Further evidence that antithrombotic therapy is beneficial with streptokinase: improved early ST resolution and late patency with enoxaparin

See doi:10.1053/euhj.2001.3083 for the article to which this Editorial refers

This issue of the Journal features a report from the Acute Myocardial Infarction–Streptokinase (AMI–SK) study[1], in which 496 patients were treated with streptokinase and randomized to receive either the low-molecular-weight heparin, enoxaparin, or a placebo for 3–8 days. Those who received enoxaparin were more likely to have ST-segment resolution at 180 min and a patent infarct-related artery at 8 days. Enoxaparin also reduced the combined incidence of death/myocardial infarction/recurrent angina at 30 days. Severe bleeding was more common in patients treated with enoxaparin (1.6% vs 0.8%) but there was no increase in intracranial haemorrhage (0% vs 0.4%). This is an important study because low-molecular-weight heparin has not previously been shown to improve the rates of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow[2,3] or of ST resolution, which is thought to relate to myocyte reperfusion[4]. However, the AMI–SK study is a small one, and so the effects of low-molecular-weight heparins on clinical end-points will need to be tested in a larger clinical trial.

A number of small trials have evaluated the use of enoxaparin in combination with fibrinolytic therapy. In the Heparin and Aspirin Reperfusion Therapy (HART)-II trial[5], 400 patients were given alteplase and randomized to receive either enoxaparin (30 mg intravenously and 1 mg . kg$^{-1}$ subcutaneously every 12 h) or unfractionated heparin for at least 3 days. The primary efficacy endpoint was TIMI-2 or -3 flow at 90 min, which was achieved in 80% of the enoxaparin group vs 75% of the unfractionated heparin group ($P=ns$). At 5–7 days there was a trend towards a lower reocclusion rate in the enoxaparin group (3.1% vs 9.1%, $P=0.12$). The rates of severe bleeding were similar in both groups, and intracranial haemorrhage occurred in 1% of both groups.

Two recent trials compared enoxaparin with unfractionated heparin in patients treated with tenecteplase, and both reported reductions in ischaemic events. In the Enoxaparin and TNK-tPA With or Without GP IIb/IIIa Inhibitor as Reperfusion Strategy in ST Elevation MI (ENTIRE-TIMI-23) trial[6] of 483 patients, enoxaparin had no effect on the incidence of TIMI-3 flow (51% vs 50% with unfractionated heparin), but did reduce the combined incidence of death/myocardial infarction.

References

from 15-9% to 4-4% (P=0.05) at 30 days. The intracranial haemorrhage rate was similar in both groups (0.6% with enoxaparin vs 0.0% with unfractionated heparin), but major bleeding was less common with enoxaparin (1.9% vs 2.4%, P=0.05).

The Assessment of the Safety and Efficacy of a New Thrombolytic Agent (ASSENT)-3 trial[5] was a moderately-sized hypothesis-generating trial, which randomized 6095 patients to receive either full-dose tenecteplase plus weight-adjusted unfractionated heparin, full-dose tenecteplase plus enoxaparin, or half-dose tenecteplase plus abciximab and weight-adjusted low-dose unfractionated heparin. Unfractionated heparin was given for 48 h, while enoxaparin was given for up to 7 days. At 30 days the combined incidence of death/in-hospital investigator-reported reinfarction/in-hospital refractory ischaemia was significantly lower in the enoxaparin group than in the unfractionated heparin group (11.4% vs 15.4%, relative risk 0.74, 95% confidence interval 0.63–0.87, P<0.01), and the in-hospital reinfarction rate was reduced from 4.2% to 2.7% (P<0.01). Intracranial haemorrhage occurred in 0.88% of the enoxaparin group vs 0.93% of the unfractionated heparin group. Although there was no significant difference in the rate of severe bleeding (3.0% with enoxaparin vs 2.2% with unfractionated heparin, P<0.01), there were significantly more transfusions in the enoxaparin group (3.4% vs 2.3%, P=0.03). In patients over 75 years of age, the intracranial haemorrhage rates were 1.5% in the enoxaparin group vs 1.0% in the unfractionated heparin group (P=ns).

Two randomized placebo-controlled trials have compared the low-molecular-weight heparin, dalteparin with a placebo as adjunctive therapy with streptokinase. In the Fragmin in Acute Myocardial Infarction (FRAMI) study[6] of 776 patients, subcutaneous dalteparin (150 IU kg⁻¹ twice daily during hospitalization) reduced the incidence of left ventricular thrombus or embolism from 21.9% to 14.2% (P=0.03) at 9 days. In the Biochemical Markers in Acute Coronary Syndromes (BIOMACS)-II study[7] of 101 patients, 68% of those given subcutaneous dalteparin (100 IU kg⁻¹ for the first dose and 120 IU kg⁻¹ at 12 h) had TIMI-3 flow at 20–28 h compared with 51% of those given a placebo (P=0.10). Recurrent ischaemic episodes (recorded by continuous electrocardiographic monitoring) were significantly less common in the dalteparin group (16% vs 38%, P=0.037). There were no differences in major bleeding or clinical events.

