CARDIOVASCULAR MEDICINE

Cost effectiveness of extended treatment with low molecular weight heparin (dalteparin) in unstable coronary artery disease: results from the FRISC II trial

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Background: In unstable coronary artery disease short term treatment with low molecular weight heparin in addition to aspirin has been shown to be effective.

Objective: To assess the cost effectiveness of extended treatment with dalteparin in patients managed with a non-invasive treatment strategy.

Design: Prospective, randomised, multicentre study.

Setting: 58 centres in Sweden, Denmark, and Norway, of which 16 were interventional.

Patients: After at least five days' treatment with open label dalteparin, 2267 patients were randomised to continue double blind treatment with either subcutaneous dalteparin twice daily or placebo for three months. The patients' use of health service resources was recorded prospectively.

Main outcome measure: Death/myocardial infarction.

Results: After one month into the double blind period there was a 47% relative reduction in death or myocardial infarction in the dalteparin group compared with the placebo group ($p = 0.002$). There was a non-significant mean cost difference, favouring the placebo group, of 849 Swedish crowns (SEK) per patient (equivalent to £58). The incremental cost effectiveness ratio for giving dalteparin treatment for one month was SEK 30 300 (range -78 000 to 139 000) (£2060, range -£5300 to £9400) per avoided death or myocardial infarction. At three months, the decrease in death or myocardial infarction was not significant, precluding cost effectiveness analyses.

Conclusions: There is a marginal and non-significant increase in costs for one month of extended dalteparin treatment compared with placebo. Extended dalteparin treatment lowers the risk of death or myocardial infarction in patients with unstable coronary artery disease. While in many countries the resources for early intervention are limited, extended dalteparin treatment up to one month is a cost effective bridge to invasive intervention.

The efficacy of short term treatment with subcutaneous low molecular weight heparin in addition to aspirin in reducing death and myocardial infarction in patients with unstable coronary artery disease has been demonstrated in several trials.¹⁻³ However, the optimal duration of this combination treatment has yet to be resolved.⁴ Thrombi at the coronary lesion and increased coagulation activity persist for months after an episode of instability.⁵⁻⁷ The risk of adverse cardiac events is increased during this period.^{1-3 8-11}

In the FRISC (Fragmin and fast revascularisation during instability in coronary artery disease) trial,¹ extended treatment with the low molecular weight heparin dalteparin resulted in additional protection against cardiac events in patients at higher risk—that is, patients with raised troponin T concentrations—who had a very low rate of early invasive procedures.¹² Thus the effects of long term antithrombotic treatment in unstable coronary artery disease may be dependent on the patient population and on the proportion of patients treated with early invasive procedures.

An economic assessment of short term treatment with the low molecular weight heparin enoxaparin versus unfractionated heparin in patients with unstable coronary artery disease has been carried out.¹³ It was found that treatment with enoxaparin improved clinical outcomes and cost less than treatment with standard unfractionated heparin.

Pharmacoeconomic analyses of dalteparin carried out in patients requiring treatment for established thromboembolic disease showed that there were cost advantages with dalteparin over unfractionated heparin from a hospital perspective.¹⁴ Cost effectiveness studies of dalteparin treat-

ment in unstable coronary artery disease have not been conducted to date, and there are no cost effectiveness studies comparing extended treatment with low molecular weight heparin versus placebo. The FRISC II invasive trial^{15 16} showed that an early invasive strategy is beneficial, especially in high risk patients. However, catheterisation laboratory capacities and resources are limited. Not all patients can get the benefit of this early approach. There is wide variation in the use of invasive procedures in Europe as well as in North America.^{17 18} In many countries, especially in general practice hospitals and in smaller hospitals, the waiting time for catheterisation and revascularisation is many weeks.¹⁷

The aim of this prospective study was to evaluate the cost and medical efficacy of extended treatment for one and three months with dalteparin compared with placebo in patients randomised to a non-invasive treatment strategy. We report the cost effectiveness of extended dalteparin treatment using data gathered during the FRISC II study.

