American Journal of Gastroenterology
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Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2004.30754.x

The Cost-Effectiveness of Hepatic Venous Pressure Gradient Monitoring in the Prevention of Recurrent Variceal Hemorrhage

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OBJECTIVE: Recurrent variceal hemorrhage is common following an initial bleed in patients with cirrhosis. The current standard of care for secondary prophylaxis is endoscopic band ligation (EBL). Combination of β-blocker and nitrate therapy, guided by hepatic venous pressure gradient (HVPG) monitoring, is a novel alternative strategy. We sought to determine the cost-effectiveness of these competing strategies.

METHODS: Decision analysis with Markov modeling was used to calculate the cost-effectiveness of three competing strategies: (1) EBL; (2) β-blocker and nitrate therapy *without* HVPG monitoring (HVPG−); and (3) β-blocker and nitrate therapy *with* HVPG monitoring (HVPG+). Patients in the HVPG+ strategy who failed to achieve an HVPG decline from medical therapy were offered EBL. Cost estimates were from a third-party payer perspective. The main outcome measure was the cost per recurrent variceal hemorrhage prevented.

RESULTS: Under base-case conditions, the HVPG+ strategy was the most effective yet most expensive approach, followed by EBL and HVPG−. Compared to the EBL strategy, the HVPG+ strategy cost an incremental $5,974 per recurrent bleed prevented. In a population with 100% compliance with all therapies, the incremental cost of HVPG− *versus* EBL fell to $5,270 per recurrent bleed prevented. The model results were sensitive to the cost of EBL, the cost of HVPG monitoring, and the probability of medical therapy producing an adequate HVPG decline.

CONCLUSIONS: Compared to EBL for the secondary prophylaxis of variceal rebleeding, combination medical therapy guided by HVPG monitoring is more effective and only marginally more expensive.

INTRODUCTION

Hemorrhage from esophageal varices is a common and clinically significant problem in patients with cirrhosis (1, 2). Moreover, up to 80% of patients surviving an initial bleed develop recurrent hemorrhage within the following 2 yr (3–5). Endoscopic band ligation (EBL) has proven efficacy in the prevention of recurrent variceal hemorrhage (6), and has emerged as the standard of care for the secondary prophylaxis of variceal hemorrhage. Alternatively, medical therapy with either β-blockers or a combination of β-blockers and long-acting nitrates have demonstrated effectiveness in decreasing the incidence of recurrent variceal bleeding (7–9). However, results from studies comparing combination medical therapy with endoscopic therapy have yielded conflicting results (8–11). Therefore, the appropriateness of combination therapy in the prevention of recurrent variceal hemorrhage is unclear.

Recent data indicate that the effectiveness of medical therapy is most pronounced in the subset of patients achieving a significant decline in their hepatic venous pressure gradient (HVPG), defined as an HVPG measurement <12 mmHg or $>25\%$ decline in HVPG from the pretreatment value (8, 9, 12–14). Patients taking the combination of β-blockers and the long-acting nitrates are more likely to have a significant decline in their HVPG than patients using β-blockers alone (15). This raises the possibility that HVPG monitoring may be a useful adjunct to medical therapy via identification of treatment failures that require alternative management. Although a recent decision analysis suggests that HVPG monitoring may not be cost-effective in the primary prevention of variceal

Presented in part at the AGA Clinical Hepatobiliary Research Forum Digestive Disease Week, May 2002, San Francisco, California. Funding Sources: Dr. Spiegel is supported by NIH Training Grant DK-07180, Dr. Dulai is supported by an NIH K23 Award NIH/NCRR K23 1618801, Dr. Gralnek is supported by a VA HSR&D Advanced Research Career Development Award and VA HSR&D IIR 01-191-1.

hemorrhage (16), the performance of this modality may improve when it is being used for secondary prophylaxis. This is due to the increased risk of variceal hemorrhage in patients who have already had a previous episode of variceal bleeding. Furthermore, recent review articles suggest that the patients surviving an initial variceal hemorrhage should receive upfront medical therapy for secondary prophylaxis along with HVPG monitoring to assess response to therapy. EBL would then be recommended for the subset of patients failing to achieve an adequate decline in their HVPG (17, 18).

However, HVPG monitoring is an invasive and expensive procedure, and its cost-effectiveness has not been established in the setting of secondary prophylaxis of variceal hemorrhage. Furthermore, there are no published trials comparing medical therapy with adjunctive HVPG monitoring *versus* standard endoscopic therapy for the prevention of recurrent variceal bleeding. We therefore sought to compare the cost-effectiveness of medical therapy with or without adjuvant HVPG monitoring *versus* the standard practice of EBL for the secondary prophylaxis of variceal hemorrhage in a decision analysis model.

