcations. Macroscopic CEA plaque ulceration frequency was significantly increased in patients with symptomatic carotid plaques, compared to the frequency in patients with asymptomatic carotid plaques.

Plasma MMP-8 levels and MMP activities were significantly increased in patients with hypoechoic carotid plaques on ultrasound. Recent intraplaque hemorrhage on histologic sections of CEA specimens was related to the significantly increased MMP activity. The gray-scale median scores were significantly decreased in the images of carotid plaque echogenicity obtained by high-resolution color duplex ultrasounds in patients with neurological symptoms and ICA stenosis >50%, compared to asymptomatic patients with ICA stenosis >50%. The gray-scale median score was considerably associated with serum osteopontin and osteoprotegerin levels in patients with carotid atherosclerosis. Carotid plaque echogenicity was significantly decreased in the −765GC genotype group of the cyclooxygenase-2 gene, compared to that in the −765GG genotype group of the cyclooxygenase-2 gene.
Plaque thickness was significantly decreased, and carotid plaque echogenicity was significantly increased, after 12 months of statin therapy in hypercholesterolemic patients with carotid plaques treated with simvastatin 10 mg/d or atorvastatin 5 mg/d. This was compared to plaque thickness in hypercholesterolemic patients with carotid plaques without statin therapy. The color duplex ultrasound characteristics of unstable stenoses were found in stenoses grade ≥70%, plaque surface ulcerations, and hypochoic or predominantly hypochoic plaques. The frequency of unstable ultrasound features of ICA stenosis was significantly increased in symptomatic patients compared to asymptomatic patients.

There was a lipid core in 71% of the plaques with a maximum thickness ≥1.5 mm by magnetic resonance imaging (MRI). A lipid core in thickened carotid walls is strongly associated with total plasma cholesterol. There were large intraplaque hemorrhages in 64% of patients who underwent CEA for carotid stenosis, and there were lipid-rich plaques in 52% of them. The sensitivities and specificities of MRI identification of large intraplaque hemorrhages, and for ¹⁸F-fluorodeoxyglucose-positron emission tomography (¹⁸FDG-PET) to identify the lipid-rich plaques, were high. There was a significant correlation between the findings on ¹⁸FDG-PET and those on immunohistochemistry against CD68 (activated macrophages) and MMP-9. CEA plaques with >40% fat frequency were significantly decreased in women compared with men. Laser-induced fluorescence spectroscopy with limited tissue penetration and histological staining revealed that elastin was significantly decreased, and arterial matrix collagen I and III were significantly increased, in unstable carotid plaque compared to those in left internal mammary arteries. Collagen I was elevated in plaques within the ICA region, compared to those in the common carotid artery (CCA) region. Fluorescence spectroscopy with microscopy analyses revealed marked regional differences in collagen I, III, and elastin in surface layers of carotid plaques. Plaque formation tendency was significantly increased in ICA/bulb segments compared with CCA segments. There was a significant positive trend between ICA/bulb IMT and total homocysteine in people ≥58 years of age. A patient’s carotid plaque score was significantly correlated with active and total MMP-3 levels in the blood.

In addition, a carotid plaque total score was significantly associated with serum MMP-9 quartiles and was high compared to those associated with serum MMP-9 quartile 1. IMT was significantly and independently associated with serum monocyte chemoattractant protein-1 concentration.

Biochemical risk factors in plaques and blood

The switch from anti-inflammatory lipocalin-type prostaglandin D synthase to pro-inflammatory Type 1 inducible membrane-bound prostaglandin E synthase-1 (mPGES-1) in carotid atherosclerotic plaque macrophages is associated with acute brain ischemia. Pro-inflammatory inducible cyclooxygenase-2/mPGES-1 are overexpressed in symptomatic plaques in association with PGE2-dependent MMP biosynthesis and release leading to plaque rupture. EP4 immunoreactivity was strong in 4 PGE2 receptors EP1-4 expression of plaques from symptomatic and asymptomatic patients undergoing CEA. EP4 was significantly increased in MMP-rich symptomatic lesions. EP4 overexpression is associated with enhanced inflammatory reaction of atherosclerotic plaques and plaque rupture. The MMP-9 level was significantly increased in symptomatic (within 1 month) plaques obtained from patients undergoing CEA and in plaques undergoing spontaneous embolization. Active MMP-8 concentrations were significantly increased in carotid plaques of symptomatic patients or emboli-positive patients. Plaque MMP-8 protein and mRNA colocalized with macrophages. Plasma MMP-7 levels were significantly increased in patients with moderate (50–69%) or severe (≥70%) ICA atherosclerotic stenosis and particularly high in patients with recent symptoms (within last 2 months), compared to those in healthy controls. The levels of MMP-7 mRNA were significantly increased in carotid plaque compared to those in nonatherosclerotic vessels. The levels of MMP-7 protein were particularly high in patients with most recent symptoms. Immunohistochemistry revealed that the MMP-7 was localized to macrophages. MMP (-8, -9) activities were significantly increased in macrophage-rich carotid atherosclerotic lesions whereas MMP-2 activity was significantly increased in smooth muscle cell-rich lesions.

