

Cost-effectiveness of Proton Pump Inhibitor Cotherapy in Patients Taking Long-term, Low-Dose Aspirin for Secondary Cardiovascular Prevention

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Background: Patients with coronary heart disease (CHD) require long-term therapy with low-dose aspirin (ASA). Although these patients are at increased risk for upper gastrointestinal bleeding (UGIB) and proton pump inhibitor (PPI) cotherapy may reduce such risk, it is not known whether lifelong PPI cotherapy is cost-effective.

Methods: A Markov model was developed to compare lifelong therapy with ASA alone vs therapy with ASA plus PPI in patients with CHD who are at least 50 years old. Base-case assumptions were (1) starting age, 65 years (range, 50-80 years); (2) UGIB risk category, average risk (range, average to 8-fold increased risk); (3) PPI effectiveness (66% (range, 25%-75%)); and (4) annual PPI cost, \$250 (range, \$250-\$1400).

Results: In the base-case analysis, ASA plus PPI resulted in fewer lifetime UGIB events (3.1% vs 9.5%) and UGIB-related deaths (0.4% vs 1.4%). At over-the-

counter (OTC) PPI cost, ASA plus PPI was cost-effective, with an incremental cost-effectiveness ratio (ICER) of \$40 090 per life-year saved (LYS). Varying PPI effectiveness from 75% to 25% resulted in ICERs of \$35 315 to \$94 578 per LYS. Varying the starting age of the cohort from 80 to 50 years resulted in ICERs of \$16 887 to \$79 955 per LYS. At prescription PPI cost, the ICER for average-risk patients was over \$100 000 per LYS across all modeled age groups and assumptions of PPI effectiveness, but the ICER for high-risk patients was \$10 433 to \$51 505 per LYS.

Conclusions: At OTC cost, PPI cotherapy is cost-effective in average-risk patients taking low-dose ASA for secondary prevention. At prescription cost, cotherapy is cost-effective for high-risk patients only.

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CURRENT GUIDELINES recommend that patients with established coronary heart disease (CHD) use low-dose (75-325 mg) aspirin (ASA) indefinitely for prevention of recurrent cardiovascular (CV) events.^{1,2} Although the CV benefits of ASA are

tor (PPI); PPIs have been shown to reduce the risk of bleeding in 2 randomized controlled trials.^{8,9} Although these trials enrolled patients at high risk for ulcer bleeding (ie, those with a history of peptic ulcer disease), observational studies¹⁰⁻¹² support a similar benefit for patients at average risk of bleeding. Despite these data supporting the effectiveness of PPI cotherapy, the question of whether such cotherapy is cost-effective remains unanswered. Although prior models have explored the role of PPI cotherapy in users of traditional-dosage, nonsteroidal anti-inflammatory drugs (NSAIDs),¹³⁻¹⁶ low-dose ASA carries a markedly lower risk of bleeding, and the role of PPI cotherapy in users of low-dose ASA alone has not been explicitly studied. The recent availability of low-cost over-the-counter (OTC) PPIs has also not been studied. The purpose of this study was to model the clinical and economic effects of PPI cotherapy in patients taking long-term, low-dose ASA for secondary prevention of cardiovascular events, from the perspective of a long-term payer such as Medicare. We explic-

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widely accepted, ASA also carries a small but clinically important risk of upper gastrointestinal bleeding (UGIB) (0.25% -1% per patient-year).³ Also, UGIB carries significant risk of morbidity and mortality, particularly in patients with CHD.⁴⁻⁶ Furthermore, low-dose ASA is the most common cause of GI bleeding-related mortality, accounting for one-third of bleeding-related deaths nationally in a recent Spanish study.⁷

One approach that can reduce the risk of UGIB in patients taking low-dose ASA is cotherapy with a proton pump inhibi-

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itly compared the cost-effectiveness of low-cost OTC PPIs, such as omeprazole magnesium, to that of higher-cost prescription (Rx) PPIs, such as esomeprazole magnesium, rabeprazole sodium, and pantoprazole sodium. We employed an age-dependent risk of UGIB and UGIB-related mortality and also studied the impact of additional risk factors for UGIB. With this approach, we defined patient subgroups for which PPI cotherapy is cost-effective and identified additional areas of research for defining a rational approach to reducing the risk of low-dose ASA therapy.