METHODS

Decision analysis is a quantitative method for estimating the cost-effectiveness of the alternative management strategies under conditions of uncertainty (19). Using decision analysis software (DATA version 3.5, TreeAge Software, Boston, MA), we evaluated three competing strategies for the prevention of recurrent variceal hemorrhage:

1. Endoscopic band ligation (EBL).
2. Combination medical therapy with nadolol and isosorbide-5-mononitrate *without* HVPG monitoring to gauge therapeutic response (HVPG–).
3. Combination medical therapy with nadolol and isosorbide-5-mononitrate *with* HVPG monitoring, with nonresponders receiving EBL (HVPG+).

Base-Case Patient Cohort

We evaluated a hypothetical cohort of cirrhotic patients following successful EBL for an index episode of esophageal variceal hemorrhage. We assumed that the severity of underlying liver disease was representative of subjects enrolled in secondary prophylaxis clinical trials. We assumed that the patients had no contraindications to β-blockers, oral nitrates, or further EBL therapy. We further assumed that the cohort did not develop early rebleeding from esophageal varices, defined as rebleeding prior to hospital discharge. The hypothetical cohort thus simulated patient populations enrolled in intervention trials for the secondary prophylaxis of variceal hemorrhage.

Markov Model

We created a Markov model with 1-month transition intervals to simulate the natural history of patients with cirrhosis following an initial variceal hemorrhage over a 24-month time horizon (Fig. 1). In this transition model, all the subjects were initially alive without an episode of recurrent variceal bleeding ("Alive—No Rebleed"). Subjects then either continued without a recurrent bleed or suffered a recurrent bleed. Those without a recurrent bleed either remained alive throughout the course of the study period or died from a nonvariceal cause. Those patients who suffered a recurrent bleed either survived the episode or died.

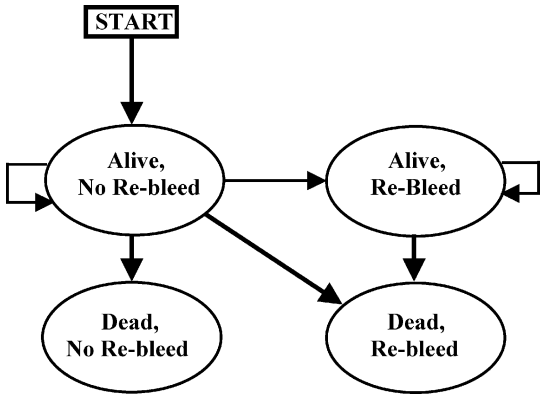

Figure 1. Markov state diagram. The base-case cohort consists of survivors of an initial variceal hemorrhage that enter the model in the health state of "Alive, No Re-bleed." The cohort is then treated with one of three competing management strategies (see text for strategy details), and progresses through the Markov model in 1-month cycles. During each cycle individual members of the cohort either remain in their assigned health state (recursive arrows), or progress to a new health state (straight arrows). Transition rates between health states were derived from the literature and were selected to represent the most likely clinical scenarios. Each patient progressed through the transition model until either the 24-month time horizon was reached or the patient died. Patients developing a recurrent hemorrhage were censored from further bleeding events in the analysis.

Outcomes

The main outcome measure was the cost per initial variceal bleed prevented by each strategy. We then calculated the incremental cost-effectiveness ratios (ICERs) for each strategy compared to the referent strategy (EBL) and to each other. The ICER between strategies represents the additional cost that must be expended to prevent one additional recurrent bleed when adopting the more expensive yet more effective of two competing strategies.

Costs

Costs were estimated from the perspective of a third-party payer, considering only direct health-care costs (Table 1). Costs for procedures and physician services were obtained from the 2001 American Medical Association Current Procedural Terminology codebook and the 2001 Medicare Fee Schedule. We also included a cost for the ongoing care of patients who survived an episode of recurrent variceal bleeding. Drug costs were obtained from the 2001 Blue Book of average wholesale prices for pharmaceuticals. Cost

Table 1. Key Base-Case Cost Estimates for Markov Model Comparing the Cost-Effectiveness of Competing Strategies for the Secondary Prophylaxis of Variceal Hemorrhage

Variable	Base-Case Cost Estimate ($US)	Range Tested ($US)
Cost of one session of endoscopic band ligation	732	0–7,320
Cost of 1 month of combination medical therapy with isosorbide mononitrate and nadolol	41	0–410
Cost of one measurement of the HVPG	1,221	0–12,210
Cost of HVPG measurement complication (modeled after pneumothorax)	12,720	0–50,000
Cost of inpatient admission for recurrent variceal hemorrhage	11,318	0–50,000
Cost of inpatient admission for nonvariceal complication of cirrhosis	14,268	0–50,000
Monthly cost of ongoing care of persons surviving an episode of recurrent variceal bleeding	797	0–5,000
Cost of an outpatient gastroenterologist visit	62.15	0–250

Costs for endoscopic procedures and physician services were obtained from the 2001 American Medical Association Current Procedural Terminology codebook and the 2001 Medicare Fee Schedule. Drug costs were obtained from the 2001 Blue Book of the average wholesale prices for pharmaceuticals.

discounting was not performed due to the short time horizon of the analysis.

