Approximately 8% to 10% of all ischemic strokes are caused by intracranial arterial stenosis (IAS). After a stroke or transient ischemic attack due to IAS, patients face a 12% annual risk of recurrent stroke on medical therapy, with most strokes occurring in the first year. Warfarin has been shown to be no better than aspirin in preventing recurrent strokes but poses a higher risk of serious bleeding and death. Groups with the highest risk of recurrent stroke are those with high-grade (>70%) stenosis, those with recent symptom onset, and women. Endovascular treatment of IAS is a rapidly evolving therapeutic option. Antiplatelet agents are currently recommended as the primary treatment for symptomatic IAS, with endovascular therapy reserved for appropriate high-risk cases refractory to medical therapy.

Introduction
Cerebral atherosclerosis is an important cause of cerebral ischemia, particularly in Asians, blacks, and Hispanics [1,2]. Intracranial arterial stenosis (IAS) is estimated to cause 8% to 10% of ischemic strokes in the United States, corresponding to approximately 40,000 events per year, with a risk of recurrent stroke as high as 15% per year [3–10]. Current therapeutic options include medical management with antithrombotic medications, risk factor modification, and endovascular treatment using percutaneous transluminal angioplasty (PTA) with or without stenting [4–8].

Natural History
A review of the natural history of intracranial atherosclerosis found that most of the available data were from relatively small retrospective case series employing divergent and often uncontrolled selection criteria and follow-up. These studies demonstrated 5% to 8% annual rates of recurrent stroke in IAS vascular territories, independent of their anatomic location [11]. This is higher than the stroke rate in the general population in a similar age range, which is estimated to be 0.39% per year for men and 0.18% per year for women [3]. More rigorous data on the natural history of medically treated IAS were provided by the prospective, controlled Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) trial (see following text) [12].

Surgery
Extracranial-intracranial (EC-IC) bypass surgery was introduced in the 1960s to treat extracranial and intracranial arterial occlusive disease [13]. The procedure was popular until the EC-IC Bypass Study results were published in 1985 [10]. Patients with a symptomatic extracranial carotid artery occlusion, intracranial internal carotid artery stenosis, or middle cerebral artery (MCA) stenosis were randomized to surgery (EC-IC bypass) combined with aspirin (1300 mg/d) or medical treatment alone (1300 mg/d of aspirin). The results demonstrated no overall benefit to surgery over medical management. Patients with a severe (>70%) intracranial internal carotid stenosis had the same rate of stroke with surgery (26 strokes in 72 patients [36%]) as with medical management (29 strokes in 77 patients [38%]). Patients with a severe (>70%) MCA stenosis fared worse with surgery (22 strokes in 50 patients, or 44%) than with medical therapy (14 strokes in 59 patients, or 24%). As a result of this trial, EC-IC bypass is rarely performed today to treat symptomatic IAS [14,15], although it is still under investigation for the treatment of complete extracranial carotid occlusion.

Medical Therapy
Antithrombotic therapy
There has been continuing controversy for more than 50 years over the optimal antithrombotic treatment for symptomatic IAS [16]. Anticoagulation was first suggested...
in 1955 [17], followed by retrospective studies indicating warfarin may be more effective than aspirin [8]. However, a randomized clinical trial showed that anticoagulation was no better than aspirin for secondary stroke prevention in patients with noncardioembolic stroke [18].

The most definitive data on the optimal antithrombotic therapy for symptomatic IAS currently available are from the WASID trial published in 2005 [12••]. WASID was a randomized, double-blinded clinical study funded by the National Institutes of Health performed at 59 North American medical centers from 1999 to 2003. WASID had two primary aims: 1) to evaluate the safety and efficacy of aspirin versus warfarin to treat symptomatic IAS; and 2) to identify patients with high risk of ischemic stroke in the IAS vascular territory while on medical therapy to target patients for a future trial comparing endovascular and medical management.

Inclusion criteria were a transient ischemic attack (TIA) or nondisabling stroke within 90 days of enrollment caused by a moderate to severe (50%–99%) atherosclerotic stenosis of a major intracranial artery (internal carotid, middle cerebral, vertebral, or basilar artery) documented by conventional cerebral angiography, a modified Rankin score of 3 or less, and age of 40 years or older. Patients were excluded for a nonatherosclerotic etiology of their IAS, a tandem moderate to severe (50%–99%) extracranial carotid artery stenosis, an unequivocal cardioembolic source, a contraindication to either aspirin or warfarin therapy, or a life expectancy of less than 5 years.

