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Cost-utility of enoxaparin compared with unfractionated heparin in unstable coronary artery disease

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Abstract

Background: Low molecular weight heparins hold several advantages over unfractionated heparin including convenience of administration. Enoxaparin is one such heparin licensed in the UK for use in unstable coronary artery disease (unstable stable angina and non-Q wave myocardial infarction). In these patients, two large randomised controlled trials and their meta-analysis showed small benefits for enoxaparin over unfractionated heparin at 30–43 days and potentially at one year.

We found no relevant published full economic evaluations, only cost studies, one of which was conducted in the UK. The other studies, from the US, Canada and France, are difficult to interpret since their resource use and costs may not reflect UK practice.

Methods: We aimed to compare the benefits and costs of short-term treatment (two to eight days) with enoxaparin and unfractionated heparin in unstable coronary artery disease. We used published data sources to estimate the incremental cost per quality adjusted life year (QALY), adopting a NHS perspective and using 1998 prices.

Results: The base case was a 0.013 QALY gain and net cost saving of £317 per person treated with enoxaparin instead of unfractionated heparin. All but one sensitivity analysis showed net savings and QALY gains, the exception (the worst case) being a cost per QALY of £3,305. Best cases were a £495 saving and 0.013 QALY gain, or a £317 saving and 0.014 QALY gain per person.

Conclusions: Enoxaparin appears cost saving compared with unfractionated heparin in patients with unstable coronary artery disease. However, cost implications depend on local revascularisation practice.

Background

Advantages of low molecular weight heparins over unfractionated heparin include convenience of administration, higher bioavailability and the lack of need for monitoring. Some varieties are now used in the treatment of unstable angina and non-Q wave myocardial infarction (henceforth referred to as unstable coronary artery disease). These conditions are common in hospital and may be increasing. Incidence of unstable angina ranges from 99 to 246 per 100,000[1,2] and approximately 20–38% of myocardial infarctions are non-Q-wave [3].

A recent meta-analysis [4] compared low molecular weight heparins (enoxaparin, dalteparin and nadroparin) with unfractionated heparin in unstable coronary artery disease. The short-term treatment comparison combined the results from 5 randomised controlled trials (12,169 patients). The overall result suggested that the low molecular varieties were no more effective than unfractionated heparin, odds ratio 0.88 (95% confidence intervals 0.69–1.12), for the combined outcome of death or myocardial infarction. This was controversial as the meta-analysis used outcomes at the end of equal duration of treatment, but this varied across the trials. In addition, some authors [5] felt that it was inappropriate to combine the different varieties due to their pharmacological differences, despite the lack of statistical heterogeneity detected between the trials.

Our current analysis considered only enoxaparin. This variety is licensed in the UK for unstable coronary artery disease and has the largest body of research evidence. Two large randomised controlled trials [6,7] and their meta-analysis [8] (comprising 7081 patients) showed small relative benefits for enoxaparin over unfractionated heparin at 30–43 days and potentially at one year [9]. This was for the primary composite outcome of death, myocardial infarction, recurrent angina or revascularisation (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty, PTCA). A third small randomised controlled trial [10], reported in an abstract, found mostly worse outcomes for the enoxaparin group.

We found no published full economic evaluations of enoxaparin compared with unfractionated heparin, only cost studies, one of which was conducted in the UK [11]. The other studies, from the US [12], Canada [13,14] and France [4], are difficult to interpret since their resource use and unit costs may not reflect UK practice and simple currency conversions can markedly affect overall costs. However, for information, their results in their base currency and when converted to UK pounds are summarised in Table 1. It should be noted that the studies are not directly comparable as, for example, they include different cost items, different patient groups (in some cases using effectiveness estimates from country sub-groups), and different cost years. The current study builds on our previous work for the former South East/South West Development and Evaluation Committee [15], but includes more extensive analyses and incorporates the most recent published evidence.

