

Minimizing Recurrent Peptic Ulcer Hemorrhage After Endoscopic Hemostasis: The Cost-Effectiveness of Competing Strategies

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OBJECTIVES: Controversy exists regarding the optimal strategy to minimize recurrent ulcer hemorrhage after successful endoscopic hemostasis. Our objective was to evaluate the cost-effectiveness of competing strategies for the posthemostasis management of patients with high risk ulcer stigmata.

METHODS: Through decision analysis, we calculated the cost-effectiveness of four strategies: 1) follow patients clinically after hemostasis and repeat endoscopy only in patients with evidence of rebleeding (usual care); 2) administer intravenous proton pump inhibitors (*i.v.* PPIs) after hemostasis and repeat endoscopy only in patients with clinical signs of rebleeding; 3) perform second look endoscopy at 24 h in all patients with successful endoscopic hemostasis; and 4) perform selective second look endoscopy at 24 h only in patients at high risk for rebleeding as identified by the prospectively validated Baylor Bleeding Score. Probability estimates were derived from a systematic review of the medical literature. Cost estimates were based on Medicare reimbursement. Effectiveness was defined as the proportion of patients with rebleeding, surgery, or death prevented.

RESULTS: The selective second look endoscopy strategy was the most effective and least expensive of the four competing strategies, and therefore dominated the analysis. The *i.v.* PPI strategy required 50% fewer endoscopies than the competing strategies, and became the dominant strategy when the rebleed rate with *i.v.* PPIs fell below 9% and when the cost of *i.v.* PPIs fell below \$10/day.

CONCLUSIONS: Compared with the usual practice of “watchful waiting,” performing selective second look en-

doscopy in high risk patients may prevent more cases of rebleeding, surgery, or death at a lower overall cost. However, *i.v.* PPIs are likely to reduce the need for second look endoscopy and may be preferred overall if the rebleed rate and cost of *i.v.* PPIs remains low. (Am J Gastroenterol 2003; 98:86–97. © 2003 by Am. Coll. of Gastroenterology)

INTRODUCTION

Upper GI tract hemorrhage (UGIH) remains a frequent and expensive condition in the United States, with an estimated direct cost of more than 1 billion dollars annually (1, 2). With the aging of the American population, UGIH will continue to significantly burden the health care system. It is therefore essential to continuously reappraise our approach to UGIH by developing cost-effective management strategies.

Peptic ulcer disease remains the most common cause of acute nonvariceal UGIH, accounting for up to one half of cases (3). Although initial endoscopic hemostasis is achieved in most patients with high-risk ulcer stigmata, including nonbleeding visible vessels and active bleeding, recurrent hemorrhage after successful therapy occurs in 10–30% of patients (3). Because rebleeding has long been recognized as the most important factor in determining patient outcomes (4, 5), several management strategies have been proposed to minimize rebleeding after successful hemostasis. However, the optimal approach remains controversial, and the current usual practice is to follow patients clinically and to repeat endoscopy only if there is evidence of rebleeding. Alternative strategies to minimize rebleeding include the use of second look endoscopy and the posthemostasis administration of intravenous proton pump inhibitors (*i.v.* PPIs).

Proponents of second look endoscopy contend that early re-examination of the bleeding site within 24 h of hemostasis allows retreatment of residual high risk stigmata and may minimize recurrent hemorrhage compared with repeating endoscopy only in patients with clinical signs of rebleeding (6). Despite arguments in favor of this approach, however, prospective studies demonstrate an inconsistent benefit when early second look endoscopy is indiscriminately performed in all patients with peptic ulcer hemorrhage (7–11). Recognizing the fact that only a subset of patients is likely to benefit from second look endoscopy, Saeed *et al.* proposed a strategy of *selective* endoscopic surveillance reserved only for patients at high risk for rebleeding, as determined by the prospectively validated Baylor Bleeding Score (10). In a randomized controlled trial comparing early second look endoscopy at 24 h to usual care for high risk Baylor Bleeding Score patients, there were no instances of rebleeding in the experimental group and 24% in the control group (10). The authors concluded that early second look endoscopy in selected high-risk patients is more effective in minimizing rebleeding than is usual care.

Despite this documented effectiveness of endoscopic surveillance, recent data indicate that the need for second look endoscopy may be significantly reduced with the use of *i.v.* PPIs after hemostasis (12, 13). A recent randomized controlled trial comparing standard medical management with a 72-h course of *i.v.* omeprazole for patients with successful ulcer hemostasis found that 22.5% of the control group developed recurrent hemorrhage compared with only 6.7% of the experimental group (13). Based on these findings, the routine use of *i.v.* PPIs after successful hemostasis may reduce the subsequent endoscopic burden by substantially reducing the risk of recurrent hemorrhage.

Once an intervention is deemed to be effective, it is important to determine whether it is *cost-effective* when applied in the appropriate clinical setting. For second look endoscopy to be cost-effective, the cost generated by additional endoscopies and their potential complications must be offset by a reduction in resource use afforded by improved effectiveness. The cost-effectiveness of second look endoscopy is therefore likely to depend on several factors, including the effectiveness of initial hemostasis and the group selected for surveillance. Similarly, in order for *i.v.* PPIs to be cost-effective, the additional cost of the medication must be offset by a reduction in the need for repeat endoscopy afforded by improved effectiveness.

In light of these factors and the lack of consensus regarding the optimal strategy to minimize ulcer rebleeding, we used decision analysis to estimate the cost-effectiveness of four competing strategies for the posthemostasis management of peptic ulcer hemorrhage: 1) follow patients clinically and repeat endoscopy only in patients with evidence of rebleeding (usual care); 2) administer *i.v.* PPIs and repeat endoscopy only in patients with clinical signs of rebleeding; 3) perform second look endoscopy at 24 h in all patients with successful endoscopic hemostasis; and 4) perform *se-*

lective second look endoscopy at 24 h only in patients at high risk for rebleeding as identified by the Baylor Bleeding Score.

