Intracranial Atherosclerosis
Current Concepts
Juan F. Arenillas, MD, PhD

Abstract—The most relevant ideas discussed in this article are described here. Intracranial atherosclerotic disease (ICAD) represents the most common cause of ischemic stroke worldwide. Its importance in whites may have been underestimated. New technical developments, such as high-resolution MRI, allow direct assessment of the intracranial atherosclerotic plaque, which may have a profound impact on ICAD diagnosis and therapy in the near future. Early detection of ICAD may allow therapeutic intervention while the disease is still asymptomatic. The Barcelonès Nord and Maresme Asymptomatic Intracranial Atherosclerosis Study is presented here. The main prognostic factors that characterize the patients who are at a higher risk for ICAD recurrence are classified and discussed. The best treatment for ICAD remains to be established. The Stenting Versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Study is currently ongoing to address this crucial issue. These and other topics will be discussed at the Fifth International Intracranial Atherosclerosis Conference (Valladolid, Spain, autumn 2011). (Stroke. 2011;42[suppl 1]:S20-S23.)

Key Words: acute stroke ■ intracranial stenosis ■ intracranial atherosclerotic disease ■ prevention ■ treatment

Intracranial Atherosclerotic Disease: A Major Cause of Stroke
Intracranial atherosclerotic disease (ICAD) is characterized by the development, progression, and complication of atherosclerotic lesions affecting intracranial large arteries. ICAD represents the most common cause of ischemic stroke among patients of Asian ancestry.1,2 Moreover, atherosclerosis is also more prone to affect intracranial compared with extracranial arteries in Hispanics and Africans.3 Thus, it has been claimed that ICAD may be the most common cause of stroke worldwide.4 Accordingly, as shown in the Figure, ICAD has become a rapidly evolving research field in the last 2 decades. ICAD may account for ≈8% to 10% of all ischemic strokes in whites.5,6 Nevertheless, the real impact of ICAD on whites may be greater than expected. A study conducted by a French group in 339 autopsies of patients who died because of an ischemic or hemorrhagic stroke showed a strikingly high prevalence of both intracranial plaques and intracranial stenoses.6 As will be discussed later on, intracranial stenosis represents only the most advanced stage of ICAD, and, as suggested by this work, nonstenotic ICAD may turn to be much more common than stenotic ICAD.

Intracranial Atherosclerotic Plaque Imaging
Our traditional understanding of ICAD is based on the detection of hemodynamically relevant intracranial stenoses. The main limitations of this approach are as follows: (1) it may be restricted to the most advanced stage of ICAD alone; (2) it is unable to differentiate atherostenoses from stenoses caused by other entities; and (3) it may not be able to provide information about the histopathologic composition and activity of the intracranial atherosclerotic plaque. This last point seems extremely relevant, because symptomatic intracranial atherosclerotic plaques are characterized not only by a higher degree of luminal stenosis but also by a richer content in lipid, intraplaque hemorrhage and inflammatory cell infiltration, all of which are well-known determinants of plaque instability in the extracranial vasculature.7

In contrast to this classical approach to ICAD, newer technical developments, such as high-resolution MRI and intravascular ultrasound, allow direct assessment of intracranial atherosclerotic plaques. The main implications of this focus on intracranial atherosclerotic plaque imaging are shown in Table 1. This new concept could have a dramatic impact on the way we will diagnose and treat ICAD in the near future. For instance, intravascular ultrasound has shown intraplaque hemorrhage in vivo in symptomatic ICAD, a finding that supports the hypothesis that intracranial atherosclerotic plaques can become symptomatic after complication by intraplaque hemorrhage analogous to coronary artery plaques.8 In line with this observation, 3T high-resolution MRI direct thrombus imaging also allows characterization of intraplaque hemorrhage in vivo and identification of other...
Primary Prevention: Asymptomatic ICAD

Atherosclerotic lesions develop silently over years until they suddenly become symptomatic. Therefore, early detection of ICAD may allow therapeutic intervention while the disease is still asymptomatic. However, the natural history of asymptomatic ICAD is still largely unknown, especially in whites. In this setting, several transcranial Doppler studies in an asymptomatic population have been conducted in Asia. The prevalence of asymptomatic intracranial stenosis ranged from 5.9% to 24.5%. Age, hypertension, and diabetes mellitus emerged as the most relevant factors associated with asymptomatic ICAD, and interestingly the odds ratio for hypertension was higher than the one for diabetes mellitus in a Chinese study.

To clarify the prevalence and natural history of asymptomatic ICAD in whites, we designed a population-based study in the metropolitan area of Barcelona, the Barcelonès Nord and Maresme Asymptomatic Intracranial Atherosclerosis Study. The main aims of the Barcelonès Nord and Maresme Asymptomatic Intracranial Atherosclerosis Study are as follows: (1) to determine the prevalence of asymptomatic ICAD in a moderate-high vascular risk population; (2) to study its prognostic impact on the risk of experiencing future major ischemic events; and (3) to identify clinical, biological, and genetic predictors of the development, progression, and clinical expression of this condition. Study subjects were obtained from an initial sample of 1503 individuals randomly selected from a population of 600,000 inhabitants. Main entry criteria were age ≥50 years, no past history of cerebrovascular or ischemic heart disease, and moderate-to-high vascular risk. Presence and severity of intracranial stenoses were determined by means of transcranial color-coded Duplex and subsequent MR angiography confirmation. Preliminary results were presented at the 2009 International Stroke Conference, showing a prevalence of asymptomatic ICAD of 9% in the first 157 subjects studied. Recruitment took place from March 2007 until June 2010.