This study aimed to compare the benefits and costs of short-term treatment (two to eight days) with enoxaparin or unfractionated heparin in the treatment of unstable coronary artery disease, using published data sources to model cost-utility. We chose to perform a cost-utility rather than cost-effectiveness analysis because there were several outcomes of interest (namely death, myocardial infarction and recurrent angina). Multiple outcomes can be combined through cost-utility analyses. A further advantage over cost-effectiveness is that the outcome of the cost-utility analysis is a cost per quality adjusted life year (QALY) that incorporates both quality and length of life. This also makes it is possible to compare within and across treatment areas (although rankings are potentially misleading where methods and settings differ) [16,17]. The analysis adopted a National Health Service (NHS) perspective, since the purpose was to assist NHS decision-makers in the UK.

Methods

Effectiveness

To assess the benefits and harms of enoxaparin, we searched the Cochrane Library, Medline and Embase for randomised controlled trials. Two large double-blind trials [6,7] and a third small randomised trial [10] were found. Full details of the searches, inclusion criteria, appraisal and data extraction methods and tables of results are available in the Additional Material 1: Section A and Additional material 3: Section C

The first trial [6] compared two to eight days treatment using enoxaparin or unfractionated heparin. The primary composite outcome of death, myocardial infarction or recurrent angina at 14 days was more common in the unfractionated heparin group, a difference maintained at one year (relative risk reduction 16.2% P = 0.02 [6] and 10.7% P = 0.02 [9] respectively). Similarly, more revascularisations (coronary artery bypass grafting or PTCA) were required in the unfractionated heparin group at 30 days and one year.

The second trial [7] included two comparisons; enoxaparin or unfractionated heparin to eight days, followed by enoxaparin or placebo to 43 days. At eight days, the triple endpoint (death, recurrent myocardial infarction or urgent revascularisation) was more frequent in the unfractionated heparin group (relative risk reduction 14.6% P = 0.048).

Both were good quality trials, scoring five and three on the Jadad scale [18]. The following limitations were detected in one study [7]; incomplete description of withdrawals and modification of inclusion criteria during the trial. Their meta-analysis [8] found the enoxaparin group's composite endpoint was significantly reduced to 43 days. However, the only outcome reported separately was death and so these results could not be used in the cost-utility model.

Table 1: Results of economic (cost) studies

Country	UK [11]	US [12]	US [12]	Canadian [14]	Canadian [13]	French [4]	French [4]
Cost year	? (1996–1997)	? (1994–1996) 1995*	? (1994–1996) 1995*	1997	1999	1996	1996
Patient group	UK only (n = 191)	US only (n = 936)	All ESSENCE patients	Canadian only (n = 1259	Canadian hypothetical cohort	French only (n = 133)	All ESSENCE patients
Cost-effectiveness assessed at	30 days	30 days	30 days	1 year	30 days	30 days	30 days
Currency	£UK	$US	$US	$CAN	$CAN	FF	FF
Cost savings							
Base case 1	23.68	763	661	1485	44	9993	1555
Base case 2	na	1172	688	na	na	2804	1014
Sensitivity analysis best case	Not available for cost differences	Net costs in only 14%** and 6%*** of 200	Not available	3167	435	12019	1876
Sensitivity analysis worst case		bootstrap samples		-174	-299	1518	542
In £UK (in cost year as above)							
Base case 1	23.68	499	432	812	25	980	152
Base case 2	na	766	450	na	na	275	99
Sensitivity analysis best case	Not available for cost differences	Net costs in only 14%** and 6%*** of 200	Not available	1733	247	1178	184
Sensitivity analysis worst case		bootstrap samples		-95. Net costs in only 3% of 1000 bootstrap samples	-170	149	53

Notes ? means unclear na = not applicable Negative cost savings indicates a net cost * taken as 1995 for currency conversion ** initial hospitalisation *** cumulative total Cost savings converted to UK pounds using Purchasing Power Parities (PPP) [23] (this eliminates the differences in price levels between countries). ESSENCE patients were the patients in the 'Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events' trial [6]

The third trial [10] was a small randomised controlled trial, but only reported in an abstract. It found mostly worse outcomes for the enoxaparin group, but differences were not statistically significant and the trial was under powered. The study did not appear to be double blind, and although patients were followed up for 30 days it was unclear when the outcomes had been measured. For these reasons it was not possible to extract data for the model.