METHODS

Study design

The FRISC II medical trial design has been published previously.¹⁹ In brief, it was a prospective, randomised multicentre trial with parallel groups. There were 58 Scandinavian centres in the study, of which 16 were interventional. The comparison of extended dalteparin treatment with placebo was double blind. Patients were eligible for inclusion if they had symptoms of ischaemia that were increasing or occurring at rest, or if suspicion of acute myocardial infarction

was warranted, with the last episode preceding the first dose of dalteparin or standard heparin by less than 48 hours. Myocardial ischaemia was always verified by ECG (ST depression or T wave inversion) or by biochemical markers.

The exclusion criteria were: an increased risk of bleeding or anaemia; an indication for thrombolysis or thrombolytic treatment given during the preceding 24 hours; angioplasty within the previous six months; being on the waiting list for coronary revascularisation procedures; other acute or severe cardiac disease; renal or hepatic insufficiency; known clinically relevant osteoporosis; other severe illness; hypersensitivity to randomised drugs; and anticipated problems concerning cooperation or participation in this or another clinical trial. There was no upper age limit.

Within 72 hours after the start of open label dalteparin (or standard heparin) the patients were randomised, using stratification by centre, to extended dalteparin or extended placebo. All patients received basic treatment with aspirin and at least five days of subcutaneous dalteparin (120 IU/kg every 12 hours) before they continued with the randomised treatment with twice daily subcutaneous injections of either dalteparin or placebo. Women weighing less than 80 kg and men weighing less than 70 kg received dalteparin 5000 IU twice daily; above these weight limits the dalteparin dose was 7500 IU twice daily. This treatment was continued for a period of three months, with patients self injecting by prefilled single dose syringes after discharge from hospital. Follow up was done in hospital, by telephone after two weeks, and by outpatient visits after six weeks and three months. The primary end points were death or myocardial infarction during the double blind period.

Use of resources

For all patients in the study we logged their consumption of health care resources prospectively in the main case report form, from the first day of double blind treatment until the three month follow up. The direct medical costs were categorised as hospital admissions, investigations, interventions, pharmaceuticals, and outpatient care. In this study we used a health care provider perspective.

Hospital admissions

The number of days for hospital admission (all reasons) was recorded. This included care in the intensive care unit/cardiac care unit (ICU/CCU), cardiology/internal medicine ward, thoracic surgery ICU, thoracic surgery ward, and general ward.

Investigations and interventions

The recorded investigations were exercise tests, echocardiograms, and coronary artery catheterisations. The predefined interventions were percutaneous transluminal coronary angioplasty with and without stenting, and coronary artery bypass grafting.

Pharmaceuticals

Pharmacological treatments including the use of thrombolytic agents (streptokinase, alteplase, and reteplase), glycoprotein IIb/IIIa blockade (abciximab), and dalteparin were recorded.

Outpatient care

Outpatient hospital visits and home care visits involving a physician, nurse, or physiotherapist were noted by the patients in a questionnaire.

Costing

To obtain the actual prices for the hospital admissions, investigations, and interventions, a costing study was conducted in 1997 at all 36 participating Swedish centres, which comprised over 80% of all patients in the trial. The hospitals in this study adequately represented the different categories of hospital in

Table 1 Prices employed to value resource use

Resource	Price (SEK)
<i>Hospital admissions (per day)</i>	
ICU/CCU	5560
Cardiology/medical ward	3335
Thoracic surgery ICU	19990
Other wards	3335
<i>Investigations (per procedure)</i>	
Exercise test	1005
Echocardiogram	1225
Coronary catheterisation	12380
<i>Interventions (per procedure)</i>	
PTCA without stent	41875
PTCA with stent	51840
CABG	96030
<i>Pharmaceuticals (per treatment episode)</i>	
Streptokinase	950
Alteplase	9530
Reteplase	9495
Abciximab	9815
<i>Intervention treatment*</i>	
Dalteparin (10 000 IU)	71
Dalteparin (15 000 IU)	113
<i>Outpatient care</i>	
Visit to physician	1215
Visit to nurse	305
Visit to physiotherapist	305
Physician home visit	2425
Nurse home visit	605

*Prices for intervention treatment are per day.

