Cost-effectiveness of prophylactic low molecular weight heparin in pregnant women with a prior history of venous thromboembolism


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
Antepartum prophylaxis with low molecular weight heparin (LMWH) and expectant management during the antepartum period without prophylaxis were examined in pregnant women with a prior history of venous thromboembolism (VTE). LMWH was given to pregnant women once daily from week 16 until delivery.

Type of intervention
Secondary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of pregnant women of 30 years of age and 16 weeks post-conception. Three patient groups were considered:

"unselected" women without stratification into different clinical risk groups;

"low-risk" women with a prior VTE associated with a transient risk factor and no known thrombophilic condition; and

"high-risk" women with prior idiopathic VTE or known thrombophilic condition.

The low-risk and high-risk categories were described in detail.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data and some resource use data came from studies published between 1974 and 2003. The price year was 2004.

Source of effectiveness data
The effectiveness data were derived from a synthesis of completed studies.

Modelling
A Markov model was constructed to assess the clinical and economic impact of the two strategies examined in the study. The health states considered were well (with or without prophylaxis), postpartum warfarin, treatment for
recurrent thromboembolism, post-treatment for recurrent thromboembolism, minor or major bleed, lifelong anticoagulation, and dead. The model took adverse events associated with prophylaxis and thromboembolism into consideration. The time horizon of the model was lifetime and the cycle length was 6 weeks. A simplified structure of the model was reported.

**Outcomes assessed in the review**
The outcomes estimated from the literature were:

- the probabilities associated with thromboembolism,
- the recurrence rates,
- the rates of bleeding or fractures,
- the long-term morbidity,
- the death rates,
- the efficacy of the treatment,
- the utility values associated with treatments, and
- the disutility associated with adverse events.

**Study designs and other criteria for inclusion in the review**
The authors stated that the clinical inputs were derived from a review of existing English-language literature. However, no details of the review were reported. The characteristics and design of only a few primary studies were reported. There were 2 randomised controlled trials, 4 prospective cohort studies and 2 retrospective chart reviews.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
Not stated.

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

**Number of primary studies included**
Forty-nine primary studies provided clinical data.

**Methods of combining primary studies**
The primary estimates appear to have been combined using a narrative approach.

**Investigation of differences between primary studies**
Not stated.
Results of the review
The probability of recurrent VTE (weeks 16 - 40) was 1.8% (range: 0 - 12.5) in unselected women, 0.5% in low-risk women, and 5.9% in high-risk women.

The short-term probability of second VTE following first recurrence while receiving anticoagulant therapy was 4.0% per 6 weeks in the period 0 - 6 weeks, 0.6% per 6 weeks in the period 6 - 12 weeks, and 0.5% per 6 weeks in the period 12 - 24 weeks.

The long-term annual rate of recurrent VTE (i.e. after the first 24 weeks) was 2.0% for overall risk, 1.0% for low risk (relative risk, RR=0.5) and 2.9% for high risk (RR=1.43).

The probability of major haemorrhage on prophylactic LMWH during weeks 16 - 40 was 0.5%.

The probability of vertebral fracture on prophylactic LMWH during weeks 16 - 40 was 2.2%.

The rate of bleeding on treatment doses of warfarin was 2.0% per year (range: 0 - 5.8).

The probabilities of pulmonary embolism and deep venous thrombosis given VTE were 25% and 75%, respectively.

The probabilities of death from deep venous thrombosis, pulmonary embolism and major haemorrhage were 3% (range: 0 - 10), 21% (range: 10 - 30) and 13.4% (range: 9.4 - 17.4), respectively.

The probability of long-term morbidity from major haemorrhage was 8.7% (range: 5 - 20). The annual excess mortality following major haemorrhage with long-term morbidity was 8% (range: 4 - 16).

The efficacy of prophylactic LMWH was 99% (range: 80 - 100).

The efficacy of inferior vena caval filter for preventing pulmonary embolism was 90% (range: 50 - 100).

The utility for treatment states was 0.99 (range: 0.90 - 1) for well while receiving LMWH or warfarin and 0.60 (range: 0.02 - 1) for permanent bleeding sequelae (intracranial haemorrhage).

The short-term disutility associated with adverse events was as follows:

major haemorrhage with short-term morbidity, 4.9 days;
major haemorrhage with long-term morbidity, 6.1 days;
symptomatic vertebral fracture, 6.4 days;
deep venous thrombosis, 5.9 days; and
pulmonary embolism, 7.1 days.

Measure of benefits used in the economic analysis
The summary benefit measure used was the number of quality-adjusted life-years (QALYs). The QALYs were calculated by combining utility weights and expected survival, both derived from the literature. No details of the sources of the utility values, or the methods used to elicit patient preferences, were given. An annual discount rate of 3% was applied. The cumulative incidences of mortality, thromboembolism and disabling haemorrhage were also reported as model outputs.

Direct costs
The perspective adopted in the study was unclear since only the direct medical costs were included in the analysis. The health services considered in the analysis were drugs, supplies, anticoagulation clinic visits, inferior vena cava filter placement, hospitalisations (for deep vein thrombosis, pulmonary embolism, or haemorrhage) and pathological fracture.
The unit costs were presented separately from the resource quantities only for some items such as medications and clinical visits. The costs were estimated mainly from Medicare reimbursement rates and average wholesale prices (medications). Outpatient cost data came from the Tufts Associated Health Plans. Resource use appears to have been based on authors’ opinions. Discounting was relevant, as the lifetime costs were calculated, and an annual rate of 3% was used. The price year was 2004. Costs occurred in other years were inflated to 2004 using the medical component of the Consumer Price Index.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
Univariate and multivariate sensitivity analyses were undertaken to assess the robustness of the base-case results to variations in all model inputs. The ranges of values used were derived from the literature.

