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Cost-effectiveness analysis: cardiovascular benefits of proton pump inhibitor co-therapy in patients using aspirin for secondary prevention

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SUMMARY

Background
Many patients with cardiovascular (CV) disease will stop aspirin (ASA) because of ASA-related dyspepsia. Proton pump inhibitor (PPI) co-therapy may reduce ASA-related dyspepsia, enhancing ASA adherence and improving CV outcomes.

Aim
To explore the impact of PPI co-therapy on CV outcomes in long-term, low-dose ASA users.

Methods
We modified a previously published Markov model to assess the long-term impact of PPI co-therapy on CV and upper gastrointestinal bleeding (UGIB) outcomes among patients using ASA for secondary CV prevention. UGIB events, recurrent myocardial infarctions (MIs) and incremental cost-effectiveness ratios (ICERs) were measured. The perspective taken was that of a long-term payer.

Results
Compared with ASA alone, ASA plus PPI resulted in fewer lifetime UGIB events (3.4% vs. 7.2%) and increased ASA adherence (74% vs. 71%). Increased ASA adherence resulted in fewer recurrent MIs (26 fewer events per 10 000 patients). On average, the ASA plus PPI strategy resulted in 38 additional days of life per patient, with the majority of this benefit (61%) because of a reduction in CV mortality (rather than UGIB-related mortality). ASA plus PPI was also more costly than ASA alone, with an ICER of $19 000 per life-year saved. Results were sensitive to cost of PPI and impact of PPI on ASA adherence.

Conclusions
Proton pump inhibitor co-therapy has the potential to impact not only GI, but also CV outcomes in patients with CV disease using ASA and such co-therapy is likely to be cost-effective. Future studies should better quantify the CV benefits of PPI co-therapy.

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INTRODUCTION

Guidelines recommend that patients with cardiovascular (CV) disease use low-dose aspirin (ASA) for secondary CV prevention.[1] However, up to 30% of patients will not consistently take their medication,[2–4] placing them at increased risk for recurrent CV events.[5, 6] In a recent trial of patients with established CV disease presenting with peptic ulcer bleeding, mortality was increased in patients in whom ASA was withheld, emphasising the hazard of even short-term ASA discontinuation.[7] Strategies to improve ASA adherence can therefore improve CV outcomes.

Several studies have suggested that ASA-related dyspepsia is an important reason for ASA discontinuation. In the British Doctors' Trial, 20% of participants discontinued ASA within 1 year, and half of these patients cited dyspepsia as the reason for discontinuation.[8] In the CAPRIE study, 40% of patients who discontinued ASA did so because of dyspepsia.[9] Similarly, another study reported that 50% of patients who stopped ASA did so because of side effects, with GI side effects being most common.[10] Unfortunately, most patients who discontinue ASA do so without consulting their physician.[11] Therefore, preemptive efforts to reduce dyspepsia are likely to be more effective than symptom-driven efforts. One preemptive strategy for reducing dyspepsia is proton pump inhibitor (PPI) co-therapy. PPIs have been widely studied for reducing NSAID-related dyspepsia.[12] However, studies of PPI co-therapy on ASA-related dyspepsia are lacking. One approach to determining whether studies on this topic are worthwhile is to use modelling techniques to define the potential effects of PPI co-therapy on ASA adherence and CV outcomes.

The purpose of this study was to model the effects of PPI co-therapy in patients taking low-dose ASA for secondary prevention. We modified a recently published Markov model,[13] modelling dyspepsia as a modifiable cause of ASA discontinuation. Prior work and has demonstrated that PPI co-therapy may be cost-effective because of a reduction in upper GI bleeding events;[13, 14] the aim of this study was to explicitly examine the potential reduction in CV events with PPI co-therapy.

