

Aspirin for the Primary Prevention of Cardiovascular Disease in Women

A Cost-Utility Analysis

Michael Pignone, MD, MPH; Stephanie Earnshaw, PhD; Mark J. Pletcher, MD, MPH; Jeffrey A. Tice, MD

Background: The cost-effectiveness of aspirin for primary prevention of cardiovascular events in women is unclear. We sought to perform a cost-utility analysis to address this issue.

Methods: We developed a Markov model, based on published literature, to compare aspirin prevention with no therapy. We used the perspective of a third-party payer and a lifetime time horizon. Our main outcome measure was cost per quality-adjusted life-year (QALY) gained. Our base case analysis considered 65-year-old women with a 7.5% 10-year risk of coronary heart disease events and a 2.8% risk of stroke.

Results: Aspirin use cost \$13 300 per additional QALY gained in the base case. Results were sensitive to age, cardiovascular disease risk, relative risk reductions with aspirin for ischemic strokes and myocardial infarction, ex-

cess risk of hemorrhagic stroke and gastrointestinal bleeding, and the disutility of taking medication. Probabilistic sensitivity analysis for 65-year-old women at moderate cardiovascular disease risk found a 27% chance that aspirin produces fewer QALYs than no treatment, a 35% chance that the cost-utility ratio was less than \$50 000 per QALY gained, and a 37% probability that it was greater than \$50 000 per QALY gained.

Conclusions: Aspirin use appears to have a favorable cost-utility ratio for older women with moderate cardiovascular risk, but firm conclusions about its effects are limited by the imprecision of available evidence, which comes mainly from 1 trial. Aspirin is indicated for women at higher risk for stroke but should not be prescribed for low-risk women, including most younger women.

Arch Intern Med. 2007;167:290-295

PREVENTION OF CARDIOVASCULAR disease (CVD) is important for women. Since 1984, the number of women dying from CVD has exceeded that for men in the United States.^{1,2} Developing effective treatment strategies for women is essential for reducing the burden from CVD, but the effect of therapies in women has been understudied.

Aspirin is effective for preventing first coronary heart disease (CHD) events, particularly nonfatal myocardial infarction, in men but does not appear to have an important effect on ischemic stroke incidence.³ Fewer data have been available for understanding the effect of aspirin in women. The recently published Women's Health Study (WHS) evaluated the effect of low-dose aspirin (100 mg every other day) for primary prevention in more than 40 000 women older than 45 years⁴; 2 previous primary prevention trials of aspirin included smaller numbers of women.^{5,6} In contrast to trials of aspirin in men, the WHS found that aspirin appeared to reduce the risk of

ischemic stroke but had no important effect on myocardial infarction; risk of adverse events, gastrointestinal bleeding, and hemorrhagic stroke was similar to that found in the trials conducted mainly in men. Integration of data on women from the 3 trials that included women produced similar estimates of effect to those seen in the WHS alone.^{4,7}

Given these data, cost-utility analysis may be helpful for deciding which women have sufficient cardiovascular risk to warrant risk reduction therapy with aspirin. We previously performed a cost-utility analysis in middle-aged men and found that aspirin was more effective and less costly than no therapy when the 10-year risk of CHD events was 7.5% or greater.⁸ To better inform clinical and policy decisions about primary CVD prevention in women, we performed a cost-utility analysis of aspirin compared with no treatment.

METHODS

To examine the costs and utilities associated with aspirin use in women, we modified our

Author Affiliations: Department of Medicine, University of North Carolina, Chapel Hill (Dr Pignone); RTI Health Solutions, Research Triangle Park, NC (Dr Earnshaw); and Departments of Epidemiology and Biostatistics (Dr Pletcher) and Medicine (Dr Tice), University of California, San Francisco.

previously described Markov state-transition model.⁸ The new model simulates initially healthy cohorts of middle-aged and older women with no history of CVD events (**Figure 1**). We took the perspective of a third-party payer and used a lifetime time horizon.

BASE CASE SCENARIO

In our base case scenario, we examined the effectiveness of low-dose aspirin compared with no aspirin in cohorts of moderate-risk 65-year-old women with the following risk factor profile: systolic blood pressure, 120 mm Hg; total cholesterol, 184 mg/dL (4.77 mmol/L); high-density lipoprotein cholesterol, 40 mg/dL (1.04 mmol/L); and no smoking, diabetes, or atrial fibrillation. Such a patient would have an estimated 10-year total CHD risk of 7.5% and a 10-year stroke risk of 2.8%.