**Estimated benefits used in the economic analysis**
Among unselected women, the average QALYs were 23.76 with no prophylaxis and 23.77 with prophylaxis (difference 0.01 in favour of prophylaxis).

In low-risk women, the average QALYs were 24.16 with no prophylaxis and 24.14 with prophylaxis (difference 0.02 in favour of no prophylaxis).

In high-risk women, the average QALYs were 23.38 with no prophylaxis and 23.46 with prophylaxis (difference 0.08 in favour of prophylaxis).

**Cost results**
Among unselected women, the average costs were $6,021 with no prophylaxis and $9,806 with prophylaxis.

In low-risk women, the average costs were $2,879 with no prophylaxis and $6,875 with prophylaxis.

In high-risk women, the average costs were $9,069 with no prophylaxis and $12,246 with prophylaxis.

**Synthesis of costs and benefits**
An incremental cost-utility ratio was calculated to combine the costs and benefits of the alternative strategies.

Among unselected women, the incremental cost per QALY gained was $5,613,300 with prophylaxis over no prophylaxis. In the group of low-risk women, no prophylaxis was more effective and less costly than prophylaxis. In the group of high-risk women, the additional cost per QALY with prophylaxis in comparison with no prophylaxis was $38,700.

The sensitivity analysis showed that the base-case results were robust to variations in the model inputs. For example, in the population of unselected women, prophylaxis did not reach a cost-utility ratio lower than $50,000, while no prophylaxis was always the dominant strategy in the sub-group of low-risk women. In the sub-group of high-risk women, the option of prophylaxis was no longer cost-effective (given a threshold of $50,000 per QALY) in the NHS Economic Evaluation Database (NHS EED) Produced by the Centre for Reviews and Dissemination Copyright © 2020 University of York
following scenarios:

the probability of haemorrhage on prophylaxis was greater than 1.0% (base-case 0.5%);

the rate of major haemorrhage on anticoagulant treatment was less than 0.5% per year (base-case 2.0% per year);

the efficacy of thrombo-prophylaxis was less than 85% (base case 99%);

the probability of death from deep venous thrombosis was less than 1% (base-case 3%), or from pulmonary embolism less than 15% (base-case 21%);

when the cost of prophylaxis was greater than $1,600 per 6 weeks of treatment (base-case $1,292), or if the costs and life expectancy were discounted at a rate greater than 4.1% (base-case 3%).

The multivariate sensitivity analysis indicated that prophylaxis became more and more attractive as the probability of recurrent VTE increased and the probability of major haemorrhage while receiving prophylaxis decreased.

Authors' conclusions
For low-risk women with prior venous thromboembolism (VTE), expectant management during pregnancy led to better outcomes than the administration of prophylactic low molecular weight heparin (LMWH). However, antepartum thromboprophylaxis was cost-effective for high-risk women.

CRD COMMENTARY - Selection of comparators
The selection of expectant management as the baseline comparator was appropriate as it reflected standard care for pregnant women with a history of VTE. However, it was noted that the use of unfractionated heparin was not investigated. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published studies, but the methods and conduct of the review were not reported. Further, information on the design and characteristics was provided for only a few of the primary studies, which limits the possibility of assessing the validity of the studies. The approach used to extract and then combine the primary estimates was not described. Key parameters were varied in the sensitivity analysis in order to address the uncertainty around some clinical measures.

Validity of estimate of measure of benefit
The benefit measure used in the analysis was appropriate since QALYs capture the impact of the interventions on the most relevant dimensions of care (i.e. survival and quality of life). A further advantage of QALYs is that they are comparable with the benefits of other health care interventions. Discounting was applied in accordance with US guidelines for economic evaluations. There was limited information on the source of the utility weights and the approach used to calculate the QALYs.

Validity of estimate of costs
The economic analysis focused on direct medical costs, although the authors stated that a societal perspective was adopted. The unit costs and the quantities of resources used were not presented separately for all items, and for some categories of costs were expressed as macro-categories. However, a detailed breakdown of items was reported, which enhances the possibility of replicating the cost analysis in other settings. The costs were treated deterministically in the base-case analysis, but extensive sensitivity analyses were performed on economic items. The source of the data was reported for all costs, but resource consumption was mainly based on authors’ assumptions. The price year was reported, which will facilitate reflation exercises in other time periods.
Other issues
The authors stated that their results were consistent with those from a previous study and current guideline recommendations. The issue of the generalisability of the study results to other settings was not addressed, although extensive sensitivity analyses were performed and these enhance the external validity of the study. While the authors noted that the decision model did not incorporate the postphlebitic syndrome as a long-term complication of deep venous thrombosis, they also noted that this omission should not alter the main conclusions of the analysis.

Implications of the study
The study results suggested that the use of antepartum thromboprophylaxis should be restricted to high-risk women with prior VTE. The authors pointed out that patients could be better served by individualising management decisions.

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Other publications of related interest


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