Cost-effectiveness of screening, surveillance, and primary prophylaxis strategies for esophageal varices

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
Screening, surveillance and primary prophylaxis strategies for oesophageal varices (OEV) were considered. Four strategies were analysed:

no screening and no prophylaxis;
universal screening and primary prophylaxis with nonselective beta-blockers for large varices detected;
universal screening and primary prophylaxis with endoscopic variceal ligation (EVL); and
universal primary prophylaxis with beta-blockers without screening.

Type of intervention
Screening and prophylaxis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised two hypothetical cohorts of 50-year-old patients with cirrhosis. The first cohort consisted of patients with decompensated or Child-Pugh A cirrhosis. The second cohort consisted of patients with decompensated or Child-Pugh B cirrhosis.

Setting
The setting was unclear. The economic analysis was carried out in Birmingham (AL), USA.

Dates to which data relate
The effectiveness data were gathered from studies published between 1981 and 2000. Resource data were gathered from studies published between 1997 and 2000. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from published studies.

Modelling
A Markov decision analytic model was created, using DATA 3.5 software, to simulate the costs and the health outcomes assigned to each strategy. The five health states described were no varices, small varices, large varices, bleed,
and death. The time horizon was 5 years and each cycle was 1 year.

**Outcomes assessed in the review**
The outcomes assessed in the review and used as model inputs were:

- the prevalence of varices;
- the probability of varice development;
- the probability of bleeding;
- the risk reduction of bleeding from large varices with beta-blockers or EVL;
- the probability of death caused by VB;
- the probability of complications caused by endoscopy;
- the risk reduction of re-bleeding on secondary prophylaxis; and
- the transition probabilities between disease states.

Health-related quality of life was also assessed in the review.

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

**Sources searched to identify primary studies**
MEDLINE was searched for primary studies. In addition, population-based mortality rates adjusted for age, gender and race were obtained from published US Vital Statistics.

**Criteria used to ensure the validity of primary studies**
Not specified.

**Methods used to judge relevance and validity, and for extracting data**
Not specified.

**Number of primary studies included**
Approximately 19 studies were included in the review.

**Methods of combining primary studies**
Not reported.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
In compensated cirrhotics:
the prevalence of varices was 0.30 (0.85 for small varices and 0.15 for large varices);
the probability of varices development was 0.045 for none to small varices, and 0.06 for small to large varices;
the probability of bleeding was 0.05 with small varices and 0.15 with large varices;
the risk reduction of bleeding from large varices was 0.50 with beta-blockers and 0.55 with EVL;
the probability of death caused by VB was 0.10 per episode;
the probability of complications caused by endoscopy was 0.001; and
the risk reduction of re-bleeding on secondary prophylaxis was 0.43.

In decompensated cirrhotics:
the prevalence of varices was 0.60 (0.50 for small varices and 0.50 for large varices);
the probability of varices development was 0.045 for none to small varices, and 0.06 for small to large varices;
the probability of bleeding was 0.10 with small varices and 0.17 with large varices;
the risk reduction of bleeding from large varices was 0.50 with beta-blockers and 0.55 with EVL;
the probability of death caused by VB was 0.30 per episode;
the probability of complications caused by endoscopy was 0.001;
the risk reduction of re-bleeding on secondary prophylaxis was 0.43; and
the transition probability from compensated to decompensated cirrhosis was 0.045.

Methods used to derive estimates of effectiveness
The authors made several assumptions to estimate model inputs. It appears that the estimates have been based on the authors' opinion.

Estimates of effectiveness and key assumptions
The main assumptions were as follows.

The authors assumed an 85% tolerance rate for pharmacological therapy with beta-blockers.

In patients undergoing EVL, the authors assumed a success rate of 95% for EVL and an 85% tolerance rate for beta-blocker therapy.

The authors assumed a linear probability for the annual development and growth of OEV in both compensated and decompensated cirrhotics.

The authors assumed a constant risk of VB throughout the time horizon.

The authors assumed that beta-blocker therapy did not affect the rates of variceal development or growth. In addition, the risk reduction for VB provided by such therapy was equal among the strategies in both patient groups.

Primary prophylaxis was assumed not to influence the probability of death associated with an episode of VB.

The authors assumed that the risk of VB among cirrhotics was similar, regardless of the underlying etiology of liver
disease. In addition, the risk reduction of beta-blocker therapy was equal between the two patient sub-groups.

**Measure of benefits used in the economic analysis**
The benefit measures were the number of life-years saved (LYS) and the quality-adjusted life-years (QALYs) saved. Quality of life was measured by health-state utility weights on a scale from 0 to 1 and was derived from the literature. The benefits were discounted at an annual rate of 3%.

**Direct costs**
The perspective of the third-party payer was adopted. The direct costs were for screening, beta-blocker therapy, VB hospitalisation and complications arising from endoscopy. The costs associated with complications arising from chronic liver diseases and portal hypertension were not included. The costs reflected Medicare reimbursement rates at the authors' institution. The cost of beta-blockers represented the average wholesale price. The unit costs were reported, whereas the quantities of resources used were not. All of the costs were adjusted to 2000 US dollars. The total costs were derived using the decision analytic model. The source of the quantities was not reported. The costs were discounted at a rate of 3%.

**Statistical analysis of costs**
No statistical analysis of the costs was performed.

**Indirect Costs**
The indirect costs were not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
One- and two-way sensitivity analyses were performed on all parameter values, using ranges obtained from the literature.