Enrolled subjects were randomized to treatment with aspirin (1300 mg/d) or warfarin (target International Normalized Ratio [INR] between 2 and 3). Patients were contacted monthly and examined every 4 months by a neurologist blinded to the therapeutic protocol. The primary endpoint for the first aim (comparison of the efficacy and safety of aspirin versus warfarin) was ischemic stroke (any vascular territory), intracranial hemorrhage, or vascular death not caused by ischemic stroke. The primary endpoint for the second aim (high-risk patients) was ischemic stroke in the vascular territory of the IAS.

The trial was terminated early because of safety concerns for the patients taking warfarin. A total of 569 patients (71% of the target) were enrolled. The two treatment groups demonstrated no significant differences in baseline characteristics, with a mean follow-up of 1.8 years. The group treated with warfarin had a significantly higher death rate (4.3% for the aspirin group vs 9.7% for those on warfarin; hazard ratio [HR] of 0.46; 95% CI, 0.23–0.90; P = 0.02). Subjects randomized to warfarin had higher rates of both vascular and nonvascular death, although only the nonvascular death rate was significantly greater (P = 0.05). In addition, the warfarin group had a significantly higher rate of major hemorrhage (3.2% for the aspirin group vs 8.3% for the warfarin group; HR of 0.39; 95% CI, 0.18–0.84; P = 0.01).

The primary endpoint (ischemic stroke in any vascular territory, intracranial hemorrhage, or vascular death not caused by ischemic stroke) for the first aim (comparison of the efficacy and safety of aspirin versus warfarin) was reached in 22% of the patients in both treatment groups (HR of 1.04; 95% CI, 0.73–1.48; P = 0.83). There were also no significant differences between treatment groups in the rates of several prespecified secondary endpoints: ischemic stroke in the territory of the symptomatic IAS (15% for aspirin vs 12% for warfarin; HR of 1.26; 95% CI, 0.81–1.97; P = 0.31); ischemic stroke in any vascular territory (20% for aspirin vs 17% for warfarin; HR of 1.23; 95% CI, 0.84–1.80; P = 0.29); and the combination of ischemic stroke, myocardial infarction, or vascular death not caused by ischemic stroke (24% for aspirin vs 25% for warfarin; HR of 0.98; 95% CI, 0.70–1.37; P = 0.90).

In the warfarin group, a post hoc analysis revealed that an INR less than 2.0 was associated with a significantly higher rate of ischemic stroke (P > 0.00001) whereas an INR greater than 3.0 was associated with a significantly higher rate of major hemorrhage (P > 0.00001). No subgroup was clearly identified that had a better outcome on warfarin versus aspirin [19].

The WASID trial demonstrates that although warfarin and aspirin have similar efficacy for the treatment of symptomatic atherosclerotic IASs, warfarin is associated with significantly higher rates of major hemorrhage and death. Therefore, aspirin is recommended rather than warfarin to treat symptomatic IAS.

The second aim of WASID was to identify patients at highest risk for stroke in the vascular territory of the symptomatic IAS [20••]. All of the patients were combined for this analysis because there was no significant difference between treatment groups. Ischemic stroke in any vascular territory accounted for most events in WASID and occurred in 106 of 569 patients (19%), most in the territory of the IAS (n = 77 [73%]). Sixty of the 77 strokes (78%) happened within the first year.

The 1-year risk of stroke in the symptomatic IAS territory was 19% for a stenosis of 70% or greater. The risk of stroke in the symptomatic IAS territory increased linearly (P for trend = 0.0026) with an increase in the severity of the IAS, but may have declined when the stenosis exceeded 90%. Age, ethnicity, location and length of the IAS, other vascular risk factors, co-morbidities, and antithrombotic drug treatment at the time of the qualifying event were not significantly associated with an increased risk of stroke in the IAS vascular territory.

Multivariate analysis showed the risk for stroke in the symptomatic IAS vascular territory was highest for a severe IAS (≥ 70%; HR of 2.03; 95% CI, 1.29–3.22; P = 0.00025) and for patients enrolled early (≤ 17 days) after the qualifying event (HR of 1.69; 95% CI, 1.06–2.72; P = 0.028). Women were also at increased risk (HR of 1.59; 95% CI, 1.0–2.55; P = 0.051). Although the type of qualifying event (stroke or TIA) was not significantly associated...