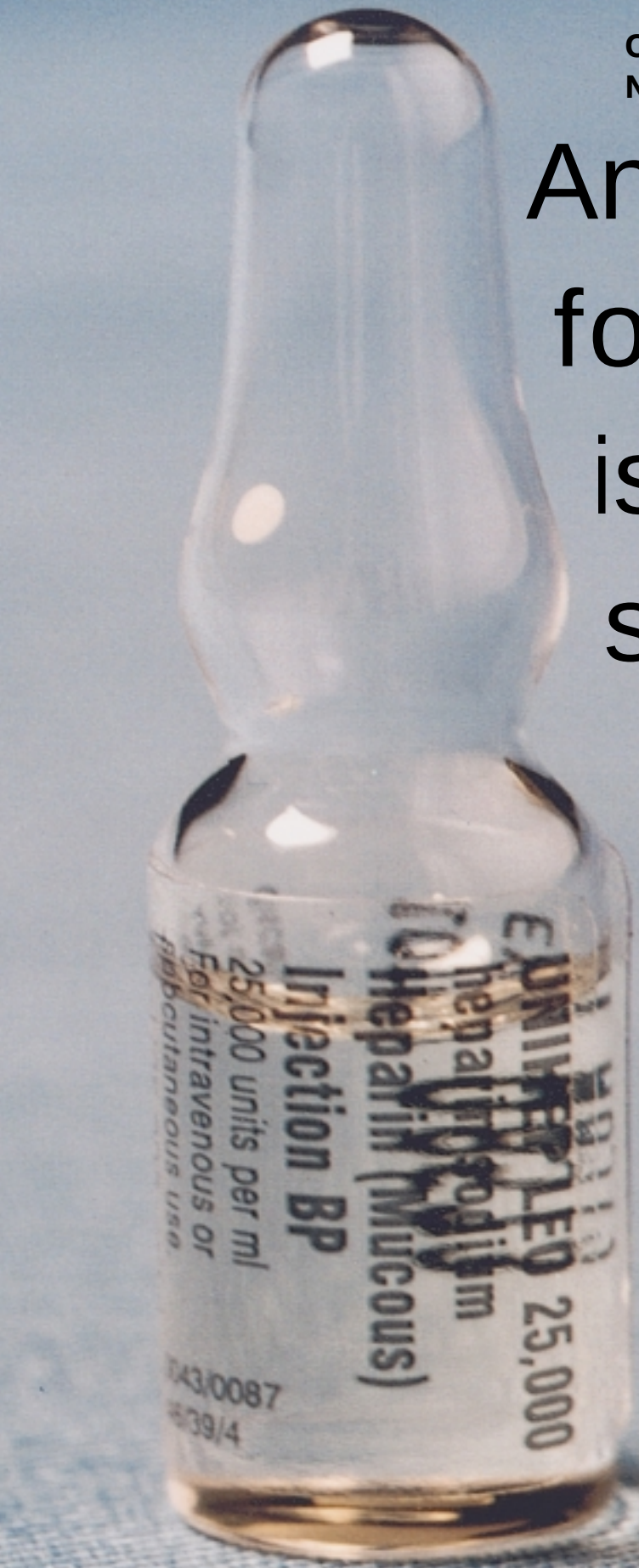

CONTEMPORARY NEUROLOGICAL DILEMMAS

Anticoagulation for acute ischaemic stroke?

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INTRODUCTION

Six years ago, in December 1955, there appeared in the *New England Journal of Medicine* an article that revolutionized the way we think of stroke. I am referring, of course, to the NINDS paper 'Tissue plasminogen activator for acute ischemic stroke' (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995), which singularly made the FDA recognize rt-PA as still the only approved treatment for stroke. Trailing behind that landmark paper was our paper from Hong Kong, 'Low-molecular-weight heparin for the treatment of acute ischemic stroke' (Kay *et al*. 1995), which showed that an anticoagulant, nadroparin, if given subcutaneously within 48 h of stroke onset could also reduce death or disability.

This paper temporarily raised the hope that there might be another treatment for stroke than thrombolysis within three hours. But as more anticoagulant trials were completed and published, that hope has evaporated. In this article, I shall revisit some of the milestones in the history of anticoagulation for stroke, review the controversies that recent trials have generated, and finally offer some thoughts on the use of anticoagulants in daily practice.

