Hepatic venous pressure gradient measurements to assess response to primary prophylaxis in patients with cirrhosis: a decision analytical study


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 two hepatic venous pressure gradient (HVPG) measurement strategies to evaluate the response to beta-blocker (BB) therapy in patients with cirrhosis, who were at risk of variceal bleeding (VB). The strategies were HVPG measurement 4 weeks after the initiation of BB therapy (strategy 1) and HVPG prior to and 4 weeks after the initiation of BB therapy (strategy 2). A HVPG measurement of greater than 12 mmHg indicated a high risk of variceal rupture.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with cirrhosis and non-bleeding, high-risk varices.

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

Dates to which data relate
The effectiveness and resource use data were obtained from studies published between 1987 and 2001. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from published studies and the authors’ assumptions.

Modelling
Two separate decision tree models were constructed to estimate the economic implications of the two strategies for HVPG measurement in a hypothetical cohort of 100 patients with cirrhosis and at high-risk of VB, for a period of one year. Each model evaluated each strategy relative to BB therapy alone. In both models the patients received BB therapy. Those patients who did not tolerate the treatment underwent endoscopic variceal ligation (EVL) to obtain variceal obliteration, while those who responded to the therapy continued it for one year. However, those patients found with a HVPG of greater than 12 mmHg (strategy 1), or with a reduction in HVPG from baseline of less than 20% (strategy 2), discontinued the BB therapy and underwent EVL. The model took into consideration mortality resulting from VB, EVL and other liver-related causes. The authors stated that a Markov model was constructed to simulate the economic impact of the two measurement strategies over a time horizon longer than one year.
Outcomes assessed in the review
The outcomes assessed in the review were the following probabilities:

HVPG decreased to less than 12 mmHg,

VB after HVPG decreased to less than 12 mmHg,

HVPG decreased to at least 20%,

VB after HVPG decreased to at least 20%,

VB while on BB therapy,

VB after EVL,

complications from EVL,

death from cirrhosis,

death from VB, and

intolerance to BB therapy.

Study designs and other criteria for inclusion in the review
Not stated.

Sources searched to identify primary studies
MEDLINE was searched using the keywords "variceal bleeding", "portal hypertension", "primary prophylaxis", "hepatic venous pressure gradient" and "portal pressure". Further relevant studies were obtained from the reference list of each study retrieved from MEDLINE.

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
Eleven studies were included in the review.

Methods of combining primary studies
The methods used to combine the primary studies were not reported.

Investigation of differences between primary studies
Not stated.

Results of the review
The probability values were:
24% (range: 0 - 50) for HVPG decreased to less than 12 mmHg,
0% (range: 0 - 25) for VB after HVPG decreased to less than 12 mmHg,
61% (range: 0 - 100) for HVPG decreased to at least 20%,
2.3% (range: 0 - 50) for VB after HVPG decreased to at least 20%,
7.5% (range: 0 - 75) for VB while on BB therapy,
5% (range: 0 - 50) for VB after EVL,
1% (range: 0 - 10) for complications from EVL,
14% (range: 0 - 50) for death from cirrhosis,
20% (range: 0 - 50) for death from VB, and
15% (range: 0 - 50) for intolerance to BB therapy.

Methods used to derive estimates of effectiveness
The authors made some assumptions due to the lack of data available in the literature. These assumptions were based on acceptable and justifiable clinical decisions reflecting expert opinion.

Estimates of effectiveness and key assumptions
It was assumed that:

adverse events associated with HVPG measurements were negligible;

BB therapy was discontinued, due to adverse events in the first two weeks after drug initiation, in 15% of the patients; and

EVL was considered as the unique alternative to BB therapy (thus excluding nitrates as monotherapy or in addition to BB).

Measure of benefits used in the economic analysis
The benefit measures used in the economic analysis were the number of VB episodes and patient mortality. Mortality due to VB was also reported. Both were calculated using the decision model. No discounting was performed due to the short time horizon of the analysis. However, a 3% annual discount rate was applied in the Markov model since the time horizon was extended.

Direct costs
Discounting was not relevant since the costs were incurred in one year. In terms of benefits, a 3% annual rate was applied in the Markov model to discount future costs, due to the extended time horizon of the analysis. The unit costs were not reported separately from the quantities of resources used. The health services included in the economic evaluation were BB therapy, treatment of VB episode, EVL, treatment of EVL complications and HVPG measurement. The cost/resource boundary adopted in the study was that of the third-party payer. Resource use was based on probability data derived from the studies used to provide the effectiveness evidence. The costs were estimated using wholesale prices for drugs and Medicare reimbursement rates at the authors' institution (the University of Alabama) for the remaining categories of costs. The price year was 2001.
Statistical analysis of costs
The costs were treated deterministically in the base-case.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
One-way and two-way sensitivity analyses were carried out to evaluate the impact of changes in several model inputs and assumptions on the estimated cost-effectiveness ratios.