MODEL ASSUMPTIONS

All women begin in the healthy state and progress through the model in annual cycles. In each cycle, a woman can remain in the healthy state, die, progress to have initial cardiovascular events (angina, myocardial infarction, or ischemic stroke), or have adverse effects from aspirin (hemorrhagic stroke or gastrointestinal bleeding). Those who have cardiovascular events or adverse events are assumed to stay in the subacute state for the remainder of that cycle and then enter a postevent state. Adherence to aspirin is assumed to be 100% in the absence of adverse effects, although the treatment efficacy estimates are based on the actual rates of adherence observed in the clinical trials. Women who experience adverse effects from aspirin discontinue its use permanently and otherwise proceed similarly to healthy patients after the initial cycle. All costs and outcomes were discounted at 3% per year in accordance with current consensus recommendations.⁹

MODEL VARIABLES

Noncardiovascular Mortality

Age-dependent noncardiovascular mortality rates for women were estimated from the National Vital Statistics life tables.¹⁰ Rates were adjusted as the cohort aged over the time horizon of the analysis.

Cardiovascular Event Rates

Baseline risks of initial cardiovascular events (ie, myocardial infarction, stroke, angina, and CHD death) were drawn from Framingham risk equations.¹¹⁻¹³ We assumed that all predicted strokes were ischemic in nature, and we created a separate rate for hemorrhagic strokes as a complication of aspirin use. The 10-year risks were translated into annual, event-related transition probabilities based on an assumed exponential distribution.

Because we were interested in primary prevention, we did not simulate the specific experience of each woman after a primary nonfatal event. Instead, we assigned women an increased risk of mortality, increased costs, and decreased utilities using literature data on the average experience (eg, increased event rate) of patients after an initial event. The increased relative risks of mortality after initial events (**Table**) were estimated based on data from population-based studies in men conducted in the United Kingdom and the United States. Although initial short-term mortality rates after events in women are greater than those in men, their age-adjusted long-term experiences are similar.^{18,19} The relative risk estimates were ap-

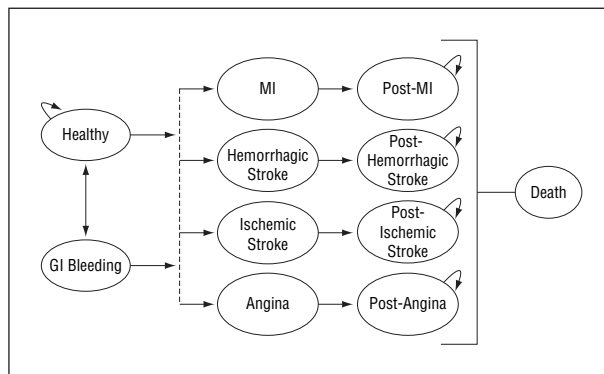


Figure 1. Markov model structure. Women begin in the healthy state and can transition to the other states in yearly cycles. Patients can progress to death from any state. GI indicates gastrointestinal; MI, myocardial infarction.

plied to the age-specific mortality rates for women from the US life tables to generate the estimated postevent mortality rates.

Adverse Effects

The excess risk of gastrointestinal bleeding with aspirin, 0.7 per 1000 per year, was estimated from a systematic review of the 5 primary prevention trials published before the WHS.¹⁴ The relative risk of major gastrointestinal bleeding in the WHS was 1.4, consistent with the risks observed in the previous trials, and the excess risk was approximately 0.1 per 1000 per year.⁴ We chose to use the higher estimate because real-world rates of substantial bleeding or peptic ulcer may be somewhat higher and because the age in our base case (65 years) was higher than the mean age in the WHS (55 years). Risks of gastrointestinal bleeding in untreated women are assumed to be zero, so only treatment-induced adverse events were modeled. Because better data were not available, we made an assumption about the risk of mortality from aspirin-related gastrointestinal bleeding and varied it in the sensitivity analysis.¹⁵ Women who had adverse effects were not prescribed alternate agents for primary prevention.