METHODS

We modified an existing Markov model of ASA and PPI use (Figure 1).[13] Two competing strategies were modelled: (i) ASA alone strategy, where the cohort began on ASA alone and PPI was added if upper GI bleeding occurred; and (ii) ASA plus PPI strategy, in which the entire cohort began on ASA plus PPI. The cohort was comprised of 50 year-old patients with no risk factors for upper GI bleeding, using ASA for secondary prevention. Our previous work, which modelled only the GI benefits of PPIs, suggested that PPI co-therapy was cost-effective in older (age >65) but not younger patients.[13] For the current study, which modelled not only GI but also CV benefits, we selected a younger population for the base-case, anticipating that the cost-effectiveness of PPI would be further improved when CV benefits were

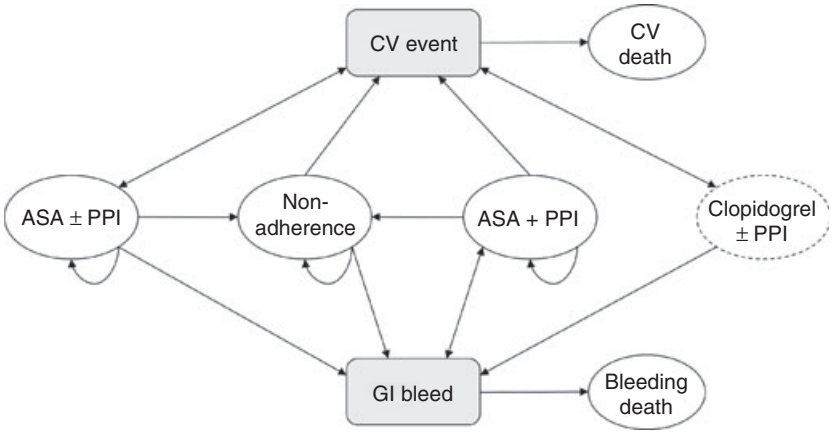

Figure 1 | Markov Model Structure. All patients begin the simulation in an ASA alone state or ASA plus PPI state (ASA ± PPI) (depending on the strategy being modelled). The non-adherence state can be entered due to ASA-related dyspepsia or for reasons unrelated to dyspepsia (see text). A CV event or GI bleed is an event that can occur within any state. A non-CV/non-GI death state can be reached from any state (not shown). The clopidogrel state is a temporary (1-year) state that ultimately returns to an ASA ± PPI state or transitions to a death state.

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taken into account. Age was varied widely in sensitivity analysis. The simulation began with the cohort in an ASA state ± PPI (depending on the strategy). The cohort could remain in the ASA state or transition to a non-adherence state [no ASA or PPI until GI bleeding or recurrent myocardial infarction (MI) occurred]. During any state, a patient could experience an upper GI bleeding event or a recurrent MI. GI bleeding resulted in transition to a high-risk state for future upper GI bleeding or to a death state.[15, 16] Recurrent MI resulted in: (i) hospitalisation followed by return to the current state; (ii) hospitalisation followed by transition to an ASA + clopidogrel state for 1 year (with PPI co-therapy only in patients at high-risk for GI bleeding); or (iii) transition to a death state.

Gastrointestinal effects

Risk of upper gastrointestinal bleeding. The risk of upper GI bleeding in low-dose ASA users was estimated from published literature (Table 1). We performed a MEDLINE search for English-language systematic reviews of ASA and GI bleeding published since the year

Table 1 | Base-case assumptions of variables in model and ranges tested in sensitivity analysis

Description	Base-case	Sensitivity analysis range	References
Costs			
Acute UGIB	$7757*	$3878 to $15 514 (G)	38
Myocardial infarction	$10 305*	$5152 to $20 610 (G)	38
Aspirin (ASA)	$2†	$1 to $4 (G)	39
Clopidogrel	$1539†	$769 to $3078 (G)	39
Generic PPI	$144†	$72 to $288 (G)	39
Branded PPI	$1515†	$757 to $3030	39
Probabilities and risks for CV events			
CV event (without ASA)	8%	6% to 10% (B)	28
RR of CV event with ASA	0.81	0.75 to 0.87 (N)	28
Death from CV event	50%	25% to 75% (B)	28
Clopidogrel × 1 year after CV event	50%	25% to 75% (B)	57
ASA discontinuation (year 1)	20%	5% to 30% (B)	2–4, 11, 30–33
Probabilities and risks for GI events			
UGIB (on ASA)	Age-dependent (0.5% at age 65)	Average to 8-fold increased	18, 21
RR of bleed on PPI	0.33	0.18 to 0.60 (N)	15, 24, 25, 58
Death following UGIB	Age-dependent (10% at age 65)	0.5 to 2.0 of base-case (N)	22, 23
RR of recurrent UGIB	4.0	2.0 to 8.0 (N)	15, 16
Other			
Absolute increase in ASA adherence with PPI	2.5%	0% to 5% (B)	8, 10, 12, 30, 36
Discount rate	3%	0% to 10% (B)	Assumed
Starting age of cohort	50 years	25 to 80 years	Assumed

UGIB, upper gastrointestinal bleeding; CV, cardiovascular; RR, relative risk; PPI, proton pump inhibitor; PCI, percutaneous coronary intervention (stent); G, gamma distribution, B, beta distribution and N, normal distribution (indicating distributions utilised for selected variables in probabilistic sensitivity analysis).

