Cost-effectiveness of combination thromboembolism prophylaxis in gynecologic oncology surgery

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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
The use of external pneumatic compression (EPC) for 5 days, with or without low molecular weight heparin (LMWH), as prophylactic therapy for deep vein thrombosis (DVT) in gynaecologic oncology surgery. LMWH (enoxaparin) was administered at a dose of 40 mg/day for 5 days.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised three hypothetical cohorts of women undergoing gynaecologic surgery. There was a 35-year-old cohort with Stage IB cervix cancer, a 55-year-old cohort with Stage IA endometrial cancer, and a 65-year-old cohort with Stage IIIC ovarian cancer.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1971 and 2002. No dates for the resource use data were reported. Some costs were derived from a database published in 1997 and a study published in 2000. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' assumptions.

Modelling
A published Markov model was modified slightly and used to determine the clinical and economic impact of the three interventions under evaluation (i.e. no prophylaxis, ECP, and ECP+LMWH) in the three hypothetical cohorts considered in the model. Each cohort comprised 100,000 women. The model took not only the impact of the interventions on DVT prevention into consideration, but also the costs of diagnosis and treatment as well as complications arising from prophylaxis. The time horizon of the model covered the period from surgery to death, or until 85 years of age. The cycle length was one year.
Outcomes assessed in the review
The outcomes estimated from the literature were:

the overall risk of DVT in patients with gynaecologic cancer;

the risk of DVT in the specific populations modelled;

the rate of symptoms if DVT developed;

the rate of symptomatic pulmonary embolism (PE) without prior DVT symptoms;

mortality from symptomatic PE;

sudden death from PE;

the relative risk of DVT in cancer patients;

the relative risk of sudden death from PE;

the rate of reduction in symptomatic DVT and PE, and in sudden death with low-dose heparin, LMWH, or EPC; and

the rate of bleeding complications.

Study designs and other criteria for inclusion in the review
The authors stated that a systematic review of the English literature was undertaken to identify relevant sources of data. However, no details on the design of the primary studies were reported.

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
Sixty-five primary studies were included in the review.

Methods of combining primary studies
Not stated.

Investigation of differences between primary studies
Not stated.

Results of the review
The overall risk of DVT was 0.24 (range: 0.04 - 0.25) in patients with gynaecologic cancer.
The risk of DVT was 0.13 in the 35-year-old cohort with Stage IB cervix cancer, 0.195 in the 55-year-old cohort with Stage IA endometrial cancer, and 0.39 in the 65-year-old cohort with Stage IIIC ovarian cancer.

The rate of symptoms if DVT developed was 0.25 (range: 0.2 - 0.4).

The rate of symptomatic PE without prior DVT symptoms was 0.013 (range: 0.01 - 0.05).

The mortality from symptomatic PE was 0.12 (range: 0.1 - 0.5).

The rate of sudden death from PE was 0.008 (range: 0.001 - 0.008).

The relative risk of DVT was 1 (range: 1 - 1.5) in the 35-year-old cohort with Stage IB cervix cancer, 1.5 (range: 1 - 2) in the 55-year-old cohort with Stage IA endometrial cancer, and 4 (range: 2 - 5) in the 65-year-old cohort with Stage IIIC ovarian cancer.

The relative risk of sudden death from PE was similar to the relative risk of DVT.

The rate of reduction in symptomatic DVT and PE was 0.68 (range: 0.6 - 0.8) with low-dose heparin and LMWH, and 0.69 (range: 0.6 - 0.8) with EPC.

The rate of reduction in sudden death was 0.68 (range: 0.6 - 0.75) with low-dose heparin, 0.68 (range: 0.55 - 0.75) with LMWH, and 0.69 (range: 0.5 - 0.75) with EPC.

The rate of medical (transfusion only) bleeding complications was 0.058 (range: 0.05 - 0.07) with low-dose heparin and 0.049 (range: 0.04 - 0.07) with LMWH.

The rate of surgical (requiring reoperation) bleeding complications was 0.024 (range: 0.02 - 0.05) with low-dose heparin and 0.018 (range: 0.01 - 0.05) with LMWH.

