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
Seven strategies for the prophylaxis of variceal re-bleeding were studied.

Strategy 1 was beta-blockers without haemodynamic monitoring. Strategy 2 was a combination of beta-blockers and isosorbide mononitrate without haemodynamic monitoring.

Strategy 3 was endoscopic variceal ligation (EVL).

Strategy 4 was beta-blockers with one hepatic venous pressure gradient (HVPG) measurement performed 3 months after drug therapy initiation. Response to therapy was defined as an HVPG of less than 12 mmHg, or a decrease of at least 20% compared with baseline. Responders continued with beta-blocker therapy, while nonresponders underwent EVL.

Strategy 5 was beta-blockers with two HVPG measurements, one prior to drug therapy and the other 3 months after drug therapy began. Responders and nonresponders followed the clinical pattern reported for strategy 4.

Strategy 6 was combination therapy with one HVPG measurement.

Strategy 7 was combination therapy with two HVPG measurements.

Type of intervention
Secondary prevention and diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients requiring secondary prevention for variceal bleeding.

Setting
The setting was likely to have been secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were derived from studies published between 1985 and 2002. The authors stated that the price year was 2002, although 2000 prices were reported in the tables.

Source of effectiveness data
The effectiveness evidence was derived from a review of completed studies and authors' assumptions.
Modelling
A Markov model was constructed to assess the clinical and economic impact of the seven prophylaxis strategies under evaluation in a typical patient aged 55 years with cirrhosis and no other significant co-morbidities, with an average Child-Pugh score of 8. The time horizon of the model was 3 years and the cycle length was 6 months. After prophylaxis was prescribed, the patient could experience recurrent variceal bleeding, procedural-related complications, death as a result of re-bleeding, or death due to the progression of liver disease. These represented the possible health states of the model.

Outcomes assessed in the review
The outcomes assessed were the probabilities of:

re-bleeding without haemodynamic monitoring (per 6 months) with EVL, beta-blockers, or combination therapy;

haemodynamic response (either 20% reduction or less than 12 mmHg) with beta-blockers or combination therapy;

re-bleeding according to haemodynamic response (either 20% reduction or less than 12 mmHg) with beta-blockers or combination therapy;

complications due to EVL (per episode);

intolerance to beta-blockers or combination therapy; and

death due to variceal bleeding (per episode) or other causes (per 6 months).

Study designs and other criteria for inclusion in the review
It was not stated whether the review of the literature was systematic. Details of the primary studies were not provided.

Sources searched to identify primary studies
MEDLINE was searched for relevant studies. The keywords included "variceal bleeding", "portal hypertension", "secondary prophylaxis", "hepatic venous pressure gradient" and "portal pressure". Further studies were identified from the reference lists of the articles retrieved from the search.

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
Twenty primary studies were included in the review.

Methods of combining primary studies
The primary estimates appear to have been combined using narrative methods.

Investigation of differences between primary studies
Not stated.
Results of the review
The rate of re-bleeding without haemodynamic monitoring (per 6 months) was 0.107 (range: 0.05 - 0.17) with EVL, 0.125 (range: 0.03 - 0.19) with beta-blockers, and 0.085 (range: 0.05 - 0.10) with combination therapy.

The rate of haemodynamic response, in terms of a 20% reduction, was 0.36 (range: 0.19 - 0.55) with beta-blockers and 0.51 (range: 0.40 - 0.67) with combination therapy. For response in terms of less than 12 mmHg, the rate was 0.12 (range: 0.10 - 0.21) with beta-blockers and 0.14 (range: 0.10 - 0.20) with combination therapy.

The rate of re-bleeding according to haemodynamic response, in terms of a 20% reduction, was 0.02 (range: 0 - 0.05) with beta-blockers and 0.04 (range: 0 - 0.05) with combination therapy. For response in terms of less than 12 mmHg, the rate was 0 with both beta-blockers and combination therapy.

The rate of complications due to EVL (per episode) was 0.001 (range: 0.0001 - 0.01).

The rate of intolerance to drugs was 0.05 (range: 0.05 - 0.20) with beta-blockers and 0.13 (range: 0.07 - 0.19) with combination therapy.

The rate of death was 0.20 (range: 0.05 - 0.30) due to variceal bleeding (per episode) and 0.035 (range: 0.016 - 0.30) due to other causes (per 6 months).

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
The rate of death due to endoscopic variceal ligation complications was 0.1 (range: 0.01 - 0.25). Morbidity caused by complications from chronic liver disease was assumed to occur with the same frequency among all strategies and was not included in the model. Similarly, the probability of liver transplantation was not accounted for as it was considered to have the same impact on all treatment options.

Measure of benefits used in the economic analysis
The summary benefit measures used were the number of life-years saved and the episodes of variceal bleeding averted. Both were derived from the decision model. Survival was discounted at an annual rate of 3%.

Direct costs
Discounting was relevant, as the costs were incurred during more than 2 years, and an annual rate of 3% was applied. The unit costs were not presented separately from the quantities of resources used and costs were reported in macro-categories. The health services included in the economic evaluation were drugs (beta-blockers and isosorbide mononitrate), oesophagogastroduodenoscopy, HVPG, hospitalisation for variceal bleeding, and the treatment of complications from endoscopy. The cost/resource boundary of the third-party payer was adopted. Resource use was mainly estimated using data derived from the literature. The costs were derived from Medicare reimbursement rates at the authors’ institution (University of Alabama) and wholesale prices. The authors stated that the price year was 2002, although 2000 prices were reported in the tables.

Statistical analysis of costs
The costs were treated deterministically in the base-case.