METHODS

DECISION ANALYTIC MODEL

We developed a Markov cohort model using TreeAge Pro decision modeling software (TreeAge Software Inc, Williamstown, Massachusetts). Two competing strategies were modeled:

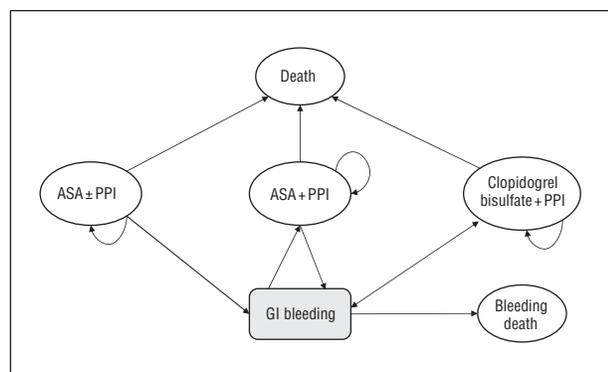


Figure 1. Basic Markov model structure. Ovals represent Markov states; gastrointestinal (GI) bleeding is a discrete event that can occur in any living Markov state; “ASA + PPI” and “clopidogrel bisulfate + PPI” represent high-risk bleeding states (owing to history of bleeding). ASA indicates aspirin; PPI, proton pump inhibitor.

led: (1) an ASA-alone strategy, in which the cohort was started on treatment with ASA alone, and gastroprotection (ASA plus PPI) was used only if a UGIB event occurred; and (2) an ASA plus PPI strategy, in which the cohort was started on treatment with ASA plus PPI and switched to clopidogrel bisulfate plus PPI in the event of UGIB. The base-case cohort was composed of a 65-year-old, adherent, ASA-tolerant population with no additional risk factors for UGIB using ASA for secondary prevention of CV events. The simulation began with the entire cohort using ASA (hereinafter, ASA state) with or without PPI (depending on the strategy being modeled). The cohort could then remain in the ASA state for the entire 1-year cycle or undergo a UGIB event. A bleeding event resulted in transition to a high-risk state for future UGIB events (“ASA plus PPI” or “clopidogrel plus PPI”) or to a death state.^{11,17} Finally, any Markov state could transition to a death state. The basic structure of the model is outlined in **Figure 1**.

UGIB RISK

The risk of UGIB in low-dose ASA users was estimated from published literature on this topic (**Table 1**). We performed a MEDLINE search for English-language systematic reviews of ASA and gastrointestinal bleeding published since 2000, using the terms *aspirin*, *gastrointestinal*, and *bleeding* or *hemorrhage*. Using this search strategy, we identified 3 recent systematic reviews^{3,5,10} from which we extracted summary relative risks and crude annual risks of UGIB in low-dose ASA users. We also extracted data on independent risk factors for UGIB in users of low-dose ASA.

Commonly accepted risk factors for UGIB in patients taking low-dose ASA include age, history of UGIB, and concomitant NSAID, warfarin sodium, or corticosteroid use. Age-related risk is unique in that it is dynamic, increasing gradually over the lifetime of the individual. We therefore modeled age-related risk separately from other “static” risk factors (**Figure 2**).²² Furthermore, we assumed that age could be multiplicatively combined with these other risk factors. Specifically, a cohort of patients with no additional risk factors was categorized as “average risk.” A cohort of patients with at least

Table 1. Base-Case Assumptions of Variables in Model and Ranges Tested in Sensitivity Analysis

Description	Base Case ^a	Sensitivity Analysis Range	Source
Annual costs of treatment, \$			
Acute UGIB	15 000 (T)	10 000-20 000	Healthcare Cost and Utilization Project ¹⁸
Aspirin	10 (T)	5-20	Consumers Union ¹⁹ ; Red Book ²⁰
Clopidogrel bisulfate	1600 (T)	500-1800	Consumers Union ¹⁹ ; Red Book ²⁰
PPI	250 (N)	250 or 1400 ^b	Consumers Union ¹⁹ ; Red Book ²⁰
Probabilities and risks			
Increased probability of death due to underlying CHD	Age dependent (N)	±25%	Goldberg et al ²¹
Probability of UGIB	Age dependent ^c	Average to 8-fold increased risk	Laine ³ ; Hernández-Díaz et al ²²
Probability of death from UGIB	Age dependent (N)	±25%	Rockall et al ^{23,24}
RR of future bleeding in patients with prior UGIB	4.0 (N)	2.0-8.0	Lanas et al ¹¹ ; Serrano et al ¹⁷
Effectiveness of PPI (RRR in UGIB), %	66 (B)	25-75	Chan et al ⁸ ; Lai et al ⁹ ; Lanas et al ¹¹ ; Hooper et al ²⁵
Miscellaneous			
Discount rate, %	3	None	Assumed ^d
Starting age of cohort, y	65	50-80	Assumed ^d

