

Aspirin improved outcome of acute stroke at 6 months but heparin did not

International Stroke Trial Collaborative Group. **The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke.** *Lancet.* 1997 May 31;349:1569-81.

Objective

To determine the benefits and risks of subcutaneous heparin and aspirin in patients with acute stroke.

Design

Randomized controlled trial with 6-month follow-up.

Setting

467 hospitals in 36 countries.

Patients

19 435 patients (54% men) who had had an acute stroke in the past 48 hours with no intracranial hemorrhage and no indications or contraindications for heparin or aspirin. Exclusion criteria were small likelihood of benefit or high risk for adverse effects.

Intervention

Patients were allocated to subcutaneous unfractionated heparin, 5000 IU twice daily ($n = 4861$) and 12 500 IU twice daily ($n = 4856$) or to avoid heparin ($n = 9718$); they were also allocated to aspirin, 300 mg daily ($n = 9720$), or to avoid aspirin ($n = 9715$).

Commentary

Randomized trials in acute stroke have been too small to detect modest intervention effects. The International Stroke Trial (IST) reported here and the Chinese Acute Stroke Trial (CAST) (1) are the first 2 megatrials of acute stroke. The absolute net risk reduction (allowing for a small increase in hemorrhagic strokes) in both trials was 13 patients who were dead or dependent at final follow-up per 1000 treated with aspirin. This effect is so modest that it barely reached statistical significance in the IST despite the size of the trial. Together, the results of the IST and CAST give definite support for immediate administration of low-dose aspirin in the routine management of patients

Main outcome measures

Death from any cause within 14 days and death or dependency at 6 months.

Main results

Patients who received heparin or aspirin did not have fewer deaths within 14 days than did patients who avoided heparin or aspirin ($P = 0.47$ and $P = 0.35$, respectively)* (Table). Death or dependency at 6 months was not reduced in patients who received heparin ($P = 0.97$)* or aspirin ($P = 0.07$)* (Table). After adjustment for baseline stroke severity, 14 fewer patients who received aspirin had died or were dependent per 1000 ($P = 0.03$).

Conclusions

In patients with recent acute stroke, heparin or aspirin did not reduce death within 14 days and heparin did not reduce death or dependency within 6 months. Aspirin reduced death or dependency at 6 months after adjustment for baseline stroke severity.

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For article reprint: Dr. P.A. Sandercock, Department of Clinical Neurosciences, Western General Hospital, Edinburgh EH4 2XU, Scotland, UK. FAX 44-131-332-5150.

* P values calculated from data in article.

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Heparin vs no heparin and aspirin vs no aspirin†

Outcomes	Heparin EER	No heparin CER	RRR (95% CI)	ARR EER - CER (CI)	NNT
Death at 14 d	9.0%	9.3%	3.2% (-5.8 to 11.4)	0.3% (-0.5 to 1.1)	NS
Death or dependency at 6 mo	62.9%	62.9%	0.05% (-2.2 to 2.1)	0.03% (-1.4 to 1.3)	NS

Outcomes	Aspirin	No aspirin	RRR	ARR	NNT
Death at 14 d	9.0%	9.4%	4.1% (-4.8 to 12.2)	0.4% (-0.43 to 1.2)	NS
Death or dependency at 6 mo	62.2%	63.5%	2.0% (-0.2 to 4.1)	1.3% (-0.1 to 2.6)	NS

†NS = not significant. Other abbreviations defined in Glossary; RRR, ARR, NNT, and CI calculated from data in article.

with acute stroke, provided that intracranial hemorrhage has been ruled out. The benefits are, however, not great.

A recent Cochrane review of 15 small trials (a total of 1599 randomized patients) of anticoagulants in acute ischemic stroke showed a significant (43%) reduction in death or dependency at follow-up in patients who received heparin and heparinoids in the acute phase (2). It is disappointing, then, that no beneficial effects of subcutaneous heparin were observed in the IST. In many countries, early administration of heparin has been a routine practice in patients who have a cardiac source of embolism, vertebrobasilar stroke, or progressing stroke. However, in

IST subgroups in which a reduction of recurrent ischemic strokes was shown, the reduction was outweighed by an increase in hemorrhagic strokes. Overall, the IST results strongly discourage the routine use of heparin in all forms of ischemic stroke.

Kjell Asplund, MD, PhD
Umeå University
Umeå, Sweden

References

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2. Counsell C, Sandercock P. In the Cochrane Collaboration; Issue 1. Oxford: Update Software; 1997.