* Costs for UGIB and myocardial infarction are weighted averages of DRG codes for Medicare admissions (see text).

† Costs for medications are per year.

2000. We identified four reviews from which we extracted summary relative risks and crude annual risks of upper GI bleeding in low-dose ASA users (0.25% at age 50, 0.5% at age 65 and 1% at age 80).[17–20]

Commonly accepted risk factors for upper GI bleeding in patients taking low-dose ASA include age, prior history of upper GI bleeding and concomitant NSAID use.[21] Age-related risk is unique in that it is dynamic, increasing gradually over the lifetime. We therefore modelled age-related risk separately from other 'static' risk factors.[22] Furthermore, we assumed that age-related risk could be multiplicatively combined with these other risk factors. The risk of death following upper GI bleeding was also age-dependent (10% at age 65).[23, 24]

Effectiveness of proton pump inhibitor co-therapy: upper gastrointestinal bleeding. The effectiveness of PPI co-therapy in reducing upper GI bleeding risk was estimated from published literature (Table 1). We performed a MEDLINE search for English-language studies of ASA, PPIs and GI bleeding published since the year 1980, identifying two randomised controlled trials of PPI co-therapy in low-dose ASA users, both of which enrolled only patients at high risk for upper GI bleeding and reported a reduction in upper GI bleeding risk of over 90%.[25, 26] Data in average-risk patients was more limited and was observational, with studies reporting a risk reduction of 60–70%.[15, 17, 27] Based on the totality of these data, we conservatively assumed that PPIs reduced bleeding risk by 66% in our base-case analysis and varied this effect widely in sensitivity analysis. A similar reduction in upper GI bleeding risk was assumed for patients using clopidogrel.[27, 28]

Effectiveness of proton pump inhibitor co-therapy: dyspepsia. The impact of PPI therapy on dyspepsia was obtained from studies of PPI co-therapy in non-ASA NSAID users. Specifically, we utilised data from a systematic review on this topic that reported a risk reduction of 66%,[12] conservatively assuming that PPI co-therapy eliminated ASA-related dyspepsia in 50% of patients.

Cardiovascular effects

Cardiovascular risk. The risk of recurrent MI was obtained from a recent meta-analysis.[29] Specifically, we assumed that the probability of a recurrent MI without ASA was 8% per year. Based on Framingham data, we assumed that this risk was independent of age.[30] We assumed that ASA reduced the risk of recurrent events by 19%.[29] We also assumed that 50% of recurrent MIs were fatal.[29]

Aspirin adherence. The probability of ASA discontinuation was obtained from the published literature on this topic. Specifically, we identified both short-term (≤1 year)[2–4, 8, 11, 31–34] and long-term (5–10 year)[8, 31, 35–38] studies that reported the rate of ASA use in patients who had been prescribed this medication for CV prevention. These studies report that approximately 20% of patients prescribed ASA after a CV event will have discontinued ASA at 1 year and that 25% to 40% of patients will have discontinued ASA by 5 years. We therefore modelled a nonlinear adherence curve as suggested by these data, assuming that the probability of ASA discontinuation was 20% at the end of year 1, with the probability of discontinuation dropping exponentially (i.e. becoming incrementally less likely) in each subsequent year. This approach yielded an adherence rate of 66% at 5 years.