In order to quantify the benefits from treatment we used the individual components of the composite outcome although the latter were not statistically significant. The base case used the first trial's most severe event rates to one year [9]. We estimated mean event free times gained for deaths, myocardial infarctions and recurrent angina using survival analysis techniques (actuarial method) to estimate the area between the survival curves. Sensitivity analyses used all events or the second trial's results [7] assuming event rates at 43 days were maintained to one year, as in the first trial (see Table 2).

Quality of life

Mean health-related quality of life changes associated with death, myocardial infarction and recurrent angina were based on preference weights of patients with suspected myocardial infarction [19] (full details in Additional material 2: Section B). We combined these with the mean event free times to estimate the QALYs gained by treatment.

Resource use and costs

All costs were in 1998 UK pounds and since data were only modelled for one year, discounting was unnecessary. The valuation of treatment-related costs and savings and average and minimum/maximum values used in the base case and sensitivity analyses are shown in the Additional material 2: Section B. To ensure generalisability within the UK, we used national costs supplemented by local costs (or resource use information) where necessary.

Table 3 shows how the cost difference between enoxaparin and unfractionated heparin was reduced when ad-

Table 2: Base case and ranges of efficacy, quality of life, resource use and cost data used (amalgamation of all models)

	Base case	Lower, Upper
Effectiveness data		
Mean event free years. Values used in sets, not individually for each outcome.		
Life years gained	0.010	0.002, same as base case
Myocardial infarction free time gained	0.007	0.008, 0.013
Time free from recurrent angina	0.018	0.014, 0.022
Quality of life data		
Values used in sets, not individually for each outcome. Quality of life change associated with		
Death	0.977	same as base case, no upper
myocardial infarction (Q-wave)	0.160	0.102, no upper
Non-Q-wave myocardial infarction	0.088	0.056, no upper
Resource use (per person)		
Treatment duration (days)	2.6	2,8
Coronary artery bypass grafting rates at one year	0.014	-0.013,0.041
Angioplasty rates at one year	0.042	0.014, 0.070
Length of stay at 30 days (days)	0.40	-0.50, 0
Myocardial infarction rates at one year (Model 3 only)	0.006	same as base case, 0.013
Recurrence of angina at one year (Model 3 only)	0.017	same as base case, 0.021
Drug treatment costs per person[1]		
Enoxaparin, drug alone per day	£12.16	£9.00, £14.29
Unfractionated heparin loading dose & saline flush	£0.52	£0.41, £0.73
Consumables for loading dose	£0.14	same as base case, £0.16
Unfractionated heparin drawn-up in saline per day	£1.83	£1.37, £2.46
Pump-related costs per day	£1.79	£1.27, £2.54
Monitoring (aPTT tests) per day	£3.67	0, £3.81
Difference in nursing time between enoxaparin and unfractionated heparin (cost over 2.6 days)	£3.39	£2.95, £4.36
Treatment costs (per person) (*including length of stay)		
Coronary artery bypass grafting*	£6,534	£5,933, £6,952
Angioplasty*	£1,803	£1,647, £2,823
Treatment of acute myocardial infarction* (Model 3 only)	£1,150	£863, £1,385
Treatment of angina* (Model 3 only)	£549	£418, £758
Per in-patient day	£399	£196, same as base case

Notes: [1] Upper value includes VAT where appropriate.

ministration costs were included. Other differences in resource use associated with enoxaparin treatment are summarised in Table 2.

We assumed that the cost per day for the length of stay included resource use for adverse events such as haemorrhage. Outpatient follow-up, ambulance transport and non-NHS costs were excluded. Where required (model 3 – see below), treatment costs of myocardial infarction and recurrent angina were based on resource use of the most severe event at one year from one trial [9] for the base case and all events for the upper value.

Model and sensitivity analyses

The sources of the base case and ranges used in the analyses are shown in the Additional Materials:

Section B. We combined these data to estimate the incremental cost per QALY of enoxaparin compared with unfractionated heparin treatment based on the following three scenarios:

1. Base case: Difference in treatment-related costs minus potential savings (from revascularisations (coronary artery bypass grafting and angioplasty) and length of stay).