Modeling Stroke

We modeled hemorrhagic stroke and ischemic stroke as separate health states. We assumed that aspirin was associated with an excess annual risk of 20 hemorrhagic strokes per 100 000 users, based on published systematic reviews and meta-analyses conducted mainly in men.^{16,17} The effect of aspirin on ischemic stroke was drawn from the meta-analysis by the WHS investigators.⁴

Treatment Efficacy

We used summary relative risk estimates from meta-analyses to estimate the effect of aspirin on cardiovascular events^{4,7} (**Table**). All patients who survive an initial CVD event are assumed to receive secondary prevention treatments, including aspirin, statins, and dietary advice. We assumed that such treatment would reduce the risk of mortality by 33%, as shown in men, but we varied this estimate widely in the sensitivity analysis to reflect data that suggested that statins have not been clearly shown to reduce all-cause mortality in women when used for secondary prevention.^{20,21}

We used the cost estimates from mixed populations of men and women to estimate costs for women. Costs, given in the **Table**, were derived from a combination of the published literature and several recent national databases and are ex-

Table. Base Case Estimates and Ranges Used in Sensitivity Analyses*

Variable (Reference)	Base Case Estimate (Range)
Relative risk of primary prevention with aspirin	
Myocardial infarction ⁴	1.01 (0.84-1.21)
Stroke ⁴	0.76 (0.63-0.93)
Angina†	1.00 (0.80-1.20)
Death from coronary heart disease†	1.00 (0.80-1.20)
Annual excess risk for adverse events with aspirin	
Gastrointestinal bleeding ¹⁴	0.0007 (0.0004-0.0100)
Death resulting from gastrointestinal bleeding ¹⁵	0.00001 (0.000001-0.0001)
Hemorrhagic stroke ^{16,17}	20/100 000 (5/100 000 to 35/100 000)
Increase in relative risk of death	
After myocardial infarction ¹⁸	3.7 (3.0-4.7)
After angina ¹⁸	3.0 (2.1-4.2)
After stroke ¹⁹	2.3 (1.6-4.6)
Relative risk for all-cause mortality with secondary prevention ^{20,21}	0.67 (0.50-0.85)
Annual cost data, \$‡	
Drug cost	
Generic aspirin ²²	5.75
Myocardial infarction	
Year 1 care ²³	14 629
Ongoing care ^{1,23,24}	3109
Stroke§	
Year 1 care ²³	10 263
Ongoing care ^{1,25}	1589
Hemorrhagic stroke	
Year 1 care ^{1,25}	21 248
Ongoing care ^{1,25}	7523
Angina	
Year 1 care ²³	3778
Ongoing care ^{23,24}	2897
Gastrointestinal bleeding	
Nonfatal ²³	7538
Fatal ²³	7538
Miscellaneous	
Physician visit ²⁵	38.66
Day institutionalized ²⁵	40.93
Utility data	
Healthy†	1.0
Death†	0
Myocardial infarction and angina	
Year 1 ^{26,27}	0.88 (0.80-0.96)
Subsequent year ^{26,27}	0.90 (0.80-0.95)
Stroke	
Nondisabling ²⁸	0.75 (0.60-0.90)
Disabling ²⁸	0.5 (0.0-0.75)
Gastrointestinal bleeding (year 1 only) ¹⁵	0.94 (0.88-1.0)
Act of taking aspirin ²⁹	1.0 (0.99-1.0)

*We assumed that patients receiving aspirin therapy did not require additional monitoring tests.

†Assumptions.

‡All costs varied by 50% in each direction in the sensitivity analysis.

§To estimate stroke costs in the main analysis, we assumed that 70% of initial strokes were nondisabling, 15% were partially disabling, and 15% were disabling. Disabling strokes were assumed to lead to 180 days of institutionalization.

pressed in 2005 US dollars.^{1,22-25,30,31} In our base case, we estimated the cost of generic aspirin to be \$5.75 per year. The costing methods are detailed elsewhere.⁸

Utilities

Because of limited data on utilities specific for women, we used published values from studies that included men or mixed populations and made assumptions when data were not available^{15,26-29} (Table). Most studies used time tradeoff techniques to generate utility weights. We included the general disutility from taking a medication in the model, but in the base case it was set at 1.0, reflecting no disutility, and was varied in sensitivity analysis.

MAIN OUTCOME MEASURE AND SENSITIVITY ANALYSES

Our main outcome measure was the cost per quality-adjusted life-year (QALY) gained.