Impact of proton pump inhibitor co-therapy on aspirin adherence

Aspirin adherence was modelled in a binary fashion (i.e., we assumed that patients were using ASA or not using ASA within a given year). We assumed that 20% of the cohort stopped ASA during the first year. Based on available data, we conservatively estimated that the majority of these patients (75%) discontinued ASA for reasons other than dyspepsia (i.e., not modifiable by PPI co-therapy).[8, 10] Assuming that 50% of dyspeptic patients would respond to PPI co-therapy and remain on ASA, we calculated a discontinuation probability of 17.5% during year 1 of the ASA plus PPI strategy (compared to 20% under the ASA alone strategy) ($0.2–0.2 \times 0.25 \times 0.5 = 0.175$). Thus, PPI co-therapy increased the proportion of patients using ASA in year 1 by 2.5% (i.e. ASA was used by 25 additional patients per 1000 in the ASA + PPI arm). We varied this PPI-mediated increase in ASA adherence between 0% and 5%.

Cost inputs

Costs of upper GI bleeding and MI were obtained from 2007 Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample Medicare data (simple weighted averages of DRG categories 174–175 and 121–123 respectively) (Table 1).[39] We used average costs for MI rather than unique costs for various acute coronary syndromes (ACS). Medication costs were obtained from the 2009 Thomson Red Book.[40] All costs were varied between half and twice the base-case value in sensitivity

analysis, discounted at 3% per year and adjusted for inflation to 2009 U.S. dollars.

Outcomes

Clinical outcomes included: (i) upper GI bleeding events and mortality; (ii) recurrent MIs and associated mortality; (iii) ASA adherence; and (iv) life years. We also calculated the proportion of PPI benefit that was attributed to reduced CV vs. GI mortality. Economic outcomes included costs and incremental cost-effectiveness ratios (ICERs). Quality-adjusted life-years (QALYs) were not measured (biasing results in favour of the ASA alone arm by overestimating quality of life after recurrent MI).

Sensitivity analysis

One-way sensitivity analysis was performed on each variable in the model. Multivariate sensitivity analysis was performed on variables found to be important in one-way analysis. Probabilistic sensitivity analysis was also performed where 15 variables were simultaneously varied over their sensitivity analysis ranges according to specified probability distributions (10 000 Monte Carlo trials).[41] Beta and gamma distributions were assumed for proportions and costs respectively. Normal distributions were assumed for log relative risks. For each distribution, we assumed that the mean was equal to the point estimate and that the standard deviation was equal to the sensitivity analysis range/[2 × 1.96].

RESULTS

Base-case analysis

The ASA plus PPI strategy resulted in fewer lifetime upper GI bleeding events than ASA alone (3.4% vs. 7.2% lifetime risk) and fewer upper GI bleeding-related deaths than ASA alone (0.4% vs. 0.8%), with relative risk reductions (RRRs) of 53% and 53% respectively (Table 2). As a result of this impact on bleeding, PPI co-therapy resulted in 14 additional days of life per patient.

Table 2 | Life-years, costs ($) and incremental cost-effectiveness ratios (ICERs) of ASA alone and ASA + PPI strategies (discounted at 3% per year)

Strategy	Cost ($)	Life-years	ICER ($)
ASA alone	$10 010	12.4534	-
ASA + PPI	$11 059	12.5086	$19 001

The ASA plus PPI strategy also resulted in enhanced ASA adherence, with the ASA plus PPI cohort using ASA an average of 245 days longer than the ASA alone cohort (4771 vs. 4526 days). The ASA plus PPI cohort spent 74% of the simulation using ASA (4771/6476 days), whereas the ASA alone cohort spent 71% using ASA (4543/6438 days). This improvement in ASA adherence resulted in a slight reduction in lifetime CV events and deaths (26 and 13 deaths avoided per 10 000 patients respectively). As a result of this improvement in adherence, PPI co-therapy resulted in 23 additional days of life related to reduced CV mortality. Overall, PPI co-therapy resulted in 38 additional days of life (14 because of reduced upper GI bleeding-related mortality and 23 because of reduced CV mortality) at an added lifetime cost of approximately $1,000 per patient, resulting in an incremental cost-effectiveness ratio (ICER) of $19 000 per life-year saved (LYS). Notably, nearly two-thirds of the observed benefit of PPI co-therapy in the base-case (23/38 days of life gained) were attributed to a reduction in CV (rather than GI bleeding-related) mortality.

