Cost-effectiveness of Proton Pump Inhibitors for Prevention of Gastrointestinal Adverse Events When Using Aspirin for Primary Cardiovascular Prevention

Stephanie Earnshaw,[1] Michael Pignone,[2] A. Mark Fendrick,[3] James Scheiman,[3] Cheryl McDade[1]

[1]RTI Health Solutions, Research Triangle Park, NC, United States; [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [3]University of Michigan, Ann Arbor, MI, United States

INTRODUCTION

- The value of aspirin for primary coronary heart disease (CHD) prevention in men depends on tradeoffs between its ability to reduce nonfatal myocardial infarction (MI) and its potential to increase the risk of hemorrhagic stroke and extracranial (primarily gastrointestinal) bleeding.[1]
- Although the increased risk of hemorrhagic stroke cannot be mitigated, the risk of upper gastrointestinal bleeding (GIB) can be reduced by acid suppressive therapy through the use of proton pump inhibitors (PPIs).[2,3]
- Previous models have confirmed the cost-effectiveness of aspirin therapy for primary prevention in men with increased CHD risk[4] but were limited by relatively crude measures of adverse effects, particularly GIB.

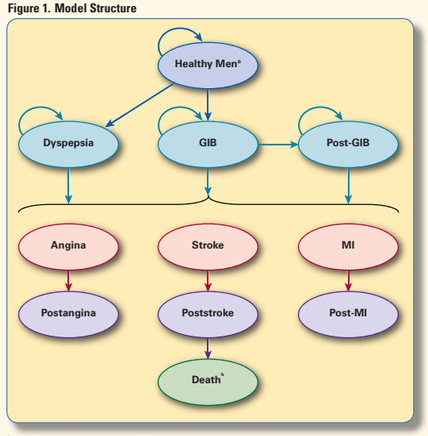
OBJECTIVE

- Examine the cost-effectiveness of the addition of routine use of PPIs to aspirin for primary cardiovascular disease (CVD) prevention in men with a range of underlying 10-year CHD risks and risk for upper GIB when modeling/not modeling dyspepsia.

METHODS

- A Markov model (Figure 1) was developed to simulate a cohort of men of varying 10-year CHD risk levels through primary prevention treatment with aspirin alone or aspirin plus a PPI (aspirin + PPI).
  - Analysis was performed from a third-party payer perspective. All costs and outcomes were discounted at 3% per annum.
  - Analysis was performed when considering/not considering dyspepsia (i.e., with and without the dyspepsia health state included).

Figure 1. Model Structure



[b] Healthy men can progress to CVD event during any cycle.
[c] Men can progress from any health state to death.

Patient Population

- Healthy, middle-aged men who were ≥ 45 years of age, had no history of CHD events, and had a 10% 10-year CHD risk.
- Men with 10-year CHD risk of 2.5%, 5.0%, 7.5%, 15.0%, and 25.0%.

Comparators

- Aspirin: 81 mg of generic aspirin daily.
- Aspirin + PPI: combination of aspirin 81 mg daily and generic omeprazole 20 mg daily.
- Men who had GIB discontinued aspirin use but did not receive a PPI if they were not in the aspirin + PPI arm.[5]

Model Parameters

- Baseline risks of initial cardiovascular (CV) events (MI, stroke, angina, and CHD death) were drawn from Framingham risk equations, using hypothetical scenarios of nonsmoking adults without diabetes with different sets of risk factors.[6]
- Age-dependent non-CV mortality was estimated from the National Vital Statistics life tables.[7] Probabilities increase as men age through the model.
- Annual baseline risks of GIB (not taking aspirin) were estimated as 0.0008, 0.0024, 0.0024, and 0.0036 for men aged 45, 55, 65, and > 65 years, respectively.[5] GIB risk increases as age increases.
- Table 1 presents the relative risk of each event as drawn from published meta-analyses and clinical trials.

Table 1. Clinical Effect of Aspirin and PPI on CV Events and GIB

Parameter	Relative Risk
Aspirin	
MI	0.70 (95% CI: 0.62-0.79)[8]
CHD death	0.87 (95% CI: 0.70-1.09)[9]
All stroke	1.06 (95% CI: 0.91-1.24)[8]
GIB	2.0 (without GIB history) 10.0 (with GIB history)[5]
GIB fatality	1/1,000 (assumption)
Aspirin + PPI	
GIB	0.2 (95% CI: 0.1, 0.9)[10]

CI = confidence interval.

- PPIs added no additional benefit and did not reduce the benefit of aspirin for avoiding CV events.
- The efficacy of combination use of aspirin + PPI was assumed to be independent.
- Men who had CV events entered a postevent health state where they received optimal secondary prevention.
- Men who had adverse effects were assumed to stop the offending agent and were not placed on alternate agents for primary prevention.
- The effect of optimal secondary prevention on all-cause mortality was estimated from meta-analyses of secondary prevention trials.[11,12]
- Health state costs and utilities were obtained from published literature (Table 2). All costs and outcomes were discounted at 3% per annum.