2. As for scenario 1, but including Value Added Tax (VAT at 17.5%), National Insurance and superannuation (ie transfer payments) since the NHS must pay these.

3. As for scenario 1, but including treatment costs of cardiac events (myocardial infarctions and recurrent angina) instead of differences in length of stay. The unit costs for length of stay should be interpreted with caution due to somewhat arbitrary accounting. This scenario was used to determine whether the alternative approach (treatment of cardiac events) produced much difference.

One-way sensitivity analyses were performed to determine how robust estimates were to the assumptions.

Results

The base case was associated with a QALY gain of 0.013 and negative net costs (ie cost savings) of £317 for each person treated with enoxaparin instead of unfractionated heparin. Table 4 shows the range of incremental net costs and QALYs resulting from the scenarios and one-way sensitivity analyses. There were net cost savings and QALY gains in all but one case. The latter was due to the longer length of stay for the UK cohort [6] that resulted in a net cost of £42 and hence cost per QALY of £3,305. However, there was still a net cost saving (£158) if there was no difference in length of stay.

Results were robust to changes in treatment duration and related costs, and the unit cost of coronary artery bypass grafting. Results were moderately sensitive to changes in the unit cost of angioplasty and very sensitive to variation in rates of revascularisation, and the duration and unit cost of length of stay. Similarly, using differences in treatment costs for myocardial infarctions and recurrent angina instead of the mean length of stay (third scenario) had a large impact on net cost savings. Changes in mean event free times reduced the QALY gain by up to three fold.

Table 3: Drug and administration costs for enoxaparin and unfractionated heparin

Average costs excluding VAT	Unfractionated heparin	Enoxaparin	Difference
Daily costs			
Drug alone	£0.95	£12.16	£11.21
Administration (saline, consumables, intra-venous pump; monitoring; nursing time)	£7.52	na	£7.52
Total cost	£8.47	£12.16	£3.69
Loading dose			
Drug alone	£0.29	na	£0.29
Administration	£0.70	na	£0.70
Total cost	£0.99	na	£0.99
Total treatment costs for base case (2.6 days)	**£23.02**	**£31.62**	**£8.60**

Table 4: Range of net costs and QALYs resulting from scenarios and one-way sensitivity analyses

Item varied	QALY or cost per person Lower	Upper
Base case (per person):	not applicable	not applicable
QALY gain 0.013		
Net cost -£317 (ie cost saving for enoxaparin)		
Event free time gained	0.004 QALYs	0.014 QALYs
Quality of life associated with event	0.012 QALYs	na
Treatment duration	-£298	-£320
Length of stay		
Difference in length of stay	£42 (ie £3,305/QALY)	-£158
Cost per length of stay	-£236	na
Revascularisations		

Table 4: Range of net costs and QALYs resulting from scenarios and one-way sensitivity analyses *(Continued)*

Difference in coronary artery bypass grafting rates	-£140	-£495
Difference in angioplasty rates	-£242	-£368
Cost of coronary artery bypass grafting	-£309	-£323
Cost of angioplasty	-£311	-£360
Unfractionated heparin costs		
Unfractionated heparin loading dose and saline flush	-£314	-£318
Unfractionated heparin drawn-up in saline	-£313	-£318
Pump-related	-£312	-£318
Monitoring (activate partial thromboplastin time tests)	-£308	-£318
Nursing time	-£314	-£318
Enoxaparin costs	-£314	-£326
Scenario 3: Treatment of cardiac events (not mean length of stay)		
Myocardial infarction rate and recurrence of angina	-£174	-£184
Cost to treat acute myocardial infarction	-£181	-£187
Cost to treat angina	-£181	-£189

Notes: See Table 2 for ranges used. As there was little difference between scenarios 1 and 2, we amalgamated the results. Negative net costs indicate cost saving if using enoxaparin. Net costs and QALY gains are not shown where unaffected by parameter changes. na means not avaliable.

Discussion

Enoxaparin treatment compared with unfractionated heparin was cost saving with increased effectiveness for the base case. Only one sensitivity analysis produced a net cost (£42 per person, cost per QALY of £3,305). The maximum cost saving per person was £495 (with a 0.013 QALY gain).