HISTORICAL PERSPECTIVE

For over 60 years, heparin has been used as a treatment for stroke. The original reason for its use was probably a matter of logic: stroke was due to 'cerebral thrombosis' and heparin was an antithrombotic drug. Doubts on its true efficacy evidently emerged in the 1950s, for clinical trials were then conducted on both sides of the Atlantic. These pre-CT era trials, which would be regarded as flawed by present-day standards, suggested that heparin might have a beneficial effect. Thus intravenous heparin became, at least in some influential quarters, the preferred treatment for acute ischaemic stroke.

Following the advent of the CT scan, in the 1970s, there were two widely quoted randomized controlled trials (RCTs) on the use of intravenous heparin for the 'immediate' treatment of stroke. Appropriately, these two trials tested the two most common conditions for which heparin was given, namely cardioembolic stroke and progressing stroke. The first trial, performed by the Cerebral Embolism Study Group (CESG) (Cerebral Embolism Study Group 1983), found that none of 24 heparinized patients and two of 21 untreated patients had an early recurrence. In addition, none of the heparinized patients and two of the untreated patients had haemorrhagic transformation of the infarct (HTI). These alarming results led to the early termination of the CESG study and to the establishment of a practice that remained largely unchallenged until recently. This practice recommended that for acute cardioembolic stroke, heparin followed by warfarin should be given to nonhypertensive patients with small to moderate strokes, provided that 48 h have passed since the onset of stroke and a CT scan performed before treatment has ruled out any HTI. Patients with large infarcts or uncontrolled hypertension were specifically excluded. The second trial, performed by Duke *et al*. (Duke *et al*. 1986) addressed the issue of stroke progression in 'acute partial stable stroke'. Despite having achieved its target sample size with 225 patients, this trial did not answer the question of whether intravenous heparin was beneficial to patients with progressing stroke, because those who were actually progressing or had atrial fibrillation had been specifically excluded (such was the conviction that heparin was needed in those circumstances). Nevertheless, 19.5% of placebo-treated patients did progress further, as compared with 17.0% of the heparin-treated patients. The absolute reduction of 2.5% was not significant (P = 0.62, 95% CI – 8.7% to 13.7%). By the end of that decade, again there were calls on both sides of the Atlantic for trials of anticoagulation for ischaemic stroke.

THE IST AND TOAST

Both launched in the early 1990s, these two trials followed very different designs. The International Stroke Trial (IST) (International Stroke Trial Collaboration Group 1997) was clearly inspired by the 'mega-trials' for myocardial infarction that were prevailing in Oxford, UK. Because of the large sample size needed, IST had to sacrifice quality for quantity. Pre-randomization CT scan was not required, treatment was given without blinding, and outcome measures like recurrence and independence were left to the trialist and patient, respectively, to define. In contrast, the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) (TOAST Investigators 1998), sponsored by the US National Institutes of Health, demanded fewer patients but a much more elaborate system of case ascertainment and treatment blinding.

The results of IST and TOAST (Table 1), published, respectively, in 1997 and 1998, and the Cochrane Systematic Review that followed (Gubitz *et al*. 2001), arguably rang the 'death knell' for heparin in acute stroke. Respectively for size and rigour, these two trials have won the approval of stroke physicians worldwide, as attested by the unanimous decisions of guideline writers in Europe (Hacke *et al*. 2000), Asia-Pacific (Organizing Committee 1998), and the United States (Albers *et al*. 2001) to exclude the

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	IST	FISS	FISS BIS	TOAST	HAEST	TAIST
Patients randomized	19435	308	767	1281	449	1486
Time window	48 h	48 h	24 h	24 h	30 h	48 h
Mean time to treatment	19 h	27 h	14 h	16 h	20 h	25 h
Main outcome measure	death or dependency	death or dependency	death or Barthel < 85	favourable outcome *	recurrent stroke at 14 days	death or dependency
Interim follow-up	none	3 m	3 m	7 d	14 d	3 m
High-dose group (%)	_	53	65	59	8.5	62
Low-dose group (%)	_	60	62	_	_	62
Control group (%)	_	64	61	54	7.5	57
	P-value	_	0.12	0.41	0.07	NS NS
Final follow-up	6 m	6 m	6 m	3 m	3 m **	6 m
High-dose group (%)	63	45	59	75	66	58
Low-dose group (%)	63	52	57	_	_	58
Control group (%)	63	65	57	74	65	57
	P-value	NS	0.005	0.62	0.49	NS NS
Main safety measure	any death	any HTI	symptomatic ICH	serious ICH	Symptomatic ICH	symptomatic ICH
Measured at	14 d	10 d	6 m	10 d	14 d	10 d
High-dose group (%)	9.3	6.2	6.1	2.4	2.7	1.4
Low-dose group (%)	8.7	8.6	3.7	_	_	0.6
Control group (%)	9.3	12.0	2.8	0.8	1.8	0.2
	P-value	NS	0.19	NS	0.05	NS < 0.05

