Clinical Perspective of Carotid Plaque Imaging

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KEYWORDS

• Carotid plaque • Imaging • Stroke • Endarterectomy • Stenting • Personalized medicine

KEY POINTS

- At present, patients with carotid disease are selected for invasive recanalization therapies mainly based on the degree of luminal narrowing and the presence or absence of recent ischemic symptoms.
- A more sophisticated risk model takes into account other clinical variables, such as age, sex, and timing and type of recent symptoms as well as presence of irregular or ulcerated plaque.
- A growing body of evidence shows that noninvasive imaging of the carotid plaque by various methods reliably identifies structural correlates of plaque vulnerability, which are associated with an increased risk of cerebrovascular events.
- These observations are in line with current understanding of the pathophysiology of atherosclerosis according to which plaque rupture and subsequent embolism, rather than reduction in flow in the stenotic vessel, are key mechanisms leading to stroke.
- Integration of plaque imaging at baseline in randomized controlled trials is needed to test the hypothesis that plaque imaging helps select patients who benefit from carotid revascularization. If this holds true, then plaque imaging should be incorporated in management guidelines.

INTRODUCTION

Stroke is the leading cause of acquired disability in adult life and represents the second most common cause of death after ischemic heart disease in developed nations.[1] Atherosclerotic disease of the carotid artery causes about 10% to 15% of ischemic strokes.[2,3] Carotid atherosclerosis in Caucasian populations is most commonly located at the carotid artery bifurcation, typically involving the distal common carotid and the proximal internal carotid artery, and to a lesser extent the proximal external carotid artery. Carotid artery atherosclerosis is more frequent in men than in women, and its prevalence increases with age. Ultrasound screening studies in Central and Northern European and North American populations have shown a prevalence of at least a moderate degree of asymptomatic carotid stenosis (narrowing the lumen by $\geq$50%) of 2.3% in 60 to 69 year old men, 6.0% in 70 to 79 year old men, and up to 7.5% in men 80 years and older; in women, the prevalence rates were 2.0%, 3.6%, and 5.0%, in the same age groups, respectively.[4] Severe carotid stenosis measuring 70% or greater was present in 0.8%, 2.1%, and 3.1% in the same age groups in men, and in 0.2%, 1.0%, and 0.9% in women.

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Despite the high prevalence of carotid disease in the community, only a small proportion of the individuals affected will ever develop a transient ischemic attack (TIA) or a stroke. Although several randomized controlled trials (RCTs) have demonstrated that carotid endarterectomy (CEA), and in selected patients, carotid artery stenting (CAS), lowers the risk of stroke in patients with symptomatic and asymptomatic carotid stenosis, the numbers of interventions (number needed to treat; NNT) necessary to prevent one stroke are rather high. The present article reviews the current treatment dilemmas faced in the management of carotid disease and highlights the potential of carotid plaque imaging in selecting patients who benefit from carotid revascularization, thus allowing for more personalized treatment decisions.

STROKE RISK AND THE EFFECT OF REVASCULARIZATION IN PATIENTS WITH CAROTID DISEASE

Symptomatic Carotid Stenosis

The bulk of evidence on stroke risk under medical therapy for symptomatic carotid stenosis stems from the medical treatment groups of RCTs, which evaluated the benefit of CEA versus medical therapy alone 2 to 3 decades ago. In a pooled analysis of the North American Symptomatic Carotid Endarterectomy Trial (NASCET),[5] the European Carotid Surgery Trial (ECST),[6] and a third, smaller trial (the Veterans Affairs trial, VA309[7]), including 6092 patients and 35,000 patient-years of follow-up, the cumulative risk of ipsilateral stroke in patients with recently symptomatic severe carotid stenosis (causing 70%–99% narrowing) randomly allocated to medical therapy was approximately 26% at 5 years after randomization.[8] This risk was reduced by an absolute difference of 16% in the group of patients randomized to undergo CEA. In patients with moderate, 50% to 69% stenosis, the 5-year risk of ipsilateral stroke was about 18% and reduced by only 4.6%.[5] The risk of periprocedural stroke or death (which by definition includes outcome events occurring up to 30 days after treatment) was 7.1% in this pooled analysis and did not vary significantly with the degree of stenosis.

Importantly though, 55% of patients in the NASCET trial were randomized more than 30 days after the qualifying event (TIA or minor stroke), and in ECST, this proportion was 65%. These RCT data therefore do not allow estimating stroke risk in the first days after initial symptoms, which may be much higher. In large prospective registries of patients presenting with TIA, up to 20% of those with large artery atherosclerosis as the underlying cause had a stroke within 90 days of the TIA, with most events occurring in the first 7 to 14 days.[2,9]

On the other hand, one has to acknowledge that ECST recruited patients between 1981 and 1994, and NASCET between 1988 and 1996. Medical therapy in these trials mainly consisted of aspirin only. In the NASCET trial, only 14% of patients were taking lipid-lowering therapy at the time of randomization. It is reasonable to assume that with more widespread use of statins and more aggressive antiplatelet regimes, the risk of early recurrent stroke in symptomatic carotid stenosis is lower today than reported in these earlier trials and TIA cohorts.

Since the time these trials were done, CAS has emerged as an alternative, less-invasive option to treat carotid stenosis and was compared against CEA in several RCTs, which enrolled mostly patients with symptomatic carotid stenosis. On average, CAS was as effective as CEA in these trials in maintaining the artery patent and preventing recurrent stroke in the long term.[10–13] However, CAS was associated with a higher risk of periprocedural stroke than surgery.[14] Subgroup analyses revealed that this excess risk in procedure-related stroke in CAS is mainly limited to patients older than 70 years, whereas CAS and CEA seem to be equally safe in younger patients.[15] Nonetheless, the fundamental problem of identifying patients in whom the risk of stroke under modern medical therapy is still high enough to warrant carotid revascularization has remained.

Asymptomatic Carotid Stenosis

Two large randomized trials, the Asymptomatic Carotid Atherosclerosis Study (ACAS), which recruited 1662 patients between 1987 and 1993, and the Asymptomatic Carotid Surgery Trial (ACST), which recruited 3120 patients between 1993 and 2003, consistently demonstrated an 11% risk of ipsilateral stroke in patients with asymptomatic carotid stenosis of 60% or higher who were assigned to initial medical management.[16,17] This risk was reduced by 6% in ACAS and 4% in ACST in patients assigned to immediate endarterectomy. Of note, fewer than 10% of patients in ACST were on lipid-lowering therapy at the beginning of recruitment in 1993, and this proportion steadily increased to more than 80% at termination of follow-up in 2008.

A meta-regression analysis of data from medical arms of randomized trials and prospective cohorts suggested that the risk of ipsilateral stroke associated with asymptomatic carotid stenosis has declined over the past 20 years and may now be only 1% per year or lower,[18] most likely