Data Sources

Our model incorporated the probability estimates derived from a systematic review of the medical literature. We performed a structured search of published reports from the MEDLINE bibliographic database to identify relevant English-language publications from January 1985 to January 2002. Where there was a range of data, we chose estimates that would tend to favor the EBL strategy, and therefore biased the model against the competing medical strategies.

Competing Strategies

1. *EBL*: Patients in this strategy, which served as the referent strategy for the analysis, received an upper endoscopy within 1 wk of hospital discharge. EBL was performed if varices remained present. We assumed that successful obliteration required an average of 3.3 sessions of EBL (20), repeated at 1–2 wk intervals. Therefore, we assumed that complete variceal obliteration would not occur before 1 month following the initial variceal bleed. During this month, we assumed persons to have the same rate of recurrent variceal hemorrhage as a person receiving no secondary prophylactic therapy. Patients who developed recurrent variceal hemorrhage were admitted to the hospital and received emergency hemostasis with EBL. We assumed that patients who were not compliant with the entire ligation regimen had the same risk of recurrent hemorrhage as those receiving no specific treatment.
2. *Medical therapy without HVPG monitoring* (*HVPG–*): Patients in this treatment strategy began medical therapy immediately prior to hospital discharge with nadolol 20 mg daily. Patients were seen weekly by their primary care physician, who titrated the dose of nadolol to reduce the systolic blood pressure by 25% or to reduce the resting heart rate to 55 beats/min. Patients who tolerated β-blocker therapy and achieved an appropriate hemodynamic response were prescribed isosorbide mono-5-nitrate 20 mg daily. This dose was also adjusted weekly until either systolic blood pressure dropped to $<$85 mmHg, any dose-limiting symptoms occurred, or the maximal dose of 40 mg twice daily was achieved. We assumed that the onset of benefit of medical therapy did not occur until the appropriate dose was achieved. We further assumed that the titration of the effective dose required 1 month. Therefore, patients were assumed to have a rate of recurrent variceal bleeding equivalent to patients receiving no specific secondary prophylactic therapy for that first month. Patients who were not compliant with therapy did not receive any therapeutic benefit. Any patient known to be either not taking the medication or intolerant of the side effects was offered a course of EBL in its place.

   Patients with recurrent variceal hemorrhage were admitted to the hospital and received emergent EBL. These patients were considered failures of medical therapy, and were offered an obliterative course of ligation as described in the EBL strategy.
3. *Pharmacological therapy with HVPG monitoring* (*HVPG+*): All patients in this strategy received a baseline measurement of their HVPG prior to hospital discharge. Once a baseline value was established, medical therapy was initiated and adjusted in the same manner as described in the HVPG– strategy 2. After achieving an optimal dose of medical therapy based on vital signs, a repeat HVPG measurement was obtained. Patients who achieved an appropriate decline, defined as an HVPG either $<$12 mmHg or $<$80% of the original value, were maintained on their medical regimen. Patients who did not have an appropriate decline were offered EBL as a treatment alternative. Patients who were noncompliant or intolerant of therapy, or who experienced recurrent variceal hemorrhage, were managed in the same manner as the HVPG–.

Clinical Inputs and Probability Estimates Derived from Systematic Review

1. *Rates of recurrent esophageal variceal hemorrhage*: Table 2 reveals our base-case estimates for the probability of recurrent hemorrhage in each arm. In order to obtain monthly transition rates for use in the Markov model,

Table 2. Key Base-Case Probability Estimates for Cost-Effectiveness Analysis

Variable	Base-Case Estimate	Range Tested in Sensitivity Analysis	References
Two-year rate of recurrent variceal hemorrhage in patients receiving no prophylactic therapy	65%	33–100%	3–5
Probability of developing an appropriate decline in HVPG in patient receiving nadolol + isosorbide therapy	55%	0–100%	8, 9, 12, 13, 22, 23
Two-year rate of recurrent variceal hemorrhage in patients receiving endoscopic band ligation	35%	17–52%	24–40
Two-year rate of recurrent variceal hemorrhage in patient receiving nadolol + isosorbide therapy			
Total (based on 55% response rate)	37.5%	7–30%	
With appropriate HVPG decline	15%	33–100%	
Without appropriate HVPG decline	65%	8, 9, 12, 13	
Probability of compliance with endoscopic band ligation regimen	85%	0–100%	24–42
Probability of compliance with combination nadolol + isosorbide mononitrate therapy	75%	0–100%	8–13
Probability of noncompliance with combination nadolol + isosorbide mononitrate therapy			
Reported noncompliance (known by physician)	18.75%	0–100%	
Unreported noncompliance (not known by physician)	6.25%	0–100%	
Total	25%		
Compliance rate with HVPG monitoring			
In patients compliant with medical therapy	90%	0-100%	
In patients noncompliant with medical therapy	30%	0–100%	8, 9, 12, 22
Probability of complication with endoscopic band ligation	2%	0–10%	6
Probability of complication with HVPG measurement using internal jugular approach	5%	0–30%	43

we converted the published rebleeding rates into 1-month rates using a life-table analysis (21). In order to approximate the natural history of recurrent variceal hemorrhage, we further assumed that 75% of the recurrent bleeds occurred within the first year following the index hemorrhage (3). We varied each of our base-case estimates between 50% and 200% of their value in sensitivity analysis (described below).

