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Prophylaxis of Esophageal Variceal Bleeding: A Cost-Utility Analysis Comparing Five Strategies

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Abstract

Objectives: **To compare the cost-utility of five strategies for preventing esophageal variceal bleeding: (1) universal primary beta-blocker prophylaxis; (2) selective primary beta-blocker prophylaxis; (3) primary endoscopic rubber band ligation (EBL) prophylaxis; (4) secondary beta-blocker prophylaxis; and (5) secondary EBL prophylaxis. The economic viewpoint was that of third-party payers.**

Methods: **A decision analysis was performed based on a six-state Markov model. Data on the transition probabilities between states for each prophylactic strategy were derived from a systematic search of the literature. Data on the cost of each strategy were from hospital charges to patients with bleeding esophagogastric varices admitted to the authors' hospital during the years 2002 to 2004. Effectiveness was measured using Quality Adjusted Life-Years (QALY). The outcome of the analysis was the incremental cost-utility ratio between the two most effective strategies. The cost-utility ratios were compared with the willingness-to-pay of Baht 10,000 (250 US dollars) or Baht 100,000 (2500 US dollars). Both one-way and multiway sensitivity analyses were performed.**

Results: **Primary EBL prophylaxis was the most cost-effective long-term (greater than five years) strategy for the prevention of bleeding esophageal varices, while universal primary beta-blocker prophylaxis was most cost-effective in the short term. Sensitivity analyses did not substantially affect this result.**

Conclusion: **Primary EBL prophylaxis is the recommended strategy for the prevention of esophageal varices bleeding in the long-term.**

Key words: **prevention; esophageal varices; hemorrhage; economics; cost-utility analysis**

INTRODUCTION

Gastroesophageal variceal bleeding due to portal hypertension is a relatively common problem in patients with cirrhosis and carries a mortality of 20% to 50% per episode,[1-4] although this number is steadily decreasing.[5] There are currently many strategies for the prevention or prophylaxis of esophageal variceal bleeding. Prophylaxis can be implemented prior to the occurrence of variceal bleeding, i.e. primary prophylaxis, or after any episode of bleeding, i.e. secondary prophylaxis. Current first line prophylactic strategies whether for primary or secondary purposes include non-operative interventions such as non-selective beta-blocker and/or nitrate medications, endoscopic band ligation (EBL), radiologic interventions such as transjugular intrahepatic portosystemic shunts (TIPS) and combinations of these options.[1,3,6-8] Surgical prophylaxis

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such as porto-systemic shunt operations or esophageal devascularization is usually reserved for failure of first line strategies.[9,10] Clinical studies including several randomized clinical trials have failed to provide clear evidence that any one type of prophylactic strategy is superior to others in terms of overall survival.[7,11-17] However, other outcomes which may have an impact on the choice of strategies such as costs and quality of life are usually not compared.

Clinical studies conducted so far also do not compare primary and secondary prophylaxis and do not compare all strategies relevant to a given clinical setting. A decision analysis provides a context within which to combine various clinical findings from diverse studies such that comparisons between prophylactic strategies not directly addressed in any clinical trials can be made.[18,19] Comparisons can be made in terms of survival, quality of life, as well as costs incurred for each strategy. Economic analyses can be done within the context of a decision analysis where the primary outcomes are the comparisons of cost-consequence differences between various strategies.[18,20]

Although there have been several recent decision-analytic studies and economic analyses looking at cost-effectiveness and cost-utility of various variceal bleeding prevention strategies,[1-4,21-24] only a few dealt with the comparison of medical and endoscopic prophylaxis within both the primary and secondary prevention contexts.[3,24] All such analyses considered costs relevant to Western countries such as North America. The aim of this article was to compare the cost-utility of five prophylactic strategies, including primary and secondary prevention as well as medical and EBL prophylaxis, from the viewpoint of the patient or third party payers in a developing country.

Methods

Model construction

A decision analytic model was constructed in which subjects in a hypothetical cohort of 10,000 patients with liver cirrhosis and good liver function (Child-Pugh class A or B) without a history of previous variceal bleeding were assigned randomly to five groups: universal primary prophylaxis with beta-blockers (group 1); selective primary prophylaxis with beta-blockers (group 2); selective primary prophylaxis with EBL (group 3); secondary prophylaxis with beta-blockers (group 4); and secondary prophylaxis with EBL (group 5). Each patient or subject was assumed to exist in only one of six states during any given period, each period lasting the length of each simulated cycle (six months in this model). These states are shown in Figure 1, where possible transitions between each state are also shown. Single, unidirectional arrows imply irreversible transitions, while double arrows pointing in opposite directions refer to reversible transitions (i.e. between states 3 and 4 in the figure). There are three recurring states (signified by the curved arrow in the figure): subjects could have large or small esophageal varices without having ever bled (states 11 and 12 in the figure), and subjects can remain free from bleeding after any episode of bleeding (state 3 in the figure). Subjects in the dead state can never leave it (state 5 in the figure); the dead state is also termed the absorbing state. The two bleeding states in Figure 1 (states 2 and 4) are transient states, meaning that a subject can not be in such states longer than one cycle period. For example, a subject with rebleeding varices in one period must either stop bleeding and survive or die in the next period; the subject can not continue bleeding into the next period. The model allowed for any number of rebleeding, as long as the subject was still alive. In the main analysis all subjects were followed till death.

