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## **Evidence Based Medicine**

### **What are the therapeutic options for strokes secondary to intracranial large artery stenosis?**

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#### **Warfarin-aspirin symptomatic intracranial disease trial-wasid and trial of cilostazol in symptomatic intracranial arterial stenosis-Toss**

#### **Why are these studies important and noteworthy?**

Atherosclerotic stenosis of the major intracranial arteries (intracranial internal carotid artery, middle cerebral artery, vertebral artery, basilar artery) is emerging as the most common cause of stroke worldwide. It causes 30% to 50% of strokes in Asians and 8% to 10% of strokes in North American Caucasians. Intracranial atherosclerosis preferentially affects Asians, Hispanics, Far East Asians and Blacks as compared to carotid bifurcation disease which affects whites more. The risk of recurrent stroke is also higher than for most other stroke subtypes and has been quoted as 15% per year.

Since intracranial atherosclerosis is the most frequent but the most under recognized cause of stroke in our population, it is important to evaluate the therapeutic options for secondary stroke prevention in this subgroup of patients.

Before WASID, there was an uncertainty regarding whether warfarin was superior to aspirin for secondary

prevention in intracranial disease. Prior studies had shown mixed results and there was a need for a randomized trial in this regard.

The other study TOSS was undertaken to assess whether cilostazol (which is a phosphodiesterase 3 inhibitor with both antiplatelet and vasodilating effects) can delay the progression of intracranial atherosclerosis and hence prevent recurrent events.

#### **Who were the participants?**

WASID was an investigator-initiated, randomized, double-blind, multicenter clinical trial conducted at 59 sites in North America. Patients were recruited if they had a TIA or a nondisabling stroke that occurred within 90 days before randomization and that was attributable to angiographically verified 50 to 99 percent stenosis of a major intracranial artery (carotid, middle cerebral, vertebral, or basilar). Patients were excluded if they had other causes for stroke like extracranial large artery disease or cardioembolic causes. They were also excluded if they had contraindication to Aspirin or Warfarin. Since the study was carried out in North America most of the patients were whites~58% with only about 30% who were blacks.

TOSS was also a multicenter, double blind placebo controlled trial carried out in 5 tertiary hospitals in South Korea. Patients with ischaemic strokes within 2 weeks from onset, and with symptomatic stenosis in the M1 segment of MCA or basilar artery were eligible for enrolment. They excluded patients with other potential causes of stroke and with anaemia and thrombocytopenia.

### What was the intervention?

In WASID the initially prescribed dose of warfarin (or its placebo) was 5 mg daily, and that of enteric-coated aspirin (or its placebo) was 650 mg twice daily. A total of 569 patients were randomized, 280 to Aspirin arm and 289 to Warfarin. Both groups were followed up for a period of approximately 1.9 years. All patients underwent blood testing for INR on a monthly basis and the dose of warfarin was then adjusted by an unblinded investigator. Patients were contacted monthly to determine whether outcome events had occurred and were examined after every four months. Imaging was done if an event was suspected.

In TOSS participants were randomly given either cilostazol 100 mg twice daily or matching placebo. All participants got Aspirin 100 mg daily. A total of 135 patients were randomized, 67 to cilostazol arm and 68 to placebo arm. They were followed at 1, 3, 5 and 6 months.

### What was the outcome?

In WASID, the primary end point (which was ischaemic stroke, brain haemorrhage or death from vascular causes) occurred in 22.1 percent of the patients in the aspirin group and 21.8 percent of those in the warfarin group (hazard ratio, 1.04; 95 percent confidence interval, 0.73 to 1.48;  $P=0.83$ ). There were no significant differences between the two groups in terms of the secondary endpoints either. Warfarin group had significantly more cardiac events compared to those getting aspirin (rate, 2.9 percent in the aspirin group vs. 7.3 percent in the warfarin group; hazard ratio, 0.40; 95 percent confidence interval, 0.18 to 0.91;  $P=0.02$ ). Also, major haemorrhages occurred significantly more often among patients assigned to warfarin (3.2 percent in the aspirin group vs. 8.3 percent in the warfarin group; hazard ratio, 0.39; 95 percent confidence interval, 0.18 to 0.84;  $P=0.01$ ).

In TOSS the primary outcome was the progression of symptomatic stenosis on MRA at 6 months. The extent of stenosis was graded and progression was defined as worsening of stenosis by 1 or more grades on final MRA. The progression

of stenosis assessed by TCD was used as a secondary outcome measure. During the follow up period no clinical events (strokes or TIAs) occurred. The progression on MRA was significantly less frequent in the cilostazol group than in the placebo group ( $p=.008$ ). TCD evaluations were also similar with less frequent progression in the cilostazol group.

### What were the conclusions?

Before WASID it was thought that certain high-risk patients such as those with severe stenosis, vertebrobasilar disease and those who have failed anticoagulation would benefit from warfarin. In WASID, however, patients with severe stenosis or those previously on antithrombotic therapy did not benefit from warfarin. Patients with basilar artery stenosis in WASID did appear to have a lower rate of the primary end point on warfarin, but there was no difference in the rate of stroke in the territory of the basilar artery between patients on aspirin versus warfarin and there was no clear evidence of a benefit of warfarin over aspirin for patients with vertebrobasilar stenosis.

TOSS concluded that cilostazol combined with aspirin may prevent the progression of intracranial atherosclerotic lesions although whether this translates into clinical effects cannot be judged from this trial.

### How does this impact our clinical practice?

Intracranial atherosclerosis is a greatly under-recognized cause of ischaemic stroke in our population. Currently available data does not prove a clear superiority of any one antithrombotic agent over the others. The three agents evaluated so far for this disease entity are aspirin, warfarin and cilostazol. Till more data becomes available, aspirin alone is sufficient for secondary stroke prevention in large artery atherosclerotic disease, although cilostazol shows promise. It is, therefore, important to recognize that other risk factors must be aggressively managed in these patients as they may have a greater effect on slowing the rate of progression of this disease.

### Recommended Reading

1. Kasner SE, Lynn MJ, Chimowitz MI, Frankel MR, Howlett-Smith H, Hertzberg VS, et al. Warfarin Aspirin Symptomatic Intracranial Disease (WASID) Trial Investigators. Warfarin vs aspirin for symptomatic intracranial stenosis: subgroup analyses from WASID. *Neurology* 2006; 67: 1275-8.
2. Kwon SU, Cho YJ, Koo JS, Bae HJ, Lee YS, Hong KS, et al. Cilostazol Prevents the Progression of the Symptomatic Intracranial Arterial Stenosis. The Multicenter Double-Blind Placebo-Controlled Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis. *Stroke* 2005; 36: 782-6.