A study on the safety, efficacy, and efficiency of sulodexide compared with acenocoumarol in secondary prophylaxis in patients with deep venous thrombosis

Cirujeda J L, Granado P C

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
Patients with deep vein thrombosis (DVT) were given low molecular weight heparin (LMWH) and urokinase. The LMWH (nadroparin) was given every 12 hours for 10 days; the dose was adjusted 4 hours after administration in the morning to anti-Xa levels of 0.8 to 1.2 U/mL. Urokinase was administered at a dose of 300,000 IU/day and was given for 5 days. After treatment with urokinase had finished, oral treatment with 30 mg sulodexide was given. Treatment finished after 3 months. The comparator technology was to initially give the same treatment of LMWH and urokinase, but to follow this with 2 mg/day acenocoumarol with the international normalised ratio (INR) adjusted every 30 days.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The patients had been diagnosed by colour echo-Doppler as having proximal DVT of the lower limbs for less than 1 month. The patients had to be at least 18 years old. Patients were excluded if they had an active haemorrhage, a contraindication to anti-thrombotic treatment, or were know to be allergic to the study medications or the contrast medium. They were also excluded if they were carriers of documented congenital haemocoagulative defects, or if they had kidney or liver failure.

Setting
The setting was secondary care. The economic study was carried out in La Rioja, Spain.

Dates to which data relate
The effectiveness and resource evidence were from 2001 to 2003. The price year was 2003.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out retrospectively on the same patients who provided the effectiveness data.

Study sample
No power calculations were reported, although the authors stated "150 patients were considered suitable to fulfil the
study objectives”. There were 75 patients in each treatment group.

**Study design**
This was a single-centred, randomised controlled trial (RCT) in which patients were randomised between the two types of treatment. The patients were followed up for 3 months after treatment ended. Sixty-eight (90.7%) patients in the sulodexide group and 67 (89.3%) in the acenocoumarol group completed the follow-up.

**Analysis of effectiveness**
The analysis was conducted on the basis of treatment completers. Effectiveness was assessed by the presence of recurring DVTs and/or pulmonary embolism. The patients were shown to be comparable at baseline.

**Effectiveness results**
One patient in each treatment group suffered from nonfatal pulmonary embolism.

Two patients in the sulodexide group and 3 in the acenocoumarol group suffered from venous recurrence.

There were no cases of haemorrhagic complications in the sulodexide group. However, in the acenocoumarol group, there were 9 (12%) minor haemorrhages and 1 major haemorrhage, (p=0.014; 95% confidence interval: 4.7% to 19.4%).

Four patients in the sulodexide group and 3 in the acenocoumarol group died from cancer during the study, (difference not statistically significant).

One patient in the sulodexide group and 3 in the acenocoumarol group suffered from an allergic reaction, (difference not statistically significant).

**Clinical conclusions**
There was no significant difference between the two groups in their effectiveness in preventing DVTs and pulmonary embolisms. Sulodexide produced fewer haemorrhages.

**Measure of benefits used in the economic analysis**
No summary measure of benefit was used as the authors carried out a cost-consequences analysis.

**Direct costs**
Discounting was not carried out as the costs were incurred during less than 2 years. The unit costs and total costs of five key cost components were given. Specifically, the drug costs of sulodexide and acenocoumarol, monitoring by haematology and vascular surgery, and prothrombin time (INR). The costs common to both treatment groups were not included. The unit costs were obtained from the Pharmaceutical Specialties Catalogue and database of Spanish health costs. The quantities of resources used by the two treatment groups were obtained through a questionnaire. Thus, the estimation of the costs was based on what resources the authors expected to be used rather than the resources actually used. The price year was 2003.

**Statistical analysis of costs**
No statistical analysis of the costs was carried out.

**Indirect Costs**
No indirect costs were estimated.
Currency
Euros (EUR).

Sensitivity analysis
A one-way sensitivity analysis was carried out to investigate the effects of calculating costs for 6 months rather than 3 months, changing the acenocoumarol dose to 1 mg/day, and of adjusting acenocoumarol once a month.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The cost per patient was EUR 109.98 in the sulodexide group and EUR 593.79 in the acenocoumarol group.

The cost-saving from using sulodexide over a 3-month period was EUR 483.81.

In the sensitivity analyses sulodexide was always cheaper, but the cost-difference ranged from EUR 248.31 to EUR 732.12.

The costs of adverse effects were not included in the analysis.

Synthesis of costs and benefits
The costs and benefits were not combined as the study was a cost-consequences analysis.

Authors' conclusions
Sulodexide was cheaper than acenocoumarol. Both patient groups had similar health outcomes, apart from haemorrhages, which were higher in the acenocoumarol group.

CRD COMMENTARY - Selection of comparators
The choice of the comparator, LMWH and urokinase followed by acenocoumarol, was justified by it being current practice for DVT patients in many settings. You should decide if the comparator represents current practice in your own setting.

Validity of estimate of measure of effectiveness
The source of the effectiveness data was a single study. The study design, an RCT, was appropriate for the hypothesis. The study sample appears to have been representative of the study population. The patient groups were shown to be comparable at analysis. The analysis of effectiveness was handled credibly, though no statistical results were given for some of the effectiveness measures.

Validity of estimate of measure of benefit
The authors did not derive a summary measure of health benefit as they carried out a cost-consequences analysis. The comments in the 'Validity of estimate of measure of effectiveness' field (above) therefore apply.

Validity of estimate of costs
For the cost perspective adopted (i.e. the hospital), the authors estimated the costs that would be incurred if everything ran to plan. They did not estimate the actual costs incurred by the patients, so it is not clear if this biased the results. The
authors did not report the costs separately from the quantities, although they reported the unit costs and total costs for the key cost components. The unit costs were taken from published sources, whilst the resource use quantities were taken from questionnaires carried out at the hospital to estimate resources necessary for the two kinds of treatment. No other sources were used for resource quantities. There was no sensitivity, statistical or any other kind of analysis of the prices, and no statistical analysis of the quantities. However, a sensitivity analysis was carried out to assess the effect of varying the dose of acenocoumarol, of adjusting it once a month, and of calculating costs for 6 months. The price year was reported.

Other issues
The authors made appropriate comparisons of their results with the findings from other studies. The issue of generalisability to other settings was not addressed. The authors did not present their results selectively. The authors’ conclusions reflected the scope of the analysis, apart from the fact that the actual costs were not estimated. The authors report several limitations of their study. For example, the costing was carried out retrospectively, patient quality of life was not assessed, and indirect costs were not calculated. The inclusion of the indirect costs would have given a bigger advantage to sulodexide as it would avoid several monitoring visits.

Implications of the study
The authors recommended using sulodexide rather than acenocoumarol for secondary prophylaxis of thromboembolic diseases, as it cost less and produced fewer haemorrhages.

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