Each simulated cycle lasted 6 months. This period was chosen in order to keep the model simple as well as reasonably realistic. That is, with a six-month cycle it would be possible to have two rebleeding episodes within a single year in the model, which is to be expected in reality. Six months was also long enough to keep the model simple in terms of the number of iterations needed to complete a model run. Transitions between states were determined only by the state immediately preceding the transition and not on any other previous states; this is the Markov assumption.[19,25] The probability of transition between each pair of states in the diagram is termed the transition probability for that pair. Strictly speaking the transition probabilities to be discussed below are cumulative transition probabilities, and thus are non-decreasing functions of time.

Primary prophylaxis would begin at the start of simulation. Secondary prophylaxis began only after a subject has reached state 3 in the figure, i.e. only after surviving an initial bleeding episode. Universal primary

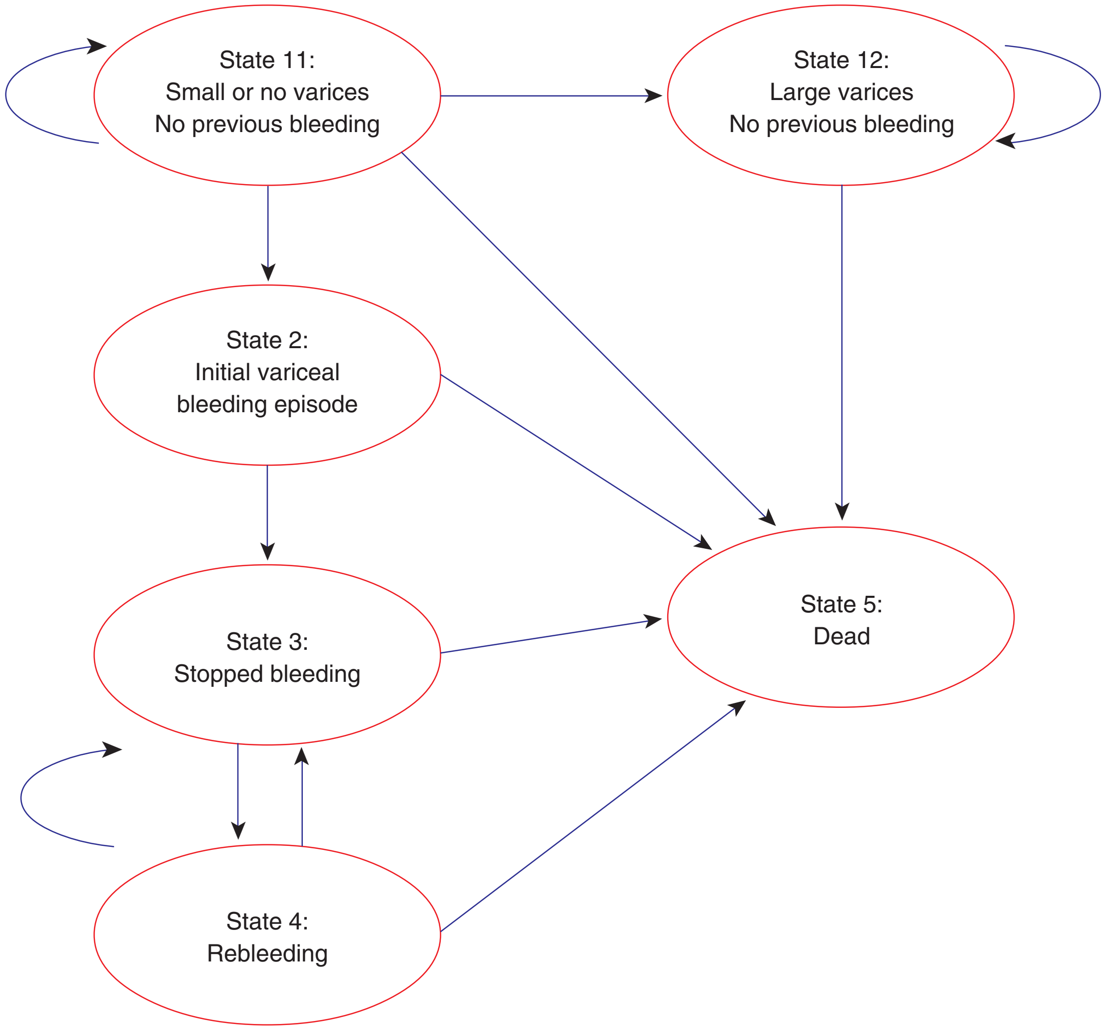

Figure 1 Diagram of transitional states in the model.

