EDITORIAL

The primacy of clinical effectiveness for cost effectiveness analysis

I P Casserly, E J Topol

Heart 2003;89:249–250

Cost effectiveness analysis has increasingly emerged as a means of evaluating new treatments with superior clinical outcomes but increased cost compared with the standard therapy

Despite the many advances in cardiovascular therapeutics over the last two decades, the incidence of death or myocardial infarction in the six months following clinical presentation with acute coronary syndromes (ACS) (excluding ST elevation myocardial infarction) remains unacceptably high at 12–15% (fig 1).¹ Most ACS trials have focused on reducing ischaemic events during the in-hospital treatment phase (usually less than one week). However, the recognition that 40% of all deaths and myocardial infarctions (MI) in the six months after presentation with ACS occur beyond the seventh day has prompted the search for treatments specifically directed at decreasing ischaemic events beyond the acute treatment phase.

Several key observations have suggested the coagulation cascade should be an attractive target for such treatments: the demonstration of a persistent prothrombotic state as reflected by raised concentrations of fibrinogen^{1,2} (a marker of factor Xa activity) up to six months following an ACS;² the angiographic finding of persistent thrombus on infarct related plaques in 80% of patients up to one month following MI, and the clinical phenomenon of rebound ischaemia following discontinuation of anticoagulant treatment.³ The attractive pharmacologic and pharmacokinetic properties of low molecular weight heparins (LMWH) led to this class of anticoagulant being tested in large clinical trials.^{4–8}

One of the major difficulties of such contemporary ACS trials is the increasing difficulty for newer treatments to demonstrate an incremental clinical benefit when tested against the current standard of care. The financial barrier to the addition of new treatments is also considerable, given the efforts of those who bear the financial burden for health care (federal governments, managed care organisations (MCOs)) to restrict the escalation of health care costs. Against this background, cost effectiveness analysis (CEA) has emerged as an economic analysis method employed in medical care to evaluate new treatments with superior clinical outcomes but increased cost compared with the standard treatment.⁹ CEA produces a ratio of incremental monetary cost per some unit of clinical effectiveness for a treatment. The “user” (physician, pharmaceutical company, government regulatory authority, health systems decision maker, MCO) of the CEA then deter-

mines whether the incremental ratio is “economically attractive” and makes decisions based on that judgement.

FRISC II STUDY

While five large studies have examined the efficacy of extended (14–90 days) LMWH treatment in ACS patients, the FRISC II study⁵ was unique in a number of respects: (1) the acute treatment in both arms was the same, making interpretation about the effect of extended treatment more straightforward; (2) with the exception of the FRAX.I.S. study,⁶ the dosing during the chronic phase was more aggressive; (3) the duration of extended treatment was for three months, compared with 14–45 days in the other studies; (4) the percentage of patients with troponin elevation at presentation was higher; and (5) all patients were managed using a predefined non-invasive strategy. The latter two factors have been shown to predict an improved outcome with LMWH treatment.^{10–11} Despite this, the trial found only a non-significant decrease in the primary end point (death and/or MI at three months) with extended dalteparin treatment.⁵ At six months follow up, there was a loss of any early benefit, with a similar incidence of death, MI, and revascularisation in both groups. Together with the findings of the other extended treatment LMWH trials and a meta-analysis of all five trials (fig 2),¹² the data suggest that the clinical efficacy of extended LMWH therapy beyond the acute treatment phase is unproven. Since CEA assumes a given treatment is more efficacious than the standard therapy, this precludes a CEA of extended LMWH therapy in ACS patients.

It is in this context that the paper presented by Janzon and colleagues¹³ in the current issue of *Heart* should be interpreted. Using the one month outcomes data (secondary end point) from the FRISC II trial, Janzon and colleagues report a CEA of one month of extended treatment with dalteparin versus placebo in patients with ACS managed using a non-invasive strategy. They found a cost saving of £2060 per avoided death or MI after one month of treatment with dalteparin and conclude that extended dalteparin treatment in patients with ACS is a cost effective bridge (up to one month) to invasive intervention.

Abbreviations: ACS, acute coronary syndrome; CEA, cost effectiveness analysis; FRAX.I.S., fraxiparine in ischaemic syndrome; FRISC, Fragmin and fast revascularization during instability in coronary artery disease; LMWH, low molecular weight heparin; MCO, managed care organisation; MI, myocardial infarction

See end of article for authors' affiliations

Correspondence to:
Eric J Topol MD,
Department of
Cardiovascular Medicine,
Desk F25, The Cleveland
Clinic Foundation, 9500
Euclid Avenue, Cleveland,
OH 44195, USA;
topole@ccf.org

Figure 1 Incidence of death, myocardial infarction (MI), and the composite of death/MI at various time points from presentation with acute coronary syndromes in patients enrolled in the PRISM-PLUS trial.¹

INTERPRETING THE FINDINGS

Some caution in the interpretation of these findings is warranted. It is likely that at the time of the design of this prospective CEA, it was hoped that the outcomes data for the primary end point at three months would prove the clinical efficacy of extended dalteparin treatment, and that CEA would then help determine the economic attractiveness of the strategy. With a non-significant reduction in the primary clinical efficacy end point, it seems unfair to now perform a CEA using secondary efficacy end points that are significant, particularly when other later secondary efficacy end points were not significantly impacted.