METHODS

Decision analysis is a quantitative method for estimating the cost-effectiveness of alternative management strategies under conditions of uncertainty (14). The technique of decision analysis is most useful in circumstances where there is an absence of prospectively derived cost-effectiveness data. Through a reliance on prespecified cost estimates (*e.g.*, Medicare reimbursement), coupled with the best available effectiveness data from the published literature, decision analysis may provide information regarding the tradeoffs between financial costs and clinical effectiveness engendered by competing management strategies.

Using decision analysis software (15), we evaluated a hypothetical cohort of patients with peptic ulcer hemorrhage in whom successful endoscopic hemostasis was performed. Patients with clean-based ulcers or flat pigmented spots do not currently receive endoscopic therapy by guidelines and were therefore not included in this analysis. Patients entered the model after achieving endoscopic hemostasis and were subsequently followed during their hospital course and for 30 days after discharge. Our model incorporated base case estimates of the most likely clinical scenarios and then used sensitivity analysis to evaluate the results over a wide range of cost and probability estimates.

Data Sources

Base case probability estimates were derived from a structured search of English language publications from January, 1990, to January, 2002, in the MEDLINE and HealthSTAR bibliographic databases (Table 1). We targeted randomized controlled trials with one or more arms investigating the use of injection therapy (epinephrine, polidocanol, ethanolamine, ethanol) or thermal contact probes (heater probe, monopolar and bipolar coagulation probe) in patients with peptic ulcer hemorrhage who were found to have active bleeding or a nonbleeding visible vessel at the time of endoscopy. Our search strategy used the keywords “randomized controlled trial (pt),” “placebo* (tw),” “random* (tw),” “double blind method (MeSH),” and “hemorrhage, peptic ulcer (MeSH).” We assessed the methodological quality of each identified study by applying the scale of Jadad *et al.* (Table 2), which is a standardized instrument focusing on features related to internal validity (16). This scale has been widely adopted in the medical literature, and we have used it in a previous systematic review of UGIH trials (17). Where available, we used summary estimates derived from pre-existing systematic reviews and meta-analyses. Where there was a range of data, we chose estimates that would tend to favor the current usual practice of reserving second look endoscopy for suspected rebleeding

Table 1. Base-Case Clinical Probability Estimates

Variable	Base-Case Estimate	Range in Literature	Range Tested	References
Probability of recurrent hemorrhage in patients receiving usual care after endoscopic therapy	18.8%	4–40%	0–100%	1, 5, 6, 8, 10, 19–51
Probability of recurrent hemorrhage in patients receiving <i>i.v.</i> PPIs after endoscopic therapy	13.2%	0–29%	0–100%	9, 10
Probability of recurrent hemorrhage in low-risk Baylor Bleeding Score patients after endoscopic therapy	5%	0%	0–100%	8
Probability of recurrent hemorrhage in unstratified all comers receiving second-look endoscopy after index hemostasis	11%	7–21%	0–100%	7, 8, 11, 22, 27, 29, 35, 37, 48–51
Probability of recurrent hemorrhage in high-risk Baylor Bleeding Score patients receiving second-look endoscopy after initial hemostasis	12%	0%	0–100%	7
Proportion of high-risk Baylor Bleeding Score patients in hypothetical cohort	56%	56%	0–100%	7
Probability of repeat hemostasis in patients with clinically evident rebleeding receiving repeat endoscopy	70%	20–80%	0–100%	1, 52
Probability of repeat hemostasis in patients with subclinical rebleeding receiving repeat endoscopy	50%	8%	0–100%	7
Probability of endoscopically induced perforation or uncontrollable bleeding	0.5%	0–3%	0–5%	1
Probability of perioperative death	10%	0–20%	0–100%	1

and therefore biased the model against the competing strategies.

Cost Estimates

Costs were estimated from the perspective of a third party payer, considering only direct health care costs (Table 3). Costs for endoscopic and surgical procedures and physician services were obtained from the 2001 American Medical Association Current Procedural Terminology codebook and the 2001 Medicare Fee Schedule. Inpatient resource use, including blood transfusions, laboratory costs, medication costs, and intensive care unit monitoring were included

under the standard Medicare Diagnosis Related Group (DRG) reimbursement for upper GI hemorrhage. Because it is not presently the standard of care to use *i.v.* PPI therapy for peptic ulcer bleeding, the current Medicare DRG does not reflect the additional cost of *i.v.* PPIs, including both the cost of the medication and the equipment required to administer it (*e.g.*, intravenous tubing and pumps). To account for the additional costs incurred by the *i.v.* PPI strategy, we itemized the costs of *i.v.* PPIs separately and added them to the standard Medicare DRG. Because the cost of *i.v.* PPI therapy has not been standardized, we used the average pharmacy cost from the buying consortiums of the six

Table 2. Scale for Quality Assessment of Controlled Clinical Trials*

Quality Indicator	Points Assessed
Was the study described as “randomized”?	If yes, score +1 If no, score 0
If randomization was performed, was there concealed allocation?	If yes, score +1 If no, score –1
Was the study described as “double blind”?	If yes, score +1 If no, score 0
If blinding was performed, was it appropriate?	If yes, score +1 If not, score –1
Was there a description of withdrawals and dropouts?	If yes, score +1 If no, score 0

* Based on Ref. 16 (Jadad *et al.*).

Poor quality studies are defined as those with a cumulative score of <3, and high quality studies are defined as those with a cumulative score of ≥3. In calculating our pooled base-case estimates, we weighted “high quality” studies twice that of “low quality” studies.