prophylaxis with beta-blockers refers to the strategy of providing non-selective beta-blockers to all subjects with documented cirrhosis, regardless of risk of bleeding from esophageal varices, who never had a variceal bleeding episode. Selective primary prophylaxis refers to the strategy of providing primary prophylaxis, either with life-long beta-blockers or several sessions of EBL, only after esophagogastroduodenoscopy (EGD) revealed sufficiently large varices or a high risk of bleeding. Subjects with small or no varices were to undergo annual EGD surveillance until the development of large varices,[1,3,6,26] upon which prophylaxis was provided. Secondary prophylaxis refers to the strategy of providing prophylaxis against rebleeding, either with life-long beta-blockers or several EBL sessions, after any episode of variceal bleeding. Subjects involved in this last strategy who have never bled would not undergo any surveillance procedure.

Subjects in the primary EBL prophylaxis group with a high risk of bleeding and who have not yet bled were to undergo semiannual EGD surveillance after initial EBL sessions.[2] Subjects who have bled at least once whether on primary EBL prophylaxis or secondary EBL prophylaxis would undergo semiannual EGD surveillance,[2] with variceal banding as appropriate. Data for subjects who developed serious EGD or EBL complications were truncated at the occurrence of these complications.

The program used to run the simulations was written in STATA version 7 (Stata Corporation, College Drive, Texas, USA) by the authors.

Model assumptions

Each transition probability between states was assumed to have the same value for all cycles, and to be valid throughout the lifetime of any given subject. All subjects were assumed to fully comply with whatever regimen of prophylaxis they were assigned. The success rate of each EBL session was assumed to be 100%. All subjects could tolerate beta-blockers although not all may respond to them. Response to beta-blockers in this study meant a significant reduction in hepatic venous pressure gradient, for example to less than 12 mmHg or greater than 20% to 25% reduction from pretreatment values.[4,22,23] These measurements, however, were assumed not to have been done on any study subject. Hepatic function was assumed not to change with time. Once a prophylactic modality was assigned it was fixed for all times for a given subject, despite repeated rebleeding episodes. These assumptions constituted those of the "main analysis".

Outcomes of the model

Outcomes consisted of costs of prophylaxis, costs of treatment during a bleeding episode as incurred by the subjects or by third party payers, the survival time of the subjects, and the overall quality of life. The survival time and quality of life were combined into a measure called the quality-adjusted life-years (QALY).[17] One unit of QALY is defined as one year of full health-equivalent survival. QALY was used since, for example, some prophylactic strategies may reduce the number of bleeding episodes within a lifetime to a greater extent than others but do not differ greatly in their effect on survival time. Therefore, QALY can better reflect bleeding tendencies than survival time by virtue of the fact that the quality of life associated with each bleeding episode is lower than that associated with no bleeding. The derived primary outcome of this study was the incremental cost-QALY ratio,[17] a special type of the cost-utility or cost-effectiveness ratio, defined as the ratio of cost difference to QALY difference between two given strategies.

The quality of life for subjects in this study was valued using two methods. The base case values for a subject with cirrhosis not actively bleeding, with mild to moderate degree of liver impairment, were based on the utilities previously obtained using a validated questionnaire.[27,28] These utilities were assumed to be the same for cirrhotics who have never bled (states 11 and 12 in the figure) as well as those who have bled several times but are not actively bleeding (state 3). Utilities for patients with active variceal bleeding (states 2 and 4) were obtained by a rating method under the constraint that the utility values must not be higher than those for non-bleeding cirrhotics, but must be higher than zero.[17] Nineteen staff and trainee surgeons in the authors' institution were asked to rate a bleeding episode subject to the stated constraints on a visual analogue scale.[12,18,28] The death state (state 5) was set to have the utility of zero.