We further assumed that 55% of patients who were compliant with the combination medical therapy achieved a significant decline in their HVPG. This value reflects the average rate of appropriate decline in trials reporting HVPG measurements in cirrhotics receiving combination medical therapy (8, 9, 13, 18, 22, 23). Furthermore, we assumed that any patient who failed to achieve an appropriate decline in HVPG subsequently bore the rate of recurrent hemorrhage equivalent to those receiving no therapy. Therefore, the composite 2-yr rate of recurrent variceal hemorrhage in the patients receiving medical therapy reflected the case-mix of 55% who achieved an appropriate decline in HVPG and the 45% who do not.

2. *Rates of compliance*: We based our compliance estimates upon the principles of intention-to-treat analysis. Specifically, the compliance estimates accounted for the rate of patient dropout, the rate of noncompliance with therapy, and the likelihood of reporting noncompliance to the physician (Table 2). We performed an additional analysis on a hypothetical cohort of patients with 100% compliance with all therapies. This analysis attempted to simulate a cohort awaiting liver transplantation, since these patients are more likely to be highly compliant.
3. *Rates of complications*: We were unable to identify any studies reporting complication rates associated with HVPG measurement. However, the most likely complications from this procedure are those associated with obtaining central venous access (*e.g.*, 1.5% risk of pneumothorax) (42). In order to reflect the increased likelihood of complications in cirrhotics, we assumed that 5% of HVPG measurements resulted in a serious complication. We modeled our serious complication after a pneumothorax, because this is a morbid and potentially expensive complication associated with HVPG measurement (assuming that an internal jugular approach is used). We assumed that the risk of dying from a pneumothorax was 20%. We also assumed that EBL would result in a complication in 2% of patients (6). A complication of EBL was modeled in our analysis as recurrent hemorrhage from a postligation esophageal ulcer. Patients with this complication were admitted to the hospital, endoscoped, and discharged 3 days later.
4. *Mortality*: A systematic review of the literature demonstrates an average mortality rate of 30% over 2 yr for patients in randomized control trials of interventions to prevent recurrent variceal hemorrhage, without any discernible difference in mortality rates between intervention groups (6, 7). Therefore, we held the mortality rate at 30% for each of the three competing strategies, and varied this estimate between 0% and 60% in sensitivity analysis.

Table 3. Results of One-Way Sensitivity Analyses

Variable	Base-Case Estimate	Threshold where HVPG+ dominates	Threshold where ICER = $20,000	Threshold where ICER = $50,000	Threshhold where EBL dominates
Two-year rate of recurrent variceal hemorrhage in patient receiving endoscopic band ligation	35%	≥40%	30%	26%	22%
Two-year rate of recurrent variceal hemorrhage in patient receiving nadolol + isosorbide who does achieve an appropriate HVPG decline	15%	10%	20%	24%	28%
Probability of achieving a significant response in HVPG in patients receiving nadolol and isosorbide	55%	63%	46%	40%	35%
Probability of serious complication with HVPG monitoring	5%	0.3%	11%	16%	22%
Probability of serious complication with EBL	2%	8%	<0%	<0%	<0%
Cost per month of medical therapy with nadolol and isosorbide	$41	$0.68	$138	$342	N/A
Cost of endoscopic band ligation	$732	$915	$293	< $0	<0%
Cost of HVPG monitoring	$1,218	$974	$1,739	$2,849	N/A
Compliance with nadolol and isosorbide therapy	75%	95%	60%	52%	44%
Compliance with EBL	85%	70%	98%	>100%	>100%

Four types of thresholds are listed: (1) the threshold where HVPG+ becomes dominant (*i.e.*, becomes the most effective and least expensive strategy), (2) the threshold where the incremental cost-effectiveness ratio (ICER) between the HVPG+ and EBL strategies becomes $20,000, (3) the threshold where the incremental cost-effectiveness ratio (ICER) between the HVPG+ and EBL strategies becomes $50,000, and (4) the threshold at which EBL becomes dominant (*i.e.*, becomes the most effective and least expensive strategy).