IL-18 was highly expressed in human carotid plaques compared to that in control normal arteries and mainly localized in plaque macrophages. Plasma IL-23 levels were significantly increased in patients with carotid atherosclerosis compared to those in healthy controls, and particularly high in patients with most recent symptoms. IL-23 and its receptor mRNA levels were significantly increased in carotid atherosclerotic plaques compared to those in nonatherosclerotic vessels. Immunostaining showed colocalization to plaque macrophages. IL-23 gave a prominent TNF release in monocytes from patients with carotid atherosclerosis.

The concentration of osteoprotegerin and osteopontin within proximal ICA part of CEA specimen removed from patients with recent (within 6 weeks) focal neurological symptoms was elevated 2- and 4-fold compared with those in asymptomatic patients. Serum lipid profile was worse, and hsCRP, fibrinogen, leukocyte count, osteopontin, and osteoprotegerin levels were significantly increased in patients with recently diagnosed ICA stenosis >50% compared with those in healthy controls. Serum osteopontin, osteoprotegerin, and hsCRP levels were significantly increased in patients with neurological symptoms and ICA stenosis >50% compared to those in patients with ICA stenosis >50% but with no symptoms and healthy controls. Only osteoprotegerin levels were significantly increased in patients with ICA stenosis >50% but with no symptoms compared with those in healthy controls.
The levels of plasma sCD36 were significantly increased in patients with high-grade ICA stenoses and clinical symptoms within the last 2 months from plaque compared to those in patients with high-grade ICA stenoses and symptoms within the last 2–6 months and asymptomatic patients. Immunohistochemistry revealed that CD36 was localized to the macrophage-rich area of intima within atherosclerotic lesion.[30] CD146 expression was mainly on the carotid intraplaque blood vessels and infiltrated macrophages and strongly correlated with MMP-9 expression in the plaques. There was a significant correlation between the increased CD146 expression in the plaques and elevated serum sCD146 level in patients with carotid plaques. The sCD146 was significantly correlated with serum MMP-9, IL-6, and hsCRP.[31]

The levels of serum enzyme chitin (YKL)-40 were significantly increased in patients with carotid atherosclerosis and particularly high in symptomatic patients. Carotid plaque YKL-40 mRNA levels were significantly increased in patients with recent ischemic symptoms within 2 months compared to those in other patients.[32] Plaque and plasma suPAR levels were significantly increased in symptomatic patients with carotid plaques compared to those in asymptomatic patients with carotid plaques.[33] Plasma S100A12 levels were significantly increased in patients with carotid atherosclerotic high-grade stenosis compared to those in healthy controls and highest in patients with the most recent symptoms within 2 months. IL-1β and interferon-γ significantly enhanced S100A12 expression.[34]

Carotid ultrasound revealed that plaque vulnerability was significantly increased in symptomatic patients with acute brain ischemia compared to that in asymptomatic patients with acute brain ischemia. Immunohistochemistry revealed that pro-inflammatory M1 macrophage concentration was significantly increased in plaques from symptomatic patients compared to that in plaques from asymptomatic patients while anti-inflammatory M2 macrophages were significantly increased in plaques from asymptomatic patients compared to those in plaques from symptomatic patients.[35]

Inflammatory biomarkers were significantly increased in patients with carotid atherosclerosis compared to those in patients with middle cerebral artery atherosclerosis. The CRP levels were significantly inversely correlated with middle cerebral artery atherosclerosis. Results indicated that inflammatory biomarkers revealed clinical and radiological differences between patients with carotid atherosclerosis and patients with middle cerebral artery atherosclerosis. The stability of plaque associated with middle cerebral artery atherosclerosis may be significantly increased compared to that of plaque associated with carotid atherosclerosis.[36] Serum IL-6, fibrinogen, erythrocyte sedimentation rate concentrations, and CRP values were significantly increased in patients with ICA stenosis compared to those in control group individuals.[37] Blood IL-6 and triglycerides were significantly increased, and TIMP-1 and high-density lipoprotein cholesterol were significantly decreased in symptomatic patients with carotid stenosis ≥50% compared to those in asymptomatic patients with carotid stenosis ≥50%. Blood osteoprotegerin and lipoprotein-associated phospholipase A2 were significantly increased in carotid stenosis with recent symptoms compared to those in carotid stenosis with remote symptoms.[38] The hematocrit levels were significantly increased in symptomatic patients with carotid plaques compared to those in asymptomatic patients with carotid plaques.[10]