Table 3. Current Procedural Terminology and Costs to Medicare

Variable	Base-Case Cost Estimate (\$)	Range Tested (\$)
Medicare DRG for uncomplicated ulcer hemorrhage	4,072	0–10,000
Medicare DRG for complicated ulcer hemorrhage	10,123	0–10,000
Cost of <i>i.v.</i> PPI therapy		0–1,000
Medical cost*	90 (30/day)	
<i>i.v.</i> tubing and pump	10	
Total cost	100	
Cost of upper endoscopy		
Endoscopist's consultation fee	252	
Endoscopist's procedure fee	231	
Total cost	483	0–2,000
Cost of surgical ulcer or perforation repair		
Medicare DRG for bowel perforation	13,744	
Initial surgical consultation	97	
Surgeon's fee	710	
Anesthesiologist's fee	299	
Total cost	14,850	0–20,000
Cost of inpatient gastroenterologist follow-up visit	53	0–500
Cost of inpatient surgical follow-up visit	53	0–500

* Cost of *i.v.* PPIs derived from average pharmacy cost of buying consortiums from six institutions represented by authors and based on PPI equivalent of 80-mg bolus followed by 8 mg/h for 72 h.

institutions represented by the authors. This base case estimate was varied over a wide range in sensitivity analysis.

Outcomes

The primary outcomes measured were the average cost per patient for each strategy and the proportion of patients with recurrent hemorrhage, surgery, or death. The effectiveness of each strategy was defined as the proportion of patients with recurrent hemorrhage, surgery, or death prevented. We also measured the number of endoscopic and surgical procedures required by each strategy. We then calculated the average and incremental cost-effectiveness ratios compared with usual care. Using the absolute risk reduction for each strategy compared with usual care, we calculated the hypothetical number of patients needed to treat to avoid one recurrent hemorrhage, surgery, or death.

Decision Model

We evaluated four strategies for the posthemostasis management of a base case patient with peptic ulcer hemorrhage in whom endoscopic therapy for a nonbleeding visible vessel or active bleeding was performed. These specific strategies were selected because each is supported by sufficient data in the literature to allow modeling without invoking assumptions. Along these lines, we did not evaluate the potential strategy of using *i.v.* PPI therapy selectively in high-risk Baylor Bleeding Score patients. Although this approach is a relevant variant of the strategies modeled in our analysis, there are presently no published data regarding the differential effect of *i.v.* PPI therapy in patients stratified by risk after endoscopic hemostasis. Modeling the selective use of *i.v.* PPI therapy would therefore be entirely conjectural.

ENDOSCOPY FOR SUSPECTED REBLEEDING (USUAL CARE). This strategy, which serves as the referent case for our analysis, limits the use of second look endoscopy to patients with clinical evidence of rebleeding, including hematemesis, fresh melena, unanticipated decline in Hct, and hemodynamic instability. Patients without clinical evidence of rebleeding after initial hemostasis are offered early resumption of feeding and are monitored clinically for evidence of rebleeding. Patients with clinical evidence of rebleeding while hospitalized receive repeat upper endoscopy with retreatment of high risk stigmata or bleeding vessels. Patients with rebleeding after discharge (during the 30-day time horizon) are first readmitted to the hospital and then receive repeat upper endoscopy. Patients with persistent or recurrent bleeding despite endoscopic retreatment receive surgical oversewing of the bleeding ulcer. Patients with endoscopy-induced perforation undergo surgical repair of the lesion.

***i.v.* PPI AND ENDOSCOPY FOR SUSPECTED REBLEEDING.** Patients in this strategy are managed in the same manner as described in the referent case. However, after initial endoscopic hemostasis is achieved, all patients receive the PPI equivalent of an 80-mg bolus injection of omeprazole followed by a continuous infusion of 8 mg/h over 72 h as described by Lau *et al.* (13)

SECOND LOOK ENDOSCOPY. In this strategy, all patients undergo second look endoscopy 24 h after initial hemostasis, regardless of whether there is clinical evidence of rebleeding. Patients found to have subclinical bleeding or a nonbleeding visible vessel at repeat endoscopy undergo retreatment of the lesion. Patients without high-risk stigmata

Table 4. Baylor Bleeding Score*

Assigned Score	Age (yr)	Number of Illnesses	Severity of Illnesses	Site of Hemorrhage	Stigmata of Hemorrhage
0	<30	0			
1	30–49	1 or 2			Clot
2	50–59				
3	60–69				Visible vessel
4		3 or 4	Chronic	Posterior bulb	
5	≥70	≥5	Acute		Active bleed

* Adapted from Saeed *et al.*, Ref. 10. Sum of scores for age and the number and severity of concurrent illnesses makes up the “pre-endoscopy score.” Sum of the scores for site and stigmata of hemorrhage make up the “postendoscopy score.” High risk is defined as a pre-endoscopy score >5, or a total score of ≥10.

at the time of repeat endoscopy are not retreated and are followed clinically. Patients with recurrent bleeding despite this intervention or with endoscopy-induced perforation are referred for surgical management as described in the referent strategy.

SELECTIVE SECOND LOOK ENDOSCOPY. Patients in this strategy are initially divided into high- and low-risk groups as determined by the prospectively validated Baylor Bleeding Score (Table 4). Patients at low risk for rebleeding are managed in the same manner as described in the referent strategy. Patients at high risk for rebleeding undergo second look endoscopy 24 h after initial hemostasis and are then managed as described in the second look endoscopy strategy.

General Model Assumptions

Our model was based on several assumptions, as follows. First, because our base case estimates were derived from studies using disparate combinations of injection therapy and thermal contact probes, we did not specify which combination was used for initial or repeat hemostasis. Because rebleeding rates may vary between different combinations, we explored the effect of changing our estimates through sensitivity analysis, as described below. Second, based on data reported by the Center for Medicaid and Medicare Services, we assumed that patients with an uncomplicated postprocedural course required an average hospital stay of 3 days (18), whereas patients with a complicated postprocedural course required an average length of stay of 6 days. These estimates were each varied from 1–20 days in sensitivity analysis. Third, all patients received a daily follow-up visit by their gastroenterologist while hospitalized. Fourth, all patients ultimately requiring surgery received an initial surgical consultation, followed by a daily follow-up visit by their surgeon while hospitalized. Fifth, patients with recurrent hemorrhage after discharge were readmitted to the hospital and therefore incurred the charges associated with a second hospitalization. Review of the evidence reveals that, on average, 90% of recurrent hemorrhage occurs within the first 72 h, regardless of the strategy used (19–47). We therefore assumed that 10% of the patients with rebleeding in each arm required readmission to the hospital, whereas the remainder was managed during the original

hospital stay. This estimate was varied between 0% and 50% in sensitivity analysis.

