Low-Molecular-Weight Heparin in Atherosclerotic Stroke
A Surprising Resurrection of Anticoagulants?

Oh Young Bang, MD, PhD; Jong S. Kim, MD, PhD

See related article, page 346.

Intracranial atherosclerosis (ICAS) is a major cause of stroke worldwide, especially in Asia. In patients with symptomatic ICAS, the risk of recurrent stroke is fairly high.1 Although stenting/angioplasty is occasionally performed, a recent randomized trial failed to find the benefit of stenting in patients with symptomatic ICAS.2 Moreover, trials using antiplatelets or anticoagulants have been rare, and results are confusing. Therefore, we still do not have well-proven, effective treatment strategies for ICAS.

A few retrospective nonrandomized studies have suggested that anticoagulation may be more effective than antiplatelets for secondary stroke prevention in patients with ICAS.3,4 However, Warfarin–Aspirin Symptomatic Intracranial Disease (WASID), a large randomized trial, demonstrated that warfarin was not more effective than aspirin and was associated with significantly higher bleeding risks in patients with ICAS.1 The Fraxiparin in Stroke Study for the treatment of ischemic stroke (FISS-tris) is another trial that compared nadroparin calcium, a form of low-molecular-weight heparin (LMWH), and aspirin in 353 Asian patients with symptomatic large artery occlusive disease, mostly ICAS (97%).5 Analysis at 6 months showed that the primary outcome (Bathel Index ≥85) was not significantly different between the LMWH (73%) and aspirin (69%) groups, whereas the secondary outcome (modified Rankin Scale score 0–1) analysis showed results favoring LMWH (LMWH group 54%, aspirin group 44%; OR, 1.55; 95% CI, 1.02–2.35). However, when a good outcome was defined as a modified Rankin Scale score of 0 to 2, this benefit was no longer significant. With these disappointing or confusing results, anticoagulation is currently rarely used in patients with noncardioembolic stroke.

In this issue of Stroke, Wang and colleagues presented the results of subgroup analyses of FISS-tris aiming at finding selected patients who would benefit from LMWH therapy.6 They found that LMWH improved outcomes in certain subgroups such as the elderly, antiplatelet nonusers, and patients with posterior circulation stroke. This benefit was not clearly documented in a WASID subgroup analysis,7 which may be attributed to differential anticoagulation administration timing. Although the median time for qualifying event to randomization was 17 days in WASID,1 anticoagulation was given within 48 hours in the FISS-tris trial.8 This result seems consistent with the previous notion that patients with basilar artery stenosis and those randomized early may fare better with warfarin than aspirin.7

Despite this encouraging result, many unresolved questions still remain. First of all, this is a subanalysis of a limited number of patients, and the sample size was not decided on the basis of subgroup analysis. Moreover, some important aspects of ICAS such as the degree of vascular stenosis were not considered, because heterogeneous vascular imaging techniques, including transcranial Doppler, were used in this study. Because severe stenosis is more closely associated with embolization than milder stenosis,8 LMWH may be more efficacious in patients with severe stenosis. The data of LMWH’s beneficial effect in the elderly and those with posterior circulation stroke may possibly be confounded if these variables are associated with severe stenosis.

Second, although thromboembolism due to rupture of an unstable plaque is the main mechanism of ischemic stroke, stroke mechanisms in ICAS are more diverse and include branch occlusion, in situ occlusion, and hemodynamic impairment. Future studies should examine the role of medications focusing on different stroke mechanisms in patients with ICAS.

Finally, both the WASID and FISS-tris compared antiplatelets with aspirin monotherapy, whereas recent pieces of evidence have suggested favorable effects of dual antiplatelet medications in the acute stage of stroke. Aspirin and clopidogrel combination was more effective than aspirin monotherapy in reducing microembolic signals detected by transcranial Doppler in patients with symptomatic carotid stenosis (Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis [CARESS])9 as well as those with predominantly ICAS (Clopidogrel plus Aspirin for Infarction Reduction in acute stroke or transient ischaemic attack patients with large artery stenosis and microembolic signals [CLAIR]).10 The results of the Fast Assessment of Stroke and Transient ischaemic attack to prevent Early Recurrence (FASTER) pilot trial showed some reduction in secondary strokes in patients treated with clopidogrel plus aspirin as compared with those receiving aspirin monotherapy, although the difference was not statistically significant.11 In addition,
aspirin plus cilostazol was found to be more effective than aspirin monotherapy in preventing early progression of symptomatic ICAS. Therefore, anticoagulants should compete with dual antiplatelets for the wider use in patients with ICAS.

Nevertheless, Wang and colleagues should be congratulated for identifying the effects of LMWH in a certain group of patients and also for not being frustrated by the failure of the FISS-tris. The “absence of evidence” of benefit may not be the same as “evidence of absence” of benefit. Although the result of FISS-tris subgroup analysis does not necessarily indicate a surprise resurrection of anticoagulants, this is a small but important step forward in our journey of a never-ending anticoagulation story. Considering the enormous burden of ICAS and the higher rate of recurrent stroke, continuous efforts, including the search for candidates for certain strategies, should be made in this particular subtype of stroke.

Disclosures

None.

References

Low-Molecular-Weight Heparin in Atherosclerotic Stroke: A Surprising Resurrection of Anticoagulants?
Oh Young Bang and Jong S. Kim

Stroke. 2012;43:293-294; originally published online November 10, 2011;
doi: 10.1161/STROKEAHA.111.638726

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/43/2/293