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
Low molecular weight heparins (LMWHs) were compared with warfarin for prophylaxis following total hip (THR) or total knee (TKR) replacement.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised hospital records from patients admitted for THR and TKR in 1992 in 57 acute-care non-federal hospitals in the USA. Patients were excluded if they had missing data, had more than one procedure, or had their surgery more than 3 days after hospitalisation.

Setting
The setting was secondary care (acute-care, non-federal hospitals in the USA). The economic study was carried out in the USA.

Dates to which data relate
The clinical outcomes and results for patients taking warfarin were gathered from patients admitted in 1992. The effectiveness of LMWH was obtained from a randomised controlled trial published in 1994. The prices used were from 1993.

Source of effectiveness data
The effectiveness data were derived from a single study and from a review of published studies. The authors also made some assumptions.

Link between effectiveness and cost data
For warfarin therapy, the costing was carried out retrospectively using the same sample as that used in the effectiveness analysis. The LMWH arm was modelled.

Study sample
No power calculations or method of sample selection were reported in the study. From the 9,663 patient records included in the HCIA's (Health Care Investment Analysis Inc.) Clinical Pathway database, 1,942 were excluded because
of missing data (n=1013), and/or multiple procedures (n=802), and/or having surgery more than 3 days after admission. The final study sample comprised 2,964 THRs and 4,757 TKRs. Of these patients, 72% were over 65 years old, 62% were female and 85% had osteoarthritis. Warfarin prophylaxis was received by 42.1% and no prophylaxis by 40.2%. Factors associated with receiving no prophylaxis were older age, polypharmacy and TKR.

Study design
This was a retrospective cohort study using a hospital dataset. The dataset was developed by HCIA with data from 57 acute-care hospitals (Clinical Pathways Database) and was used to assess complication rates and resource use. The duration of follow-up was not stated, but it appears to have been restricted to the acute hospitalisation phase.

Analysis of effectiveness
As this was a retrospective analysis, it was based on the type of prophylaxis actually received preoperatively. The patients were segmented into three categories according to the prophylaxis received, in other words, no prophylaxis, warfarin prophylaxis, and other (heparin or aspirin, intermittent pneumatic compression, compression stockings or other). The patients were classified into two categories (definitely complicated and possibly complicated) according to the certainty of thromboembolic complications (DVT or PE).

The definitely complicated group comprised:

- patients coded for DVT or PE who either received treatment levels of heparin, or were transferred from the hospital or died;
- patients coded for related disorders (e.g. atrial fibrillation) who received treatment levels of heparin;
- patients coded for DVT or PE who received intermediate levels of heparin; and
- patients not coded for DVT or PE, but who received treatment levels of heparin, had a lung scan, stayed at hospital more than 10 days, or were transferred.

The possibly complicated group comprised:

- patients coded for DVT or PE who received less than treatment levels of heparin and were neither transferred from the hospital nor died;
- patients who received treatment levels of heparin, but who were not coded for DVT or PE; and
- patients coded for DVT or PE related disorders who received less than treatment levels of heparin, and were transferred or died.

Characteristics that significantly affected the decision to administer no prophylaxis were having a TKR, being older, and mainly receiving more concurrent pharmacological therapy. Adjustment for confounding factors was not reported.

Effectiveness results
The overall rates of symptomatic DVT and/or PE ranged from 1.1 to 4.1% in THR patients and from 1.4 to 4.4% in TKR patients, depending on the outcome definition. The low end of the range represented definitely complicated patients and the high end possibly complicated ones.

Differences between TKR and THR were not statistically significant.

Warfarin prophylaxis was found to be significantly more effective than no prophylaxis, (p<0.001). In THR patients, patients who received warfarin (n=1,273) had a 0.8% incidence of definite DVT or PE, a 0.5% incidence of possible DVT or PE, and a 1.3% incidence of total DVT or PE. The corresponding figures in the no prophylaxis group (n=1,059) were 0.9% (definite), 2.7% (possible), and 3.6% (total) in the no prophylaxis group.
In TKR patients who received warfarin (n=1,975), the incidence rates of DVT or PE were definite 0.8%, possible 0.9%, and total 1.7%. In the no prophylaxis group (n=1,059), these figures were definite 1.1%, possible 2.8%, and total 3.9%.

The overall complication rate was higher in patients receiving more interactive drugs with warfarin, patients who were obese, and those with congestive heart failure.

Clinical conclusions
Patients receiving warfarin prophylaxis had significantly fewer complications than those having no prophylaxis. The complication rate was higher in patients receiving more interactive drugs with warfarin, patients who were obese, and those with congestive heart failure.