Clinical Inputs and Probability Estimates Derived From Systematic Review

REBLEEDING PROBABILITY IN PATIENTS RECEIVING USUAL CARE AFTER ENDOSCOPIC THERAPY. Recurrent peptic ulcer hemorrhage after successful hemostasis remains the single most important determinant of patient outcomes (4, 5). A previous comprehensive review of 27 prospective trials using combinations of injection therapy and thermal contact probes found a mean rebleeding probability of 21% in patients managed by usual care after initial hemostasis (3). We identified 39 subsequently published randomized controlled trials with at least one arm using injection therapy or thermal contact probes (2, 7–9, 11, 13, 19–51). The mean probability of rebleeding from these reports, weighted by study size and quality, is 18.8%. Because the strategy of usual care is most likely to be cost-effective when the probability of rebleeding is low, we adopted the latter value as our base case estimate to bias the model in favor of usual care. We varied our estimate from 0% to 100% in sensitivity analysis to help account for the fact that the probability of rebleeding depends on several factors, including operator skill and the specific endoscopic modality used.

REBLEEDING PROBABILITY IN PATIENTS RECEIVING *i.v.* PPIs AFTER ENDOSCOPIC THERAPY. The use of high dose PPI therapy in the posthemostasis setting may reduce the risk of recurrent hemorrhage compared with usual care. A recent large, double-blind, randomized, controlled trial comparing standard medical management with a 72-h course of *i.v.* omeprazole for patients receiving endoscopic ulcer hemostasis found that 22.5% of the control group developed recurrent hemorrhage compared with only 6.7% of the experimental group (13). A recent meta-analysis of eight randomized controlled trials using *i.v.* PPIs for peptic ulcer hemorrhage calculated a pooled rebleeding probability of 13.2% (12). To bias the model in favor of usual care and against the *i.v.* PPI strategy, we adopted the latter value as our base case estimate.

REBLEEDING PROBABILITY IN PATIENTS STRATIFIED BY BAYLOR BLEEDING SCORE AFTER ENDOSCOPIC THERAPY. The Baylor Bleeding Score is an index based on readily available clinical data and is designed to predict rebleeding in patients receiving endoscopic hemostasis for peptic ulcer hemorrhage (Table 4) (10). Saeed *et al.* found that 31% of patients with a pre-endoscopy score of >5 or a postendoscopy score of ≥ 10 developed recurrent bleeding, whereas 0% of the patients achieving a lower score developed this outcome (10). To bias the model against the strategy of selective second look endoscopy, we assumed a more conservative estimate of 5% rebleeding in patients deemed to be at low risk by the Baylor Bleeding Score. This estimate is comparable to the probability of recurrent hemorrhage for patients with clean-based ulcers (3) and is consistent with the pooled probability of rebleeding identified by a systematic review of trials allowing early hospital discharge of low-risk patients (17). We further assumed that 44% of our hypothetical cohort was low risk as reported in the original series by Saeed *et al.* (10). However, because the proportion of high- and low-risk patients varies between populations, we varied this estimate from 0% to 100% in sensitivity analysis.

EFFECT OF ELECTIVE SECOND LOOK ENDOSCOPY IN UNSTRATIFIED PATIENTS AFTER ENDOSCOPIC THERAPY. Second look endoscopy 24 h after initial hemostasis with retreatment of residual high-risk stigmata has been suggested as a technique to reduce the risk of rebleeding. When this practice is applied without stratification to all comers with peptic ulcer hemorrhage, the probability of rebleeding ranges between 5% (11) and 29% (7). We identified 12 studies that used second look endoscopy in unstratified patients with peptic ulcer hemorrhage (7, 8, 11, 22, 27, 29, 35, 37, 48–51). The mean probability of rebleeding from these reports, weighted by study size and quality, is 11%. We adopted this value as our base case estimate.

EFFECT OF ELECTIVE SECOND LOOK ENDOSCOPY IN HIGH-RISK BAYLOR BLEEDING SCORE PATIENTS AFTER ENDOSCOPIC THERAPY. The use of selective second look endoscopy in patients at high risk for rebleeding was reported in only one study. In a randomized controlled trial of high-risk patients as determined by the Baylor Bleeding Score, Saeed *et al.* found no instances of clinically apparent rebleeding in the group receiving second look endoscopy and 24% in the control group (9). However, 8% of the experimental group had endoscopically apparent rebleeding at the time of second look endoscopy that was not otherwise clinically evident. Based on this rate of subclinical bleeding, we assumed a more conservative base case estimate of 12% clinically evident rebleeding in high risk patients receiving second look endoscopy (rather than 0%). By adopting this potentially inflated estimate, we biased the model in favor of usual care and against the second look endoscopy strategies.

PROBABILITY OF REPEAT HEMOSTASIS IN PATIENTS WITH CLINICALLY EVIDENT REBLEEDING. Recurrent hemorrhage after initial hemostasis may present with hematemesis, fresh melena, unanticipated decline in Hct, or hemodynamic instability. The current usual practice for the management of clinically evident rebleeding is to repeat therapeutic endoscopy (52). We assumed that 70% of the patients with clinically evident recurrent hemorrhage achieved successful and persistent hemostasis with repeat endoscopy, whereas the remaining 30% required surgical repair of the ulcer (52).