In the ASSENT-Plus trial, 439 patients were given alteplase and randomized to receive either subcutaneous dalteparin (120 IU kg⁻¹ every 12 h for 4–7 days) or an intravenous infusion of unfractionated heparin for 48 h[8]. Similar proportions of the dalteparin and unfractionated heparin groups had TIMI-3 flow at 4–7 days (69.3% vs 62.5%, P=0.16), but patients in the dalteparin group were less likely to have TIMI-0 or -1 flow (13.4% vs 24.4%, P=0.003). Although there were fewer reinfarctions within 7 days in the dalteparin group (1.4% vs 5.4%, P=0.01), there was no difference in the reinfarction rates at 30 days (6.5% vs 7.0% respectively, P=ns). Intracranial haemorrhage occurred in 0.9% of the dalteparin group vs 1.9% of the unfractionated heparin group (P=0.43), and major bleeding occurred in 7.2% vs 9.5% respectively (P=0.37).

An increase in the incidence of myocardial infarction after the cessation of dalteparin treatment was observed in the BIOMACS-II study of dalteparin with streptokinase[7], the ASSENT-Plus trial of dalteparin with alteplase[9], and the Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease (FRISC II) study of dalteparin in patients with non-ST-elevation acute coronary syndromes[9]. It is interesting to note that rebound ischaemia has not been observed to the same extent in trials of enoxaparin. Although preliminary data from the ASSENT-3 trial[5] indicated that there was a reactivation of thrombotic events following the cessation of enoxaparin, the AMI–SK Investigators found that the benefit of enoxaparin was sustained at 30 days.

In the AMI–SK study, enoxaparin was compared with a placebo rather than with unfractionated heparin. There has been controversy as to whether adjunctive heparin is necessary with streptokinase. The 1999 American College of Cardiology/American Heart Association guidelines[10] recommend the use of unfractionated heparin with fibrin-specific fibrinolytic agents, but where streptokinase is being used this recommendation is limited to patients with large or anterior myocardial infarctions. However, streptokinase induces extensive plasmin activity, and may be associated with more marked procoagulant effects than fibrin-specific agents such as alteplase, which activate plasminogen to a lesser extent[11]. In a meta-analysis of approximately 68,000 patients (all of whom received aspirin and 93% of whom received a fibrinolytic — mostly streptokinase), heparin significantly reduced the rates of death (five events per 1000 patients, P=0.03) and reinfarction (three events per 1000 patients, P=0.04). There was no significant increase in stroke, but there was a significant increase in bleeding (three transfusions per 1000 patients treated)[12]. Considering that no fibrinolytic regimen trialled since the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-I trial[13] a decade ago has produced a further reduction in
mortality, it is interesting that the mortality reduction observed with unfractionated heparin (P=0.03) was at the time judged to be only a small benefit[12].

Besides comparing alteplase with streptokinase, GUSTO-I was designed to evaluate the adjunctive use of intravenous heparin with streptokinase, and patients who received streptokinase were randomized to receive either immediate intravenous heparin or subcutaneous heparin begun at 4 h. However, 36% of the patients randomized to subcutaneous heparin were electively given intravenous heparin (not counting the use of intravenous heparin for cardiac catheterization, which occurred in 54% of patients), and this reduced the power of the study to detect a difference between these two treatment randomizations to 71%. It is perhaps not surprising, therefore, that there was no difference in clinical endpoints. However, at 5–7 days, 84% of patients randomized to intravenous heparin had TIMI-2 or -3 flow in the infarct-related artery compared with 72% of those randomized to subcutaneous heparin (P<0.05). This patency benefit is greater than that observed with intravenous heparin vs placebo in patients treated with alteplase[14,15], and may partly explain why patients randomized to streptokinase plus intravenous heparin in GUSTO-I had a 5-year survival rate equal to that of those randomized to alteplase (but with two fewer non-fatal disabling strokes per 1000 patients treated) and a 1% higher absolute survival rate than those randomized to streptokinase plus subcutaneous heparin[16].

Where are we with fibrinolysis in 2002? Firstly, no fibrinolytic agent has been shown to be more effective than alteplase, and there appears to be a ceiling for TIMI-3 flow of 54–65% at 90 min depending on the angiographic population studied and the reporting angiographic core laboratory[17–19]. Tenecteplase produces similar clinical outcomes to those seen with alteplase, but has the advantages of bolus administration and a lower associated incidence of non-cerebral bleeding[20]. With the patent on alteplase expired and with half-dose reteplase in GUSTO-V (16 588 patients)[22] and with half-dose tenecteplase in ASSENT-3 (6095 patients)[23]; enoxaparin, used in conjunction with tenecteplase in ASSENT-3[24]; and bivalirudin, used in conjunction with streptokinase in HERO-2 (17 073 patients)[25]. The reduction in infarction has ranged from 30% to 48%, with an absolute reduction of 8–22 reinfarctions per 1000 patients treated.

