Cost-Utility of Aspirin and Proton Pump Inhibitors for Primary Prevention

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Background: Aspirin reduces myocardial infarction but increases gastrointestinal tract (GI) bleeding. Proton pump inhibitors (PPIs) may reduce upper GI bleeding. We estimate the cost-utility of aspirin treatment with or without a PPI for coronary heart disease (CHD) prevention among men at different risks for CHD and GI bleeding.

Methods: We updated a Markov model to compare costs and outcomes of low-dose aspirin plus PPI (omeprazole, 20 mg/d), low-dose aspirin alone, or no treatment for CHD prevention. We performed lifetime analyses in men with different risks for cardiovascular events and GI bleeding. Aspirin reduced nonfatal myocardial infarction by 30%, increased total stroke by 6%, and increased GI bleeding risk 2-fold. Adding a PPI reduced upper GI bleeding by 80%. Annual aspirin cost was $13.99; the generic PPI cost was $200.00.

Results: In 45-year-old men with a 10-year CHD risk of 10% and 0.8 per 1000 annual GI bleeding risk, aspirin ($17,571 and 18.67 quality-adjusted life-years [QALYs]) was more effective and less costly than no treatment ($18,483 and 18.44 QALYs). Compared with aspirin alone, aspirin plus PPI ($21,037 and 18.68 QALYs) had an incremental cost per QALY of $447,077. Results were similar in 55- and 65-year-old men. The incremental cost per QALY of adding a PPI was less than $50,000 per QALY at annual GI bleeding probabilities greater than 4 to 6 per 1000.

Conclusions: Treatment with aspirin for CHD prevention is less costly and more effective than no treatment in men older than 45 years with greater than 10-year, 10% CHD risks. Adding a PPI is not cost-effective for men with average GI bleeding risk but may be cost-effective for selected men at increased risk for GI bleeding.

Arch Intern Med. 2011;171(3):218-225
OVERVIEW AND MODEL STRUCTURE

We updated a previously developed Markov model, programmed in version 2003 SP3 of Microsoft Excel© (Redmond, Washington) to examine the costs and outcomes of primary prevention treatment with aspirin alone or aspirin plus PPI (aspirin PPI) for men (eFigure 1; http://www.archinternmed.com). In the updated model for the present study, men began treatment in the healthy state and transitioned through the model annually. During each cycle, men could remain in the healthy state; progress to initial, nonfatal cardiovascular events such as angina, myocardial infarction, or stroke; have upper GI bleeding; or die. Men who had cardiovascular events were assumed to stay in the subacute state for the remainder of that cycle and then entered a postevent health state during which they received optimal secondary preventive care. Because we were interested in primary prevention, we did not simulate or examine the additional treatment course of patients after primary nonfatal events. Instead, we assigned those patients an increased risk for mortality, increased costs, and decreased utilities, using data from published literature on the average experience of patients after an initial event.5,9,10

Men with GI bleeding discontinued aspirin use but did not receive PPIs if they were not in the aspirin plus PPI arm. They then entered a postevent health state during which they progressed through the model as healthy men. However, these men were at greater risk for subsequent GI bleeding.6,9

Men were observed for the remainder of their lifetimes to estimate costs, cardiovascular and adverse events, life-years, and quality-adjusted life-years (QALYs). Efficacy data were taken from published literature.6,9,14 Resource use and costs were drawn from published literature and standard United States (US) costing sources and updated to 2009 dollars.5,15 The analysis was performed from a third-party payer perspective. All costs and outcomes were discounted at 3% per annum.

PATIENT POPULATION

Men in the base-case analysis were assumed to be healthy, middle-aged men with starting age of 45 years, no history of CHD events, and 10%, 10-year CHD risk (eg, nonsmoker; no diabetes; systolic blood pressure 120 mm Hg; total cholesterol level, 220 mg/dL; high-density lipoprotein level, 30 mg/dL; to convert high-density lipoprotein to micromoles per liter, multiply by 0.0357). Men were observed for the remainder of their lifetimes to estimate costs, cardiovascular and adverse events, life-years, and quality-adjusted life-years (QALYs). Efficacy data were taken from published literature.6,9,14 Resource use and costs were drawn from published literature and standard United States (US) costing sources and updated to 2009 dollars.5,15 The analysis was performed from a third-party payer perspective. All costs and outcomes were discounted at 3% per annum.