The other UK study [11] found net cost savings of £23.68 per person in contrast to the £317 in the present study. This appears to be due to the use of alternative unit costs for revascularisations and length of stay, further reinforcing the sensitivity of the results to these variables. Perhaps paradoxically, in the first trial [6], the UK enoxaparin sub-group had a longer length of stay than the unfractionated heparin group, although the authors of the US study [12] suggested that enoxaparin may have helped save the sickest patients who therefore required more treatment.

Interpretation from an UK viewpoint of the other economic studies [4,12–14] is difficult due to their resource use and unit costs being potentially unrepresentative of the UK and the variation in cost year (possibly 1994–1999). All these studies were based on the first trial [6] and used outcomes at 30 days in all but on case [14]. In contrast, we used results from the second large trial [7] to inform the sensitivity analysis. In addition, sub-group analyses of patients by country are also problematic since the trials were powered for a triple composite of death, myocardial infarction and recurrent angina (or urgent revascularisation). They were not powered for cost outcomes or to detect country differences. Furthermore, unlike the other cost studies, ours was a full economic evaluation.

As noted before, the studies are not directly comparable. However, the majority of results from the other studies were also cost saving with a maximum of £1,733 (in the Canadian patient sub-group [14]). In a minority of results there were net costs [12–14] with a maximum reported cost of £170 per person [13].

Our study results were moderately sensitive to changes in the unit cost of angioplasty and very sensitive to variation in rates of PTCA. This was similar to both the French study [4] and Canadian sub-group study [13]. Our results were also very sensitive to variation in the duration and unit cost of length of stay. This was also found in the French study [4] for both stay in the intensive care unit and non-intensive care for the ESSENCE [6] patients and French sub-group respectively. In our third scenario, similarly to the Canadian sub-group study [13], results were particularly affected by changes in the composite end-point. These similarities are unsurprising given that all the studies used data from one trial.

Limitations of the study

All models have limitations. These can be separated into general modelling issues and those specific to the current study.

There are three general limitations of modelling, all of which may be relevant here. Firstly, the potential biases from amalgamation of multiple data sources (in this study effectiveness, quality of life and costs). Secondly,

the simplifications required may lead to models being unrepresentative of reality. Thirdly, potentially inadequate sensitivity analyses where data variances are unknown, that also may be applicable here and is discussed below. Furthermore, external validity (generalisability) may be weak as results used from international randomised controlled trials reflect efficacy rather than effectiveness. Patient populations, staff in-puts, settings and therapies that differ from the UK, compound this. Shifts in other treatment or lifestyle aspects also influence relative effectiveness. For example, stent rates during angioplasty have increased dramatically since the trials, with improved results but additional costs.

The above limitations of modelling are not specific to this study and are unavoidable in most models. Currently, few models are subsequently validated due to lack of time and resources for data collection and testing. However, alternatives – economic evaluations alongside trials – are usually more expensive and are not always the 'gold standard' since resource use may not reflect routine practice and they may be no more informative than modelling. We do not believe that the study results would be changed, although the magnitude of the potential savings may be smaller – an issue that we return to in the Policy implications section.

A main limitation of the current study was that sensitivity analyses for treatment-related costs principally involved variation in unit costs as ranges for resource use were unavailable. Furthermore, the one-way analyses risked missing possible interactions between variables.

The overall effectiveness estimated in the model was from randomised controlled trials rather than the UK sub-group. There was some variation in effectiveness (eg revascularisation rates) between country sub-groups. However, this was not a prior hypothesis (ie post hoc finding) and to assume that such differences were genuine could have been seriously misleading. The extent of certainty around the effectiveness data was unknown as the simple survival analysis to estimate mean event free times did not take into account censoring and confidence intervals could not be calculated. Similarly, the small range of QALY gains (0.004 to 0.014) reflected limited data available rather than a true effect as it was not possible to calculate confidence intervals for the mean changes in quality of life from the source study [19]. Longer-term data were also unavailable and so extrapolation from 100 days to one year was based on assumptions. In addition, the quality of life estimates were not derived in an ideal manner as they used the Rosser classification [20]. Although widely used, this classification is not based on choice (the 'gold standard' for measuring preferences), it is insensitive to subtle changes [21] and valuations are not exactly reproducible [22]. Nonetheless, these data were the best available as the only published valuations found for the patient group in question.