Sensitivity Analysis

We performed sensitivity analyses over a wide range of values (Table 3). We evaluated two types of threshold values: (1) the threshold value for each variable at which the most effective strategy became dominant over the next most effective strategy (*i.e.*, became more effective and less expensive than the comparator), and (2) the thresholds at which the ICER was $20,000 or $50,000 per bleed prevented.

RESULTS

Base-Case Results

Figure 2 reveals the base-case results. The strategy using HVPG monitoring as an adjunct to medical therapy **(**HVPG+**)** was the most effective approach, as only 33% of the cohort developed a recurrent variceal hemorrhage at the end of the 2-yr study period. The EBL and HVPG– strategies were the second and third most effective, as 38% and 39% of the patients developed a recurrent hemorrhage in each strategy, respectively. Although all three strategies were similarly expensive, the HVPG– approach cost marginally less ($11,744 per patient) than either EBL or HVPG+ strategies ($12,525 and $12,818 per patient, respectively). Under base-case conditions, it cost an additional $5,974 per year to avoid one additional recurrent hemorrhage when using the HVPG+ strategy instead of the EBL strategy. Similarly, it cost an additional $16,984 per year to avoid one additional bleed when using the HVPG+ instead of the HVPG– strategy.

Simulated Pretransplant Cohort

Patients listed for liver transplantation may be more likely to comply with the therapy than the general clinical trial populations on which our base-case estimates were founded. In order to simulate this patient cohort, we performed an additional analysis in which the compliance was maximized. When we assumed 100% compliance with all interventions, the most effective strategy for preventing recurrent hemorrhage was again the HVPG+ approach, with a rate of 26% over 2 yr. This was followed by EBL (33%) and HVPG– (37%). This increase in effectiveness was associated with a commensurate drop in the ICER between the HVPG+ and EBL strategies from $5,974 to $5,270 per variceal bleed prevented.

Sensitivity Analysis

We performed sensitivity analysis to determine whether our findings were robust to changes in the base-case probability estimates. Table 3 displays the results from one-way analyses of additional variables that impacted the model results. The HVPG+ strategy remained the most effective approach in one-way analyses over a wide range of values. However, the order of strategy preference was sensitive to several probability estimates. For example, the probability of achieving an appropriate HVPG decline from medical therapy impacted the model results when varied over a wide range. Figure 3 demonstrates the results of varying this probability on the ICER between the HVPG+ strategy and the EBL strategy. As the probability of HVPG decline from medical therapy decreased, the ICER between the strategies increased rapidly. For example, the ICER increased to $50,000 when the probability of HVPG decline fell to 40% (base-case = 55%).

Compliance with the prescribed therapies plays a pivotal role in determining the cost-effectiveness of competing strategies and therefore also impacted the model results. Figure 4 displays the results of simultaneously varying both

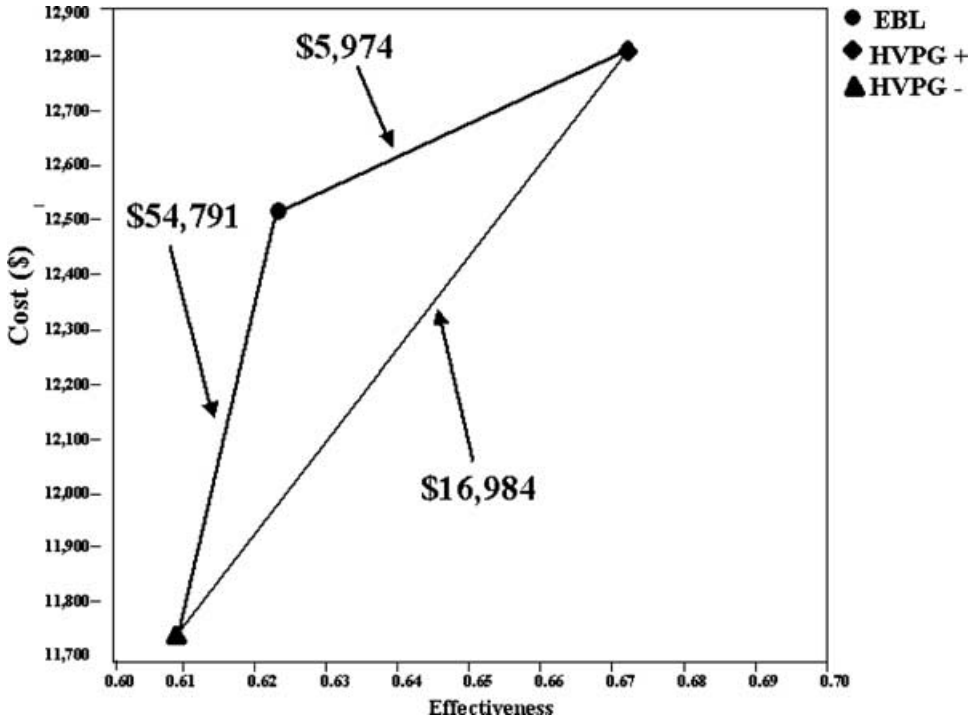

Figure 2. Results of base-case cost-effectiveness analysis. The vertical axis displays the 2-yr cumulative cost and the horizontal axis displays the proportion of patients avoiding a recurrent variceal hemorrhage. Each line represents the incremental cost-effectiveness ratio (ICER) between the connected strategies. The ICER between strategies represents the additional cost that must be expended to prevent one additional recurrent bleed when adopting the more expensive yet more effective of the two compared strategies. Under the base-case conditions, it cost an additional $5,974 per year to avoid one additional recurrent hemorrhage when using the HVPG+ strategy instead of the EBL strategy.