Sensitivity analysis

Results were sensitive to two variables: (i) the cost of PPI (base: $144 per year, range: $72 to $3030); and (ii) the absolute increase in ASA adherence with PPI co-therapy (base: 2.5%, range: 0% to 5%). As PPI cost decreased, the ICER of the ASA plus PPI strategy also decreased, with PPI co-therapy becoming cost-neutral (equivalent in cost to the ASA alone strategy) at a PPI cost of $25 per year (Figure 2). At branded PPI cost, PPI co-therapy was only cost-effective in patients at increased risk for GI bleeding (Figure 2). Increased ASA adherence due to PPI co-therapy also had strong effects on the ICER of the ASA plus PPI strategy (Figure 3). Specifically, improving ASA adherence by as little as 0.2% (2 additional patients using ASA per 1000) reduced the ICER of the ASA plus PPI strategy below $50 000 per LYS. With only 1% improvement in ASA adherence, approximately one-third of the benefit of PPI co-therapy was attributed to reduced CV mortality and this proportion increased with further improvements in ASA adherence (Figure 4). Notably, these results were independent of the underlying probability of ASA discontinuation. Probabilistic sensitivity analysis confirmed our results, with a median ICER of $19 180 per LYS ($11 683 to $31 991) and 87% of Monte Carlo trials costing less than $50 000 per LYS. The ASA plus PPI strategy remained cost-effective regardless of the starting age of the cohort.

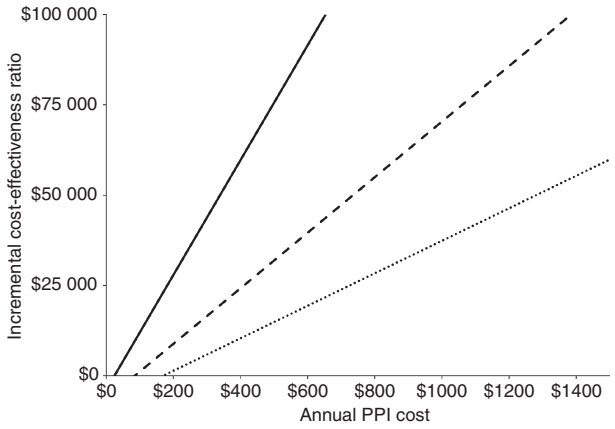

Figure 2 | Sensitivity analysis on PPI cost and risk of upper GI bleeding. Solid black line indicates ICERs for patients at average risk for UGIB (base-case assumption), dashed line = 4X increased risk and dotted line = 8X increased risk.

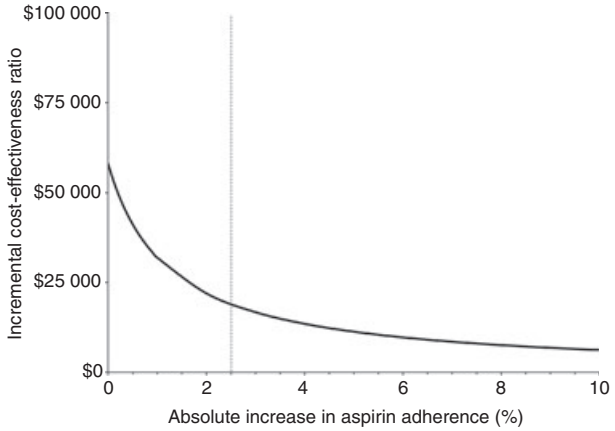

Figure 3 | Sensitivity analysis on absolute increase in proportion of patients using aspirin. Dashed vertical line indicates base-case value for improvement in adherence (2.5%).

DISCUSSION

Summary of key findings

Low-dose ASA is recommended in patients with CHD to decrease recurrent CV events.[1] Unfortunately, a substantial minority of patients discontinue ASA without consulting a physician.[2–4, 11] One important reason for non-adherence is dyspepsia, an adverse effect that could be mitigated by PPI co-therapy.[8–10, 12] Our study suggests that PPI co-therapy could reduce both GI and CV events in patients with CHD, making it cost-effective at generic

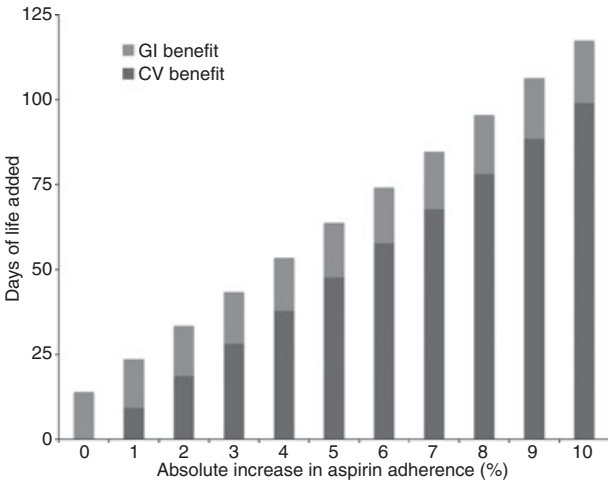

Figure 4 | Days of life gained due to PPI-mediated reduction in gastrointestinal and cardiovascular events.