Indirect Costs
The indirect costs were not considered.
Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were carried out to investigate the issue of uncertainty arising from variability in the model inputs. The inputs were varied in a univariate sensitivity analysis, and then two-way sensitivity analyses were conducted with the most influential parameters. The ranges of probability values were derived from the literature. However, no justification for the ranges of costs was provided. Changes in the length of the time horizon were also studied. A first-order Monte Carlo simulation based on 1,000 iterations was also performed.

Estimated benefits used in the economic analysis
The estimated life expectancy per patient was:

- 2.25 with combination therapy,
- 2.20 with beta-blockers,
- 2.22 with EVL,
- 2.24 with combination therapy plus 1 HVPG measurement,
- 2.24 with beta-blockers plus 1 HVPG measurement,
- 2.28 with combination therapy plus 2 HVPG measurements, and
- 2.27 with beta-blockers plus 2 HVPG measurements.

In a sample of 100 patients, the episodes of bleeding were:

- 67 with beta-blockers,
- 52 with combination therapy,
- 61 with EVL,
- 54 with beta-blockers plus 1 HVPG measurement,
- 53 with combination therapy plus 1 HVPG measurement, and
- 44 with beta-blockers plus 2 HVPG measurements.

The rate of bleeding with combination therapy plus 2 HVPG measurements was 0.2% lower than that associated with beta-blockers plus 1 HVPG measurement. Undiscounted results were also reported.

Cost results
The estimated per patient costs were:

- $9,504 with combination therapy,
- $11,186 with beta-blockers,
- $12,043 with EVL,
- $12,829 with combination therapy plus 1 HVPG measurement,
$13,147 with beta-blockers plus 1 HVPG measurement,

$13,605 with combination therapy plus 2 HVPG measurements, and

$13,826 with beta-blockers plus 2 HVPG measurements.

Undiscounted results were also reported.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the alternative preventive strategies. The incremental analysis revealed that the cheapest strategy (combination therapy) strongly dominated (less costly and more effective) all the other strategies, with the exception of one. This exception was combination therapy with 2 HVPG measurements, which had an incremental cost of $136,700 per life-year saved relative to combination therapy and an incremental cost of $51,262 per episode of re-bleeding prevented. Similar results were obtained in the undiscounted analysis.

The sensitivity analysis revealed that the results of the base-case were quite robust. The only parameter that had a strong influence on the incremental ratios was the model time horizon. When the time horizon of the study was 5 years, the incremental cost per life-year saved with combination therapy plus 2 HVPG measurements relative to combination therapy was $21,000, while when the time horizon was 1 year it was $2,274,000. The Monte Carlo simulations showed that HVPG strategies had, in general, a cost-effectiveness ratio above the commonly used threshold of $50,000 per life-year saved. At willingness-to-pay thresholds of $200,000, $100,000 and $50,000, the probability for combination therapy plus 2 HVPG measurements to be cost-effective relative to combination therapy was 98%, 45% and 19%, respectively.

Authors' conclusions
The cost-effectiveness of haemodynamic monitoring to assist secondary prophylaxis of recurrent variceal bleeding was well above the threshold of $50,000 per life-year saved. It depended on specific factors, such as monitoring costs, life expectancy, and re-bleeding rates. Both strategies that involved only one hepatic venous pressure gradient (HVPG) measurement were found to be less efficacious and more expensive than combination therapy alone. The model results enabled those variables that could improve the cost-effectiveness of the prophylaxis strategies to be identified. Patients with an extended life expectancy and those at high risk for recurrent variceal bleeding were identified as those who could benefit the most from HVPG-based strategies.

CRD COMMENTARY - Selection of comparators
The selection of the comparators appears to have been appropriate since it covered the most commonly used treatment options for prophylaxis of variceal bleeding. One of the options was considered as current practice. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a review of the literature. The methods and conduct of the review were not reported and only the search strategies were described. The authors did not state whether the review was systematic and no information on the primary studies was given. Therefore, it is difficult to assess the validity of the sources used. Narrative methods were used to combine the primary estimates. Most of the probability values were varied in the sensitivity analysis.

Validity of estimate of measure of benefit
The use of survival as a summary benefit measure was appropriate for capturing the impact of the interventions on the patients' health. Discounting was performed, as recommended in US guidelines. Undiscounted figures were reported. A disease-specific summary benefit was also used. The issue of quality of life was not addressed, which would have been
interesting. However, the authors noted that quality of life data were not available. The use of survival enables comparisons with the benefits of other health care interventions.

**Validity of estimate of costs**
The authors stated explicitly which perspective was adopted in the study. It appears that all the relevant categories of costs have been included in the analysis. Limited information on the unit costs and resource use was provided. The costs were presented as macro-categories for some items, which limits the possibility of replicating the study. Discounting was relevant and was carried out. The price year was reported, which aids reflation exercises in other settings. Reimbursement rates were used as proxies for costs. The source of the data was reported. The costs were treated deterministically in the base-case, but variability in economic data was investigated in the sensitivity analysis.

**Other issues**
The authors did not make extensive comparisons of their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. Sensitivity analyses were carried out, which had a positive impact on the external validity of the analysis. The authors noted some limitations to the validity of their analysis. First, some of the variables used in the model had a non-linear development over time, which could reduce the robustness of those conclusions of the analysis that were based on the results of the extended time horizon. Second, some data used in the model were not exhaustive and could have differed in sub-group analyses. Finally, the hypothesis that a reduction in variceal bleeding resulted in a reduction in mortality was controversial in the literature.

**Implications of the study**
The authors suggested that further studies should investigate the cost-effectiveness of haemodynamic monitoring until portal pressure can be assessed by an alternative technique, or pharmacotherapy related to a more uniform decrease in portal pressure is available.

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