

CLINICAL UPDATE

ASA or low-molecular-weight heparin in the initial management of acute ischemic stroke complicating atrial fibrillation?

Berge E, Abdelnoor M, Nakstad PH, Sandset PM, on behalf of the Heparin in Acute Embolic Stroke Trial (HAEST) Study Group. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. *Lancet* 2000;355:1205-10.

Background: Atrial fibrillation (AF) is the most common cause of cerebral embolism and is responsible for up to 20% of all ischemic strokes.¹ Anticoagulation has been shown to achieve relative risk reductions in the order of 60%–70% in both primary and secondary prevention of stroke in patients with AF.² However, the optimal timing of anticoagulant therapy following AF-related ischemic stroke has remained controversial. Traditionally, clinicians considering early anticoagulation have weighed the likelihood of reducing the estimated 10%–20% risk of recurrent stroke within 14 days against the potential for hemorrhagic transformation of the index stroke.³

Question: Is low-molecular-weight heparin (LMWH) superior to ASA in preventing early recurrent ischemic stroke in patients with atrial fibrillation?

Design: In this multicentre, double-blind, double-dummy controlled trial, 449 patients admitted to hospital with acute ischemic stroke and atrial fibrillation were randomly assigned, within 30 hours of stroke onset, either to LMWH (dalteparin 100 IU/kg subcutaneously twice daily) plus placebo tablets once daily, or to ASA tablets 160 mg once daily plus subcutaneous placebo injections twice daily. Treatment was continued for 14 days (or until earlier discharge), whereupon treating physicians were encouraged to initiate, at their discretion, long-term oral anticoagulation therapy with warfarin.

The primary outcome event was recurrent ischemic stroke within the first 14 days. This was defined as a sudden and persistent clinical neurologic deficit occurring more than 48 hours after the

index stroke and accompanied by a loss of 3 or more points on the Scandinavian Stroke Scale (SSS) and no evidence of cerebral hemorrhage on CT scan. Secondary outcomes included cerebral hemorrhage within 14 days, progression of symptoms, death from any cause within 14 days and a combined end point incorporating all 3 of these outcomes. Neurologic outcome was assessed at 14 days using 4 stroke scales (the SSS, the modified Rankin Scale, the Barthel Index and the International Stroke Trial scale) and at 3 months using the International Stroke Trial scale. Outcomes were compared using intention-to-treat analysis, and treatment effects were expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

Results: Subjects had a median age of 80 years (range 44–98) and a median SSS score of 39 (range 22–49). There were more women in the ASA group than in the LMWH group (61% v. 50%). Treatment with LMWH or ASA was begun a median of 21 and 20 hours respectively from the onset of the index stroke. The 2 groups were comparable in the prevalence and severity of such risk factors and comorbid conditions as smoking, hypertension, serum cholesterol levels, coronary artery disease, heart failure, diabetes and premorbid stroke or transient ischemic attack.

The 14-day incidence of recurrent ischemic stroke did not differ significantly between the 2 groups (LMWH 8.5% and ASA 7.5%; OR 1.13, 95% CI 0.57–2.24). Adjustment for the sex imbalance between the groups did not alter the OR significantly (1.19, 95% CI 0.60–2.36). Of the secondary outcomes, only the combined end point (OR 1.60, 95% CI 1.01–2.54, $p = 0.048$) and the incidence of extracerebral hemorrhage (OR 3.40, 95% CI 1.09–10.61, $p = 0.028$) were significantly different, in each case occurring more frequently in the LMWH group. The number of deaths at 14 days did not differ significantly between the groups, nor did neurologic outcomes at 14 days and 3 months.

Commentary: This well-designed study showed no evidence that immediate anticoagulation with LMWH is beneficial over once-daily ASA in preventing early recurrent stroke or in improving neurologic outcomes in patients with AF-related acute ischemic stroke. The results are consistent with those from previous studies evaluating LMWH⁴ and unfractionated heparin⁵ in patients with other types of ischemic stroke. Although this trial was designed to detect a relative risk reduction of 67% in the 14-day incidence of recurrent ischemic stroke, the observed incidence of recurrent stroke in the ASA group (7.5%) was significantly less than the estimated incidence of 12% assumed in the authors' power calculation; hence, the possibility of a type II error (missing a true difference) remains.

Practice implications: Early anticoagulation treatment with LMWH appears to confer no benefit over 160 mg of ASA once daily in preventing early (within 14 days) recurrent acute ischemic stroke or in improving short-term neurologic outcomes in patients with atrial fibrillation, but it does increase the risk of hemorrhage. The optimal timing of initiation of oral anticoagulation therapy was not addressed in this trial and remains to be determined. — Donald Farquhar

The Clinical Update section is edited by Dr. Donald Farquhar, head of the Division of Internal Medicine, Queen's University, Kingston, Ont. The updates are written by members of the division.

References

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