CABG, coronary artery bypass graft; CCU, cardiac care unit; ICU, intensive care unit; PTCA, percutaneous transluminal coronary angioplasty.

Scandinavia, ranging from small county hospitals to university hospitals. The price for an inpatient day in hospital was based on the annual cost of running the ward, including physicians' fees, divided by the number of bed occupancy days over the year (table 1).

The prices of pharmacological treatment were collected from pharmacy prices in Sweden.²⁰ The price per visit to a physician, a nurse, and a physiotherapist (including home visits) was obtained from nine hospitals in south eastern Sweden.²¹

Costs were inflated to year 2000 prices using the consumer price index (CPI) 2000. The inflation factor between 1997 and 2000 was 1.1%.²² (£1 was equivalent to 14.71 Swedish crowns (SEK) on 14 March 2002).²³

Analyses and statistics

Analyses of clinical outcome and costs were on an intention to treat basis.¹⁹ All costs were expressed as current costs, and no discount rate was used because the follow up period was less than one year.

Cost analysis was based on resource use recorded after the start of the double blind treatment until the three month follow up, or until death within three months. Following the clinical study¹⁹ we made an additional analysis at one month. The prices we used in the analyses indicate the cost of treating a patient and are not charges or payments but reflect opportunity costs.²⁴ The hospitals' median average prices were used as estimates for the real unit costs, and these were later tested in a sensitivity analysis.

We used *t* tests to compare the treatment groups in terms of mean costs. This method is known to be fairly robust with respect to non-normality, especially if the sample size is as large as in this study.²⁵ The clinical results are presented as odds ratios with 95% confidence intervals. Data processing

Figure 1 Disposition of the patients in the FRISC II study.

was undertaken independently in the Department of Biostatistics and Data Management, Pharmacia Corporation, Sweden, and by us. All our own statistical analyses were done using the SPSS 10.1 statistical programs for personal computers.

Data management, quality, and ethics

The trial was run according to good clinical practice. The quality of the data was ensured by continuous source data verification of all case report forms by external monitors employed by the sponsoring pharmaceutical company. All cardiac events (efficacy end points) were sent to the independent end point adjudication committee, and adverse events were also continuously sent directly from the centres to the Data and Safety Monitoring Board. Randomisation was done by telefax contact with an independent organisation (Clinical Data Care, Lund, Sweden). The study complied with the Declaration of Helsinki and all local ethics committees approved the protocol.

RESULTS

Patients

Between June 1996 and August 1998, 2267 patients were randomised to extended dalteparin treatment or placebo. Of these, 1235 constituted the non-invasive part of the invasive/non-invasive randomisation. Also included in the non-invasive (medical treatment) arm of the trial were 366 patients who were included late, after the recruitment period for the invasive and non-invasive comparison, and 666 patients who had contraindications to invasive treatment. Of the 2267 patients who entered the medical treatment arm, 162 were withdrawn before the double blind treatment period (fig 1).

Baseline characteristics

There were no significant differences in baseline characteristics between the two groups (table 2). The median age was 67 years and 68% of the participants were men. A majority of the patients could be considered at high risk: 81% had chest pain at rest; 59% had elevation of troponin T ($\geq 0.1 \mu\text{g/l}$) and, at entry, 48% showed ST segment depression on ECG. However, the majority of patients had normal left ventricular function.

Costs: one month follow up

For both treatment arms, 4% of the patients were admitted to hospital during the first month. There were no significant differences between the measured variables in the dalteparin group and the placebo group after one month of double blind

treatment (table 3). While the cost of intervention with dalteparin for one month was significantly greater than the cost for the placebo group, the overall cost of resources per patient in the dalteparin group did not differ significantly from the placebo group. The mean difference for the first month was SEK 849 (£58) per patient.

Costs: three months follow up

A detailed breakdown of the number of events and direct medical costs per patient is given in tables 4 and 5, respectively. Both groups of patients spent on average four days in hospital. Patients treated with dalteparin had a significantly lower need for exercise tests but the need for echocardiograms and coronary catheterisation was similar in the two groups. There were no significant differences in total costs for investigations.