COMPARATORS

Men in the aspirin arm received 81 mg/d of generic aspirin. Patients taking aspirin plus PPI were treated with a combination of aspirin, 81 mg/d, and generic omeprazole, 20 mg/d. We did not consider use of other CHD preventive strategies (smoking cessation, hypertension treatment, or statin use) in this analysis, nor did we examine the effect of aspirin in patients with diabetes or previous cardiovascular events. Treatment efficacy was based on actual effects observed in clinical trials; we did not model effects of different levels of adherence.

MODEL PARAMETERS

Baseline Event Probabilities

Baseline risks of initial CHD events (myocardial infarction, angina, and CHD death) and stroke were drawn from Framingham risk equations, using hypothetical scenarios of nonsmoking adults without diabetes and with different sets of other risk factors.16 We examined scenarios for men aged 45, 55, and 65 years with up to 6 risk levels: 2.5%, 5.0%, 7.5%, 10.0%, 15.0%, and 25.0%. Assuming an exponential distribution, these 10-year risks were translated into annual, event-related transition probabilities. These probabilities were allowed to change annually to reflect increasing CHD and stroke risk over the time horizon of the analysis.

Age-dependent, noncardiovascular mortality was estimated from National Vital Statistics life tables.17 Probabilities were adjusted as the cohort aged over the analysis time horizon.

Baseline risk of upper GI bleeding (not taking aspirin) was calculated according to the parameters set out by Hernández-Díaz and García Rodríguez.6 Annual risks were estimated as 0.0008, 0.0024, 0.0024, and 0.0036 for men aged 45, 55, 65, and over 65 years, respectively.6 In the model, a man started with the baseline GI bleeding risk for his age, and his GI bleeding risk increased as he aged.

Treatment Efficacy

The RRs, as drawn from published meta-analyses and clinical trials,6,9,11 are listed in Table 1. Aspirin was assumed to have no effect on angina and to reduce men’s risk of nonfatal myocardial infarction by 30% and CHD death by 13%. It increased the combined risk of stroke (ischemic and hemorrhagic considered together) by 6%.11 More recent sex-specific analyses have found similar estimates for men.16 We did not model the effect of aspirin on stroke-related mortality or on initial use of revascularization procedures. The changes in each parameter were tested extensively in sensitivity analyses.

Table 1. Clinical Parameters and Risks of Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base-Case Finding, RR (95% CI)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>1.00 (0.80-1.20)</td>
<td>Assumption</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.06 (0.91-1.24)</td>
<td>Sammuganathan et al11</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.70 (0.62-0.79)</td>
<td>Sammuganathan et al11</td>
</tr>
<tr>
<td>CHD death, males</td>
<td>0.87 (0.70-1.09)</td>
<td>Hayden et al13</td>
</tr>
<tr>
<td>GI bleeding, no history of GI bleeding</td>
<td>2.00 (NR)</td>
<td>Hernández-Díaz and García Rodríguez6</td>
</tr>
<tr>
<td>GI bleeding, with history of GI bleeding</td>
<td>10.00 (NR)</td>
<td>Hernández-Díaz and García Rodríguez6</td>
</tr>
<tr>
<td>Aspirin + PPI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>0.15 (0.10-0.20)</td>
<td>Lanas and Scheiman12</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal hemorrhagic stroke, proportion (95% CI)</td>
<td>0.33 (0.10-0.50)</td>
<td>Expert clinical opinion</td>
</tr>
<tr>
<td>Death due to GI bleeding</td>
<td>0.001 (0.00001-0.00100)</td>
<td>Expert clinical opinion</td>
</tr>
<tr>
<td>Increase in risk of mortality after initial CHD event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After myocardial infarction</td>
<td>3.7 (3.0-4.7)</td>
<td>Lampe et al9</td>
</tr>
<tr>
<td>After angina</td>
<td>3.0 (2.1-4.2)</td>
<td>Lampe et al9</td>
</tr>
<tr>
<td>After stroke</td>
<td>2.3 (1.0-4.6)</td>
<td>Dennis et al13</td>
</tr>
<tr>
<td>Reduction in number of deaths due to aspirin therapy after a CV event</td>
<td>0.85 (0.80-0.90)</td>
<td>He et al14</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; GI, gastrointestinal tract; NR, not reported; PPI, proton pump inhibitor; RR, relative risk.