IL-1 receptor antagonist gene allele 2 frequency was significantly increased in patients with carotid atherosclerosis compared to that in nonatherosclerotic individuals.[39] A dominant genotype MMP-3 -1612 6A/6A is associated with significantly increased blood active MMP-3 levels.[39] BRAP gene GG genotype was significantly associated with an increased risk for having at least one carotid plaque compared to BRAP gene carrying an A allele.[39] T245G polymorphism GG genotype, T950C polymorphism CC genotype, and G1181C polymorphism CC genotype were significantly increased in osteoprotegerin gene TNFRSF11B polymorphisms in patients with ICA stenosis who underwent CEA compared to those in controls, and significantly associated with high serum osteoprotegerin levels.[40]

**Infection risk factor**

*C. pneumoniae* burden in carotid plaques was significantly associated with plaque IL-6 expression and serum IL-6 and CRP levels.[41] The lipoprotein-associated phospholipase A2 in carotid plaque was correlated with serum homocysteine levels and plaque macrophages and *C. pneumoniae* which infected predominantly macrophages colocalizing with lipoprotein-associated phospholipase A2.[42]

**Association of therapy and risk factors**

Serum total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, and CRP levels, as well as plaque IL-6 expression and plaque prevalence, were significantly decreased in patients with carotid plaques and statin therapy compared to those in patients with carotid plaques but without statin therapy.[43] Serum total cholesterol, triglyceride, hsCRP, and IL-18 levels were significantly decreased after 12 months of statin therapy in hypercholesterolemic patients with carotid plaques treated with simvastatin 10 mg/d or atorvastatin 5 mg/d compared to those in hypercholesterolemic patients with carotid plaques but without statin therapy.[12]

The frequency of low macrophage staining was significantly increased in CEA plaques obtained from women. Plaque interleukin-8 concentration and MMP-8 activity were significantly decreased in women compared to those in men. Smooth muscle cell content was significantly increased in a large proportion of plaques obtained from asymptomatic women. The prevalence of stable plaques was the highest in asymptomatic women. The stability of plaque was significantly increased, and inflammation of plaque was significantly decreased in women, especially asymptomatic women compared to those in men, resulting in a decreased...
The prevalence of plaque and plasma oxidized low-density lipoprotein levels and pathologically vulnerable plaque incidence were significantly increased in stroke patients with a variety of symptoms who underwent early CEA within 4 weeks of the last symptom compared to those in stroke patients who received CEA in a late stage beyond 4 weeks from last symptom. Some of the vulnerability biomarkers, especially those reflecting an active systemic inflammatory process of plaque such as pregnancy-associated protein A, hsCRP, and IL-6, were significantly increased before and after carotid stenting, and significantly decreased after 30 days.

**Consequences of Human Carotid Atherosclerotic Plaque**

Outcomes of human carotid atherosclerotic plaque

Outcomes of human carotid atherosclerotic plaque include acute ischemic stroke or acute brain infarction, transient ischemic attack, cardiovascular death, myocardial ischemia, or myocardial infarction. For example, frequency of acute brain ischemia including acute ischemic stroke or transient ischemic attack was significantly increased in elderly type 2 diabetes mellitus patients with carotid stenosis and heat shock protein 70-2 gene B' allele genotype (at position 1267) compared to that in elderly type 2 diabetes mellitus patients with carotid stenosis and heat shock protein 70-2 gene B- allele genotype (at position 1267). Ipsilateral stroke or cardiovascular death incidence was significantly increased in patients with carotid stenosis ≥50% and elevated plasma MMP-9 levels compared to that in patients with carotid stenosis ≥50% but without elevated plasma MMP-9 levels. Serum MMP-9, sCD40 ligand (sCD40L), and hsCRP levels were significantly increased, and TIMP-1 levels were significantly decreased in stroke patients compared to those in asymptomatic patients. The prevalence of stroke or myocardial infarction was significantly increased in hypertensive patients with carotid atherosclerosis compared to that in hypertensive patients without carotid atherosclerosis. Complex carotid plaques in patients with stable angina pectoris may be associated with ischemic stroke risk. Plaque T-cells accumulation and IL (-6, -17A, -21, and -23) and vascular cell adhesion molecule-1 expression were significantly increased in patients with carotid plaques and ischemic symptoms compared to those in patients with carotid plaques but without ischemic symptoms. Event rates of newly developed myocardial ischemia, cardiovascular death, and ischemic stroke were significantly increased in coronary disease patients with high hsCRP and carotid echolucent plaque on the far wall from CCA to proximal ICA compared to those in coronary disease patients with high hsCRP but without carotid echolucent plaque on the far wall from CCA to proximal ICA. The incidence of cerebrovascular events >6 months before carotid surgery was significantly increased in chronic kidney disease patients with advanced carotid stenosis >70% compared to that in patients with advanced carotid stenosis >70% but without chronic kidney disease. CD40L expression was the highest on peripheral blood monocytes in patients with large artery atherosclerotic acute brain infarction, and significantly increased in patients with carotid atherosclerotic brain infarction compared to that in patients without carotid atherosclerosis. Serum sCD40L was significantly increased in patients with acute brain infarction compared to that in patients with carotid stenosis or healthy controls, and significantly correlated with increased disability. Stroke incidence rates were significantly decreased in patients with essential hypertension and mild hyperlipidemia receiving lipid-lowering agent and antihypertensive treatment for 24 months compared to those in control group.