Modelling
To compare the actual results with warfarin with the estimated results with LMWH, the authors modelled the expected effects and cost implications of using LMWH. The main effects considered were complication rates and complications, more specifically, deep venous thrombosis (DVT) or pulmonary embolism (PE). The authors assumed no significant difference in bleeding complications. These were not included in the analysis as they are rare and earlier studies have suggested no significant differences.

Outcomes assessed in the review
The outcomes assessed in the review were the DVT and PE incidence with warfarin or ardeparin (LMWH), and bleeding complications.

Study designs and other criteria for inclusion in the review
DVT and PE incidence were obtained from a randomised trial. Individual studies and meta-analyses of clinical trials provided information on bleeding complications.

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
A randomised trial provided DVT and PE incidence, as well as bleeding rates. Five individual studies and 3 meta-analyses of clinical trials were cited for bleeding complications.

Methods of combining primary studies
As a single trial was used to compare DVT and PE incidence, a synthesis was not carried out. Bleeding complications were assumed to be similar using a narrative method.

Investigation of differences between primary studies
Not stated.

Results of the review
Prophylaxis with ardeparin resulted in 41% fewer incidents of asymptomatic DVT and PE than prophylaxis with warfarin, (p<0.001). Bleeding complications were reported to be similar.

Methods used to derive estimates of effectiveness
The authors made assumptions on the basis of the literature.

Estimates of effectiveness and key assumptions
The authors made two key assumptions. First, the expected incidence of symptomatic DVT or PE would be similarly reduced to asymptomatic DVT or PE found in the trial results. Second, bleeding complications were similar, and were thus excluded from the study. Complicated patients were also assumed to be twice as likely to have DVT as PE.

Measure of benefits used in the economic analysis
The measure of benefits used in the economic analysis was the rate of DVT or PE.

Direct costs
Discounting was not carried out, which was appropriate due to the short time horizon of the study. The quantities and the cost/charges were analysed separately. The average utilisation of medical resources was calculated from the HCIA data on 3,199 uncomplicated patients receiving warfarin prophylaxis and 2,984 uncomplicated patients receiving no prophylaxis. The resources included laboratory tests for prothrombin time (PT), activated partial thromboplastin time, and complete blood count. Inpatient resource use for DVT and/or PE treatment was calculated using data from the 107 definitely complicated patients. The resources included heparin and warfarin, ultrasonograms, lung scans, chest radiographs, arterial blood gas analyses, and laboratory monitoring tests for coagulation. Interviews with hospital personnel informed estimates of the related laboratory technician, nursing, pharmacy and physician time associated with each of the aforementioned prophylaxis or treatment procedures. Some tests were excluded as the authors assumed that the tests were common to both treatments. The incremental cost of warfarin prophylaxis was assumed to include six additional PT tests in a week. LMWH was assumed to need no additional PT. An inpatient treatment protocol for treating DVT or PE was assumed. This comprised heparin, warfarin, activated partial thromboplastin time, PT and complete blood count tests, diagnostic tests (ultrasonograms, lung scans, chest radiographs, arterial blood gas analyses), and 7 additional days of hospitalisation (3 spent in a critical care unit in the case of PE).

The analysis considered both the costs and charges for medical resources. The costs of medical procedures and inpatient and outpatient visits were estimated from base fees in the 1993 Medicare RB-RVS national fee schedule, adjusted upwards by 10% to account for average geographic adjustments made to the base rate. The cost of heparin and warfarin for treating DVT or PE was assumed to be equal to the average wholesale price. Pharmacy dispensing, nursing administration and medical technician time costs were estimated using wage data from the American Hospital Association. The cost of additional inpatient days was estimated through weighted average per diem costs of acute-care hospitals of the Maryland Hospital Association.

Charge data for procedures were obtained from the 1994 50th percentile charges of third-party payers reported by the Practice Management Information Corporation. Hospital per diem charges were obtained from the Maryland Hospital Services Cost Research Commission. Inpatient laboratory test charges were taken from HCIA. The charge for heparin and warfarin for treating DVT or PE was assumed to be 30% higher than the average wholesale price. The analysis compared the average total costs of medical care for each prophylaxis alternative, excluding the cost of the pharmaceuticals consumed in the prophylaxis. The average total cost of care was equal to the cost of prophylaxis plus the expected costs of complications (rate of symptomatic DVT or PE multiplied by the costs of treatment). A hospital perspective was adopted, and both costs and charges were reported. Pharmacological costs of prophylaxis with warfarin and LMWH were not considered, so that each institution could evaluate the results using their local drug costs/charges.
Statistical analysis of costs
Resource use was treated stochastically to compare warfarin to no prophylaxis. It was then treated deterministically to estimate the cost implications of warfarin versus LMWH.