PROBABILITY OF REPEAT HEMOSTASIS IN PATIENTS WITH SUBCLINICAL REBLEEDING. Subclinical rebleeding, by definition, cannot be detected by standard clinical monitoring. However, when second look endoscopy is performed as an adjunct to clinical monitoring, the endoscopist may find ongoing hemorrhage that was otherwise clinically undetectable. There are limited data regarding the rate of repeat hemostasis when this subclinical bleeding is treated. Saeed *et al.* reported an 8% probability of subclinical oozing found with second look endoscopy, all of which was successfully treated without clinically evident recurrent hemorrhage (9). Although the effect of repeat hemostasis is likely to be more robust for subclinical bleeding than for clinically evident bleeding, we conservatively assumed that only 50% (rather than 100%) of patients with subclinical bleeding achieved persistent hemostasis, thereby further biasing the model against the second look endoscopy strategies.

PROBABILITY OF COMPLICATIONS OF ENDOSCOPY. Notable complications of urgent therapeutic endoscopy for bleeding peptic ulcers include perforation and induction of uncontrollable bleeding. Based on a previous comprehensive review of prospective data (3), we assumed a probability of 0.3% and 0.5% for perforation and bleeding, respectively. These estimates were varied from 0% to 5% in sensitivity analysis.

PROBABILITY OF COMPLICATIONS OF SURGERY. Between 4% and 12% of patients requiring surgical intervention for bleeding peptic ulcers die from either the severity of their illness or, less commonly, from the surgery itself (3). We assumed that 10% of the patients that underwent surgery died.

Sensitivity Analysis

One-way sensitivity analyses were performed to evaluate the effect on our results of varying individual cost and probability estimates over ranges exceeding the degree of uncertainty expected based on the medical literature. Two-way sensitivity analyses were performed on the most clinically significant and potentially influential variables. Finally, we conducted a Monte Carlo simulation to evaluate the second order uncertainty around our base case estimates. We evaluated the mean cost and effectiveness for each

Table 5. Results of Base-Case Cost-Effectiveness Analysis

Strategy	Cost/Patient Treated	Marginal Cost*	Effectiveness†	Marginal Effectiveness‡ (NNT)	Average Cost-Effectiveness§	Incremental Cost-Effectiveness¶
Endoscopy for suspected rebleeding (usual care)	\$7943		81%		\$ 9,806	
<i>i.v.</i> PPIs	\$7412	-\$531	87%	+6% (NNT = 17)	\$ 8,539	Negative value
Second-look endoscopy	\$8856	+\$913	89%	+8% (NNT = 13)	\$10,000	+\$11,412
Selective second-look endoscopy	\$7262	-\$681	91%	+10% (NNT = 10)	\$ 7,995	Negative value

NNT = Number Needed to Treat, defined as the number of patients needed to treat in each strategy to prevent one recurrent hemorrhage, surgery, or death compared to usual care. The NNT is the inverse of the absolute risk reduction or marginal effectiveness.

* Cost per patient vs usual care.

† Proportion of patients with recurrent hemorrhage, surgery, or death prevented.

‡ Proportion of patients with recurrent hemorrhage, surgery, or death vs usual care.

§ Cost per additional recurrent hemorrhage, surgery, or death prevented.

¶ Cost per additional recurrent hemorrhage, surgery, or death prevented vs usual care.

strategy from 1000 trials using random samples of variable estimates.

RESULTS

The potential clinical and economic impact of implementing the four alternative strategies was estimated through cost-effectiveness analysis (Table 5). The strategy employing usual care, in which repeat endoscopy is reserved for patients with clinical signs of rebleeding, was the least effective approach because it prevented recurrent hemorrhage, surgery, or death in only 81% of the cohort, and was the second most expensive at \$7943 per patient treated. Compared with usual care, the selective second look endoscopy strategy was more effective and less expensive, as it prevented recurrent hemorrhage, surgery, or death in 91% of the cohort and cost \$7262 per patient treated. The *i.v.* PPI strategy was 87% effective and cost \$7412 per patient treated. The second look endoscopy strategy cost the most per patient treated at \$8856 and was 8% more effective than usual care. The second look strategy therefore cost an incremental \$11,412 per unit of effectiveness compared with usual care. Overall, the use of selective second look endoscopy for high-risk patients was the most effective and the least expensive of the four competing strategies, and therefore dominated the analysis. Compared with usual care, 10 patients needed to be treated with selective second look endoscopy to prevent one recurrent hemorrhage, surgery, or death.

The cost-effectiveness of competing strategies for GI hemorrhage depends partly on the use of invasive procedures, including endoscopy and surgery. Compared with usual care, the *i.v.* PPI strategy required 50% fewer endoscopic and surgical procedures, which partially offset the additional cost of the medication. In contrast, the selective and nonselective second look endoscopy strategies required 100% and 400% more endoscopic procedures, respectively, compared with usual care.

We performed one-way sensitivity analysis to determine whether our findings were robust to changes in the clinical probability estimates (Table 6). The probability of rebleeding after initial hemostasis plays a pivotal role in determining the effectiveness of competing strategies and therefore affected the model results. When the probability of rebleeding in unstratified patients managed by usual care fell below 10% (base case, 18.8%), the strategy employing usual care dominated the analysis (*i.e.*, became the most effective and least expensive of the competing strategies), reflecting the decreased need for second look endoscopy when the effect of initial hemostasis is robust. We further tested our conclusions by varying the probability of rebleeding in patients receiving *i.v.* PPIs. The *i.v.* PPI strategy dominated the analysis when the probability of rebleeding for unstratified all comers receiving *i.v.* PPIs fell below 9% (base case, 13.2%).

Our model was also affected when we altered the proportion of high- and low-risk patients in the hypothetical cohort. The selective second look endoscopy strategy remained the dominant strategy when less than 66% of the cohort was high risk as determined by the Baylor Bleeding Score, whereas the *i.v.* PPI strategy became the dominant strategy for values above this threshold (base case, 56%). In other words, as the proportion of high-risk patients increased, the use of *i.v.* PPIs gained cost-effectiveness.

Although the risk of severe endoscopic complications is rare, the economic repercussions of bowel perforation or uncontrolled bleeding induced by endoscopy are significant, and the probability of complications therefore affected the model results. When the likelihood of severe complications exceeded 3% (base case, 0.05%), the *i.v.* PPI strategy became the dominant approach, reflecting its minimal reliance on endoscopic procedures.