Abbreviations: B, beta distribution; CHD, coronary heart disease; N, normal distribution; OTC, over the counter; PPI, proton pump inhibitor; RR, relative risk; RRR, RR reduction; T, triangular distribution; UGIB, upper gastrointestinal bleeding.

^aThe abbreviation in parentheses indicates the type of distribution used in probabilistic sensitivity analysis; the OTC PPI cost was varied 25% in either direction for this analysis.

^bThe OTC PPI cost (base case) is \$250, and prescription PPI cost is \$1400.

^cThe precise relationship between age and UGIB is displayed graphically in Figure 1.

^dThese values were selected by the authors.

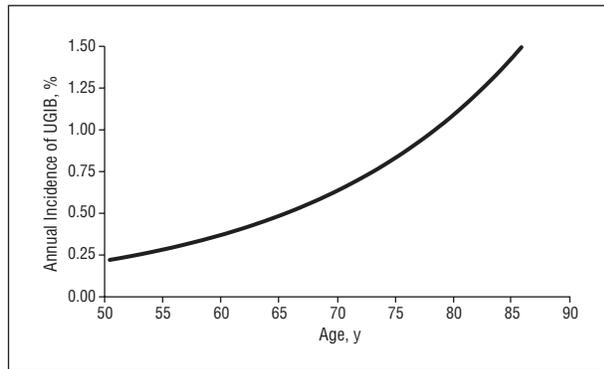


Figure 2. Risk of upper gastrointestinal bleeding (UGIB) by age in users of low-dose aspirin (average-risk population).

1 additional risk factor was categorized as “high risk,” with the precise risk increase expressed as a multiple of average risk (eg, $4 \times$ or $8 \times$ average risk). The risk of death from UGIB was also age dependent (based on data from the Rockall cohort).^{23,24}

EFFECTIVENESS OF PPI COTHERAPY

The effectiveness of PPI cotherapy in reducing UGIB risk was estimated from published literature (Table 1). We performed a MEDLINE search for English-language studies of ASA, PPIs, and gastrointestinal bleeding published since 1980, using the terms *aspirin*, *gastrointestinal*, *bleeding* or *hemorrhage*, and *proton pump inhibitor*. The generic name for each commonly used PPI was also employed in the search. Using this search strategy, we identified 2 randomized controlled trials^{8,9} of PPI cotherapy in low-dose ASA users, both of which enrolled only patients with a personal history of peptic ulcer disease. Data in average-risk patients were more limited and were observational.¹⁰⁻¹² Only 1 of these studies⁸ explicitly used “high-dose” PPI (ie, more than once daily or at higher than the widely accepted starting dosage). Using the point estimate from the study reporting the smallest effect size,¹² we assumed that PPIs reduced bleeding risk by 66% in our base-case analysis. We then varied this effect from 25% to 75% in a sensitivity analysis based on the confidence intervals reported across these studies.^{8,9,11,12} A similar benefit was assumed for patients using clopidogrel.^{12,26}

CV RISK

Because CV events would be expected to occur at the same rate under both strategies (both cohorts taking an antiplatelet agent throughout the simulation), CV events were not explicitly modeled. However, the annual age-dependent probability of death was adjusted (increased in an age-dependent fashion) to account for the assumption of underlying CHD in the cohort.²¹