We examined the effect of changing several different variables in 1-way sensitivity analyses, including the effect of different starting ages (55 and 75 years) and different levels of cardiovascular risk factors. We also examined the effect of varying individual values for all of our main efficacy, adverse event, cost, and utility estimates, using plausible ranges of values from the literature with their 95% confidence intervals or by varying the estimates by at least 20% in each direction. In addition to 1-way sensitivity analyses, we also performed probabilistic sensitivity analyses.³² The variables used in these analyses included relative risks of myocardial infarction, CHD death, ischemic stroke, and hemorrhagic stroke; excess gastrointestinal bleeding with aspirin; mortality after an initial cardiovascular event; and utilities for all health states.

RESULTS

Aspirin produced 10.963 QALYs in the base case analysis of moderate-risk women, with mean costs of \$3145. No treatment produced 10.957 QALYs and mean costs of \$3069. The cost per additional QALY gained with aspirin was \$13 300.

ONE-WAY SENSITIVITY ANALYSES

We examined the effect of varying several key variables on the model's results. The patient's age and the risk of cardiovascular events had strong effects on the cost-utility ratios. At a starting age of 55 years with the same risk factor profile as the base case (and thus a 10-year stroke risk of 1.4%), aspirin was less effective and more costly than no treatment. For women 75 years old with the same risk factor profile (10-year stroke risk of 5.5%), the cost per QALY gained improved to \$2532. In 65-year-old women with increased stroke risk (5.2% over 10 years) due to elevated systolic blood pressure of 160 mm Hg, aspirin was more effective and less costly than no treatment.

Changes in the risk reductions associated with aspirin for ischemic stroke or myocardial infarction had important effects on the results (**Figure 2** and **Figure 3**), as did changes in the risk reduction with secondary prevention (data not shown). If secondary prevention is more effective than in the base case (ie, a risk reduction of >33%), the cost-effectiveness for aspirin as primary prevention becomes less favorable, whereas if it is less effective than estimated, cost-effectiveness improves.

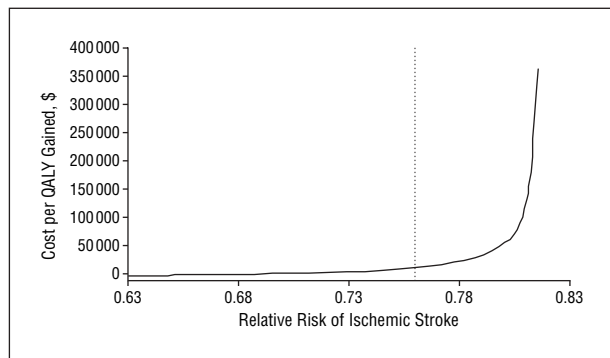


Figure 2. Variation in cost per quality-adjusted life-year (QALY) gained with aspirin compared with no treatment (represented on the y-axis) across the range of potential values for the relative risk of ischemic stroke in those taking aspirin (represented on the x-axis). The vertical broken line represents the base case value. Costs are expressed in 2005 US dollars.

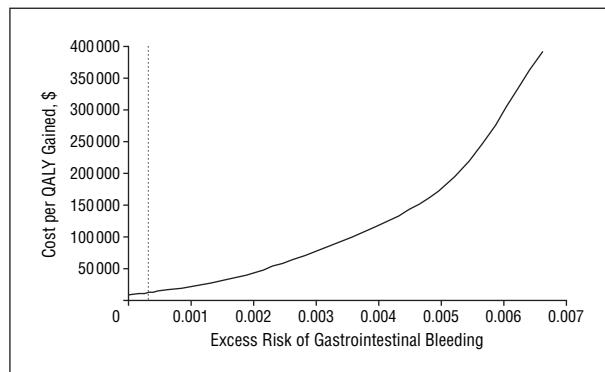


Figure 4. Variation in cost per quality-adjusted life-year (QALY) gained with aspirin compared with no treatment (represented on the y-axis) across the range of potential values for the excess risk of gastrointestinal bleeding in those taking aspirin (represented on the x-axis). The vertical broken line represents the base case value. Costs are expressed in 2005 US dollars.