Data used in the model

Data used to estimate the transition probabilities in the model were derived from a literature search through MEDLINE. The sources of data were all recent decision and economic analyses on variceal bleeding prophylaxis published after the year 2000.[1-4,21-24] These sources were supplemented by a few recent meta-analyses and randomized clinical trials providing additional data on the transition probabilities.[6,7,11-17,30,31] The search terms used for the MEDLINE search included "decision analysis", "hemorrhage", "prophylaxis", "esophageal and gastric varices", "prevention", "economics" and their combinations. Each author independently performed the search. Disagreement was resolved by consensus. The relevant transition probabilities for the current model are listed in Table 1. Data from a retrospective review of medical records of adult patients (aged 18 years or older) admitted to the authors' hospital with the diagnosis of bleeding esophagogastric varices during the years 2002 to 2004 were also used in the estimation of the transition probabilities.

Cost data were of those charged to the same adult patients mentioned previously. The data also reflected costs paid by third party payers. Cost data used in this study must necessarily reflect costs typically incurred in a Government sponsored public hospital, and may not generalize to the situation of private hospitals in Thailand. At the time of writing, one US dollar equaled approximately 40 Baht.

Base case values

Base case values of the transition probabilities and costs of each bleeding or rebleeding episode were median values[2,29] of the available data abstracted from the literature and medical records review. Transition probabilities at six months were derived from the annual probabilities by assuming constant

Table 1 Parameter values

Parameters	Base case values (range)	Reference(s)
(1) Prevalence of no/small varices	84% (60-90%)	1,3,7,24
(2) Annual prob. of varix transition (small to large)	12% (6-19%)	1,3,24,35,36
(3) Probability of beta-blocker response	53% (37-61%)	4,7,11,23
(4) Probability of serious EBL complications	0.14% (0.03-1.4%)	1-3,14,23,24
(5) Annual mortality, absence of variceal bleeding	6% (2-30%)	1,2,21,23
(6) Mortality of initial bleeding	30% (15-51%)	1,3,7,13,24,35
(7) Mortality of rebleeding	21% (10-50%)	2-4,6,11,23
Annual probabilities of initial bleeding		
(8) Small varices (Natural history)	3% (1-16%)	1,3,35
(9) Large varices (Natural history)	17% (10-40%)	1,3,12,13,21,37
(10) Beta-blocker prophylaxis	11% (7-25%)	1,3,4,7,13-15,21
(11) EBL prophylaxis	7% (4-10%)	4,7,8,12-15,21
Annual probabilities of rebleeding		
(12) Natural history	60% (48-75%)	1,2,6,9,11
(13) Beta-blocker prophylaxis	36% (6-50%)	1,11,22,23
(14) EBL prophylaxis	20% (10-34%)	22,23
No. of EBL sessions for variceal eradication		
(15) Initial prophylaxis	3 (1-5)	2,7,12-15,23,24,31
(16) After a bleeding episode	2 (1-3)	2,7,14
Dose & cost of drugs and procedures		
(17) Prophylactic dose of beta-blockers (mg.)	60 (40-120)	7,12,14,16
(18) Annual cost of beta-blockers (Baht/Dollars)	B600 (B400-1,200) $15 ($10-30)	Authors' institution
(19) Cost of a single EGD (Baht/Dollars)	B1,500 (B1,000-2,000) $38 ($25-50)	Authors' institution
(20) Cost of a single EBL (Baht/Dollars)	B2,500 (B2,000-3,000) $63 ($50-75)	Authors' institution
Cost of a single episode of variceal bleeding		
(21) Subject survived the episode (Baht/Dollars)	B24,977 (B3,956-309,170) $624 ($99-7729)	Authors' institution
(22) Subject died (Baht/Dollars)	B102,264 (B21,687-435,112) $2557 ($542-10878)	Authors' institution
Utilities		
(23) Cirrhosis without variceal bleeding	0.7 (0.5-0.9)	2,27
(24) Cirrhosis with variceal bleeding	0.35 (0.2-0.5)	Physician rating

EBL: endoscopic band ligation; EGD: esophagogastroduodenoscopy; prob: probability

instantaneous transition probabilities (i.e. constant hazards), using the equation: Pr(6months) = 1-[1-Pr(1year)], $\frac{1}{2}$, where Pr(6 month) and Pr(1 year) are transition probabilities at six months and one year, respectively.[32] Transition probabilities, costs and utilities are collectively termed parameters in this article. Base case cost of beta-blockers and costs for each session of EGD or EBL were according to current hospital charges for these medications and procedures. Average values of utilities calculated or derived using the quality of life questionnaires and the average of physicians' ratings as described above were used as base case utilities. Utilities and costs were discounted annually at the recommended rate of three percent in the base case scenario.[2,3,18,23] Generally, the "best prophylactic strategy" was defined as the strategy with the highest QALY and "acceptable incremental cost-QALY ratio" relative to the strategy with the next highest QALY.[2] In the base case analysis, the best strategy was defined as one with the highest average

QALYand "acceptable average incremental cost-QALY ratio" relative to the strategy with the next highest average QALY.