COST INPUTS

Cost estimates used in the model included the cost of hospitalization for UGIB and the costs of the various medications studied in the model (ASA, OTC PPI, Rx PPI, and clopidogrel) (Table 1). The cost of UGIB was obtained from the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (DRG categories 174-178).¹⁸ This cost was varied by 33% in either direction in sensitivity analysis. The cost of OTC PPIs was based on current OTC wholesaler prices as reported by the Consumers Union,¹⁹ an independent consumers group. Such prices are likely to reflect those available to large health insurance companies or governmental payers (Medicare or the Department of Veterans Affairs) because these groups

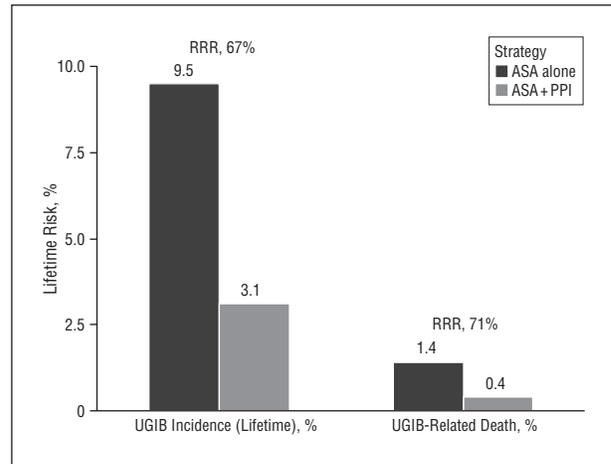


Figure 3. Predicted upper gastrointestinal bleeding incidence (UGIB) and death. ASA indicates aspirin; PPI, proton pump inhibitor; RRR, relative risk reduction.

are capable of negotiating for collective price reductions. The cost and range for sensitivity analysis of ASA, Rx PPIs, and clopidogrel were derived from the 2007 Thomson Red Book²⁰ and from data reported by the Consumers Union.¹⁹ All costs were discounted at a rate of 3% per year and adjusted for inflation to 2007 US dollars based on the Consumer Price Index.²⁷

OUTCOMES

Under each strategy, clinical and economic outcomes were measured and reported. Clinical outcomes included (1) UGIB events, (2) UGIB-related mortality, and (3) years of life saved. Economic outcomes included costs and incremental cost-effectiveness ratios (ICERs). Because GI bleeding represents a discrete, time-limited event without a well-defined disutility, quality-adjusted life-years were not measured.

SENSITIVITY ANALYSIS

Ranges for sensitivity analysis were based on published literature whenever possible. For areas in which the published literature was limited (eg, the effectiveness of PPI therapy in average-risk patients), expert opinion was also sought (A.M.F. and J.S.) and the range was widened to account for the additional uncertainty. One-way sensitivity analysis was performed on each variable in the model. Multivariate sensitivity analysis was performed on variables found to be important in 1-way sensitivity analysis. Probabilistic sensitivity analysis was also performed to assess the overall impact of uncertainty in the variables used in the model. In this analysis, 8 variables were simultaneously varied over 10 000 iterations in a cohort of average-risk, 65-year-old patients using OTC PPIs. Variable distributions for this analysis were based on the type of variable (cost, risk, or probability), point estimate, and range (Table 1).

RESULTS

In the base-case analysis, at an OTC PPI cost of \$250 per year, the ASA plus PPI strategy resulted in fewer lifetime UGIB events than ASA alone (3.1% vs 9.1% lifetime risk) and fewer UGIB-related deaths than ASA alone (0.4% vs 1.4%), with a relative risk reduction (RRR) of 67% and 71%, respectively (**Figure 3**). An ASA plus PPI was also more costly than the ASA alone (**Figure 4**), with

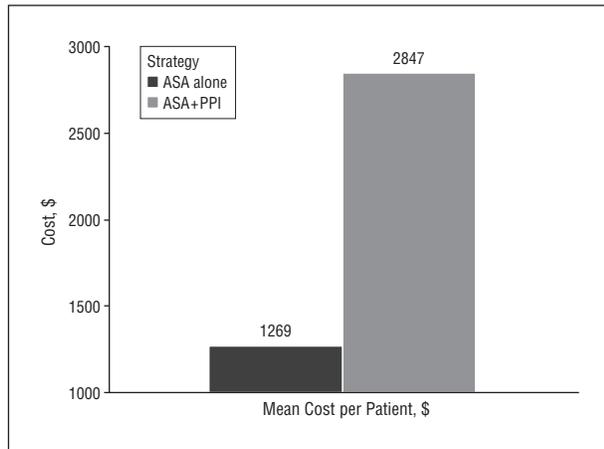


Figure 4. Predicted mean lifetime cost per patient. This includes cost of aspirin (ASA) plus clopidogrel, proton pump inhibitor (PPI), and hospital admissions related to upper gastrointestinal bleeding.