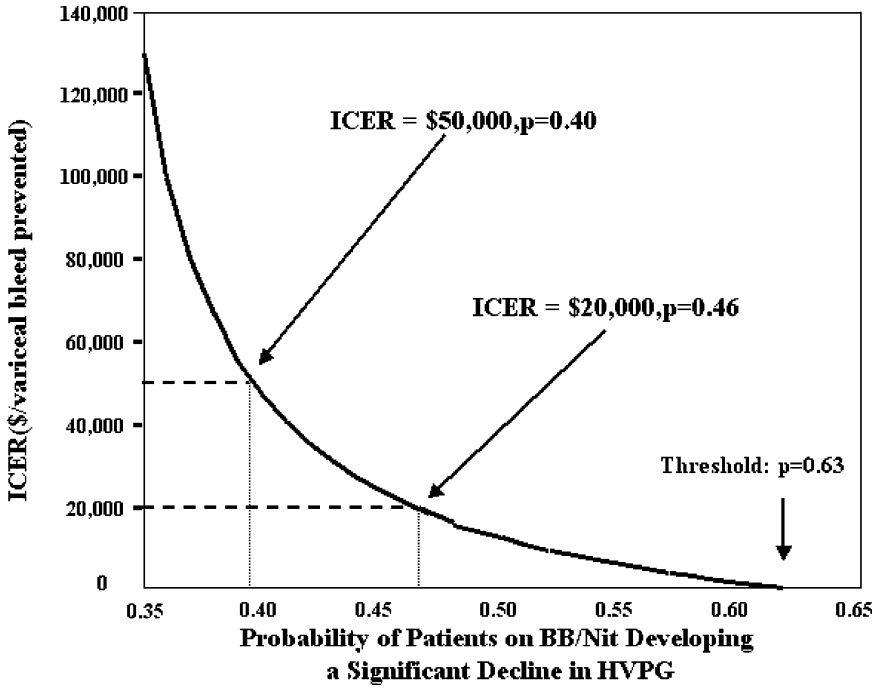

Figure 3. One-way sensitivity analysis comparing the incremental cost-effectiveness (ICER) between the HVPG+ and EBL strategies as the probability of achieving an appropriate HVPG response is varied. Under base-case conditions (55% response to medical therapy), the HVPG+ strategy cost an additional $5,974 per additional rebleed prevented compared to the EBL strategy. However, the ICER increases to $20,000 when the probability of response falls to 46%, and increases to $50,000 when the probability falls to 40%. Conversely, the HVPG strategy becomes both more effective *and* less expensive (*i.e.*, dominates) when the probability exceeds 63%.

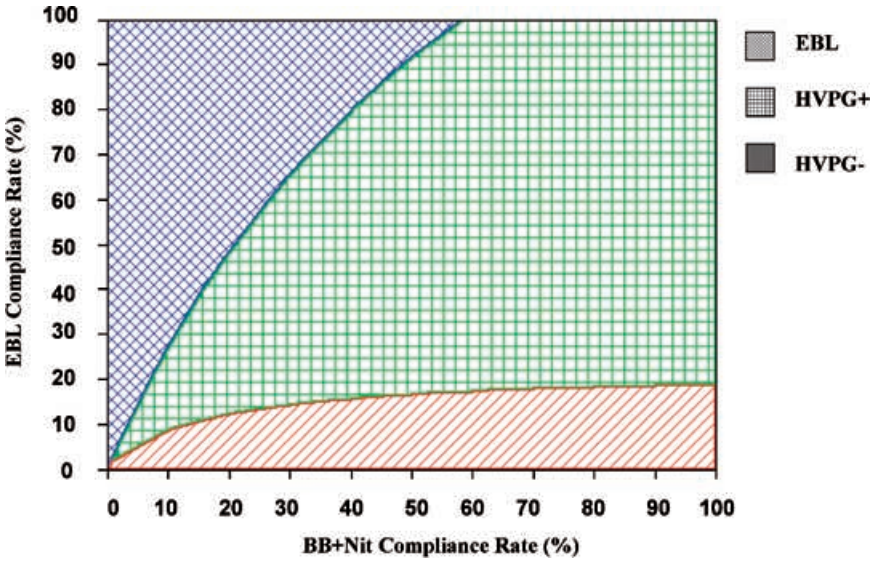

Figure 4. Two-way sensitivity analysis of compliance rates with endoscopic band ligation and combination β-blocker and nitrate therapy (BB + Nit). The striped portions of the graph represent domains where one strategy is more effective than the other. For example, the HVPG+ strategy is most effective when compliance with BB + Nit exceeds 58% and compliance with endoscopic band ligation simultaneously exceeds 20%. Conversely, the EBL strategy dominates the analysis when compliance with medical therapy is minimized, and compliance with endoscopic band ligation is concurrent maximized.