**Estimated benefits used in the economic analysis**
In compensated cirrhotics, discounted life expectancy was 3.953 years per patient in the 'no screening/no prophylaxis' strategy, 4.13 years with EVL, 4.154 years with universal screening, and 4.155 years with universal primary prophylaxis.

In decompensated cirrhotics, discounted life expectancy was 1.912 years per patient in the 'no screening/no prophylaxis' strategy, 2.115 years with EVL, 2.130 years with universal screening, and 2.143 years with universal primary prophylaxis.

**Cost results**
In compensated cirrhotics, the total cost was $1,079 per patient with 'no screening/no prophylaxis', $1,795 with EVL, $1,837 with universal screening, and $1,903 with universal primary prophylaxis.

In decompensated cirrhotics, the total cost was $2,363 per patient with 'no screening/no prophylaxis', $2,027 with EVL, $2,043 with universal screening, and $2,058 with universal primary prophylaxis.

**Synthesis of costs and benefits**
In compensated cirrhotics, the incremental cost-effectiveness ratio (ICER) of EVL compared with 'no screening/no prophylaxis' was $4,045 per LYS. The ICER of universal screening compared with EVL was $1,750 per LYS, whereas the ICER of universal primary prophylaxis compared with universal screening was $66,000 per LYS. Hence, EVL was dominated (extended-dominance). The ICER of universal screening compared with 'no screening/no prophylaxis' was $3,771 per LYS.

The ICER of EVL compared with 'no screening/no prophylaxis' was $2,869 per QALY, whereas the ICER of universal screening compared with EVL was $4,700 per QALY. The ICER of universal primary prophylaxis compared with universal screening was $88,000 per QALY.

The sensitivity analysis showed that the results were most sensitive to the prevalence of varices and the risk of VB.

In decompensated cirrhotics, 'no screening/no prophylaxis' was dominated by the other strategies. The ICER of universal screening compared with EVL was $1,067 per LYS, whereas the ICER of universal primary prophylaxis compared with universal screening was $1,154 per LYS.

The ICER of universal screening compared with EVL was $4,000 per QALY, whereas the ICER of universal primary prophylaxis compared with universal screening was $2,000 per QALY. Then, universal screening was dominated (extended-dominance). The ICER of universal primary prophylaxis compared with EVL was $2,727 per QALY.

The sensitivity analysis showed that the results were most sensitive to the cost of beta-blockers and endoscopy.

Authors' conclusions
Universal screening for varices is a cost-effective strategy in compensated liver disease, whereas universal primary prophylaxis with beta-blockers is cost-effective in decompensated patients.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator (no screening and no prophylaxis) was clear. You should decide whether it represents a currently used approach in your own setting.

Validity of estimate of measure of effectiveness
It appears that a systematic review of the literature had been undertaken, although some relevant details surrounding the methodology of the review were not reported. The source searched to identify the primary studies was reported. The criteria used to ensure the validity of the primary studies were not reported, nor were the methods used to judge the relevance and validity of the data. Also, there was little commentary on the quality of the retrieved studies, making it difficult to comment on the quality of the efficacy estimates. However, the impact of differences between the primary studies and the relevance of the assumptions made on estimates were assessed through sensitivity analyses. These analyses improved both the internal validity and the generalisability of the study by demonstrating the robustness of the results to changes in the base-case estimates.

Validity of estimate of measure of benefit
The number of LYS was derived from the model. The number of QALYs gained in each strategy was also estimated in the model using health-state utility weights derived from the literature. Hence, it was unclear whether quality of life estimates were derived from patients’ preferences or expert opinion, which limits the relevance of the QALY estimates and thus the cost-effectiveness results. The efficacy and benefit measures were reported separately, thus making it easy for the reader to recreate the results and to understand the key factors impacting on the cost-effectiveness ratios. The authors did not justify the time horizon of 5 years and, from the original paper, it was not obvious why it was selected. Discounting was performed and was relevant.

Validity of estimate of costs
All the categories of costs relevant to the perspective adopted (the third-party payer) appear to have been included in the analysis. The costs associated with some complications were not included, but a justification was provided for their exclusion (they were common among all four strategies). This exclusion might have led to the underestimation of the cost-effectiveness ratios, unless these costs were equal for all strategies. The quantities and the costs were not reported separately and the sources of the quantities were not reported. These factors limit the possibility of replicating the study in other settings. The price year was reported, which will assist reflation exercises. Statistical tests were not carried out and the costs were treated deterministically. Sensitivity analyses were performed on the costs, using ranges of variation obtained from the literature. Discounting was performed, which was appropriate as the costs were incurred during more than 2 years.

Other issues
The authors made appropriate comparisons of their effectiveness results with those from other studies, reporting consistency in their results. The issue of generalisability to other settings was addressed in that the authors reported that, in the setting of a population-based programme, the small cost and life expectancy differences will amplify and become greater. The results were not reported selectively and the conclusions reflected the scope of the study. The authors highlighted some limitations of their study. These focused on inclusion criteria (only patients without absolute contraindications to beta-blockers before screening), on the limitation of data on health-related quality of life weights, and on the assumption of linear probability of bleeding from OEV which would introduce bias toward aggressive initial screening and/or early initiation of primary prophylaxis.

Implications of the study
The authors suggested that their results support the economic feasibility of current practice guidelines recommending endoscopic screening for varices in compensated cirrhotics. They also suggested that there is a need for data on the specific effects of VB and beta-blockers side effects on the patient(s health-related quality of life. In addition, they mentioned that further studies addressing the natural history of varices and bleeding, as well as the value of haemodynamic monitoring, are likely to provide further insight into minimising costs associated with the prevention of VB.

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