Estimated benefits used in the economic analysis
The numbers of VB episodes, deaths due to VB and total deaths were estimated for the cohort of 100 patients:

- with BB therapy alone, there were 7 VB episodes, 1 death due to VB and 15 deaths in total;
- with strategy 1, there were 4 VB episodes, 1 death due to VB and 14 deaths in total;
- with strategy 2, there were 4 VB episodes, 1 death due to VB and 15 deaths in total.

Cost results
The estimated annual costs in the cohort of 100 patients were $1,464 per patient with BB therapy alone, $5,015 per patient with strategy 1, and $8,657 per patient with strategy 2.

Synthesis of costs and benefits
An incremental cost-effectiveness analysis was carried out to combine the costs and benefits of each measurement strategy relative to BB therapy alone.

- The incremental cost per VB episode prevented with strategy 1 relative to BB therapy was $108,185. The incremental cost per death prevented with strategy 1 relative to BB therapy was $355,100.
- The incremental cost per VB episode prevented with strategy 2 relative to BB therapy was $202,796. The incremental cost per death prevented with strategy 2 relative to BB therapy was $719,300.

These figures did not vary substantially in the one-way sensitivity analysis. The variables with the greatest impact were the cost of HVPG and the probability of bleeding while receiving BB therapy. The two-way sensitivity analysis showed that both HVPG measurement strategies were preferred to BB therapy alone when the cost of HVPG was very low and the overall probability of VB while on BB therapy was very high. The long-term analysis (based on the Markov model) showed that the cost-effectiveness ratio fell below the threshold value of $50,000 per life-year saved after 5.5 years for strategy 2 (two measurements) and after 3.5 years for strategy 1 (one measurement).

Authors’ conclusions
At one year, both hepatic venous pressure gradient (HVPG) measurement strategies were extremely expensive relative to routine beta-blocker (BB) therapy in patients with cirrhosis who were at risk of variceal bleeding (VB). However, they may represent cost-effective strategies under specific conditions, such as an extended time horizon, in patient populations in whom endoscopic findings suggest a very high risk of VB, and in settings were the cost of HVPG
measurement is low.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparator was clear. BB therapy alone was selected as it represented the routine treatment for patients with cirrhosis. It was also chosen to evaluate the extra value of adding HVPG measurement. The authors noted that the use of combination therapy (BB plus nitrates) was not evaluated, although it may represent a feasible option as basic therapy for patients with cirrhosis. You should decide whether it represents a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness analysis used a review of the literature. However, the authors only described the search methods and not the methodology and conduct of the review. The method used to combine the primary studies was not stated. It was unclear whether the authors took into account differences in the primary studies when estimating the effectiveness. The primary studies were not described. Some assumptions were made due to the lack of available information in the literature. The authors stated that all the assumptions were based on actual treatment patterns, and uncertainty in the estimates was investigated in the sensitivity analysis.

**Validity of estimate of measure of benefit**
The benefit measures used in the economic analysis were the number of VB cases prevented and the deaths avoided. The former (VB cases prevented) represents a disease-specific end point. The latter (deaths avoided) ensures the comparability of the benefits of the present study interventions with those associated with other technologies funded in the health care system. Both measures were obtained using a decision model, which was described in detail in the paper. Discounting was appropriately applied when the time horizon of the analysis was extended.

**Validity of estimate of costs**
The perspective adopted in the study was reported. It appears that all the relevant categories of costs have been included in the economic evaluation. However, the unit costs and the quantities of resources used were not reported separately, which may hinder generalisability. The source of the cost data was reported, but resource consumption was presumably derived from the probability values used in the effectiveness study and the authors’ assumptions. The costs were treated deterministically in the base-case, but were varied in the sensitivity analysis. The price year was reported, thus facilitating reflation exercises in other settings. The authors stated that the cost estimates represented estimates valid across the USA. However, they noted that their estimate of HVPG measurement cost may have been higher than that observed in other institutions. The impact of including the indirect costs was not evaluated.

**Other issues**
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other countries, although their findings should be transferable to other US institutions. The authors noted some limitations of their analysis, which have been reported already. The use of an incremental cost-effectiveness analysis was appropriate to evaluate the extra costs and benefits of the two strategies under examination relative to standard treatment patterns. The use of a Markov model to extend the time horizon of the analysis was helpful in understanding the long-term implications of the analysis, which represented the key results of the study.

**Implications of the study**
The main implication of the study is that both strategies for HVPG measurement may be cost-effective, but only in specific patient populations and settings. The authors suggest that future studies should evaluate the long-term clinical and haemodynamic effects of prophylaxis for VB in cirrhotic patients.
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