Since there was no consensus on "acceptable incremental cost-utility ratios" in Thailand, "acceptable incremental cost-utility ratio" in this study was defined relative to two values of "willingness-to-pay": Baht 10,000 (250 US dollars) and Baht100,000 (2500 US dollars) per QALY gained. Willingness-to-pay refers to the amount of money a patient is willing to forego in order to gain an additional year of full-health life. Since a study of willingness-to-pay has also never been done in Thailand, these two ratios were chosen for their plausibility. To put in perspective the choice of these two ratios, the average household income in Thailand in 2002 was Baht 14,000 (350 US dollars) per month and the average per capita income was Baht 4000 (100 US dolars) per month.[33] It was assumed that in one year a thrifty household might save up to Baht 100,000.

As an alternative definition, the "best strategy" was also defined as one with the most frequent highest individual QALY and acceptable incremental cost-utility ratio for a given set of values of the parameters.[2] By "individual" it was meant that the costs and QALY's for a set of five subjects who shared the same set of parameter values, one subject taken from each of the five strategies, were compared within the set. For example, if the simulation consists of 50,000 subjects, there will be 10,000 subjects in each strategy. Thus there will be 10,000 individual cost-QALYcomparisons, and the frequency of "best strategy" status will be in counts out of 10,000, expressed as a percentage (see Table 3). This definition of best strategy was used in the multiway sensitivity analysis described below.

Sensitivity analysis

Values of transition probabilities were varied in a sensitivity analysis according to the range of values found from the literature. The range of a given transition probability was formed by ordering all the values obtained from the literature for that probability, removing the most extreme value at either end, and taking the next extreme value at both ends as defining the range. The range of values for the cost of a bleeding episode was obtained from the medical record review of patients presenting with variceal bleeding in the authors' hospital. Utilities were varied according to ranges given in the source literature for non-bleeding cirrhotics[2,27] and according to the range of the physician ratings for bleeding cirrhotics. The range of the cost of beta-blocker prophylaxis was according to the variation of doses found in the literature, as well as doses ordinarily prescribed to Thai patients. Costs for EGD and EBL were only modestly varied to reflect relatively minor differences in charges between public hospitals. Discounts were varied from zero to five percent per year, according to recommendations.[2,3,18]

In the simulations the above parameters were varied by randomly choosing values from their assumed distributions. This is termed Monte-Carlo sensitivity analysis.[2,21] In order to minimize the effect of clustering of simulated parameter values in the Monte-Carlo sensitivity analysis, the distribution of the parameter values was assumed to be uniform within the given range. Oneway sensitivity analysis, in which the parameters in the model are varied one at a time, was performed to identify individual parameters which were important in determining outcomes of the decision analysis.[18,19] In the multiway sensitivity analysis, all parameters of interest were varied simultaneously; 10,000 random combinations of parameter values were used.[2,21] For the multiway sensitivity analyses the prophylactic strategy of choice was defined to be the strategy which was most frequently the çbest strategyé according to the individual cost-QALY comparisons described above.

In addition to the main analysis, two other analyses were also performed. In one, it was assumed that the subject would drop out of the study after three rebleeding episodes to simulate the decision to change treatment after repeated failure. In another, the duration of the simulated trial was set at five years, since most of the data used in this study was obtained from clinical studies with median observation time less than five years. The latter analysis should address the possibility that the main analysis might be generalizing the available data beyond the range of their validity. In both secondary analyses other parameters were set at their base case values.

Results

Data used in the model are presented in table 1. Both the base case values and ranges of values are presented. For the most part, the data for transition probabilities correspond to well known numbers often quoted in the literature.

In the main analysis, the number of sessions of EBL needed to obliterate esophageal varices was set to be three for primary prophylaxis and two for rebleeding episodes, although EGD surveillance after rebleeding episodes were extended indefinitely and performed semiannually. These numbers were held constant throughout the main analysis since according to table 1 there was little variation in the number of EBL sessions between studies.

Data on costs as well as additional data on mortality rates of a variceal bleeding episode were obtained from 88 adult patients, admitted to the authors' hospital with the diagnosis of bleeding esophagogastric varices during the years 2002 to 2004, in whom 113 bleeding episodes occurred. The cost for a bleeding episode in which the patient survived the bleeding was more likely to be much less than the cost of an episode in which the patient did not survive the bleeding. Hence, these costs were not combined but entered separately into the model. The first admission mortality rate was 15% (13 of 88), whereas the readmission mortality rate was 20% (5 of 25).