The duration of double blind treatment was similar in the dalteparin and placebo groups (table 4). Two thirds of the

Table 2 Baseline characteristics of the double blind treatment groups

Variable	Dalteparin (n=1049)	Placebo (n=1056)
Age (years), median (range)	67 (37–91)	67 (38–87)
Male/female (%)	68/32	69/31
<i>Coronary risk factors</i>		
Hypertension	33%	33%
Cholesterol $>5.5 \text{ mmol/l}$	53%	57%
Current smoker	25%	27%
Diabetes mellitus	14%	12%
<i>Previous and current cardiac disease</i>		
Previous MI	30%	27%
Previous PTCA	4%	4%
Previous CABG	14%	13%
Angina $>48 \text{ h}$	70%	70%
Chest pain at rest	82%	80%
ST depression at entry	46%	50%
Troponin T $\geq 0.1 \mu\text{g/l}^*$	57%	60%
LVEF $<45\%^\dagger$	14%	17%

*Blood samples for central troponin T analysis were obtained at randomisation in 999 and 1015 patients, respectively.

† Determined echocardiographically in 842 and 860 patients, respectively.

CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

Table 3 Mean costs (in Swedish crowns) per patient during the first month

Item	Dalteparin (n=1049)	Placebo (n=1056)	p Value	CI for difference
Hospital admissions	8388	8825	NS	−2067 to 1193
Investigations	803	973	NS	−443 to 103
Interventions	4013	4809	NS	−2317 to 725
Pharmaceuticals	56	117	NS	−145 to 23
Intervention treatment	2313	0	<0.001	2265 to 2359
All costs	15573	14724	NS	−2191 to 3889

CI, confidence interval.

patients received the higher dose of dalteparin (7500 IU twice daily). The significantly higher total cost for pharmaceuticals for patients treated with dalteparin reflected the per protocol intervention with dalteparin: the difference compared with the placebo group was SEK 7723 (£525) per patient.

The overall costs for three months of extended dalteparin treatment were significantly higher than for placebo. The cost difference was SEK 6739 (£458) per patient.

Clinical end points

At one month of extended treatment there was a 47% relative and a 2.8% absolute reduction in the primary combined end point of death or myocardial infarction in favour of dalteparin ($p = 0.002$). At three months there was a non-significant 19% relative and 1.3% absolute reduction in death or myocardial infarction in the dalteparin group. There were nine cardiac

deaths in the dalteparin group (0.9%) and 16 in the placebo group (1.5%).

Cost effectiveness

Considering a cost increase of SEK 849 (£58) per patient with extended treatment with dalteparin for one month compared with placebo, the incremental cost effectiveness ratio for giving dalteparin treatment for one month after an episode of unstable coronary artery disease was SEK 30 300 (£2060) per avoided death or myocardial infarct. Taking the cost confidence interval into consideration, the cost effectiveness ratio of giving dalteparin for one month varied between cost saving of SEK −78 000 (−£5300) and an expense of up to SEK 139 000 (£9400) per patient. At the three months follow up the decrease in death or myocardial infarction was not significant, precluding cost effectiveness analyses.

Table 4 Number of events and mean drug consumption per patient at the three months follow up