We used one-way sensitivity analysis to examine whether altering the cost estimates affected our results. When the cost of endoscopy increased by a factor of 2.5 (from \$483 to \$1225), the *i.v.* PPI strategy became the dominant approach,

Table 6. Results of One-Way Sensitivity Analyses*

Variable	Base-Case Estimate	Threshold Value	Comment
Probability of recurrent hemorrhage in patients receiving usual care after endoscopic therapy	18.8%	10%	If less than threshold, then usual care becomes dominant
Probability of recurrent hemorrhage in patients receiving <i>i.v.</i> PPIs after endoscopic therapy	13.2%	9%	If less than threshold, then <i>i.v.</i> PPI strategy becomes dominant
Proportion of high risk patients in hypothetical cohort	56%	66%	If greater than threshold, then <i>i.v.</i> PPI strategy becomes dominant
Probability of bowel perforation or uncontrollable bleeding induced by endoscopy	0.05%	3%	If greater than threshold, then <i>i.v.</i> PPI strategy becomes dominant
Cost of upper endoscopy	\$483.11	\$1225	If greater than threshold, then <i>i.v.</i> PPI strategy becomes dominant
Cost of <i>i.v.</i> PPI therapy	\$30/day	\$10/day	If less than threshold, then <i>i.v.</i> PPI strategy becomes dominant

* Listed thresholds are values at which a strategy other than the selective second-look endoscopy strategy becomes dominant (*i.e.*, becomes the most effective and least expensive strategy).

again reflecting its minimal reliance on endoscopy. This strategy also dominated when the cost of *i.v.* PPIs fell by 66% (\$30/day to \$10/day).

We also estimated the effect on outcomes when the values for pairs of the most important clinical variables were changed conjointly. The two-way sensitivity analyses were most useful to delineate circumstances under which the *i.v.* PPI strategy was preferred over the selective second look endoscopy strategy. For example, the selective second look endoscopy strategy became cost-effective compared to the *i.v.* PPI strategy when the cost of *i.v.* PPIs was \$100 and the proportion of high risk patients was 30%, whereas the *i.v.* PPI strategy was preferred when the cost of *i.v.* PPIs was \$50 and the proportion of high risk patients was 50% (Fig. 1). Likewise, the selective second look strategy was more cost-effective than the *i.v.* PPI strategy when the cost of

upper endoscopy was \$450 and the probability of rebleeding on *i.v.* PPIs was 20%, whereas the *i.v.* PPI strategy was preferred when the cost of endoscopy was \$800 and the probability of rebleeding on *i.v.* PPIs was 10% (Fig. 2).

We performed Monte Carlo simulation to evaluate the second-order uncertainty around our base case estimates. The mean cost-effectiveness from 1000 trials using random combinations of variable estimates was similar to the data derived from our base case analysis. The data were comparable when 100, 500, and 2000 trials were simulated.

DISCUSSION

There is presently no consensus regarding the optimal strategy to minimize recurrent peptic ulcer hemorrhage once endoscopic hemostasis is achieved. The current usual prac-

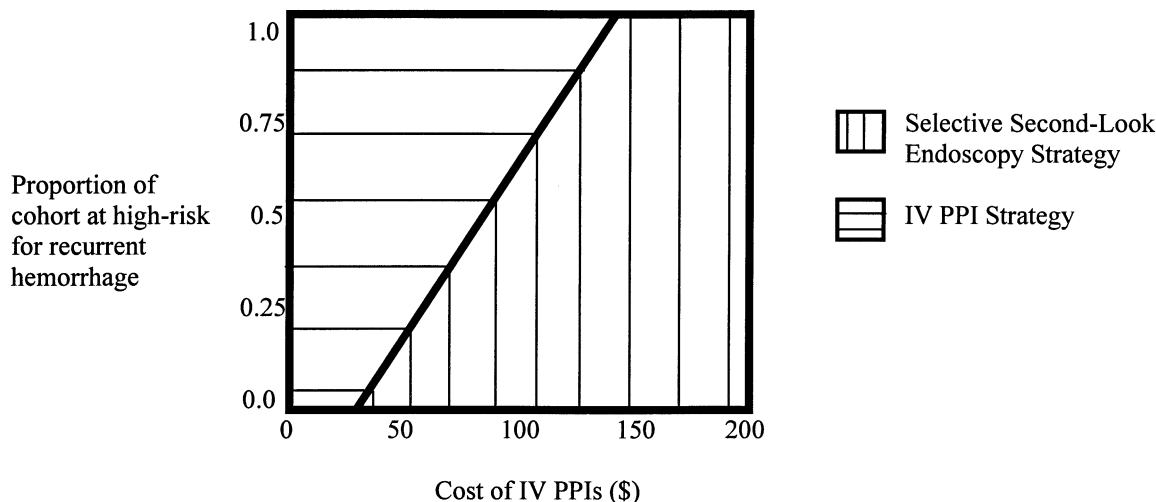


Figure 1. Two-way sensitivity analysis comparing the cost of *i.v.* PPIs with the proportion of the cohort at high risk for recurrent hemorrhage as defined by the Baylor Bleeding Score patients. Striped portions of graph represent domains where one strategy is more cost-effective than the other. For example, the selective second-look endoscopy strategy was more cost-effective than the *i.v.* PPI strategy when the cost of *i.v.* PPIs was \$100 and the proportion of high risk patients was 30%.