There were also limitations in other resource use, eg the lack of confidence intervals for nursing times, and separate revascularisation rates from the second trial [7]. Furthermore, whilst most analyses used the most severe event rates in order to avoid double counting, this risked under-estimating QALYs and treatment-related costs for cardiac events.

There are also drawbacks to the unit costs. These were predominantly national costs, a heterogeneous group (NHS hospitals and pay scales, and manufacturers, and published sources) occasionally supplemented by local costs. It is difficult to estimate what the impact of this costing approach may be. The analysis shows enoxaparin had a favourable economic impact under a wide range of assumptions, however there were small differences between the alternatives that could be overturned by estimation errors that may appear small in isolation. Furthermore, the overheads element of the unit costs (for administration, cleaning, electricity, etc.) involves somewhat arbitrary accounting principles. Allocation methods vary between hospitals and therefore cost differences may not reflect true deviations. In addition, contracted prices for drugs, especially non-patented unfractionated heparin, and consumables may be considerably lower but are difficult to obtain, despite moves in the NHS for greater openness about costs.

Policy implications

Given the robustness of the results to changes in assumptions, a move from unfractionated heparin to enoxaparin appears cost saving and more beneficial in this patient group. We calculated full costs (ie including nursing time and a share of equipment costs (pumps)) that reduce the overall cost difference between the two strategies. However, this also involves a judgement on the opportunity cost of such components. Some potential cost or resource use savings such as consumables and test reagents are clearly realisable. However, other savings (eg staff and the hotel portion of hospital stays) depend on the period of change and whether resources freed can be redeployed efficiently or transferred between budget areas. Short-term increases or decreases in workload may not equate to changes in staffing as people adapt, although they may be released for other tasks. Similarly, savings from pumps are not full realisable until purchase of new ones, although there may be an impact on the staff time involved in obtaining a pump if supplies are shared. Whilst this evaluation adopted a NHS perspective to assist decision-makers, this approach could be criticised

since a broader, societal view is less likely to reinforce artificial budgetary boundaries.

The purpose of this study was to consider the cost-utility of enoxaparin since decision makers are facing the choice of substituting the traditional unfractionated heparin. However, dalteparin is another low molecular weight heparin licensed in the UK, but the licensing arrangements of other varieties is likely to be different on other countries. Furthermore, this paper was prepared for NHS decision makers and should not be generalised to other health care systems without caution. We noted the impact of revascularisation practices, but there may be other differences in health care politics and reimbursement.

Conclusions

Moving from unfractionated heparin to enoxaparin appears cost saving and more beneficial in patients with unstable coronary artery disease, although cost implications depend on local revascularisation practice. Further research is needed into the extent that potential savings are realisable and the effect of treatment on risk stratified groups as, with use, treatment thresholds may lower thus increasing total spending without necessarily gaining benefit.

Abbreviations

ESSENCE Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events

PTCA percutaneous transluminal coronary angioplasty

QALYs quality adjusted life years

TIMI Thrombolysis in Myocardial Infarction

VAT Value Added Tax (VAT)

Competing interests

None declared

Additional material

Additional material 1: Section A: Information about systematic review methods

This gives fuller explanation to allow readers to assess the adequacy of the methods used to obtain data for the cost-utility model.

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Additional material 2: Section B: Additional information about health economics methods

This additional information complies with the Drummond et al (1996) guidelines for reporting health economic papers http://www.bmj.com/cgi/content/full/313/7052/275. Furthermore, this section allows readers to test the effect of substituting their own variables.

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Additional material 3: Section C: Data extraction tables for clinical trials

These have been added for completeness as they give full details (including comments about their quality) of the trials used for the effectiveness estimates.

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Contributors:

Guarantor: Tricia Nicholson

TN: Conception, design, data collection (including literature search), analysis and interpretation, drafting article.

AM: Design, data interpretation, revising article, final approval of version to be published.

RM: Conception, design, data interpretation, revising article, final approval of version to be published.

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