Data on the utility of the variceal bleeding state obtained from a questionnaire administered to a group of physicians did not differ substantially from those obtained in a recent study.[3,29]

In the base case analysis, the model predicted that with an average followup time of approximately 7 years, the occurrence of variceal bleeding was approximately one episode per subject (data not shown). The average QALY was highest for primary EBL prophylaxis, exceeding other primary prophylactic strategies which involved the use of non-selective beta-blockers (Table 2). Primary EBL prophylaxis also dominated all other strategies, i.e. primary EBL had the highest average QALY as well as the lowest average cost. Of note, primary prophylactic strategies using either beta-blockers or EBL seem to be more cost-effective than their respective secondary prophylaxis counterparts.

According to one way sensitivity analyses, using the range of values in table 1 for each parameter, primary EBL prophylaxis continued to generally dominate other strategies in terms of (higher) average QALY and (lower) average cost (analysis not shown). Hence, the conclusion of the base case analysis remained unchanged - the conclusion was insensitive to any single parameter variation. However, additional exploration of the model using extreme parameter values beyond those found in the literature revealed sensitivity of the conclusion to some of these parameters. It was found that beta-blocker prophylaxis, especially universal prophylaxis, was more economical in terms of acceptable incremental cost-QALY ratio than EBL prophylaxis in the following extreme cases. (1) The probability of dying in absence of variceal bleeding (probability 5 in Table 1) exceeds the probability of dying due to variceal bleeding (probabilities 6 & 7 in Table 1). This condition is unlikely to be realistic. (2) The probabilities of initial bleeding (probability 11 in Table 1) and rebleeding (probability 15 in Table 1) when on EBL prophylaxis uniformly exceed those associated with beta-blockers. (3) The complications of EGD or EBL exceed 10%, which is unlikely to happen. (4) The cost of EGD and EBL is of the order of the cost of a variceal bleeding episode. This last condition is also unrealistic.

In the multiway sensitivity analysis, with 10,000 random sets of parameter values drawn from the range of values in Table 1, the conclusion remained the same as for the base case analysis. That is, primary EBL prophylaxis continued to be the best strategy whether using the willingness-to-pay of Baht 10,000 per QALY gained, or Baht 100,000 per QALY gained (Table 3).

A secondary analysis using base case values of the

Table 2 Base case analysis

Strategy	Average QALY	Average Cost (Baht)
Primary universal beta-blocker prophylaxis	5.27	56,450
Primary selective beta-blocker prophylaxis	5.17	61,756
Primary EBL prophylaxis	5.70	51,700
Secondary beta-blocker prophylaxis	4.92	58,260
Secondary EBL prophylaxis	5.40	52,538

parameters but having subjects dropping out of the hypothetical trial after three rebleeding episodes revealed that primary EBL prophylaxis had the highest average QALY. However, the average cost of primary EBL prophylaxis was now relatively high compared with other strategies (Table 4). Therefore although primary EBL prophylaxis tended to be the best strategy, universal primary prophylaxis with beta-blockers was now comparable in economic terms. This was even more clearly bought out in the analysis where the follow-up time was limited to five years. According to this analysis, the average QALYs were not clearly different between primary EBL prophylaxis and universal primary beta-blocker prophylaxis, but the cost of the latter was lower (Table 5; incremental cost-QALY ratio for primary EBL prophylaxis versus universal beta-blocker prophylaxis is Baht 22,525 per QALY).

Discussion

The present cost-utility analysis provided a rather robust conclusion that, at least in Thailand, the strategy of providing primary prophylaxis with EBL to prevent variceal bleeding should be the most economical option in the long term, when compared with primary beta-blocker prophylaxis and secondary prophylaxis either with beta-blockers or EBL. Sensitivity analyses using

Table 3 Multiway sensitivity analysis

Strategy	Average QALY	Average Cost (Baht)	Percentage Best Strategy*	
			B 10,000	B 100,000
Primary universal beta-blocker prophylaxis	2.84	157,574	20%	18%
Primary selective beta-blocker prophylaxis	2.77	156,641	17%	17%
Primary EBL prophylaxis	3.17	98,666	25%	27%
Secondary beta-blocker prophylaxis	2.83	170,502	18%	17%
Secondary EBL prophylaxis	2.95	138,184	20%	21%

**The frequency of best strategy expressed as percentage is calculated from counts out of 10,000 computer simulations; B 10,000 and B 100,000 refer to the willingness-to-pay in Baht.*

Table 4 Secondary analysis: dropout after three failures

Strategy	Average QALY	Average Cost (Baht)
Primary universal beta-blocker prophylaxis	4.87	44,902
Primary selective beta-blocker prophylaxis	4.88	51,797
Primary EBL prophylaxis	5.72	50,848
Secondary beta-blocker prophylaxis	4.82	47,570
Secondary EBL prophylaxis	5.22	50,951

Table 5 Secondary analysis: five-year follow-up

Strategy	Average QALY	Average Cost (Baht)
Primary universal beta-blocker prophylaxis	2.62	15,879
Primary selective beta-blocker prophylaxis	2.58	20,783
Primary EBL prophylaxis	2.66	16,780
Secondary beta-blocker prophylaxis	2.60	17,324
Secondary EBL prophylaxis	2.59	16,596

the range of values of the parameters available from the literature and the authors' institution did not change this conclusion.