The conclusion that extended dalteparin treatment is a cost effective bridge to invasive intervention is also somewhat misleading. All patients in the FRISC II study were managed using a non-invasive approach. They were not bridged for a period of time and then directed towards an invasive strategy. Because this hypothesis was not tested, no conclusions about its cost effectiveness can be made.

As the authors concede, the use of the effectiveness unit of death and/or MI in this CEA is somewhat unorthodox, and makes it difficult to compare the economic attractiveness of this treatment to other therapies where the effectiveness unit is usually expressed in life or quality adjusted life years gained. Investigators often devise models to predict the long term survival of patients included in studies to allow such effectiveness measures of survival to be used.¹⁴ The almost complete convergence of the incidence of mortality in the dalteparin and placebo arms of the FRISC II study at six months did not allow such modelling in this paper, making a purely survival based effectiveness measure impossible.

In summary, we feel the primary issue of efficacy of extended LMWH treatment in ACS needs to be further clarified before economic data can contribute to the decision making process in ACS management.

Authors' affiliations

I P Casserly, E J Topol, Department of Cardiovascular Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio, USA

REFERENCES

- 1 **PRISM-PLUS Study Investigators.** Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet receptor inhibition in ischemic syndrome management in patients limited by unstable signs and symptoms (PRISM-PLUS) study investigators. *N Engl J Med* 1998;**338**:1488-97.
- 2 **Merlini PA, Bauer KA, Oltrona L, et al.** Persistent activation of coagulation mechanism in unstable angina and myocardial infarction. *Circulation* 1994;**90**:61-8.
- 3 **Theroux P, Waters D, Lam J, et al.** Reactivation of unstable angina after the discontinuation of heparin. *N Engl J Med* 1992;**327**:141-5.
- 4 **FRISC Study Group.** Low-molecular-weight heparin during instability in coronary artery disease. Fragmin during instability in coronary artery disease (FRISC) study group. *Lancet* 1996;**347**:561-8.
- 5 **FRISC II Investigators.** Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Fragmin and fast revascularisation during instability in coronary artery disease investigators. *Lancet* 1999;**354**:701-7.
- 6 **FRAXIS Investigators.** Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q wave myocardial infarction: FRAXIS. (fraxiparine in ischaemic syndrome). *Eur Heart J* 1999;**20**:1553-62.
- 7 **Antman EM, McCabe CH, Gurfinkel EP, et al.** Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation* 1999;**100**:1593-601.
- 8 **Klein W, Buchwald A, Hillis SE, et al.** Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). *Circulation* 1997;**96**:61-8.
- 9 **Mark DB, Simons TA.** Economics and cost-effectiveness in evaluating the value of cardiovascular therapies. Fundamentals of economic analysis. *Am Heart J* 1999;**137**:S38-40.
- 10 **Lindahl B, Venge P, Wallentin L.** Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. The FRISC study group. *Circulation* 1996;**93**:1651-7.
- 11 **FRISC II Investigators.** Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Fragmin and fast revascularisation during instability in coronary artery disease investigators. *Lancet* 1999;**354**:708-15.
- 12 **Eikelboom JW, Anand SS, Malmberg K, et al.** Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 2000;**355**:1936-42.
- 13 **Janzon M, Levin L-A, Swahn E, and the FRISC II Investigators.** Cost effectiveness of extended treatment with low molecular weight heparin (dalteparin) in unstable coronary artery disease: results from the FRISC II trial. *Heart* 2003;**89**:287-92.
- 14 **Mark DB, Hlatky MA.** Medical economics and the assessment of value in cardiovascular medicine: part I. *Circulation* 2002;**106**:516-20.

	LMWH	Control
FRISC I	46/738 (6.2%)	45/755 (5.9%)
FRISC II	70/1049 (6.7%)	85/1056 (8.0%)
FRIC	24/562 (4.3%)	26/561 (4.6%)
TIMI IIB	65/1953 (3.3%)	59/1957 (3.0%)
FRAXIS	23/1151 (2.0%)	42/2317 (1.8%)
Pooled results	228/5453 (4.2%)	257/6646 (3.9%)

Figure 2 Death or myocardial infarction in placebo controlled randomised trials of extended low molecular weight heparin (LMWH) treatment in patients with acute coronary syndromes (excluding ST elevation myocardial infarction). CI, confidence interval; OR, odds ratio.