Life expectancy was reported only for a 55-year-old woman (25 years) and a 35-year-old woman (55 years).

Methods used to derive estimates of effectiveness
The authors made some assumptions that were used in the decision model.

Estimates of effectiveness and key assumptions
It was assumed that EPC did not result in bleeding complications. In addition, the rate of developing PE after symptomatic DVT was assumed to be 0.005 (range: 0.001 - 0.1).

Measure of benefits used in the economic analysis
The benefit measures that were estimated using the decision model were the number of events (DVT plus PE cases) prevented per 100,000 and incremental life expectancy. However, only the number of life-years gained was considered as the summary benefit measure in the economic analysis and was combined with the costs. Expected survival was discounted at an annual rate of 3%.

Direct costs
The costs were incurred over a lifetime horizon and discounting was relevant. An annual discount rate of 3% was applied. The unit costs were reported separately from the quantities of resources used for most cost items. However, some costs were presented as macro-categories. The health interventions examined in the study were LMWH (enoxaparin), EPC, tests for the diagnosis of thromboembolism, therapy for thromboembolism, and postsurgical treatment of underlying disease. The diagnostic tests included Doppler ultrasound, venography, ventilation or perfusion scan, chest X-ray, pulmonary angiogram, arterial blood gas, and electrocardiogram. The diagnosis of thromboembolism distinguished between DVT and PE. Therapy for thromboembolism covered heparin, warfarin, activated partial thromboplastin time (aPTT), and anticoagulant treatment. The surgical interventions included surgery for the underlying disease, resection of the affected organ, and reoperation for PE. The cost of medical and surgical complications was incurred during the lifetime horizon and was discounted at an annual rate of 3%.
thromboplastin time, INR, hospital stay, and the treatment of complications. Postsurgical treatment covered medications, equipment, staff, laboratory tests, and chemotherapy.

The cost/resource boundary of the study was not reported. The costs came from several sources, including gynaecologic malignancy-related diagnosis-related groups in the Health Care Financing Administration Medicare Provider Analysis and Review database, and published studies. When charges were used as the source of cost data, a 60% cost-to-charge ratio was applied. Resource use was mainly based on authors' assumptions. All the costs were presented in 2001 values using the medical cost component of the Consumer Price Index.

**Statistical analysis of costs**
No statistical analyses of the costs were performed.

**Indirect Costs**
The indirect costs were not considered in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were carried out to address the issue of variability in the data. The analysis focused on the risk of thromboembolism and the charges associated with chemotherapy. There was little information on the type of sensitivity analysis conducted, but both one- and two-ways analyses appear to have been performed. Some of the ranges used were derived from the literature.

**Estimated benefits used in the economic analysis**
In the 35-year-old cohort with Stage IB cervix cancer, the mean life expectancy was 21.484 with no prophylaxis, 21.637 with EPC, and 21.664 with EPC+LMWH.

The number of total events prevented per 100,000 was 3,922 (1,533 PE events only) with EPC over no prophylaxis, and 279 (273 PE events only) with EPC+LMWH over EPC.

In the 55-year-old cohort with Stage IA endometrial cancer, the mean life expectancy was 19.80 with no prophylaxis, 20.01 with EPC, and 20.05 with EPC+LMWH.

The number of total events prevented per 100,000 was 5,882 (2,300 PE events only) with EPC over no prophylaxis, and 419 (428 PE events only) with EPC+LMWH over EPC.

In the 65-year-old cohort with Stage IIIC ovarian cancer, the mean life expectancy was 6.586 with no prophylaxis, 6.729 with EPC, and 6.754 with EPC+LMWH.

The number of total events prevented per 100,000 was 11,700 (4,600 PE events only) with EPC over no prophylaxis, and 2,100 (820 PE events only) with EPC+LMWH over EPC.

**Cost results**
In the 35-year-old cohort with Stage IB cervix cancer, the average cost per patient was $1,075 with no prophylaxis, $1,127 with EPC, and $1,406 with EPC+LMWH.