Indirect Costs
The indirect costs were not considered in the study.

Currency
US dollars ($).

Sensitivity analysis
One- and two-way sensitivity analyses were used to estimate the difference in the cost implications due to reasonable variations in certain parameters, such as a difference in the complication rates or laboratory test costs.

Estimated benefits used in the economic analysis
The symptomatic complication rate for patients (TKR and THR) receiving warfarin was assumed to be 1.15%, the midpoint of the range between definitely complicated and definitely plus possibly complicated patients. Assuming a 41% reduction with LMWH, a complication rate of 0.68% would be expected with LMWH.

Cost results
There were no significant difference in resource use for prophylaxis between patients in the TKR and THR groups.

The inpatient costs (or charges) were $2,785 ($5,114) for DVT treatment and $4,710 ($7,836) for PE treatment.

The outpatient costs (or charges) were $376 ($409) for DVT and $753 ($817) for PE.

The expected total costs (or charges) in all patients were $97.04 ($237.75) for warfarin prophylaxis and $47.44 ($44.73) for LMWH prophylaxis. Of the $50 ($193) expected difference in the total cost, 63% (84%) was due to expected savings in laboratory costs as a result of using LMWH.

Savings in blood monitoring costs and improvements in efficacy were key to the cost-savings. For example, if laboratory tests were processed singly rather than in batches, the difference in expected total costs (charges) would increase to $70 ($193).

If complication rates doubled from 1.15 to 2.3%, the difference in expected total costs would rise to $68 ($224).

Small hospitals, especially prone to both higher complications and laboratory costs, would expect a difference of $88 ($224) in favour of LMWH.

The total costs were very sensitive to the length of hospital stay. A decrease in stay of one day would increase the difference to $226 ($624).

Synthesis of costs and benefits
The costs and benefits were not combined. When excluding the pharmacological costs of prophylaxis, LMWH was estimated to prevent complications and have a lower cost.

Authors' conclusions
Low molecular weight heparin (LMWH) has the potential to offer cost-advantages in comparison with warfarin, mostly
due to the lower test costs associated with prophylaxis and the reduced complication rates.

**CRD COMMENTARY - Selection of comparators**
The comparator, warfarin, was appropriately selected as being routinely and widely used in the US setting before the introduction of LMWH.

**Validity of estimate of measure of effectiveness**
The main aim of the study was to evaluate the cost implications of LMWH, and warfarin versus LMWH. Effectiveness was based on the results of a single trial, and relative benefit was treated deterministically. This could have altered, if not the main results, then the sensitivity analysis. The authors did not state whether a systematic review of the literature was conducted, and did not state the methods used to select the final trial.

**Validity of estimate of measure of benefit**
The expected benefits of LMWH were modelled by applying the LMWH complication rate point estimate reduction from a single trial to the complication rate observed in the administrative database of patients using warfarin.

**Validity of estimate of costs**
The authors included the relevant cost categories in the analysis, except for the cost/charges of the prophylactic drugs evaluated (warfarin and LMWH). This exclusion would certainly have affected the main results, as the authors stated that generic warfarin can be purchased at a lower price than branded warfarin. The authors suggested that each institution compute its own costs by adding the costs of warfarin or LMWH treatment to the study's main results (table 5 of the original paper). Some laboratory costs common to both strategies were omitted. The quantities and the cost/charges were analysed separately, which helps transferability to other settings. Resource used was derived from a large retrospective database analysis and authors' assumptions. The authors reported both the costs and charges. Costs may be more useful for hospitals and staff model health maintenance organisations who receive a fixed payment for services provided (e.g. capitated or diagnostic-related groups). Charges may be more useful for payers or providers using a fee-for-service basis. The costs and charges were taken from published sources and the price year was reported. This makes reflation exercises possible.

**Other issues**
The authors partially compared their study with other cost-effectiveness studies. Generalisability to other settings was addressed by the study mainly using administrative data collected during routine care, and in the sensitivity analysis where laboratory processing capability was evaluated. The authors reported some further limitations of the study. First, the reliance of the results on coding and billing data which makes it impossible to confirm what actually happened to the patients. Second, the results were derived from a non-random population and were, therefore, susceptible to selection bias. This may underestimate warfarin benefit versus no prophylaxis.

**Implications of the study**
There were considerable variations in prophylaxis practices and outcomes. This suggests the need for protocols and guidelines that explicitly consider patient risk factors, such as the concurrent use of pharmaceuticals and the appropriate choice of prophylactic methods, including LMWH. This study helps hospitals and third-party payers to evaluate possible cost implications of warfarin versus LMWH, which could be very different in the two scenarios.

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