Item	Dalteparin (n=1049)	Placebo (n=1056)	p Value	Mean difference	CI for the difference
<i>Hospital admissions (days)</i>					
ICU/CCU	0.67	0.76	NS	−0.09	−0.28 to 0.10
Cardiology/medical ward	2.39	2.23	NS	0.16	−0.29 to 0.61
Thoracic surgery ICU	0.18	0.17	NS	0.01	−0.06 to 0.08
Thoracic surgery ward	0.57	0.58	NS	−0.01	−0.20 to 0.18
Other wards	0.47	0.47	NS	0.00	−0.22 to 0.22
All admissions	4.28	4.21	NS	0.07	−0.69 to 0.83
<i>Investigations</i>					
Exercise test	0.86	0.90	0.03	−0.04	−0.08 to 0.00
Echocardiogram	0.05	0.05	NS	0.00	−0.02 to 0.02
Coronary catheterisation*	0.13	0.15	NS	−0.02	−0.05 to 0.01
<i>Interventions</i>					
PTCA without stent	0.03	0.03	NS	0.00	−0.01 to 0.01
PTCA with stent	0.04	0.05	NS	−0.01	−0.03 to 0.01
CABG	0.06	0.06	NS	0.00	−0.02 to 0.02
<i>Pharmaceuticals (treatment episodes)</i>					
Streptokinase	0.004 (4)	0.010 (10)	NS	−0.006	−0.013 to 0.001
Alteplase	0.005 (5)	0.012 (13)	NS	−0.007	−0.016 to 0.002
Reteplase	0.001 (1)	0.001 (1)	NS	0.000	−0.002 to 0.002
Abciximab	0.006 (6)	0.005 (5)	NS	0.001	−0.005 to 0.007
<i>Intervention treatment</i>					
Dalteparin (10 000 IU per day)/placebo	79.3	81.6	NS	−2.3	−4.6 to 0.0
Dalteparin (15 000 IU per day)/placebo	75.8	80.2	0.024	−4.4	−8.1 to −0.7
<i>Outpatient care</i>					
Visits to physician	3.66	3.63	NS	0.03	−0.10 to 0.16
Visits to nurse	0.85	0.91	NS	−0.06	−0.21 to 0.09
Visits to physiotherapist	0.64	0.70	NS	−0.06	−0.27 to 0.15
Physician home visits	0.06	0.05	NS	0.01	−0.02 to 0.04
Nurse home visits	0.18	0.36	NS	−0.18	−0.46 to 0.10

*Coronary catheterisations that led to PTCA ad hoc are listed under interventions.

CABG, coronary artery bypass graft; CCU, cardiac care unit; CI, confidence interval; ICU, intensive care unit; PTCA, percutaneous transluminal coronary angioplasty.

Table 5 Mean costs in Swedish crowns per patient at the three months follow up

Item	Dalteparin (n=1049)	Placebo (n=1056)	p Value	Mean difference	CI for the difference
<i>Hospital admissions (days)</i>					
ICU/CCU	3743	4210	NS	-467	-1541 to 607
Cardiology/medical ward	7962	7452	NS	510	-988 to 2008
Thoracic surgery ICU	1927	1845	NS	82	-676 to 840
Thoracic surgery ward	1575	1612	NS	-37	-576 to 502
Other wards	1584	1576	NS	8	-723 to 739
All admissions	16791	16695	NS	96	-2970 to 3162
<i>Investigations</i>					
Exercise test	862	909	0.03	-47	-93.6 to -0.4
Echocardiogram	64	58	NS	6	-21.6 to 33.6
Coronary catheterisations*	1640	1852	NS	-212	-580 to 156
All investigations	2566	2819	NS	-253	-622 to 116
<i>Interventions</i>					
PTCA without stent	1158	1388	NS	-230	-920 to 460
PTCA with stent	2224	2504	NS	-280	-1 205 to 645
CABG	5950	6184	NS	-234	-2 232 to 1764
All interventions	9332	10076	NS	-744	-3 009 to 1521
<i>Pharmaceuticals</i>					
Streptokinase	3.6	9.0	NS	-5.4	-12.0 to 1.2
Alteplase	45.4	117.0	NS	-71.6	-154.6 to 11.4
Retepase	9.1	9.0	NS	0.1	-24.9 to 25.1
Abciximab	56.0	46.0	NS	10.0	-51.0 to 71.0
<i>Intervention treatment</i>					
Dalteparin 10 000 IU per day/placebo	1753	0	<0.001	1753	1587 to 1919
Dalteparin 15 000 IU per day/placebo	6037	0	<0.001	6037	5753 to 6321
All pharmaceuticals	7904	181	<0.001	7723	7518 to 7928
<i>Outpatient care</i>					
Visits to physician	4451	4410	NS	41	-120 to 202
Visits to nurse	259	276	NS	-17	-63 to 29
Visit to physiotherapist	194	213	NS	-19	-82 to 44
Physician home visits	137	119	NS	17	-53 to 87
Nurse home visits	110	216	NS	-106	-274 to 62
All outpatient care	5151	5234	NS	-83	-350 to 184
All costs	41744	35005	0.008	6739	1739 to 11739

*Coronary catheterisations that led to PTCA ad hoc are listed under interventions.