In the 55-year-old cohort with Stage IA endometrial cancer, the average cost per patient was $1,105 with no prophylaxis, $1,132 with EPC, and $1,406 with EPC+LMWH.
In the 65-year-old cohort with Stage IIIC ovarian cancer, the average cost per patient was $38,000 with no prophylaxis, $38,900 with EPC, and $39,400 with EPC+LMWH.

The substantial higher costs for ovarian cancer were mainly due to the inclusion of chemotherapy costs.

**Synthesis of costs and benefits**

An incremental cost-effectiveness ratio (ICER), namely an incremental cost per life-year saved, was calculated to combine the costs and benefits of the preventive strategies under evaluation.

In the 35-year-old cohort with Stage IB cervix cancer, the ICER was $304 with EPC versus no prophylaxis and $10,091 with EPC+LMWH over EPC.

In the 55-year-old cohort with Stage IA endometrial cancer, the ICER was $129 with EPC versus no prophylaxis and $7,150 with EPC+LMWH over EPC.

In the 65-year-old cohort with Stage IIIC ovarian cancer, the ICER was $19,479 with EPC versus no prophylaxis and $50,181 with EPC+LMWH over EPC.

The sensitivity analysis showed that if charges associated with chemotherapy were excluded for patients with Stage IIIC ovarian cancer, the ICER with combination therapy would be approximately $12,600.

For all patient groups, as long as the risk of thromboembolism was decreased from 6.4% to 4% by adding LMWH to EPC, the ICER was less than $50,000.

Variations in other model inputs, such as changes in the cost and efficacy of LMWH, did not alter substantially the base-case results.

**Authors’ conclusions**

External pneumatic compression (EPC) remained the most cost-effective method of thromboembolic prophylaxis in gynaecologic oncology patients. The combined prophylactic strategy of EPC and low molecular weight heparin (LMWH) may be cost-effective (cost per life-year saved below the threshold of $50,000 - $60,000), even in women with a short life expectancy and designated as at "high risk" (diagnosis of cancer and older than 60 years of age), only if an appropriate clinical study can verify the estimates of risk reduction used in the current analysis.

**CRD COMMENTARY - Selection of comparators**

The authors justified the choice of the comparators, which represented traditional and new prophylactic options for the prevention of DVT in gynaecologic oncology surgery. The option of no prophylaxis was included for comparative purposes. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

The analysis of the effectiveness came mainly from a systematic review of the literature. However, the methods and conduct of the review were not reported, and no information on the design of the primary studies was provided. Therefore, it is difficult to assess the validity of the sources used. Further, many studies included in the review were published more than 20 years ago and might not accurately reflect today's clinical data. Some key model inputs were varied in the sensitivity analysis.

**Validity of estimate of measure of benefit**

The use of survival as the main summary benefit measure was appropriate since this is the most relevant dimension of health for cancer patients. Survival was calculated using a modelling approach, but limited information on the model, which had been published, was provided. Discounting appears to have been applied to survival, as US guidelines suggest.
Validity of estimate of costs
The perspective adopted in the study was not stated clearly and limited information on the source of the data (especially resource consumption) was reported. Nevertheless, the unit costs were, in general, presented separately from the quantities of resources used, although a breakdown of the costs was not presented for all categories. For example, chemotherapy costs were presented as a single category. The price year was reported, which aids reflation exercises in other settings. However, the costs were treated deterministically and only some cost items were varied in the sensitivity analysis.

Other issues
The authors reported the results of published studies that showed the benefits associated with combination therapy for the prevention of thromboembolism. However, no formal comparison with the results of the current study was carried out. The issue of the generalisability of the study results to other settings was not addressed and only a few sensitivity analyses were performed. This affected the external validity of the analysis. The study referred to gynaecologic oncology patients and this was reflected in the authors’ conclusions.

Implications of the study
The study results suggested that thromboembolism prevention using EPC and LMWH may be a cost-effective strategy for gynaecologic oncology patients, even high-risk patients. The authors pointed out the need for well-designed clinical trials to provide robust evidence for gynaecologic oncologists. The results of the analysis suggested also that clinical trials should be sufficiently powered to demonstrate a difference in risk reduction of 40%.

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Other publications of related interest


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