the probability of compliance with medical therapy and the probability of compliance with EBL. The HVPG+ strategy remained more effective than the EBL approach when compliance with medical therapy remained above 58%, independent of the degree of compliance with EBL. However, as compliance with medical therapy fell below this threshold, the probability of compliance with EBL determined the most effective strategy. For example, if the probability of compliance with EBL remained stable (at base-case of 85%), then the EBL strategy became dominant when compliance with medical therapy fell below 44%.

The cost of HVPG monitoring also impacted the model results when varied over a wide range. Figure 5 displays the results of one-way sensitivity analysis as the cost of HVPG monitoring is varied. As the cost of monitoring increased, the ICER between the HVPG+ and EBL strategies increased concurrently. For example, the ICER reached $50,000 when the cost of HVPG monitoring increased by a factor of 2.3 (from $1,218 to $2,849). Conversely, the HVPG+ strategy dominated the analysis when the cost of monitoring fell by 20% (from $1,221 to $974).

DISCUSSION

The results of this study suggest a definite role for the use of HVPG monitoring as an adjunct to medical therapy in the prevention of recurrent variceal hemorrhage. Our analysis suggests that the use of HVPG monitoring in conjunction with medical therapy is more effective than the current practice of EBL, and may only cost an additional $5,974 per year to prevent one additional recurrent variceal bleed. HVPG monitoring in conjunction with medical therapy (HVPG+) remained the preferred strategy despite explicitly biasing our model in favor of the EBL strategy. These findings persist despite varying the base-case model estimates over a wide range in sensitivity analysis. Therefore, our findings appear robust, and they tend to support the recent suggestion that HVPG monitoring be more widely adopted into current practice (16, 17).

Our results are highly dependent upon whether or not medical therapy adequately reduces the HVPG. We assumed that 55% of compliant patients receiving combination medical therapy achieved an adequate HVPG decline (8, 9, 13, 18, 22, 23). However, if the rate of response falls below 31% in our model, then the EBL strategy is preferred. To date, there are few studies examining the rate of HVPG decline to medical therapy, and most of these studies were performed in Europe. Therefore, the generalizability of our base-case estimate may be limited. Given our findings, further studies in diverse populations are warranted.

Our results are also dependent upon the probability of compliance with medical therapy. For example, if the rate of compliance falls below 44% (base-case = 75%), then the EBL strategy becomes most effective. Therefore, the use of HVPG monitoring may not be optimally cost-effective in patients with low compliance, and should be reserved for patients most likely to remain compliant with medical therapy, such as those listed for liver transplantation.

There is one other published analysis of the role of HVPG monitoring in the prevention of variceal hemorrhage. The authors of this study report that HVPG monitoring is not cost-effective in the primary prevention of variceal hemorrhage. Their findings on the cost-effectiveness of HVPG monitoring are divergent from ours for several important reasons. First,

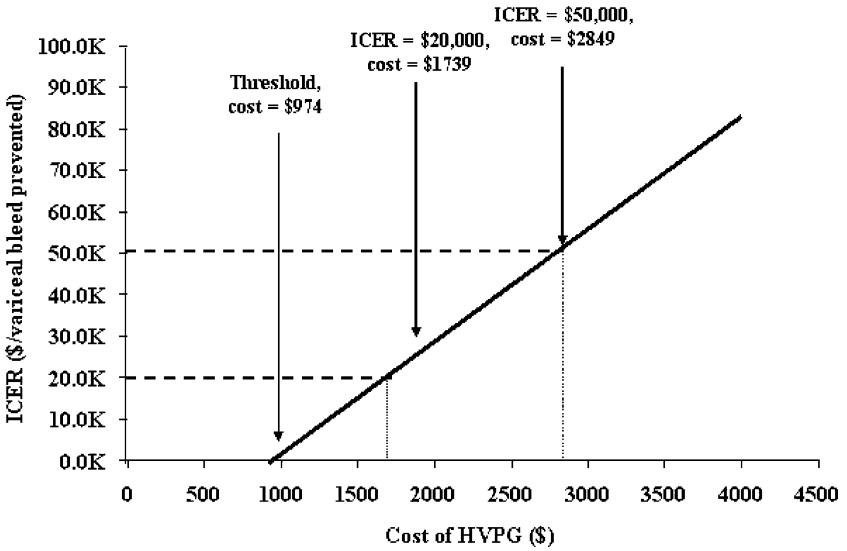

Figure 5. One-way sensitivity analysis comparing the incremental cost-effectiveness (ICER) between the HVPG+ and EBL strategies as the cost of HVPG monitoring is varied. Under base-case conditions ($1,218 for HVPG measurement), the HVPG+ strategy cost an additional $5,974 per additional rebleed prevented compared to the EBL strategy. However, the ICER increases to $20,000 when the cost increases to $1,739 and increases to $50,000 when the cost increases to $2,849. Conversely, the HVPG strategy becomes both more effective *and* less expensive (*i.e.*, dominates) when the cost falls below $974.