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The primary benefit of the PPI was assumed to be an 80% reduction in upper GI bleeding (ie, occurrence of hospitalization owing to GI bleeding) (RR, 0.20; range, 0.10-0.90), based mainly on 1 small randomized controlled trial in patients at high risk for GI bleeding.\textsuperscript{3,11} The efficacy of combination use of aspirin plus PPI was assumed to be independent: the PPI added no additional benefit and did not reduce the benefit of aspirin for avoiding CHD events. We did not assume any direct adverse effects from the PPI, nor did we include benefits of PPI for treating symptomatic conditions such as dyspepsia or reflux. Our analysis applied to men without symptomatic upper GI conditions; thus, we assumed that patients would adopt such treatments equally in both groups if they became symptomatic.

All men who survived an initial CHD event received optimal secondary preventive treatment, including aspirin or alternate antithrombotic agents if they were not able to tolerate aspirin. The effect of optimal treatment after initial events was the same between groups in the model.

Adverse Effects

Aspirin increased stroke risk by 6%.\textsuperscript{11} Increase in GI bleeding risk in aspirin users with and without a history of GI bleeding was 10.0 and 2.0, respectively.\textsuperscript{6} Although some data suggested no increased risk of fatal GI bleeding with low-dose aspirin,\textsuperscript{7} we conservatively assumed a risk of GI bleeding mortality of 1 of 1000 patients, and we tested a range of values in sensitivity analyses. Men who had adverse effects were assumed to stop taking the offending agent and were not given alternate agents for primary prevention.

Mortality

The effect of optimal secondary prevention on all-cause mortality was estimated as RRs after initial cardiovascular events (Table 1), drawn from population-based meta-analyses and from mortality rates reported in US life tables.\textsuperscript{9,10}

Costs

Costs are listed in Table 2 and include outpatient physician visits, events, and drug costs. Costs were similar to those in our groups' previous analyses\textsuperscript{5,8} and updated to 2009 US dollars using the Medical Consumer Price Index.\textsuperscript{13} Additional cost details are presented in the eAppendix.

Utilities

The utilities for the model were drawn from the literature.\textsuperscript{5,8} In most cases, they were estimated using time-trade-off techniques in original studies (Table 2 and eTable 1). Where no data existed, we made estimates and examined a wide range of values in sensitivity analyses.

OUTCOME MEASURES

To test the robustness of model assumptions and specific parameters, we examined the effect of changing several parameters in 1-way sensitivity analyses. Parameters analyzed included the RR of myocardial infarction, stroke, and CHD death for patients taking aspirin; increase in baseline risk of GI bleeding; RR of GI bleeding, given treatment with aspirin, PPI, or aspirin plus PPI; RR of cardiovascular death with optimal secondary prevention; increase in mortality due to hemorrhagic stroke and GI bleeding; costs of events and treatment; and utility weights for each health state. The effect of varying individual parameters was examined using plausible ranges of values (Table 1) from the literature, where 95% confidence intervals (CIs) were available, or by varying the estimates by 20% in each direction.

In addition to 1-way sensitivity analyses, we performed probabilistic sensitivity analysis (second-order Monte Carlo simulation). The parameters varied in these analyses were similar to those in the 1-way sensitivity analysis. We assumed that parameter estimates followed a \( \alpha \) distribution for all RRs of events, increases in GI bleeding, increases in mortality, health-state costs, and drug costs. A \( \beta \) distribution was assumed for all health-state utilities. Analyses were run 10,000 times to capture stability in results. Scatter plots were developed to represent uncertainty, and cost-effectiveness acceptability curves were created.

RESULTS

BASE CASE

For 45-year-old men with 10-year, 10% CHD risk and annual GI bleeding risk of 8 in 10,000, men taking aspirin gained more QALYs in their remaining lifetime than men undergoing no treatment (18.67 vs 18.44 QALYs).
Treatment with aspirin also was less costly ($17,571) over a man’s remaining lifetime than no treatment ($18,483). Men taking aspirin plus PPI gained more QALYs (18.68) but incurred higher costs ($21,037) than men assigned to aspirin alone. As a result, the incremental cost per QALY with aspirin plus PPI compared with aspirin alone was $447,077, suggesting that addition of PPI prophylaxis was not cost-effective.