an ICER of approximately \$40 000 per life-year saved (LYS) (cohort starting at age 65 years) (**Figure 5** and **Table 2**). These base-case results were robust to uncertainty in the input variables in probabilistic sensitivity analysis, with nearly 75% of trials remaining below a willingness-to-pay threshold of \$50 000 per LYS (**Figure 6**).

These results were highly sensitive to (1) the effectiveness of PPIs in reducing UGIB risk (reported as an RRR in UGIB), (2) the starting age of the cohort, (3) the UGIB risk category (average risk vs high risk), and (4) the cost of PPIs (OTC vs Rx). In an average-risk population, starting PPI therapy at a younger age was marginally cost-effective (\$80 000 per LYS at age 50 years), and starting PPI therapy at an older age was highly cost-effective (\$17 000 at age 80 years) (Table 2). These results varied according to the effectiveness of PPI cotherapy in reducing UGIB risk, with assumptions of lower PPI effectiveness resulting in higher ICERs (**Figure 7**). Increasing the UGIB risk of the population 3-fold or higher resulted in ICERs of less than \$25 000 across all modeled age groups and assumptions of PPI effectiveness (Figure 7 and Table 2).

Increasing the cost of PPIs to Rx prices markedly increased the cost of the ASA plus PPI strategy, making the strategy cost-ineffective for all but the highest-risk, oldest patients (**Figure 8** and Table 2). At Rx prices, the ICER of the ASA plus PPI strategy for patients with a 4-fold higher risk of UGIB (compared with the average population) was \$100 000 per LYS for the 50-year-old cohort, \$51 000 per LYS for the 65-year-old cohort, and \$25 000 for the 80-year-old cohort. At an 8-fold higher-than-average risk, the ICER remained less than \$50 000 per LYS across all modeled age groups and assumptions of PPI effectiveness.

COMMENT

SUMMARY

Long-term, low-dose ASA is universally recommended in patients with a history of CHD to decrease the risk of recurrent CV events.^{1,2} Although the benefit of ASA is

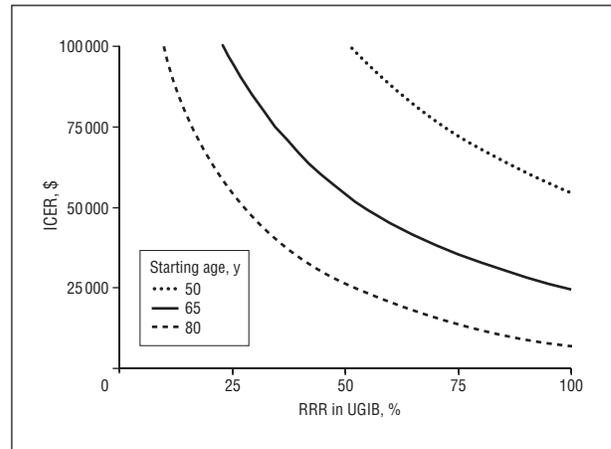


Figure 5. One-way sensitivity analysis of the relative risk reduction (RRR) in upper gastrointestinal bleeding (UGIB) for those taking a proton pump inhibitor in an average-risk population. ICER indicates incremental cost-effectiveness ratio. The middle line represents the base case, and the upper and lower lines represent the extremes of the sensitivity analysis range.

widely accepted, it also carries a clinically important risk of UGIB.³ This infrequent but serious adverse effect can be minimized with PPI cotherapy.^{8,9,11,25} Our study demonstrates that, provided that PPIs are available at OTC prices, PPI cotherapy is a cost-effective strategy for patients older than 65 years who are taking ASA for secondary prevention and may be cost-effective for patients as young as 50 years. At Rx prices, however, cotherapy seems to be cost-effective only in high-risk patients, such as those with prior ulcer disease or those taking an additional NSAID. Our results were robust across a wide range of assumptions in sensitivity analysis and should help guide physicians in caring for their patients who are taking ASA for secondary prevention.