The reason for the long-term economic advantage of EBL over beta-blockers seems to be related to lower cumulative bleeding or rebleeding rates associated with EBL. This difference between EBL and beta-blockers increases with time, and hence the expense for the higher number of bleeding or rebleeding episodes for beta-blocker prophylaxis also increases with time. In this analysis, the long-term advantage of EBL was apparent only after five years. It should also be noted that long-term prophylaxis using EBL is less likely to be superior to prophylaxis using beta-blockers if it were decided that after three failures (i.e. three rebleeding episodes) the prophylactic strategy would change or other treatments instituted (i.e. liver transplantation). The reason for this is simply that the follow up is likely to be shorter if subjects dropped out after three consecutive failures of a prophylactic strategy.

Other decision and economic analyses provided a general conclusion that primary prophylaxis of variceal bleeding is probably more cost-effective or more economical than secondary prophylaxis.[1,3,24] The result of the current study supported this conclusion. However, while many studies concluded that primary beta-blocker prophylaxis was the best overall strategy,[1,3,24] the current study instead supported primary EBL prophylaxis. The difference in the conclusions seems to be related mainly to the difference in the time frame between the studies, i.e. to shorter or longer follow-up time.

Two decision analytical and economic studies compared EBL prophylaxis with beta-blocker prophylaxis in both primary and secondary preventive contexts.[3,24] Both studies focused only on short term results, e.g. results obtained within five years. Primary beta-blocker prophylaxis was found to be more cost-effective than primary EBL prophylaxis in both studies. In one study[3] selective beta-blocker prophylaxis (termed universal screening in that study) was slightly more cost-effective than universal beta-blocker prophylaxis for patients with compensated cirrhosis, while universal prophylaxis was more cost-effective for those with decompensated cirrhosis. In another study,[24] universal primary beta-blocker prophylaxis (termed empiric beta-blocker therapy in that study) was the most cost-effective option for all patients with cirrhosis. These results are not incompatible with the current study, where universal primary beta-blocker prophylaxis was slightly more cost-effective than primary EBL prophylaxis in the short term.

Another important difference between those studies and the current study, besides the time frame, was the use of relatively more favorable rebleeding rates for the EBL strategy in the current study.

A decision analysis comparing primary EBL prophylaxis and primary beta-blocker prophylaxis looking at long-term (i.e. life-long) bleeding free survival found EBL to be more effective.[20] A similar result was found in the current study. The bleeding/rebleeding rates on EBL or beta-blockers used in that study were numerically similar to those used in the current study. Another study addressed the long-term comparison between primary and secondary beta-blocker prophylaxis.[1] The base case result of that study was similar to that of the current study. Universal primary beta-blocker prophylaxis was the most cost-effective (where effectiveness was measured in terms of QALY as in the current study) when compared with selective primary beta-blocker and secondary beta-blocker prophylaxis.

Economic studies of secondary prophylaxis tended to show that beta-blocker prophylaxis was less expensive but with higher rebleeding rates in the short term than EBL prophylaxis (some of these studies also compared other combined modalities: EBL plus medications or medications plus hepatic venous pressure gradient (HVPG) monitoring).[2,4,22,23] The current study, however, showed that in the base case analysis secondary EBL prophylaxis dominated secondary beta-blocker prophylaxis both in the short term and the long term, although less so for the short term. The reason for this discordancy seems to be because the bleeding/rebleeding rate for beta-blocker prophylaxis used in the current study was twice that of EBL prophylaxis (see Table 1). When this rate was equalized, secondary beta-blocker prophylaxis was considerably less expensive than secondary EBL prophylaxis (analysis not shown).