Aspirin remained more effective and less costly than no treatment at 5%, 10-year CHD risk and above (Table 3). However, across CHD risk levels, aspirin plus PPI remained expensive compared with aspirin alone. The patterns were similar for 55- and 65-year-old men with base-case GI bleeding risk of 24 in 10,000 (Table 4). Shorter time horizons (5, 10, and 20 years) had no appreciable effect on the cost-effectiveness of aspirin alone and led to even higher costs per QALY gained with aspirin plus PPI.

**EFFECT OF GASTROINTESTINAL BLEEDING RISK**

We examined the effects of men’s baseline risk of GI bleeding on the incremental cost per QALY (Figure 1). In 45-year-old men with 10%, 10-year CHD risk, aspirin compared with no treatment remained cost-saving and cost-effective until a man’s risk of GI bleeding was greater than 5%. Although use of aspirin plus PPI is expensive, the incremental cost per QALY of aspirin plus PPI vs aspirin alone is less than $50,000 when annual GI bleeding risk is 4 in 1000 and cost-saving when GI bleeding risk is greater than 7 in 1000.

In 55- and 65-year-old men, the incremental cost per QALY of aspirin plus PPI was less than $50,000 when baseline GI bleeding risk increased as little as 2- to 3-fold above baseline (eFigure 2 and eFigure 3). Overall, as GI bleeding risk increased, the incremental cost per QALY of aspirin plus PPI compared with aspirin alone was lower in younger men because they received cardiovascular benefits of aspirin over longer periods of time (their lifetime).

**SENSITIVITY ANALYSES**

**1-Way Sensitivity Analysis**

Sensitivity analyses (Figure 2) showed that the cost-effectiveness of aspirin compared with no treatment was robust to changes to all key parameters within their plausible ranges. In particular, aspirin’s effect on nonfatal myocardial infarction and CHD deaths had minimal impact on cost-effectiveness of aspirin compared with no treatment. The cost-effectiveness of aspirin plus PPI compared with aspirin alone was sensitive to changes in GI bleeding-related parameters, such as the effect of aspirin and aspirin plus PPI on GI bleeding and utility of GI bleeding (Figure 2B). However, within their plausible ranges, the...
incremental costs per QALY remained in the $300 000 to $800 000 range. Incremental cost per QALY also was insensitive to changes in risk of mortality due to GI bleeding until risk increased to more than 1% (eFigure 4). We found that lowering the annual cost of PPIs to under $50 (less than 20% of the base-case value) resulted in an incremental cost per QALY of less than $100 000 for aspirin plus PPI compared with aspirin alone; in contrast, at higher PPI prices, aspirin was not cost-effective even for those at increased bleeding risk (eFigure 5). Two-way sensitivity analyses that used newer meta-analysis with sex-specific RRs of stroke (RR, 1.13; 95% CI, 0.96-1.33) and myocardial infarction (RR, 0.68; 95% CI, 0.54-0.86) for aspirin showed that results remained unchanged (eTable 2).

Probabilistic Sensitivity Analysis

We performed probabilistic sensitivity analyses to examine the collective effect of parameter uncertainty (Figure 3). We observed incremental costs per QALY for aspirin vs no treatment of less than $50 000 in 99.8% and 97.4% of men aged 45 and 65 years, respectively. Compared with aspirin alone, incremental costs per QALY of aspirin plus PPI vs aspirin alone was less than $50 000 for 0.0% and 0.5% of the time in 45- and 65-year-old men, respectively. However, incremental costs per QALY crossed all 4 quadrants. Scatter plots and cost-effectiveness acceptability curves for men aged 45 and 65 years with 10-year, 10% CHD risk are presented in the eAppendix and eFigures 6, 7, and 8.