LITERATURE REVIEW

Despite the much lower risk of UGIB with low-dose ASA compared with higher-dose NSAIDs, the results of our study are consistent with those of prior studies¹³⁻¹⁶ that have investigated the cost-effectiveness of PPI cotherapy in patients using nonselective standard-dose NSAIDs. A study by Spiegel et al¹⁵ compared various strategies for minimizing GI bleeding risk in patients taking NSAIDs, including PPI cotherapy. Assuming an Rx PPI cost and a static bleeding risk across age groups, the authors concluded that cotherapy was not cost-effective in patients at low risk for bleeding but was cost-effective for patients at high risk. Furthermore, PPI cost was noted to be an important factor in sensitivity analysis. Similarly, a study by Ko and Deyo¹⁴ that also compared strategies to reduce NSAID-related GI complications found that Rx PPI cotherapy was cost-effective in patients older than 65 years but less cost-effective in younger patients. This study employed an age-related stepwise increase in UGIB-related mortality rather than a static rate across age groups. Finally, a similar study by El-Serag et al¹³ found that Rx PPI cotherapy was likely to be cost-effective in patients at low risk for ulcer bleeding but cost-effective in patients at high risk for bleeding. This study assumed an increased risk of ulcer bleeding in patients older

Table 2. Life-Years, Costs, and ICERs of ASA Alone and ASA Plus PPI Strategies

UGIB Risk	Age, y	Strategy	Mean Lifetime Cost per Patient, \$	Life-Years	ICER, \$
PPI Cost, OTC (\$250)					
Average	50	ASA alone	1206	13.77	
		ASA + PPI	3883	13.80	79 955
	65	ASA alone	1269	9.60	
		ASA + PPI	2847	9.64	40 090
	80	ASA alone	1261	5.86	
		ASA + PPI	1902	5.90	16 887
3×	50	ASA alone	3519	13.67	
		ASA + PPI	4460	13.77	9 118
	65	ASA alone	3750	9.48	
		ASA + PPI	3512	9.60	D
	80	ASA alone	3731	5.75	
		ASA + PPI	2621	5.86	D
PPI Cost, Rx (\$1400)					
4×	50	ASA alone	6702	13.62	
		ASA + PPI	20 565	13.76	99 964
	65	ASA alone	6566	9.42	
		ASA + PPI	14 863	9.58	51 505
	80	ASA alone	5929	5.69	
		ASA + PPI	9695	5.84	24 619
8×	50	ASA alone	12 960	13.41	
		ASA + PPI	21 625	13.69	30 728
	65	ASA alone	12 697	9.18	
		ASA + PPI	16 079	9.51	10 433
	80	ASA alone	11 448	5.47	
		ASA + PPI	11 011	5.77	D

Abbreviations: ASA, aspirin; D, dominant strategy (ie, more effective and less costly); ICER, incremental cost-effectiveness ratio; OTC, over the counter; PPI, proton pump inhibitor; Rx, prescription; UGIB, upper gastrointestinal bleeding.