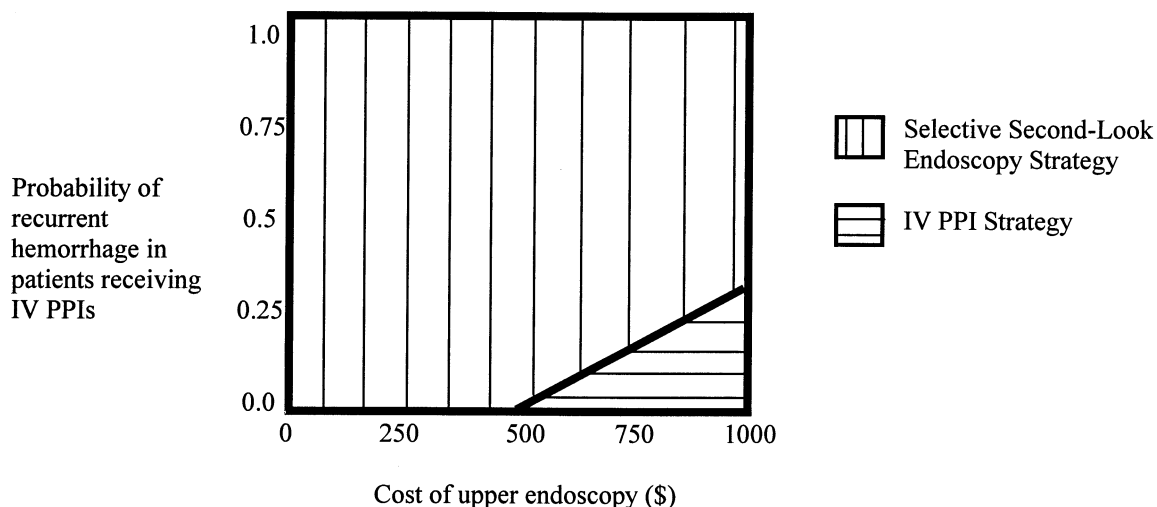


Figure 2. Two-way sensitivity analysis comparing the cost of upper endoscopy with the probability of recurrent hemorrhage in patients receiving *i.v.* PPIs after endoscopic hemostasis. Striped portions of graph represent domains where one strategy is more cost-effective than the other. For example, the selective second-look strategy was more cost-effective than the *i.v.* PPI strategy when the cost of upper endoscopy was \$450 and the probability of rebleeding on *i.v.* PPIs was 20%.

tice is to follow patients clinically after hemostasis and to repeat endoscopy only in subjects with evidence of recurrent hemorrhage. However, our analysis of alternative strategies for the posthemostasis management of peptic ulcer hemorrhage suggests that this practice may not be the most cost-effective approach. Compared with usual care, performing selective second look endoscopy in patients at high risk for rebleeding as identified by the Baylor Bleeding Score may prevent more recurrent hemorrhage, surgery, or death at a lower overall cost. Our analysis reveals that use of the Baylor Bleeding Score may serve as an effective *and* cost-effective filter to identify high-risk patients who can benefit from targeted early second look endoscopy. The additional cost generated by committing a subset of patients to repeated endoscopy seems to be offset by the significant effectiveness of this strategy. We estimate that only 10 patients need to be treated with selective second look endoscopy to prevent one recurrent hemorrhage, surgery, or death compared with usual care.

Our analysis further suggests that the use of *i.v.* PPI therapy during the 72 h after successful hemostasis may be a cost-effective strategy. Under base case conditions, this strategy is the least expensive per patient treated and is the second most cost-effective strategy. Sensitivity analysis suggests that the use of *i.v.* PPIs may be the dominant strategy (most effective and least expensive of the competing strategies) if the probability of rebleeding in patients receiving the infusion falls below 9%, a value that is marginally higher than the proportion documented by Lau *et al.* (13) Despite our conservative estimate of a 13% rebleed probability in patients receiving *i.v.* PPIs, this strategy remains nearly equivalent to selective second look endoscopy under base case estimates. Based on our sensitivity analysis, the use of *i.v.* PPIs may reduce the need for second look

endoscopy if the probability of recurrent hemorrhage by Lau *et al.* can be reproduced. This strategy may also be preferred if the proportion of patients at high risk for rebleeding exceeds 66%. This finding suggests that using *i.v.* PPIs in high-risk populations may significantly reduce the subsequent endoscopic burden compared with competing strategies and therefore offset the relatively modest up-front cost of the medication.

Because the preferred strategy to minimize rebleeding is dependent on the unique composition of a patient cohort, the optimal strategy may vary among different populations and different centers. In particular, selecting the optimal strategy is partly dependent on the proportion of high-risk patients in the cohort and on the likelihood that high-risk patients will rebleed. Figure 3 represents a two-way sensitivity analysis comparing these variables, and may serve as a nomogram to help clinicians in selecting the most cost-effective strategy in their own population. For example, clinicians caring for a predominantly elderly population with multiple comorbidities and a high rebleeding rate might consider using selective second look endoscopy or *i.v.* PPIs, whereas those caring for a predominantly young population with few comorbidities and a low rebleeding rate (<10%) might consider the usual practice of “watchful waiting.”

There are several limitations to this study. As with any decision analysis, the results depend on the validity of the base case estimates. In particular, the effectiveness of endoscopic hemostasis has improved with the advent of advanced therapeutic techniques and novel modalities, and the current literature may not yet accurately reflect these trends. Because the likelihood of rebleeding after endoscopic hemostasis largely dictates the relative cost-effectiveness of competing strategies, an inaccurate base case estimate may lead to inaccurate conclusions. For example, underestimat-

