

Low-Molecular-Weight Heparin versus Aspirin in Patients with Stroke and Atrial Fibrillation

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

Study Overview

Objective. To determine if acute stroke patients with atrial fibrillation (AF) benefit from low-molecular-weight heparin (LMWH) compared with aspirin.

Design. Randomized, double-blind, double-dummy clinical trial.

Setting and participants. 449 patients from 45 centers in Norway. All patients were older than 18 years, presented within 30 hours of onset of stroke symptoms, and had AF documented by electrocardiogram either on admission (89%) or within 24 months prior to admission (10%). Subjects were excluded if they had a clear indication for anticoagulation or antithrombotic therapy or if an initial computed tomography scan revealed intracranial bleeding. Other exclusionary criteria included prior treatment with anticoagulants; very severe stroke (Scandinavian Stroke Score [SSS] < 8), persistent severe hypertension (systolic > 200 mm Hg or diastolic > 110 mm Hg), previous severe mental or physical disability, or other serious disease; life expectancy less than 6 months; or pregnancy or breastfeeding.

Intervention. Patients received either 100 IU/kg of dalteparin subcutaneously twice daily or 160 mg of aspirin once daily. A placebo version of the nonassigned medication was also administered.

Main outcome measures. Recurrent ischemic stroke was the primary endpoint. Secondary endpoints included cerebral hemorrhage; progression of symptoms; death from any cause; combined frequency of recurrent ischemic stroke, symptom progression, and death; and a number of functional outcome measures (SSS, Barthel Index, modified Rankin Scale, and the International Stroke Trial Scale) measured at randomization and at 14 days. The researchers added symptomatic cerebral hemorrhage post hoc to the combined outcome measure. An intention-to-treat model was used for analysis.

Main results. The rate of recurrent ischemic stroke was not significantly different between LMWH patients (8.5%) and aspirin patients (7.5%). Extracerebral hemorrhage was the only prespecified outcome that differed significantly between the 2 groups (5.8% LMWH versus 1.8% aspirin). There was a significant difference ($P = 0.048$) in the modified combined frequency outcome that included symptomatic cerebral hemorrhage (24.6% LMWH versus 16.9% aspirin). Cerebral hemorrhage tended to be more severe in the LMWH group. The original combined frequency outcome showed a trend favoring aspirin (22.8% LMWH versus 16.0% aspirin [$P = 0.074$]).

Conclusion

LMWH offers no advantage over aspirin and may even be harmful for the treatment of acute ischemic stroke in a subgroup of patients with AF.

Commentary

LMWH has generally been shown to be equivalent or superior to unfractionated heparin in a variety of conditions. In this study, Berge et al investigated whether patients with ischemic stroke and AF might benefit from LMWH. They used a strong randomized design that included placebo versions of both study drugs. Appropriately, they did not incorporate a placebo-only arm, given the results of the International Stroke Trial (IST) [1] and Chinese Acute Stroke Trial [2], which demonstrated a small but significant benefit from administering aspirin within 48 hours of hospital admission for acute stroke. In particular, the IST showed small but significant decreases in recurrent stroke that favored unfractionated heparin versus placebo; however, this benefit was offset by an increase in intracerebral hemorrhages.

The Berge et al study was mid-sized and thus may have been underpowered to detect very small yet clinically significant benefits of either therapy. However, given the large studies cited above and others, it seems unlikely that larger numbers or modifications in the protocol would have shown a benefit of LMWH without a concomitant increase in seri-

ous bleeding events. The larger problem with the numbers relates to the generalizability of this study. Of 7570 patients screened, 27% had AF. This number is somewhat higher than might have been expected [3]. However, only 21% of patients with AF—6% of the total patients screened—were enrolled. The authors did not provide data on race or socioeconomic status, but it can be presumed that the vast majority of subjects were white. Otherwise, the subjects were probably similar to the “average” stroke patient: 40% had hypertension, 35% had coronary artery disease, 24% had heart failure, 15% had diabetes mellitus, and 24% had a previous stroke or transient ischemic attack.

Applications for Clinical Practice

This study adds to the growing literature denying a benefit of any heparin product in acute ischemic stroke, especially compared with aspirin. Although its benefit is small, aspirin does not seem to lead to an excess of cerebral hemorrhages. Furthermore, aspirin is inexpensive, easy to administer, and

has proven long-term benefits for secondary prevention of vascular disease. The current evidence strongly suggests that heparin products should not be used for acute ischemic stroke. Their use for comorbid conditions or to prevent venous thromboembolism in carefully selected patients may be considered.

References

1. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19,435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. *Lancet* 1997;349:1569–81.
2. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. *Lancet* 1997;349:1641–9.
3. Sandercock P, Bamford J, Dennis M, Burn J, Slattery J, Jones L, et al. Atrial fibrillation and stroke: prevalence in different types of stroke and influence on early and long term prognosis. *BMJ* 1992;305:1460–5.

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