Decisions about which men should receive low-dose aspirin for CHD prevention involve trade-offs between aspirin’s adverse effects and its beneficial effects. Some investigators have attempted to estimate the benefit-harm trade-off by determining RRs of each event through meta-analyses and then informally “weighing up” likely benefits and disadvantages for patient populations with different CHD and GI bleeding risk profiles. Such informal processes, however, are difficult to perform because main outcomes of interest (stroke, myocardial infarction, and GI bleeding) each have different health effects. Our group and others have attempted to rigorously model effects of aspirin and have found aspirin to be cost-saving or cost-effective for men with moderate and greater CHD risk levels.

Recent data, however, have suggested that GI bleeding risk may be higher than levels observed in clinical trials and that patients with elevated CHD risk may be at higher risk for GI bleeding. Some decision makers have advocated using PPI therapy concurrently with aspirin to reduce the risk of bleeding after considering clinical trial evidence from patients at high risk for GI bleeding and after conducting decision-analytic modeling studies suggesting that PPI use is beneficial in secondary CHD prevention. In the present updated analysis, we attempted to address some of these concerns and better estimate the net effect of aspirin use with or without PPI for patients at different levels of CHD and GI bleeding risk. In modeling an age-dependent GI bleeding risk, we found that aspirin remained cost-saving compared with no treatment across a wide range of CHD and GI bleeding risk levels for men aged 45 to 65 years who are considering initiation of aspirin therapy. We also found that adding generic PPI therapy to aspirin regimens for all men was not cost-effective in most cases because risk of GI bleeding was not large enough to warrant routine prophylaxis. However, under favorable assumptions about PPI efficacy and pricing, adding PPI when GI bleeding risk is 5 per 1000 per year for men aged 45 years (and slightly higher for older men) had a favorable cost-effectiveness ratio of $22 000 per QALY gained. This represents about a 4-fold increase in baseline bleeding risk. Assuming a branded cost of a PPI at $1951 per year, a man’s GI bleeding risk would need to be 6.7 per 100 per year (over 10 times higher than our base case) for the addition of a PPI to be cost-effective in a man with the same CHD risk.

Our analysis highlights that some men who are at increased GI bleeding risk may benefit from adding PPI when using low-dose aspirin for CHD risk reduction. Providers should assess the risk of GI bleeding by considering the patient’s age, history of GI bleeding, and use of other medications that increase bleeding risk (Table 5). For example, a 55-year-old man taking naproxen (a nonsteroidal anti-inflammatory drug) for arthritis and a selective serotonin reuptake inhibitor for depression would have a
4.8 per 1000 annual risk of bleeding and would be a reasonable candidate for PPI treatment if therapy with those medications could not be discontinued.20

Our findings were robust across a range of CHD risk levels and were not affected by factors such as a reduced relative benefit of aspirin on nonfatal CHD or an increased risk of fatal GI bleeding. In addition, results were insensitive to changes in aspirin risk of MI and stroke, as obtained from a sex-specific meta-analysis.18 However, if the PPIs actual GI bleeding risk reduction is much lower than the modeled effect, or its pricing is much higher than the modeled effect, or its pricing is much higher than $200 per year, the benefits of adding PPI to aspirin would be small or negligible, even for those at increased risk.

Figure 2. One-way sensitivity analysis in a 45-year-old man with a 10-year 10% coronary heart disease (CHD) risk. A. Aspirin vs no treatment. B. Aspirin plus proton pump inhibitor (PPI) vs aspirin alone. CVD indicates cardiovascular disease; GI, gastrointestinal tract; HS, health state; MI, myocardial infarction; QALY, quality-adjusted life-year.

Our study has a number of limitations. Given the lack of trials of PPIs in aspirin users without a history of ulcer bleeding, we estimated the benefit of PPI therapy among aspirin users on the basis of a single, randomized controlled trial among high-risk users.3 This estimate is supported by a large body of observational data that informed the recommendation that PPIs be given to patients with high GI bleeding risk.2 A recent clinical trial22 that examined the use of clopidogrel with and without omeprazole and showed a significant reduction in GI events for patients taking omeprazole (ie, relative risk reduction was just as high as in small trial) provided further evidence of benefit of PPI therapy.
We used data on upper GI bleeding for our analysis; aspirin may increase the risk of lower GI bleeding, as well as other extracranial bleeding, but we did not model these directly. However, aspirin remains cost-effective compared with no therapy, even if the annual risk of GI bleeding is 5%, so not including other, less common sources of GI bleeding is unlikely to change our results.