CABG, coronary artery bypass graft; CCU, cardiac care unit; CI, confidence interval; ICU, intensive care unit; PTCA, percutaneous transluminal coronary angioplasty.

Sensitivity analysis

The prices reported in the costing study differed among the centres. To test the impact of different prices on the results, the minimum and maximum prices reported were applied to the cost calculations. When varying the price levels, the mean total cost range at the one month follow up was between SEK 513 ± 3677 (£35 ± 250) and SEK 1185 ± 2290 (£81 ± 156) per patient, which gives a cost effectiveness ratio between SEK 18 300 (£1200) and SEK 42 300 (£2900) per avoided event.

DISCUSSION

Following one month of extended treatment with dalteparin there was a significant relative risk reduction of 47% in the combined end point of death or myocardial infarction in patients with unstable coronary artery disease, as previously reported.¹⁹ This reduction equated to a cost effectiveness ratio of SEK 30 300 (range -78 000 to 139 000) (£2060, range -£5300 to £9400) per avoided death or myocardial infarct. Our predefined end point of death or myocardial infarction as the measure of effectiveness makes the interpretation of this ratio slightly complicated with respect to the cost effectiveness analyses, as the value of an avoided death differs from the value of an avoided myocardial infarct. Comparison with other interventions is difficult. In some similar studies the effectiveness measure has also included revascularisations,²⁶ which complicates interpretation even further as the cost for revascularisation is in both the numerator and denominator of cost effectiveness calculations.

Ideally, the effectiveness measure should have been expressed as life years or quality adjusted life years gained. However, in the FRISC II medical trial the relatively short follow up period makes the chosen end point relevant.

A marginal increase in costs in order to avoid such a serious event as death or myocardial infarction is justified. Thus one month of dalteparin treatment is a cost effective strategy for patients with unstable coronary artery disease who are not revascularised early after hospital admission.

At the end of the three months' dalteparin treatment period there was no significant reduction in death or myocardial infarction, precluding the calculation of the cost effectiveness ratio for that period.

An invasive strategy for patients with unstable coronary artery disease has previously been shown to be cost effective.²⁷ Owing to limited health care resources, both material and in terms of personnel, invasive procedures during the first seven days after admittance to hospital with unstable coronary artery disease are often not available.¹⁷ In cases where invasive procedures are delayed our current results show that it is clinically beneficial and cost effective to extend treatment with dalteparin while waiting for an invasive evaluation and, if appropriate, revascularisation.

Conclusions and implications

This is the first prospective economic evaluation on a large randomised trial, in which the cost effectiveness of extended dalteparin treatment has been compared with placebo in unstable coronary artery disease. All resource use was

prospectively documented in the patients' main case report forms. During the first month of extended treatment with dalteparin there was a significantly reduced risk of death or myocardial infarction. This has now also been shown to be cost effective. Therefore, in clinically stabilised patients with unstable coronary artery disease, extended dalteparin treatment can be used as a cost effective bridge to invasive procedures.

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APPENDIX

Executive committee

L Wallentin, Uppsala (chairman); E Swahn, Linköping (co-chairman); F Kontny, Oslo; S Husted, Aarhus; B Lagerqvist, Uppsala (chairman invasive procedures committee) Elisabeth Ståhle, Uppsala (co-chairman invasive procedures committee).

Other members of the steering committee

J D Nielsen, Hellerup; M Dellborg, Göteborg; O Geiran, Oslo; P Grande, Copenhagen; J Hulting, Stockholm; J Kyst-Madsen, Copenhagen; J-E Nordrehaug, Bergen; U Näslund, Umeå; H Pilegaard, Aarhus; A Rollag, Nordbyhagen; T Toftegaard Nielsen, Aarhus; H Saetre, Falun; Agneta Siegbahn, Uppsala; H Öhlin, Lund.

Other members of the invasive procedures committee

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Independent end point adjudication committee

U Näslund, Umeå (chairman); S Persson, Malmö; K-A Jacobsson, Umeå; K Thygesen, Aarhus; G von der Lippe, Bergen.

Data monitoring and safety committee

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