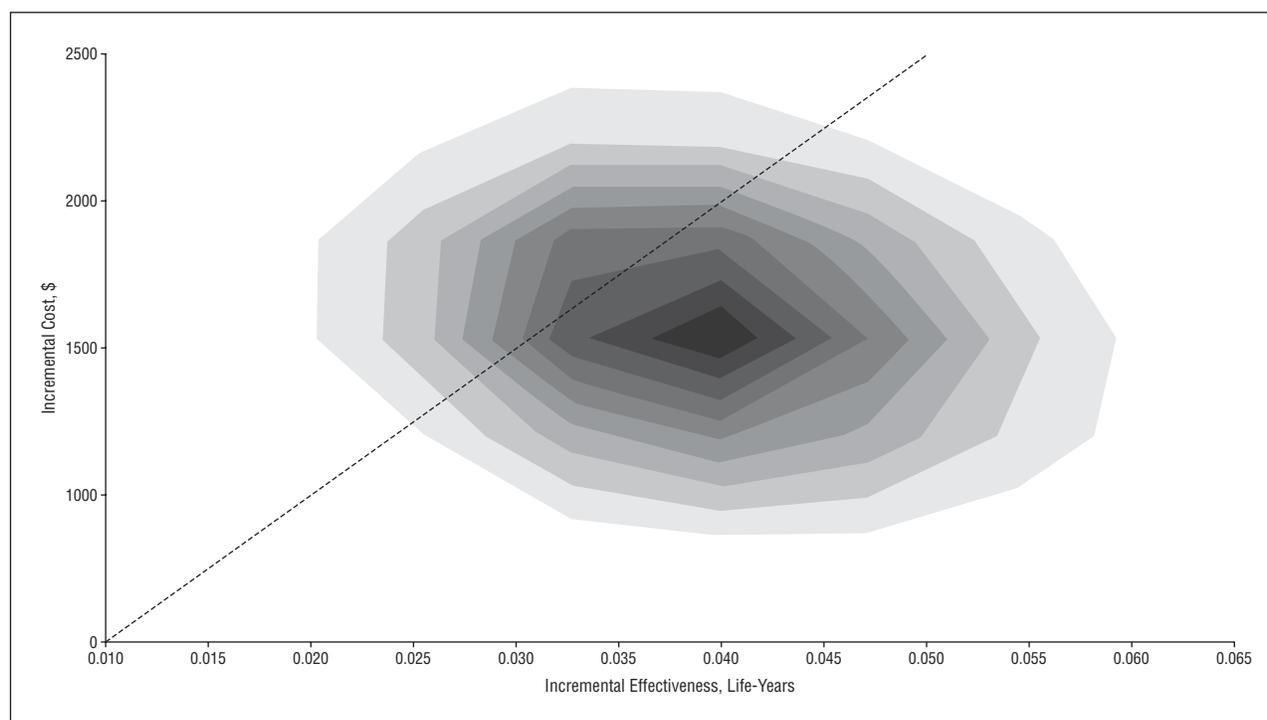


Figure 6. Probabilistic sensitivity analysis of the incremental cost and incremental effectiveness of 10 000 Monte Carlo trials. The dashed line represents a willingness-to-pay threshold of \$50 000 per life-year saved, with results to the right of the line favoring an aspirin plus proton pump inhibitor strategy. Shades of gray represent deciles of the Monte Carlo trial results.

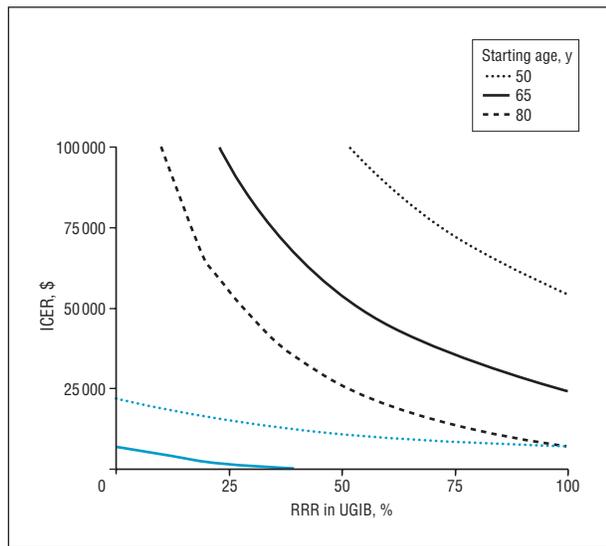


Figure 7. Two-way sensitivity analysis of the relative risk reduction (RRR) in upper gastrointestinal bleeding (UGIB) and UGIB risk category (average-risk or 3-fold increased risk). ICER indicates incremental cost-effectiveness ratio. The black lines represent the average-risk group, and the blue lines represent the increased-risk group for various starting ages.