**Role of human carotid atherosclerotic vulnerable or unstable plaque components**

The MMP-9 level was significantly increased in plaques with histological evidence of carotid plaque instability. The prevalence of carotid plaque instability associated significantly with serum MMP-9 quartiles was significantly increased compared to that associated with serum MMP-9 quartile 1. Active MMP-8 concentrations were significantly increased in carotid plaques of patients showing histological evidence of rupture compared to those in carotid plaques of patients without showing histological evidence of rupture. Plaque MMP-8 protein and mRNA were colocalized with macrophages. Active intraplaque MMP-8 levels were significantly increased in asymptomatic patients with carotid plaque progression compared to those in asymptomatic patients without carotid plaque progression. Carotid plaque oxidized low-density lipoprotein levels and MMP-9 activity were significantly increased in the vulnerable group compared to those in the stable group. MMP (-1, -9, -12, and -14) were significantly increased in vulnerable carotid plaques compared to those in stable carotid plaques. TIMP-3 expression was the highest in stable carotid plaques. Vulnerable plaque formation risk was significantly decreased in carotid plaque with MMP-14 position + 7096 TC + CC genotype compared to that in carotid plaque with MMP-14 TT genotype.

IL-18 mRNA levels were significantly increased in symptomatic unstable carotid plaques compared to those in asymptomatic stable carotid plaques. Vulnerable and ruptured complicated carotid plaques in patients with ischemic symptoms were significantly associated with high IL-17A expression levels. Pro-inflammatory M1 macrophages expressed in unstable plaques defined by carotid ultrasound were significantly increased compared to those expressed in stable plaques, while anti-inflammatory M2 macrophages expressed in stable plaques were significantly increased compared to those expressed in unstable plaques. Serum osteoprotegerin levels, as well as TNF-α, IL-6 and fibrinogen concentrations, leukocyte count, monocyte count,
and CRP values,[13] were significantly increased in patients with unstable plaques compared with those in patients with stable plaques. There is a relationship between selected serum inflammatory biomarkers’ activity and unstable ICA atherosclerotic stenosis.[13]

Plaque criteria

So far, the criteria of IMT defining plaques were not concordant worldwide from IMT 1.0 mm to 1.5 mm. For example, a distinct area protruding into vessel lumen with ≥50% significantly increased thickness compared with surrounding areas,[20] or IMT ≥1.0 mm,[53] or IMT ≥1.1 mm,[54] or IMT ≥1.3 mm,[6] or IMT >1.4 mm,[55] or IMT ≥1.5 mm[66] was defined as plaque. The only concordant criterion of IMT defining plaque worldwide should be determined from IMT ≥1.0 mm or ≥1.1 mm or ≥1.2 mm or ≥1.3 mm or ≥1.4 mm or ≥1.5 mm.

Progress

So far, very little is known about the pathogenesis of human carotid atherosclerotic plaque vulnerability. This review describes the latest researches regarding the interactive effects of both traditional and novel risk factors and outcomes of human carotid atherosclerotic plaques, molecular and cellular mechanism of human carotid atherosclerotic plaque vulnerability, and whether the changes of biomarkers are truly necessary and sufficient to cause human carotid atherosclerotic plaque vulnerability.

Conclusion

This review describes the latest researches regarding the interactive effects of both traditional and novel risk factors for human carotid atherosclerotic plaques, novel insights into human carotid atherosclerotic plaque composition and blood components, and consequences of human carotid atherosclerotic plaque. Carotid plaque biology and serologic biomarkers of vulnerability can be used to predict the risk of cerebrovascular events. Furthermore, plaque composition, rather than lesion burden, seems to most predict rupture and subsequent thrombosis.

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Conflicts of interest

There are no conflicts of interest.

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