*Combination of Glasgow Outcome Scale of I or II and Modified Barthel Index of 12 or greater.
** As a secondary outcome, death or dependency at 3 months.
HTI, haemorrhagic transformation of the infarct; ICH, intracranial haemorrhage; NS, not significant.

Table 1 Trials of anticoagulants for the acute treatment of ischaemic stroke

routine use of heparin (including low-molecular-weight heparin and heparinoid) from the acute management of stroke.

LOW-MOLECULAR-WEIGHT HEPARINS

Low-molecular-weight heparins are fractionated heparin with the pharmacokinetic advantages of rapid absorption, good bioavailability, and long half-life. In clinical trials of venous thrombosis and unstable angina, they have been shown to be superior to unfractionated heparin. To date, four major RCTs of acute stroke treatment involving a low-molecular-weight heparin have been completed: FISS (Kay *et al*. 1995) and FISS bis (Hommel 1998), which tested nadroparin vs. placebo, HAEST (Berge *et al*. 2000), testing dalteparin vs. aspirin, and TAIST (Bath *et al*. 2001), testing tinzaparin vs. aspirin (Table 1). With the exception of FISS, all failed to show that low-molecular-weight heparin had any superiority over placebo or aspirin, other than a reduction in deep venous thrombosis or pulmonary embolism.

RECURRENT STROKE AND HAEMORRHAGIC TRANSFORMATION

One of the key arguments against anticoagulants is that they cause as many haemorrhagic strokes as the number of recurrent strokes they prevent. The Cochrane review found that 'Although anticoagulant therapy was associated with about 9 fewer recurrent ischaemic strokes per 1000 patients treated, it was also associated with a similar sized 9 per 1000 increase in symptomatic intracranial haemorrhages' (Gubitz *et al*. 2001). Prevention of early recurrence used to be the major rationale for using heparin acutely, for it was felt that without treatment it could be as high as 1% per day during the first 2 weeks, especially after a cardioembolic stroke. However, successive reports from the late 1980s suggested that the true recurrence rate was no higher than 4% in the first 30 days, although the proportion of patients anticoagulated in those observational studies was unknown (Kay 2000). What the anticoagulant trials (excluding the unfinished CESG) have shown is that the early recurrence rate after cardioem-

bolic stroke was 1.6–6.3% among placebo-treated patients, and 0.0–3.7% among anticoagulated patients. Regarding haemorrhagic transformations, with CT scanning asymptomatic ones are commonly seen regardless of coagulation status. Symptomatic HTIs were found in 3.6% of 417 anticoagulated patients in six observational studies published between 1986 and 1995 (Kay 2000). In the anticoagulant trials, symptomatic HTI occurred in 0.0–2.8% of placebo-treated patients, and in 0.0–6.1% of anticoagulated patients. Thus, despite the considerable variability in the way ischaemic recurrences and haemorrhagic transformations were defined and identified, clearly there was a reduction of the former and an increase of the latter with the administration of anticoagulants. However, the balance between the two is not constant and is affected by the dose of anticoagulants and by the underlying pathology of the stroke. In the IST, the number of recurrent ischaemic strokes per haemorrhagic stroke was 1.8 for the 12500 IU twice-daily heparin group, 3.7 for the 5000 IU twice-daily heparin group, and 9.5 for the no heparin group. Among the subgroup of patients with atrial fibrillation, this number went from 1.3 to 12.3 between heparinized and nonheparinized patients. Before using these figures to decide whether heparin does any good or not, it should be remembered that ischaemic recurrence (often underestimated) and haemorrhagic transformation (often overestimated) are really surrogate markers, and may have little bearing on the eventual outcome in terms of death and disability.