Although PPI therapy may increase the risk of various adverse clinical outcomes among long-term users, we did not include such effects in our model. Specifically, observational studies have demonstrated a modest but significantly increased risk for community-acquired pneumonia as well as enteric infections, particularly involving *Clostridium difficile.* In addition, high-dose, twice-daily PPI therapy has been proposed to increase risk of osteoporotic fractures. Existing data on these effects remain controversial, and robust data to model their risk are limited.

### CONCLUSIONS

This updated analysis supports the role of aspirin for primary prevention of CHD events in middle-aged men across a range of CHD and GI bleeding risk levels. Increased risk of GI bleeding does not reduce aspirin’s net benefit until GI bleeding risk becomes quite high, such as the level seen in men with previous GI bleeding. Adding PPI therapy does not appear to be cost-effective for those patients at low or average risk for GI bleeding but may be valuable for those with a GI bleeding risk over 4 per 1000 per year. Further efforts to include GI bleeding risk assessment when prescribing low-dose aspirin for CHD protection are warranted.

Accepted for Publication: June 18, 2010.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Earnshaw, Scheiman, Fendrick, McDade, and Pignone. Acquisition of data: Earnshaw, Fendrick, and McDade. Analysis and interpretation of data: Earnshaw, Scheiman, Fendrick, McDade, and Pignone. Drafting of the manuscript: Earnshaw, Scheiman, Fendrick, McDade, and Pignone. Critical revision of the manuscript for important intellectual content: Earnshaw, Scheiman, Fendrick, McDade, and Pignone. Statistical analysis: Earnshaw, Fendrick, and McDade. Obtained funding: Fendrick. Administrative, technical, and material support: Earnshaw and McDade. Study supervision: Scheiman.

Financial Disclosure: Drs Scheiman and Fendrick are paid consultants to RTI Health Solutions. Dr Scheiman also is a consultant to AstraZeneca, Bayer Inc, Pozen Inc, and other pharmaceutical companies with products not relevant to this work. Dr Earnshaw and Ms McDade are employees of RTI Health Solutions, an independent contract research organization that has received research funding for this and other studies from Bayer Inc and other

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Table 5. Estimated Baseline Risk per 1000 Patient-Years of GI Bleeding in Men With No History of Ulcer

<table>
<thead>
<tr>
<th>Patient Age, y</th>
<th>No NSAID or SSRI</th>
<th>SSRI Use, No NSAID</th>
<th>NSAID Use, No SSRI</th>
<th>NSAID and SSRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>0.8</td>
<td>1.9</td>
<td>3.2</td>
<td>4.8</td>
</tr>
<tr>
<td>60-69</td>
<td>2.4</td>
<td>5.8</td>
<td>9.6</td>
<td>14.4</td>
</tr>
<tr>
<td>70-79</td>
<td>3.6</td>
<td>8.6</td>
<td>14.4</td>
<td>21.6</td>
</tr>
<tr>
<td>80-89</td>
<td>6.0</td>
<td>14.4</td>
<td>24.0</td>
<td>36.0</td>
</tr>
</tbody>
</table>

Abbreviations: GI, gastrointestinal tract; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

The risk in this table is for men with no ulcer-related bleeding and assumes that the relative risks approximate the odds ratios and that the relative risks are independent. For estimating GI bleeding risk for patients with a history of uncomplicated ulcer, multiply by 6; for a history of complicated ulcer, multiply by 10.

From the study by Hernández-Díaz and García Rodríguez.

Odds ratio, 2.4, 25

Odds ratio, 6.0, 25
pharmaceutical companies that market drugs to prevent cardiovascular events and other conditions.

**Funding/Support:** Funding for this study was provided by Bayer Inc. Dr Pignone was supported by the Foundation for Informed Medical Decision Making and a K05 Established Investigator Award from the National Cancer Institute.

**Role of the Sponsor:** Bayer Inc did not participate in the development of the model or in the collection, management, analysis, and interpretation of the data. The preparation and editing of the manuscript was performed solely by the authors. Bayer received a copy of the draft manuscript but had no role in decisions about submission and revision.

**Online-Only Material:** Supplemental material is available at http://www.archinternmed.com.

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**REFERENCES**


