Cost/death averted with venous thromboembolism prophylaxis in patients undergoing total knee replacement or knee arthroplasty

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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
Two prophylaxis modalities for deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients who had undergone total knee replacement (TKR) were studied. The use of low molecular weight heparin or adjusted-dose warfarin was considered.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a cohort of 42,962 patients aged over 40 years old who underwent TKR or knee arthroplasty, with a subsequent length of stay of at least 1 day, and who did not die postoperatively.

Setting
The setting was secondary care. The economic study was carried out in the Department of Biomedical Sciences and Clinical and Administrative Pharmacy, University of Georgia, USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1976 and 1997. The length of stay (LOS) and the cost estimates were obtained from the Healthcare Utilization Project-3 (HCUP-3), Nationwide Inpatient Sample (NIS), Release 4, 1995, sponsored by the Agency for Health Care Policy and Research, and from literature sources. The price year was 2000.

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

Modelling
A decision analytic model was developed to assess the comparative impact of warfarin and enoxaparin on expenditures and mortality rates for patients who had undergone TKR. The model was based on conditional probabilities of clinical events occurring after TKR.

Outcomes assessed in the review
The following clinical and epidemiological data were obtained from the literature and were included as inputs in the
model:

the total DVT rates,

the proximal DVT rates,

the distal DVT rates,

bleeding episodes,

DVT progression rates, and

mortality rates.

**Study designs and other criteria for inclusion in the review**
The studies included in the review had to meet several criteria. More specifically, randomised design, study population comprising patients older than 40 years who underwent TKR or knee arthroplasty, and use of contract venography for diagnosis. They also had to have postoperative administration of placebo, warfarin, or enoxaparin to the patients in at least one arm of the trial for at least 5 days and for no longer than 14 days. Trials in which concurrent mechanical prophylaxis was implemented were excluded.

**Sources searched to identify primary studies**
MEDLINE was searched for all English-language clinical trial reports and abstracts of DVT prophylaxis conducted in North America from January 1990 to January 2000. A second MEDLINE search of English-language articles was performed to obtain epidemiologic data on DVT complications, such as progression rates and mortality.

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

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

**Number of primary studies included**
Thirteen studies were included in the review.

**Methods of combining primary studies**
Not reported.

**Investigation of differences between primary studies**
Not investigated.

**Results of the review**
The following parameters were obtained from the systematic review.

With no prophylaxis (placebo rates), the total DVT rate was 65%, the proximal DVT rate was 20%, the distal DVT rate was 45%, and the frequency of major bleed was 2%.

With warfarin, the total DVT rate was 47%, the proximal DVT rate was 10%, the distal DVT rate was 37%, and the
frequency of major bleed was 3%.

With enoxaparin, the total DVT rate was 29%, the proximal DVT rate was 6%, the distal DVT rate was 23%, and the frequency of major bleed was 2%.

Epidemiologic estimates of DVT progression and mortality were obtained from an ad hoc review.

Forty per cent of proximal DVT are symptomatic.

Five per cent of distal DVT are symptomatic.

The PE progression rate was 50% for asymptomatic proximal DVT to PE.

The distal DVT to proximal DVT propagation rates were 29% (placebo arm) and 28% (therapy arm).

The 1-hour survival rate with PE was 89%.

Twenty-nine per cent of nonfatal PEs are symptomatic, diagnosed, and treated.

Mortality due to long-term anticoagulation treatment for either proximal or distal DVT was 0.25%.

Mortality of undiagnosed and untreated PE was 30%.

Mortality after diagnosis and treatment of PE was 8%.

Measure of benefits used in the economic analysis
The main benefit considered in the economic analysis was the number of deaths averted due to DVT prophylaxis.

Direct costs
The cost/resource boundary adopted was that of the hospital. Broad expenditure areas included resources consumed during hospitalisations (dependent on the number of days of hospitalisation), number of physician visits, resources related to prophylactic venous thromboembolism drug administration during the inpatient stay, laboratory tests for monitoring international normalised ratio, complete blood cell counts (for warfarin), and resources consumed in managing major bleeding episodes associated with prophylaxis. Postoperative consequences of venous thromboembolism prophylaxis failure including DVT and PE were also assessed. Additional medical expenses incurred by patients experiencing these complications were longer hospital stay to treat postoperative clinical events, diagnostic tests for confirming DVT or PE, and treatment costs associated with DVT or PE. Discounting was not relevant because of the short time horizon considered. The quantities and the costs were reported separately. The price year was 2000.

Statistical analysis of costs
The costs were treated stochastically.

Indirect Costs
No indirect costs were included.