Paradoxically, heparin, which is normally given intravenously in adjusted doses, was given subcutaneously in fixed doses in IST; and danaparoid (a heparinoid), which is normally given subcutaneously in fixed doses, was given intravenously in adjusted doses in TOAST. These unconventional ways of administration may have contributed to the final lack of success for both trials. In IST, the excess of symptomatic HTI came mostly from the 12500 IU twice-daily heparin group. As absorption of subcutaneous heparin is known to be quite unpredictable, in many patients this might have resulted in insufficient drug entering the circulation whilst for the few with side-effects the drug levels could have been very high (Cohen 1997). In TOAST, danaparoid was given as an infusion after an initial bolus dose. Patients who weighed less than 125 lb were found to have higher anti-factor Xa activities and more bleeding events, suggesting that this method of administration had caused some overshooting.

Thus, if anticoagulants are to be used acutely for stroke, the following caveats may be pertinent:

- large doses of heparin, even if given subcutaneously, should be avoided;
- low-molecular-weight heparins and heparinoids are not safer alternatives, and need not be given intravenously;
- because of the danger of overshooting, bolus doses of either heparin or its low-molecular-weight counterparts should be avoided

Because intravenous heparin therapy requires a bolus to saturate the plasma protein binding sites, this leaves subcutaneous low-molecular-weight heparin as the only safe method of rapid anticoagulation.

POSSIBLE INDICATIONS FOR GIVING ANTICOAGULANTS ACUTELY AFTER ISCHAEMIC STROKE (TABLE 2)

Cardioembolism

While it is generally accepted that anticoagulants should not be given routinely for acute ischaemic stroke, many physicians believe that cardioembolic stroke should be treated differently. Such deviation is not supported by current evidence. In the HAEST study, which enrolled only patients with atrial fibrillation, the frequency of recurrent ischaemic stroke was actually higher in the dalteparin-treated than aspirin-treated patients (8.5% vs. 7.5%, NS). In the subgroup of IST patients with atrial fibrillation, 2.8% vs. 4.9% ($2P < 0.01$) of heparinized vs. nonheparinized patients had a recurrence, but the risk of haemorrhagic stroke among the heparinized patients was correspondingly higher. However, in neither of these studies were other causes of cardioembolism considered, and it would be reasonable to contemplate anticoagulation if, for example, an intracardiac thrombus or an aortic plaque with thrombus is found on echocardiography.

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Cardiac source of emboli*	valvular heart disease artificial valves after recent myocardial infarction atrial fibrillation with or without spontaneous echo contrast
Arterial disease*	aortic plaques arterial dissection extracranial stenosis or occlusion intracranial stenosis or occlusion
Progressing stroke	
Hypercoagulable states	
Intracranial venous thrombosis	

* Especially in the presence of mural or intraluminal thrombi.

Table 2 Possible indications for giving anticoagulants acutely after ischaemic stroke

Large artery atherosclerosis

Although not as well known as cardioembolism, recurrence following large-artery atherothrombosis is well documented. In the Rochester Epidemiology Project (Petty *et al.* 2000), 18.5% of large-artery infarctions had a recurrence within 30 days, significantly more than the 5.3% following cardioembolic infarctions. Subgroup analysis of the TOAST results showed that among patients with large-artery atherosclerosis, those who received danaparoid had significantly better outcomes at three months than those who received placebo (OR = 1.77; 95% CI 1.04–3.03). For stroke patients with significant internal carotid artery stenosis, therefore, some authorities are suggesting early anticoagulation (Hacke *et al.* 2000). This bears on the question why FISS was positive, was it the 'play of chance' or could it be related to the fact that nearly half of Chinese ischaemic stroke patients have intracranial large-artery occlusive disease (Wong *et al.* 2000)? One putative mechanism is that anticoagulants help to clear away emboli from the stenotic segment which are otherwise lodged in the internal border zones (Fig. 1).

Progressing stroke

Since the study by Duke *et al.* (1986) there has been no further RCT attempting to address this ill-defined multifactorial condition. Open studies, however, showed that even with the use of intravenous heparin, 21–50% of patients continue to deteriorate (Kay 2000). The rates of serious HTI (under 3%) given in these observational studies were no higher than expected. Of interest is a recent Swedish study which showed that although patients who progressed stayed longer in the stroke unit, their mortality was similar to that of stable patients (Rödén-Jüllig & Britton 2000). Thus, there seems to be no particular reason to anticoagulate patients for progressing stroke unless they have cardiac or large-artery disease (see above).