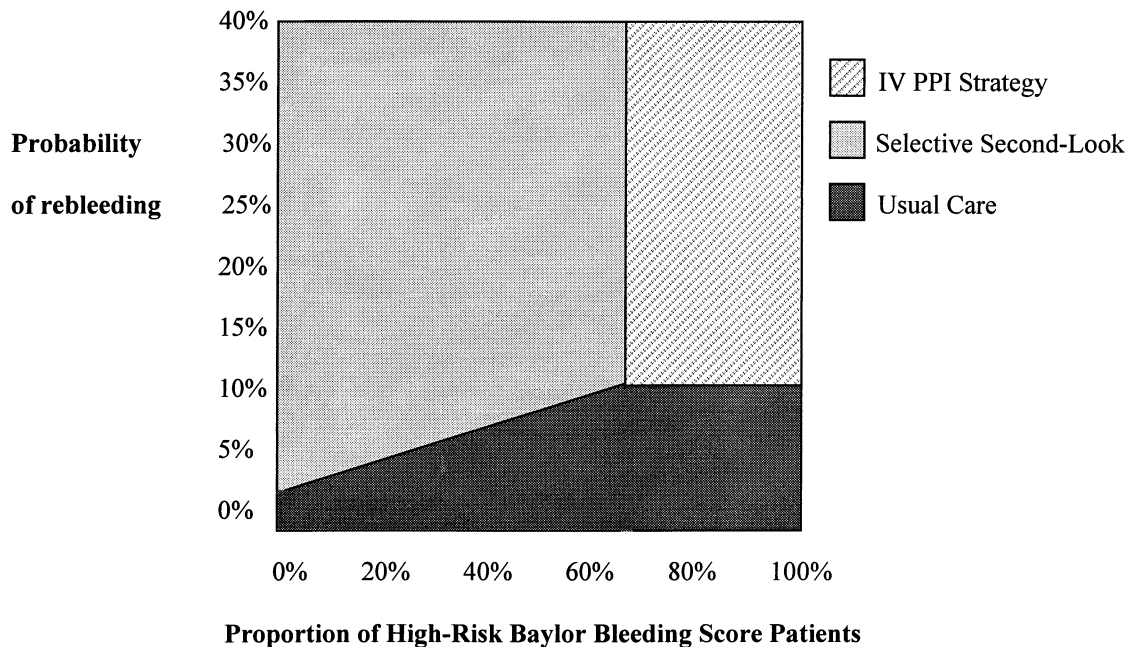


Figure 3. Two-way sensitivity analysis comparing the probability of rebleeding in high risk Baylor Bleeding Score patients with the proportion of high risk patients in the cohort. Shaded portions of graph represent domains where one strategy is preferred over another. The strategy of reserving repeat endoscopy for clinically evident rebleeding (usual care) is more cost-effective than the competing strategies when the rate of recurrent hemorrhage remains below 10%, regardless of the proportion of high risk patients. The selective second-look endoscopy strategy is most cost-effective when the rate of rebleeding is more than 10%, and when less than two thirds of the cohort is at high risk, whereas the *i.v.* PPI strategy is preferred when the rate of rebleeding is more than 10% and when more than two thirds of the cohort is at high risk.

ing the rate of rebleeding favors usual care, whereas overestimating favors strategies using second look endoscopy. We have attempted to guard against this by systematically reviewing the literature and selecting conservative estimates that tend to bias the model in favor of the usual practice. Despite this bias, our model indicates that the current usual practice of reserving second look endoscopy for clinically evident rebleeding may not be cost-effective compared with alternative strategies. This finding persists when key clinical assumptions are varied over a range of values exceeding clinical likelihood.

We limited our analysis to the use of injection therapy and thermal probes, and did not consider alternative modalities including fibrin glue, laser coagulation, or hemoclips. In particular, recent data indicate that hemoclips may significantly reduce the rate of recurrent hemorrhage compared with injection therapy or thermal probes, and the use of this modality may therefore reduce the cost-effectiveness of second look endoscopy (53, 54). Our model indicates that a rebleeding rate of less than 10% for patients receiving endoscopic therapy would favor the "watchful waiting" approach employed by usual care. Because recurrent hemorrhage in patients receiving hemoclips is reported to be as low as 1.8% (53), the strategy employing usual care may be most cost-effective if this technology is used. However, these preliminary data await confirmation with additional randomized controlled trials, and the use of hemoclips is presently not considered standard practice. It may therefore

be premature to explore the cost-effectiveness of hemoclips before their effectiveness has been firmly established.

Our analysis does not consider all possible clinical outcomes, including personal discomfort as a result of an invasive procedure or a complication of therapy. Health-related quality of life is an important consideration in all areas of medicine, as it may affect costs in a manner that is not accounted for by simple economic modeling. Strategies using elective second look endoscopy are likely to decrease health-related quality of life compared with alternative approaches because patients are, on average, subjected to additional invasive procedures. We did not incorporate utilities or calculate quality-adjusted life years in this model, and therefore we may have overestimated the cost-effectiveness of second look endoscopy. However, although utility calculations are important for conditions that are not likely to affect life or life expectancy, they are of lesser importance for peptic ulcer hemorrhage, a condition that directly threatens life expectancy.

We have assumed the perspective of a third-party payer and have used Medicare reimbursement costs. There are several limitations to this approach. The Medicare DRG for GI hemorrhage is a fixed reimbursement that is designed to account for routine costs, including blood transfusions, intensive care monitoring, nursing care, and blood draws. Competing strategies are likely to require these resources at different rates, and tabulating the individual cost components may have generated different cost-effectiveness val-

ues. Furthermore, costs are variable and depend on the managed care plan. However, Medicare reimbursement rates are the benchmark used by most managed care organizations to determine their reimbursement.

In conclusion, this analysis reveals that the current usual practice of reserving repeat endoscopy for patients with clinically evident rebleeding may not be cost-effective. Compared with usual care, using selective second look endoscopy in high-risk patients as determined by the Baylor Bleeding Score may prevent more adverse outcomes at a lower overall cost. However, the use of *i.v.* PPIs for patients with peptic ulcer hemorrhage is likely to reduce the need for second look endoscopy after successful hemostasis, and may be the dominant strategy if the risk of recurrent hemorrhage with *i.v.* PPIs is less than 9%. Because there are no available data regarding the differential effect of *i.v.* PPI therapy in patients stratified by rebleeding risk, we did not model the potential strategy of reserving *i.v.* PPIs only in high-risk Baylor Bleeding Score patients. However, given the apparent cost-effectiveness of *indiscriminate i.v.* PPI administration after hemostasis, the use of *selective i.v.* PPIs in high-risk Baylor Bleeding Score patients may be optimally cost-effective. We suggest that these findings should be confirmed with a prospective trial comparing the effectiveness and accrued costs of these competing management strategies.

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