Symptomatic ICAD: New Predictors of Recurrence

Symptomatic ICAD is burdened with a high clinical recurrence rate. The annual recurrence rates for any ischemic stroke reported in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Trial were as high as 15% and 14% in the aspirin and warfarin arms, respectively. Moreover, most subsequent strokes in patients with symptomatic intracranial artery stenosis occurred in the same arterial territory, were nonlacunar, and nearly half of them were disabling. Therefore, it seems crucial to identify those prognostic factors that characterize high-risk patients to stratify preventive therapies. These prognostic factors could be classified in 2 main categories, local factors that confer vulnerability to the intracranial atherosclerotic plaque itself (vulnerable intracranial stenosis) and systemic factors and basic pathways that render the patient more prone to ICAD recurrence (vulnerable patient). Probably the latest contributions in this field, not collected in the referred book chapter, are the observation of racial differences in recurrence risk in the WASID cohort, with black patients having a higher risk than whites, and the
Table 2. Main Predictors of ICAD Recurrence

<table>
<thead>
<tr>
<th>Vulnerable Intracranial Stenosis</th>
<th>Vulnerable ICAD Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Severity of intracranial stenosis (&gt;70% lumen reduction)</td>
<td>● Diabetes mellitus associated with greater ICAD extent in whites</td>
</tr>
<tr>
<td>● Concomitant intracranial and extracranial stenosis</td>
<td>● Deficient vascular risk factor control</td>
</tr>
<tr>
<td>● Disease extent: No. of intracranial stenoses</td>
<td>● Metabolic syndrome and insulin resistance may have a greater effect on intracranial vs extracranial athero</td>
</tr>
<tr>
<td>● Symptomatic vs asymptomatic intracranial stenosis</td>
<td>● Sex: women (WASID)</td>
</tr>
<tr>
<td>● Intracranial stenosis causing hemodynamic compromise</td>
<td>● Race: black (WASID)</td>
</tr>
<tr>
<td>● Detection of microembolic signals</td>
<td>● Failure of antithrombotic therapy</td>
</tr>
<tr>
<td>● Composition of atherosclerotic plaque: inflammation, lipid core, neovascularization, intraplaque hemorrhage</td>
<td>● Inflammation: leukocyte count, C-reactive protein, adhesion molecules</td>
</tr>
<tr>
<td>● Endogenous fibrinolysis inhibitors: high plasminogen activator inhibitor 1</td>
<td>● Inhibited endogenous angiogenic response</td>
</tr>
<tr>
<td>● Genetic factors: C-reactive protein gene C1444T polymorphism</td>
<td></td>
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</tbody>
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description of an association between a common polymorphism in the C-reactive protein gene and a higher recurrence risk.19

Table 2 summarizes ICAD prognostic factors.

Symptomatic ICAD: Best Treatment
The optimal preventive therapy for symptomatic ICAD remains yet to be clarified. Although the WASID Trial was not designed to evaluate the importance of risk factor control in symptomatic ICAD, the results of some WASID substudies strongly suggest that this stroke subgroup may benefit from aggressive risk factor management.20 Contrary to what had been postulated classically, the lower the blood pressure values are kept during follow-up, the more reduced is the recurrence risk.21 Regarding lipid management, it remains controversial whether ICAD patients may benefit from intense low-density lipoprotein cholesterol reduction, as shown by the Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study, because the location of the symptomatic vessel was not assessed in the that study.22 Moreover, a recent study failed to show a beneficial effect of 20 mg of simvastatin daily on the evolution of asymptomatic middle cerebral artery stenosis over 2 years.23 Given this profound impact of risk factor control, the benefit of future therapies for this disease should be proven on top of optimal risk factor management.

Following the results of the WASID Trial, antiplatelets are the antithrombotic drug of choice for ICAD patients. Recent studies have shown that double antiplatelet therapy is more effective than single therapy in reducing microembolic signals caused by a symptomatic intracranial stenosis, but the clinical benefit of this association in terms of diminishing early recurrence risk remains to be proven.24 The trial of Cilostazol-Aspirin Therapy Against Recurrent Stroke With Intracranial Artery Stenosis is currently ongoing to test whether combined cilostazol-aspirin therapy is superior to aspirin alone in the prevention of recurrent stroke in symptomatic ICAD. Previously, the multicenter double-blind, placebo-controlled Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis showed that progression of symptomatic intracranial stenosis was significantly lower in the cilostazol-plus-aspirin group versus in the placebo-plus-aspirin group.25

Continuous progress in intracranial angioplasty and stenting has led to high rates of technical success. However, as has been reviewed extensively, adverse event rates vary widely, in-stent restenosis is common, and the impact of stent devices on long-term outcome has not been clarified.26 To address this critical issue, the Stenting Versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (www.clinicaltrials.gov) is currently ongoing.

In conclusion, ICAD is the most common cause of ischemic stroke worldwide, but its optimal treatment has not been established. ICAD has become a fascinating and rapidly evolving research field, with relevant advances in basic mechanisms, imaging, and treatment. These and other topics will be discussed at the Fifth International Conference on Intracranial Atherosclerosis, which will be held in Valladolid in autumn 2011.

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References
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