PPI cost. Notably, clinically important improvements in CV outcomes are seen even with small increases in ASA adherence.

Literature review

Cessation of ASA has been shown to increase the risk of recurrent CV events in multiple studies. Collet and colleagues followed 1358 patients status-post recent MI.[42] These authors found that the short-term risk of a recurrent CV event was doubled (OR = 2.05) in patients who stopped ASA. Similarly, Ferrari and colleagues studied 1236 patients admitted with ACS.[43] These authors also found that the risk of a recurrent CV event increased two-fold in patients who stopped ASA, and such patients tended to have more severe disease on presentation. In another prospective study, authors found that ASA non-adherence had not only short-term, but also long-term implications, with non-adherent patients again having nearly twice the risk of a recurrent CV event compared with adherent patients.[2] Most recently, Sung *et al.* reported that the risk of recurrent CV events was markedly increased in patients with peptic ulcer bleeding in whom ASA was temporarily withheld.[7]

If long-term ASA adherence (ASA *persistence*) is sub-optimal, how can ASA persistence be enhanced? Although several studies have investigated interventions to improve prescription of ASA at the time of hospital discharge after an acute CV event,[44–46] the literature on improving persistence is more sparse. Theories of behavioural change and chronic disease management suggest that the optimal approach is likely to be multi-factorial. However, these approaches do not address the

issue of ASA intolerance. Furthermore, the CV events related to ASA non-adherence often occur within mere weeks of drug cessation.[5] The use of PPI co-therapy circumvents these issues, albeit at increased cost. However, our study suggests that the benefits of co-therapy are likely to be worth this added cost, with an ICER of $19 000 per LYS.

Strengths and limitations

Several important limitations of our study should be highlighted. First, as a modelling exercise, our study is limited by the logic and assumptions of the model. However, assumptions were tested in multiple sensitivity analyses and we were conservative with our base-case estimates (e.g. RR of upper GI bleeding with PPI co-therapy) and our model structure (e.g. assuming that CV events did not reduce quality of life in the ASA alone arm). We also did not model CV events other than MI, essentially assuming that ASA had no effect on stroke and other forms of vascular disease. As a result, however, our findings are likely to underestimate the benefit of PPI co-therapy on CV outcomes. Second, data on ASA-related dyspepsia and the effectiveness of PPI co-therapy in reducing dyspepsia are limited. To address this point, we explored the importance of these variables in sensitivity analysis. Finally, we assumed no long-term adverse effects from PPI therapy. Recent observational studies have raised concerns about an increased risk of community-acquired pneumonia and hip fractures in patients on long-term PPI therapy.[47–52] *Clostridium difficile* and other enteric infections have also been reported.[53–55] However, many of these associations are linked to high-dose PPI therapy (which is not necessary for reduction of ASA-related adverse effects). We also did not model the potential interaction between PPIs and clopidogrel.[56] However, we assumed that patients using clopidogrel would only receive PPI if they were at increased risk for bleeding, an assumption supported by a recent joint consensus statement.[57] 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 utilised a continuous, age-dependent risk of upper GI bleeding. Prior studies have used a static or step-wise risk, which may overestimate the benefit of PPI co-therapy in younger patients and underestimate the benefit in older patients. Most importantly, we also explored the impact of PPI co-therapy on CV events rather than simply GI events, which have been the focus of prior studies.

CONCLUSIONS

In summary, PPI co-therapy is cost-effective by traditional standards in patients taking long-term, low-dose ASA for secondary prevention provided that the PPI is available at generic prices. Notably, PPI co-therapy has the potential to improve not only GI but also CV outcomes. Future studies of PPI co-therapy should better quantify the CV benefits of these medications.

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