THE DILEMMA IN PRACTICE

Discussions in the literature inevitably lead to the larger subject of evidence-based medicine. Amidst the debates on 'heparin', we are reminded that a properly designed RCT of adjusted-dose intravenous heparin has yet to be performed (a European trial is underway). Recommendations for using anticoagulants, such as those listed in Table 2, are at best based on 'level 4' evidence. Physicians who give heparin or similar compounds are following 'hope over experience' (Hachinski 1999). Finally we should all be doing clinical trials if we use heparin or give aspirin if we don't.

What is the reality? Since we published our FISS paper, there have been palpable improvements: radiographers are glad to do CT scans and patients are happy that 'something is being done'. Of course, neither is a good reason for us to continue using low-molecular-weight heparin but for the fact that FISS was positive, at least in Hong Kong. To test the hypothesis that the positivity of FISS came from patients with intracranial large-artery stenosis, we have recently obtained support from our Hospital Authority to conduct a 'FISS tris' trial in which enrolled patients will all have transcranial Doppler evaluation of the intracranial arteries. Selected patients will also have magnetic resonance angiography. Unfortunately, we could not persuade the drug company to provide us with the placebo.

What if you don't live in Hong Kong, Singapore, or the part of Europe that is investigating unfractionated heparin, where you can participate in anticoagulant trials? What justification have you got if you want to use anticoagulants for your acute stroke patient? I suggest there are two. The first one is that you are not doing this indiscriminately. Before and during anticoagulation, you will have investigated and monitored your patient thoroughly. In so doing, the extra care and attention you give him or her should more than enough compensate for any risk your treat-

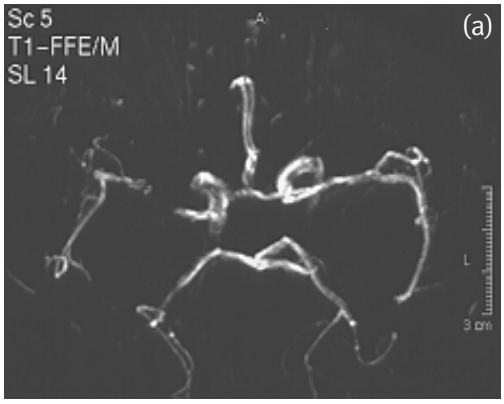
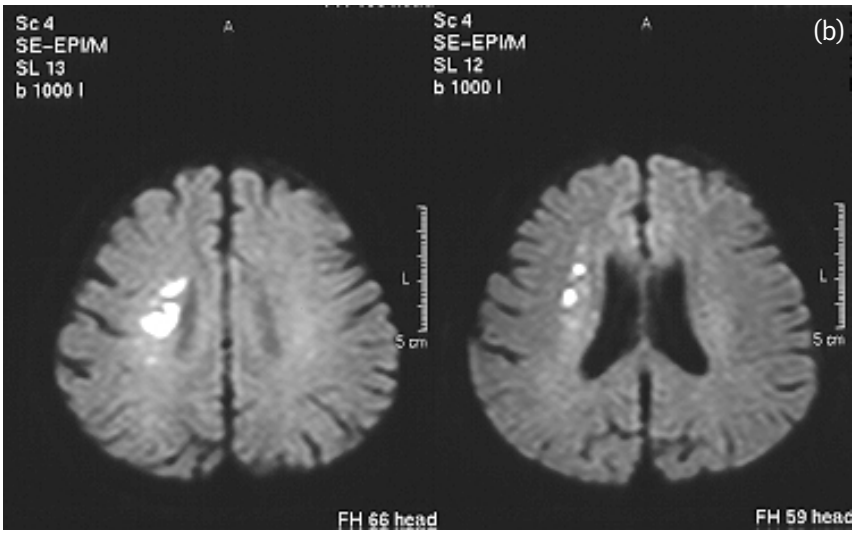


Fig. 1 Embolism from the intracrannial arterial stenosis: a 73-year-old man presented with mild left hemiparesis. Transcrannial Doppler examination of his right middle cerebral artery showed increased velocity with presence of microembolic signals. (a) MR angiography showed severe stenosis of the proximal right middle artery. (b) Diffusion-weighted MR showed multiple acute infarcts along the right internal border zone region.



ment conferred. Secondly, think of Dr Caplan's patient X, who has 'individual characteristics that might differ in many ways from patients studied in published trials' (Caplan 1999). Dr Caplan's eclectic approach to the treatment of individual patients stands in apparent conflict with evidence-based reductionism, but isn't that the sort of hope *and* experience with which we jobbing neurologists practise much of the time anyway?

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