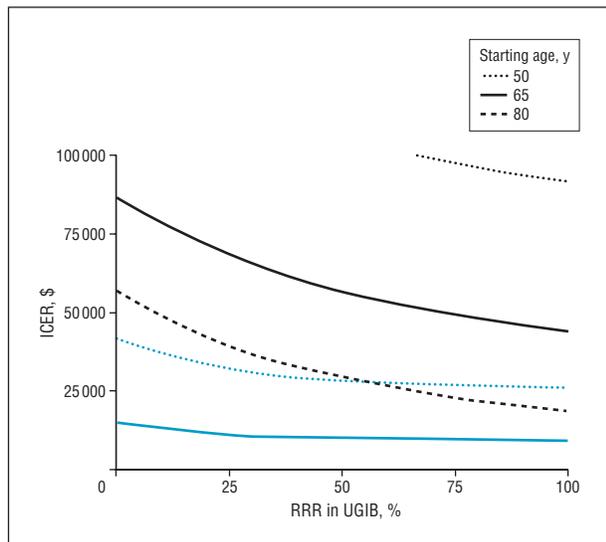


Figure 8. Two-way sensitivity analysis of the relative risk reduction (RRR) in upper gastrointestinal bleeding (UGIB) and UGIB risk category (4 \times or 8 \times) under prescription proton pump inhibitor cost (\$1400 per year). ICER indicates incremental cost-effectiveness ratio. The black lines represent the 4 \times group, and the blue lines represent the 8 \times group for various starting ages.

than 65 years. Together, these data support the notion that at Rx prices, PPI cotherapy is likely to be cost-effective only in high-risk (and older) patients, a conclusion that is consistent with the results of our study. However, our study suggests that at OTC prices, PPI cotherapy becomes increasingly cost-effective even in patients at average risk of bleeding despite the lower GI risk of low-dose ASA.

STRENGTHS AND LIMITATIONS

Several important limitations of our study should be highlighted. First, as a modeling exercise, our study is limited by the logic and assumptions of the model. How-

ever, these assumptions were tested in sensitivity analysis, and the impact of important variables was further tested in multivariate sensitivity analysis. Second, we assumed a patient population that was tolerant of and adherent to the prescribed medications. By excluding the impact of PPI cotherapy on reductions in ASA-related dyspepsia, the bias in our analysis is likely to be in favor of the ASA-alone strategy. Specifically, compliance with ASA may be enhanced by a reduction in dyspepsia with PPI cotherapy. Furthermore, this reduction in dyspepsia is likely to lead to fewer physician visits and endoscopic evaluations, again favoring the ASA-alone strategy. We also assumed compliance with the PPI, which may not always occur if patients are asymptomatic. Here, competing considerations likely counterbalance and require a well-designed trial for accurate assessment. Finally, we assumed no long-term adverse effects from PPI therapy. Recent observational studies²⁸⁻³⁰ have raised concerns about an increased risk of community-acquired pneumonia and hip fractures in patients taking long-term PPI therapy. *Clostridium difficile* and other enteric infections have also been reported, although these infections seem to primarily affect hospitalized rather than ambulatory patients.^{31,32} Whether these adverse effects are true complications of PPI therapy or spurious associations remains to be seen, but the safety of long-term PPI therapy may ultimately have important implications for the cost-effectiveness of PPI-based gastroprotective strategies.

Several important strengths of our study should also be mentioned. First, we utilized a continuous, age-dependent risk of UGIB. Prior modeling studies used a static or step-wise risk, which may have overestimated the benefit of PPI cotherapy in younger patients and underestimated the benefit in older patients. We also specifically studied the economic effect of OTC vs Rx PPIs. Our study shows that low-cost agents have the potential to substantially improve GI outcomes for patients taking long-term, low-dose ASA for secondary prevention of CV events, at costs acceptable to society and payers as well.

In summary, PPI cotherapy is cost-effective by traditional standards in patients taking long-term, low-dose ASA for secondary prevention provided that the PPI is available at OTC prices. At Rx prices, cotherapy is cost-effective only in high-risk and elderly patients. These results were sensitive to the effectiveness of PPIs in reducing UGIB risk. Future studies are needed to better quantify the effectiveness of PPI cotherapy in reducing UGIB in average-risk patients as well as the impact of PPI cotherapy on ASA-related dyspepsia and compliance.

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Author Contributions: Dr Saini had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Saini, Schoenfeld, Fendrick, and Scheiman. *Acquisition of data:* Saini. *Analysis and interpretation of data:* Saini, Schoenfeld, Fendrick, and

Scheiman. *Drafting of the manuscript: Saini. Critical revision of the manuscript for important intellectual content: Saini, Schoenfeld, Fendrick, and Scheiman. Statistical analysis: Saini. Study supervision: Schoenfeld, Fendrick, and Scheiman.*

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