Sensitivity analyses in this study revealed that important parameters influencing the outcome of the study were similar to those found in other studies. The most important probability parameters were the bleeding/rebleeding rates when on beta-blocker or

EBL prophylaxis.[1-4,21,23] The effectiveness of EBL and beta-blocker strategies in terms of QALY tended to equalize when their bleeding /rebleeding rates were similar. Also important but unlikely to be of practical concern was the probability of death in the absence of bleeding.[21] When this probability was high enough to be comparable to mortality rates of bleeding states, an unrealistic scenario except for patients with hepatic failure, beta-blocker prophylaxis became more cost-effective. Time frame of the analysis was also important in the current study, confirming an observation made earlier.[4] The most important cost data influencing the result of the current study was the cost of EBL in relation to the cost of a bleeding episode. EBL strategies tended to be less cost-effective if the cost of EBL approached that of a bleeding episode. However, this scenario is also unlikely to be realistic. Hence, for practical purposes the most important parameters influencing the results of the current study were the bleeding/rebleeding probabilities.

Although the willingness-to-pay values used in this study may seem rather low, to the average rural family in Thailand these numbers may possibly approach the maximum willingness-to-pay. Nonetheless, a criterion of Baht 1,000,000 (25,000 US dollars) per QALY gained was also examined in the base case and multiway analyses to simulate decisions made in a more affluent family. No significant changes to the results were noted (analysis not shown). A more theoretically appropriate measure of willingness-to-pay can be obtained using the process of contingent valuation of the benefits gained from the prophylatic strategies.[18]

The utilities of the non-bleeding states used in the current analysis were obtained from the available literature.[27,28] These values were used as best available data as no studies on utility valuations of cirrhosis states have ever been done in Thailand. Utilities obtained via physician valuations may not be appropriate in theory,[18,29] but the finding that utility values of bleeding states were lower compared with non-bleeding states is intuitively reasonable. The average value of the utilities for bleeding states in the current study is similar to those obtained in a recent study.[29] The uncertainty or variability associated with this parameter was addressed using a sensitivity analysis (Table 3), but the effect of these variations on the conclusions of the current analysis was not apparent.

In practice beta-blocker or medical prophylaxis of variceal bleeding is often advocated because of the ease of administration and the non-invasive nature of these strategies, in contrast to EBL strategies which require the use of a procedure with rare but potentially serious complications.[11,12,26] However, the relatively frequent intolerance of patients to beta-blockers, as well as a significant prevalence of non-response to these medications, must be taken into account-an issue not addressed in the current analysis. A recent study from Japan highlighted the possibility that Asians may not tolerate beta-blockers very well.[30] In addition commitment to a long term beta-blocker regimen and the need for dosage titration may discourage some patients from complying with the regimen. Beta-blockers and nitrate medications, however, can be used as a first line prophylactic strategy, and EBL can be used when beta-blockers and other medications can not be tolerated or compliance to medications is unlikely.[26]

Certain prophylactic strategies were not included in the current analysis. These strategies included the combination of beta-blockers and EBL, and the combination of beta-blockers and nitrates. The main reasons for not doing so were that (1) combination strategies have not been as extensively studied as the strategies employing solely EBL or beta-blockers and that the combination strategies have not been clearly shown to be superior to monotherapy,[1,16,17] (2) combined medications may be less tolerable than either alone,[7,30,34] and (3) combination strategies are rarely used in the authors' practice. The routine use of hepatic venous pressure gradient (HVPG)[4,11,23] measurement is probably not practicable in countries like Thailand in the foreseeable future. Similarly, TIPS is not an economically viable prophylactic option in many institutions.

Important limitations of the current analysis were related to the assumptions made in performing the analysis. Subjects in this analysis were assumed to be patients with good liver function. Therefore the results of this study may not apply to poor risk patients with decompensated cirrhosis. Although it is unlikely that transition probabilities will remain constant throughout the duration of any clinical trial, there is no evidence that the variability in the transition probabilities will be large enough to affect the conclusions of decision analyses, especially if the duration is relatively short.

However, extending the validity of this assumption throughout the duration of a subject's lifetime may be too extreme. The assumptions that beta-blockers are always well tolerated and that EBL is always successfully performed were unrealistic. Although there is limited data on beta-blocker tolerance in Thailand, more realistic models may need to incorporate this idea into the analysis if questions of effectiveness of these interventions are to be more accurately answered. More realistic models may also have to consider deteriorating liver function, hepatic failure, development of hepatocellular carcinoma, surgical prophylaxis of variceal rebleeding and liver transplantation, but whether these considerations will have an important impact on the conclusion of the current analysis is unclear.

Conclusion

A cost-utility analysis comparing five strategies of esophageal variceal bleeding prophylaxis was performed. It was found that, under the assumptions of the model, the strategy of long-term primary prophylaxis with EBL was the best strategy in terms of cost-utility. However, short term results (less than five years) revealed that universal primary prophylaxis with non-selective beta-blockers was slightly more economical. It is recommended that primary prophylaxis with EBL be the strategy of choice for the long-term prevention of bleeding esophageal varices, especially in a developing country.

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