Currency
US dollars ($).

Sensitivity analysis
Variability in the data was investigated. One-way sensitivity analyses were performed on:
per-diem rates;
LOS for the base-case analysis;
drug charges for enoxaparin prophylaxis;
drug charges for warfarin prophylaxis;
physician services charges;
incremental LOS for distal DVT;
incremental LOS for proximal DVT;
incremental LOS for PE;
the probability of developing a PE;
the probability of developing a symptomatic proximal DVT;
the probability of propagation of distal DVT to the proximal veins;
the development of DVT with no prophylaxis;
the development of DVT with warfarin prophylaxis; and
the development of DVT with enoxaparin prophylaxis.

For estimates derived from empirical data NIS, 95% confidence intervals were used to identify the lower and upper limits.

Estimated benefits used in the economic analysis
The number of deaths per 10,000 patients was 316 with no prophylaxis, 192 with warfarin and 122 with enoxaparin.

This translated into 124 deaths averted per 10,000 patients by warfarin and 194 deaths averted per 10,000 patients by enoxaparin.

Cost results
The authors reported the total expected medical charges. These were $26,455 for enoxaparin therapy, $27,360 for warfarin therapy and $28,766 for no prophylaxis. The costs of relevant venous thromboembolism complications were considered in the costing exercise.

Synthesis of costs and benefits
Both treatment options, warfarin and enoxaparin, were cost-saving and more effective than the option of not offering prophylaxis.

Enoxaparin was the dominant strategy in comparison with warfarin, as it cost $905 less per patient and averted 70 more deaths per 10,000 patients than warfarin.

The sensitivity analysis showed that variations in the drug costs had an insignificant impact on the incremental cost-effectiveness ratios. Even when the cost of warfarin was lowered to 1% for the base-case of 5.58 days, enoxaparin remained the cost-saving option.

Varying the probabilities of complications associated with prophylaxis failure had little influence on the incremental
cost-effectiveness ratios. Even when the PE development rate was lowered to 10% (mortality in each arm decreased to 66, 40 and 26 deaths per 10,000 for the no prophylaxis, warfarin and enoxaparin strategies, respectively), enoxaparin remained the dominant strategy.

On the other hand, when the probability of experiencing a DVT during warfarin prophylaxis approached 30.9%, break even was achieved and the expected number of deaths in the two arms became equivalent (both strategies prevented 194 deaths). Similarly, when the probability of developing a DVT with enoxaparin reached 46%, break even was achieved.

Using the worst-case estimates for DVT development after enoxaparin prophylaxis (probability of DVT with enoxaparin prophylaxis at 60%), warfarin dominated enoxaparin, as it was less costly and more effective.

Authors' conclusions
The authors stated that a wide range of model estimates and assumptions identified enoxaparin as the prophylaxis modality of choice for preventing venous thromboembolism and subsequent clinical complications following total knee replacement (TKR) surgery.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear. They represented standard practice for DVT and PE prophylaxis therapies, as recommended by the American College of Chest Physicians, in patients who have undergone TKR.

Validity of estimate of measure of effectiveness
Although the authors searched the literature using MEDLINE, a full systematic review was not reported to have been undertaken. While this is common practice in modelling studies, it does not always ensure that the best data available are used in the model. The authors appear to have used epidemiologic estimates of DVT progression and mortality rates from the available studies selectively. However, to compensate for this limitation, the authors undertook sensitivity analyses to explore the impact of variability in the data estimates.

Validity of estimate of measure of benefit
The number of deaths averted appears to have been a valid measure of benefit. However, these data might have been selectively obtained from the available studies.

Validity of estimate of costs
Relevant cost categories for the perspective adopted in the study were included. The resource quantities and the costs were reported separately. The dates to which the prices referred were also reported.

Other issues
According to the authors, this was the first study to use empirical estimates from a nationally representative sample to estimate hospitalisation charges, the largest driver of direct costs for patients who undergo TKR. Hence, the findings of this research were not compared with those of prior published studies. The authors acknowledged that the use of secondary retrospective data for determining hospital usage patterns was subject to several potential drawbacks. In addition, a primary limitation of the modelling exercise was the unavailability of venous thromboembolism progression rates for a patient who had undergone TKR, therefore published epidemiologic rates from disparate sources (mostly from orthopaedic studies) were used to populate the model.

Implications of the study
The authors suggested that a wide range of model estimates and assumptions identify enoxaparin as the prophylaxis...
modality of choice for preventing venous thromboembolism and subsequent clinical complications following TKR surgery.

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Bibliographic details

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Other publications of related interest


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