Fourthly, what about primary percutaneous coronary intervention (PCI) as an alternative to fibrinolytic therapy? In the Primary Coronary Angioplasty Versus Intravenous Thrombolysis for Treatment of Acute Myocardial Infarction (PCAT) meta-analysis[26] comparing PCI with fibrinolytic therapy in 2725 patients, the 6-month mortality rate was lower with PCI (P=0.04). Although this difference was no longer significant when missing data from several of the trials were imputed (P=0.054), there was a significant reduction in reinfarction (assessed mostly in hospital) (P<0.01). In the recent Danish Multicenter Randomized Study on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2)[27], which compared transport to a referral hospital for primary stenting with administration of accelerated alteplase in a community hospital, there was also no significant reduction in mortality (6.6% with primary stenting vs 7.6% with alteplase, P=0.35), but there was a significant reduction in reinfarction (1.6% vs 6.3%, P<0.001). However, rescue PCI was performed in only 2.5% of the patients who received accelerated alteplase. These data suggest that the major benefit of PCI may be due to decreased reocclusion of the infarct-related artery rather than improved patency rates at 90 min.

When two competing therapies are evolving side by side, it is common for one to gain a temporary advantage with some new advance, but the situation may subsequently be reversed when it is surpassed by the gains of the other. This could be what has just happened to reperfusion treatment. While stenting and the introduction of IIb/IIIa inhibitors have been major advances in the field of PCI, they have not yet translated into reduced rates of death or infarction[28–30], whereas the development of adjunctive therapies for use in patients undergoing fibrinolysis has reduced the risk of reocclusion, and consequently reinfarction[5,22,25]. The issue of whether primary PCI is a superior treatment strategy when performed in a timely manner needs to be revisited
with a new series of trials, including trials with adjunctive use of clopidogrel and trials evaluating the combination of fibrinolytic therapy with facilitated or rescue PCI. Low-molecular-weight heparin regimens will need to be incorporated into these trials to provide further information about the risks and benefits of these agents compared with unfractionated heparin or bivalirudin, particularly in patient subgroups such as the elderly. A transition to long-term oral low-molecular-weight heparin therapy may also be possible, with the potential to avoid reactivation or rebound of thrombotic events and to maintain infarct artery patency long-term.

**References**


Health care costs . . .

See doi:10.1053/euhj.2001.3075 for the article to which this Editorial refers

Policy makers in the industrialized world have become acutely conscious of the rising costs of health care. Over the past few decades, the average growth of health care spending has consistently exceeded that of the economy in every country. Having come to the conclusion that such relative growth will prove unsustainable over the longer term, policy makers have been intent on devising cost-control strategies. In public care systems, where individual purchasing capacity is not the criterion for care supply, forms of rationing are being introduced. Such rationing is often covert and is occurring in spite of the opinions of populations grown accustomed to the manifestly-unrealistic expectation of unlimited health care on demand[1].

In an attempt to establish a rational basis for rationing, governments have looked to the economic evaluation of existing and innovative health care technologies. In essence, economic evaluation is the search for value-for-money, a consideration of the clinical outcomes resulting from the use of the technology, in relation to the resources required to realize those outcomes. Evaluation thus informs the judgement as to whether or not such outcomes are actually worth paying for and whether, indeed, better health outcomes might be achieved by using the same resources in a different way.

If clinical outcomes and resource costs are the two necessary elements of an assessment determining whether or not an intervention should be provided within the health care system, it is immediately evident that the information base provided by the published medical literature is extremely asymmetric. Modern clinical research findings constitute primarily a corpus of descriptions of diverse health care technologies and their outcomes for patients. Until recently, relatively little effort has been devoted to finding out how much these health care technologies might cost. In some degree, this is a consequence of orientation and training. The clinician tends to interpret the problem of disease in terms of the well-being of the individual patient, rather than the worthiness of the intervention in relation to the resources employed. Clinicians typically see themselves as care providers, not as care rationers. Thus, clinical research has involved looking for effective solutions to individual health problems, rather than for cost-effective solutions to society’s health care problems. Moreover, a basic course in economics seldom figures in a clinician’s training (despite the fact that many find they require such a knowledge in later years when they come to adopt a managerial role).

Accepting that costs are just as important as outcomes for rational health policy making requires that we take cost analysis seriously. The methodology of costing is by no means mystical and builds on that of clinical research[2]. The essential augmentation is that, whilst the clinician is interested in recording events which trigger changes in process or outcome, the cost analyst records events entailing resource use. Compared with process or outcome measurement, however, there are potential stumbling blocks. For example, costs are considerably less universal than clinical outcomes. Typically, we accept that the nationality of a patient does not affect his or her response within a given treatment protocol: clinical results obtained from trials using American populations are thus transferred to the British or French context. With costing, however, this is highly unlikely.