Table 2. Cost and Utility Parameters, Values, and Plausible Ranges

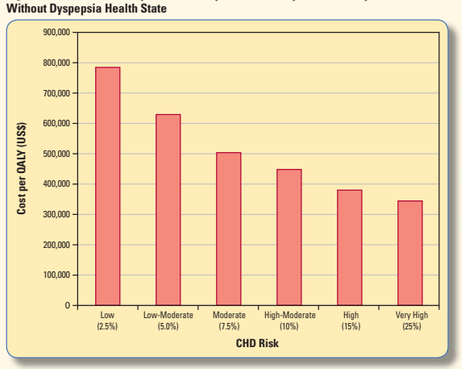
Parameter	Base-Case Value (Range)
Aspirin[13]	$13.99
Generic PPI[14]	$199.79
Outpatient physician visit[15,16]	$62.76
Healthy[a]	$62.76
GIB[17-19]	$13,342
Post-GIB[b]	$62.76
Angina[17-19]	$13,372
Postangina[19,20]	$5,993
Stroke[17-19]	$21,706
Poststroke[18,21]	$1,835
MI[17-19]	$32,625
Post-MI[18,21]	$3,590
Healthy[21]	1.000
GIB[22]	0.94 (95% CI: 0.880-1.000)
Post-GIB[c]	1.000
Dyspepsia[23]	0.996 (95% CI: 0.997-1.000)
Angina[24]	0.929 (95% CI: 0.923-1.000)
Postangina[24]	0.997 (95% CI: 0.997-1.000)
Stroke[22]	0.610 (95% CI: 0.480-0.830)
Poststroke[25]	0.830
MI[26]	0.870 (95% CI: 0.820-0.920)
Post-MI[26]	0.910 (95% CI: 0.860-0.960)

[a] Assumed to be one outpatient physician visit a year.
[b] Assumed similar to healthy patient.
[c] Assumption.

RESULTS

- When modeling/not modeling dyspepsia, aspirin is cost-savings (i.e., less costly and more efficacious) compared with no treatment in 45-year-old men with a 10-year CHD risk ≥ 5%.
- Aspirin is cost-effective compared with no treatment in 45-year-old men with a 10-year CHD risk < 5% when dyspepsia is modeled ($7,270) and not modeled ($5,714).
- When dyspepsia is not modeled, the addition of PPI to aspirin is not cost-effective compared with aspirin alone in men at any CHD risk level (Figure 2).

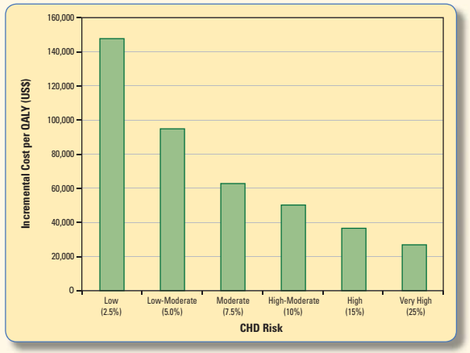
Figure 2. Incremental Cost per QALY of Aspirin + PPI Compared With Aspirin Alone Without Dyspepsia Health State



QALY = quality-adjusted life year.

- When dyspepsia is modeled, the addition of PPI to aspirin is cost-effective compared with aspirin alone in men with a 10-year CHD risk ≥ 10% (Figure 3).

Figure 3. Incremental Cost per QALY of Aspirin + PPI Compared With Aspirin Alone With Dyspepsia Health State

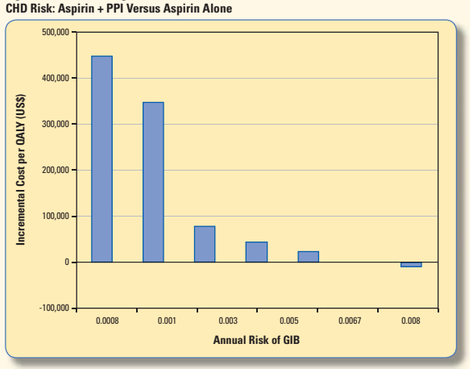


- Sensitivity analyses show that aspirin compared with no treatment and aspirin + PPI compared with aspirin alone are robust to changes to all parameters within their plausible ranges.

Effect of GIB Risk

- When modeling dyspepsia, aspirin + PPI is cost-effective compared with aspirin when GIB risk is > 0.0024.
- When dyspepsia is not modeled, aspirin + PPI compared with aspirin alone is cost-effective when GIB risk is > 0.004 and cost-savings when GIB risk is > 0.007 (Figure 3).

Figure 4. Effect of Change in Baseline GIB Risk in a 45-Year-Old Man With a 10-Year, 10% CHD Risk: Aspirin + PPI Versus Aspirin Alone



CONCLUSIONS

- When modeling dyspepsia, primary CHD prevention with aspirin is cost-saving compared with no treatment in men ≥ 45 years of age with a 10-year CHD risk of ≥ 5% as seen in previous published analyses without dyspepsia modeled.
- When the benefits from treating dyspepsia are not included, adding PPI is not cost-effective as a routine means of preventing GIB.
- However, considering dyspepsia, adding PPI to aspirin therapy may be cost-effective in 45-year-old men with a 10-year CHD risk ≥ 10%.
- The cost-effectiveness of adding PPI to aspirin depends on PPI cost and protective effect against gastrointestinal adverse events.

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CONTACT INFORMATION

Stephanie Earnshaw, PhD
Vice President, US Health Economics

RTI Health Solutions
200 Park Offices Drive
Research Triangle Park, NC 27709

Phone: +1.919.485.2730
Fax: +1.919.541.7222
E-mail: searnshaw@rti.org

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