the incidence of variceal hemorrhage is much higher in persons who have already had an episode of variceal bleeding, as in our study. Thus a greater absolute number of bleeds are prevented at roughly the same cost, thereby improving the cost-effectiveness of a given intervention. Second, the cost of HVPG monitoring used by Hicken *et al.* ($4,000 per HVPG measurement) is a local estimate, and is significantly lower than the cost of HVPG reported in our study. We used the 2001 Medicare fee schedule to obtain our cost-estimates for the model, as these reimbursement rates are generalizable for clinicians practicing in the United States. As HVPG measurement was not included in the 2001 Medicare Fee Schedule, we substituted the reimbursement rate of performing transhepatic-intravenous portosystemic shunt (TIPS), as performing TIPS encompasses a measurement of HVPG in addition to construction of the portosystemic shunt. The model is sensitive to changes in the cost of HVPG monitoring as well as the baseline rate of variceal hemorrhage, therefore it is not surprising that our analyses have differing conclusions.

Although our results suggest that medical therapy with HVPG monitoring may be the preferred strategy for the prevention of recurrent variceal hemorrhage in a compliant population, there are several barriers to its successful implementation in clinical practice. In particular, HVPG monitoring requires the availability of specialized equipment and personnel. Alternate methods of HVPG measurement have been evaluated, but none have demonstrated an acceptable level of accuracy or ease of use to be implemented in general practice (44–47). Therefore, the availability of this technique is generally limited to tertiary care settings. In contrast, EBL is now a commonly practiced technique that is widely available. In light of this discrepancy, clinicians in the community setting may be initially reluctant to adopt the HVPG+ strategy.

Although we limited our analysis to three strategies, there are several other techniques available for preventing recurrent variceal hemorrhage, including endoscopic sclerotherapy, combination endoscopic modalities, and TIPS. The superiority of band ligation over sclerotherapy in this setting has been proven (6), whereas TIPS may be suboptimal due to the high incidence of encephalopathy and stent restenosis (48–50). For these reasons, we limited our analysis to strategies with proven effectiveness and limited risk of adverse outcomes.

Another limitation of our analysis is that we did not incorporate quality adjusted life years (QALYs) as a measure of effectiveness. Although we agree that health-related quality of life (HRQOL) is an important outcome in chronic liver disease, we chose not to include it in our analysis for several reasons. First, accurate calculations of QALYs require that a value, or utility, be assigned to the HRQOL of a specific health state. While published utility values exist for patients with cirrhosis (51), there are no published utilities for patients with acute variceal bleeding. Second, cirrhosis is a chronic condition, whereas an episode of acute variceal bleeding is short and self limiting. Although there is a short-term disutility associated with developing an episode of recurrent variceal hemorrhage, there is no reason to believe that the HRQOL of a patient with cirrhosis who has recovered from an episode of recurrent variceal hemorrhage will be significantly different from a cirrhotic patient without previous hemorrhage. Therefore, QALYs may be unable to capture the true value of preventing recurrent variceal bleeding. Finally, although it is generally assumed that the side effects of β-blocker and the

nitrate therapy will depress HRQOL relative to endoscopic therapy, the incremental disutility from these side effects is unknown in cirrhotics. Also, it could be assumed that most of the patients who develop HRQOL-limiting side effects would become noncompliant with their therapy or choose alternate therapy. This increased risk of noncompliance with medical therapy was accounted for in the current analysis. In lieu of cost per QALY data, we instead chose to report our findings in terms of the cost per episode of variceal hemorrhage prevented, a unit that is meaningful to more practicing clinicians. Furthermore, by providing multiple willingness-to-pay levels, we allow the practitioner to determine the value of preventing an episode of recurrent variceal hemorrhage.

In conclusion, this analysis suggests that the adjunctive use of HVPG monitoring may be cost-effective in the secondary prophylaxis of variceal hemorrhage. Our findings are most sensitive to changes in probability of compliance with medical therapy, suggesting that patients listed for liver transplantation may be among the more appropriate candidates for this strategy. Further prospective trials comparing the effectiveness and accrued costs of these competing management strategies are needed.

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Received June 26, 2003; accepted May 25, 2004.

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