Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Enoxaparin, warfarin and a combination of the two as prophylaxes for deep vein thrombosis (DVT) and pulmonary embolism (PE), following total hip arthroplasty (THA).

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population was a hypothetical population of 1000 patients who had undergone THA.

Setting
The setting was hospital and community. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were taken from studies published between 1994 and 1997. The cost of prophylactic drugs was taken from the 1997 Red Book. The resources used and cost of treating DVT and PE were taken from two studies published in 1995 and 1996. Prices were reported in 1998 US dollars ($).

Source of effectiveness data
Effectiveness data were derived from a review of the literature and from the authors' assumptions.

Outcomes assessed in the review
The outcomes assessed in the review were:
the incidences of total and proximal DVT;
the incidence of nonfatal PE; and
the number of major bleeding episodes observed

Study designs and other criteria for inclusion in the review
Randomised trials, published in English between 1994 and 1997, evaluating low-molecular weight heparin, warfarin or a combination as DVT prophylaxis following hospital discharge in THA patients, were included in the review. Inclusion criteria were that:
the treatment was available in the US;

follow-up diagnosis of DVT was by bilateral ascending contrast venography within 30-45 days of surgery;

suspected non-fatal PE had to be diagnosed by ventilation-perfusion scanning or pulmonary angiography; and

major bleeding was defined as a drop in haemoglobin values of at least 2g/dL.

Studies reported as abstracts were excluded.

Sources searched to identify primary studies
The databases MEDLINE and Current Contents were searched to identify primary studies.

Criteria used to ensure the validity of primary studies
The trials were all randomised.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Five studies were included in the review.

Methods of combining primary studies
For each parameter of effectiveness, the average value from the studies was taken.

Investigation of differences between primary studies
The authors noted the differences, between studies, in predischarge and postdischarge prophylaxes received, but no further investigations were reported.

Results of the review
The incidence of proximal DVT was 6.2% (standard deviation (SD)=0.67) for enoxaparin and 2.9% (SD=0) for warfarin.

The incidences of PE and major bleeding were zero for both enoxaparin and warfarin.

Methods used to derive estimates of effectiveness
The authors’ own assumptions were used to derive estimates of effectiveness.

Estimates of effectiveness and key assumptions
Where the combination prophylaxis was evaluated against a single drug, its effectiveness was assumed to be equal to the single drug prophylaxis.

Measure of benefits used in the economic analysis
The outcome measure used in the comparison of enoxaparin and warfarin was Proximal DVTs avoided.

Other analyses assumed equality of effectiveness: no measure of benefits was used and a cost-minimisation analysis was...
performed.

**Direct costs**
Direct costs included in the analysis were the prophylaxes and the direct medical costs associated with the diagnosis and treatment of non-fatal PEs and major bleeding episodes. The authors determined prophylaxis dosages. The costs of prophylactic drugs were the average of wholesale prices. The quantities of resources used in the diagnosis and treatment of complications were not analysed separately from their costs. An average was taken of the universal costs reported in two studies. The price year was 1998; published costs were reflated at a rate of 5% per year. Discounting was not relevant.

**Indirect Costs**
No indirect costs were included in the analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were performed on the cost of prophylaxes and the incidence of thromboembolic events. The generalisability of the results was investigated. Simple sensitivity analyses and an analysis of extremes were carried out.

**Estimated benefits used in the economic analysis**
The benefits used were the number of proximal DVTs avoided by 1,000 patients during a 30-day follow-up. Side effects of prophylaxes, tests and treatment were not considered.

With warfarin, 33 cases of proximal DVT were avoided relative to enoxaparin.

For the combination prophylaxis no cases of proximal DVT were avoided relative to either enoxaparin or warfarin alone.

**Cost results**
The total direct cost incurred by 1,000 patients was $872,569.32 (enoxaparin) and $164,161.94 (warfarin), over the 30 days from initiation of prophylaxis.

For the combination prophylaxis, the total direct cost incurred by 1,000 patients was $94,010 greater than for warfarin alone and $18,618.10 lower than for enoxaparin alone, over the 30 days from initiation of prophylaxis.

The treatment of major bleeding and thromboembolic events during the 30-day follow-up was included in the total cost.

**Synthesis of costs and benefits**
An incremental analysis was performed for enoxaparin compared to warfarin, and the authors calculated the cost per proximal DVT avoided. For warfarin there was a cost saving of $21,466.89 per proximal DVT avoided.

Warfarin was no longer cost-effective when the cost of enoxaparin was reduced by a third, and the incidence of proximal DVT with enoxaparin was zero.

Cost-minimisation analyses showed that, with the combination prophylaxis, an additional cost of $94,010 was incurred over warfarin alone, but a cost saving of $18,618.10 was demonstrated over enoxaparin.

The combination prophylaxis became more cost-effective than warfarin alone when the frequency of thromboembolic
events, for combination therapy, was reduced to 1.1%.

**Authors’ conclusions**
Using warfarin alone for 30 days is the most cost-effective regimen. However, clinicians may continue to use the combination therapy (enoxaparin for four days and warfarin for 30 days) until the results of more ‘warfarin alone’ studies are available.

**CRD COMMENTARY - Selection of comparators**
Although a justification was given for the prophylactic drugs used (having been recommended by the ACCP and previously evaluated for the population studied), no justification was given for the duration of prophylaxis. You as a user of the database, should decide whether 30 days represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The authors stated that a systematic review of the literature had been undertaken, however, the conduct of the review was not reported sufficiently clearly to be able to ascertain whether all biases were minimised. Effectiveness estimates were combined: results were pooled and the average value was calculated. The method adopted was largely satisfactory. However, the duration of follow-up differed between studies and no attempt was made to scale the incidence rates to 30-day figures before pooling. The authors did not consider the impact of differences between primary studies when estimating effectiveness. The authors justified their assumption that combination therapy was as effective as single-drug therapy. They refer to an absence of data confirming that combination therapy is more effective. Estimates were investigated by sensitivity analysis although the range used was not reported.

**Validity of estimate of measure of benefit**
For the comparison of single drug prophylaxes, the estimation of benefits was obtained directly from the effectiveness analysis. The choice of estimate was justified. For the comparison of the combination therapy with single drug prophylaxes, the analysis of benefits was based upon the therapeutic equivalence of prophylactic alternatives, hence the economic analysis performed was cost-minimisation.

**Validity of estimate of costs**
All categories of cost relevant to the perspective adopted were included in the analysis. Costs and quantities were not reported separately. A sensitivity analysis of quantities was not conducted, and this may limit the interpretation of the study findings. However, the authors used published aggregate costs and so may not have been able to ascertain the cost of individual resources. A sensitivity analysis of prices was conducted. Discounting and currency conversions were not required. The authors reported the price year.

**Other issues**
The authors did not make appropriate comparisons of their results with those from other studies and the issue of generalisability to other settings was not addressed. The authors did not present their results selectively. The study modelled a hypothetical cohort of patients undergoing THA and this was reflected in the conclusions. The authors reported a number of further limitations to their study:

The results for low-dose warfarin were based on a single study with a small sample size, and which may have understated the true incidence of proximal DVT due to the limitations of the diagnostic test used. Consequently, low-dose warfarin therapy may be less cost-effective than found in the study.

No data were available for the combination prophylaxis, and therapeutic equivalence with the single drug had to be assumed.
Implications of the study
Although 'warfarin alone' appears to be the most cost-effective prophylaxis, larger studies are needed before a definitive recommendation can be made. Clinicians may choose combination prophylaxis until the results of more definitive studies become available.

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Other publications of related interest


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Subject indexing assigned by NLM

MeSH
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