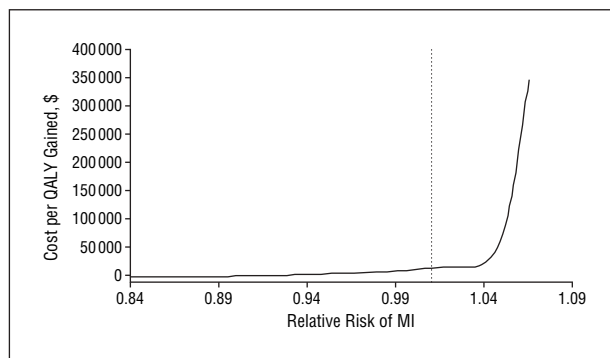


Figure 3. Variation in cost per quality-adjusted life-year (QALY) gained with aspirin compared with no treatment (represented on the y-axis) across the range of potential values for the relative risk of myocardial infarction (MI) in those taking aspirin (represented on the x-axis). The vertical broken line represents the base case value. Costs are expressed in 2005 US dollars.

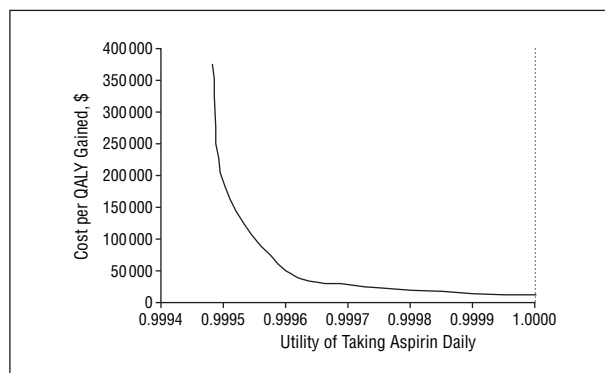


Figure 5. Variation in cost per quality-adjusted life-year (QALY) gained with aspirin compared with no treatment (represented on the y-axis) across the range of potential values for the utility of taking aspirin (represented on the x-axis). The vertical broken line represents the base case value. Costs are expressed in 2005 US dollars.

The excess rate of gastrointestinal bleeding with aspirin (0.7 per 1000 per year in the base case) also had an important effect on the cost-effectiveness ratio for aspirin therapy (**Figure 4**). If the excess risk of gastrointestinal bleeding were 2.5 per 1000 per year, the cost per QALY gained with aspirin would be increased to almost \$50 000. If it were as high as 1% per year, aspirin would be less effective than no treatment. If the excess risk of death from gastrointestinal bleeding were more than 4 per 100 000 per year, aspirin again would become less effective than no therapy. Similarly, if the risk of hemorrhagic stroke were more than 28 per 100 000 per year, aspirin would be less effective than no therapy. Assuming even a small disutility (<0.0001) from taking a pill each day increased the cost-utility ratio substantially, if the utility of taking a pill were lower than 0.9995, aspirin would become less effective than no treatment (**Figure 5**).

PROBABILISTIC SENSITIVITY ANALYSIS

We found that simultaneously varying estimates of efficacy, harm, and utilities in probabilistic analysis produced a wide range of results for women at moderate (2.8%) 10-year stroke risk. **Figure 6** shows the plot of the probabilistic analysis and the cost-effectiveness acceptability curve.

Using the range of values examined in the probabilistic model, there was a 35% chance the cost per QALY gained was less than \$50 000, a 37% chance that aspirin had a cost per QALY gained greater than \$50 000, and a 27% chance that aspirin was less effective and more costly than no treatment. The main factors leading to this uncertainty appeared to be the relative risks of stroke and myocardial infarction with aspirin (data not shown).

COMMENT

The effectiveness of aspirin for primary prevention of cardiovascular events in women is controversial. Recent meta-analyses, based largely on data from the WHS, suggest that low-dose aspirin can prevent ischemic stroke, but not myocardial infarction, in a population of middle-aged and older women.^{4,7} On the basis of these estimates of efficacy and relatively conservative assumptions about harm, we found that aspirin had a cost-utility ratio of \$13 300 per QALY gained in 65-year-old women with a moderate (7.5% CHD risk; 2.8% stroke risk) 10-year cardiovascular risk. Probabilistic sensitivity analyses, however, suggest that there is a moderately high probability (27%) that aspirin could be less effective than no treatment for these moderate-risk women, making definitive conclusions about the effec-

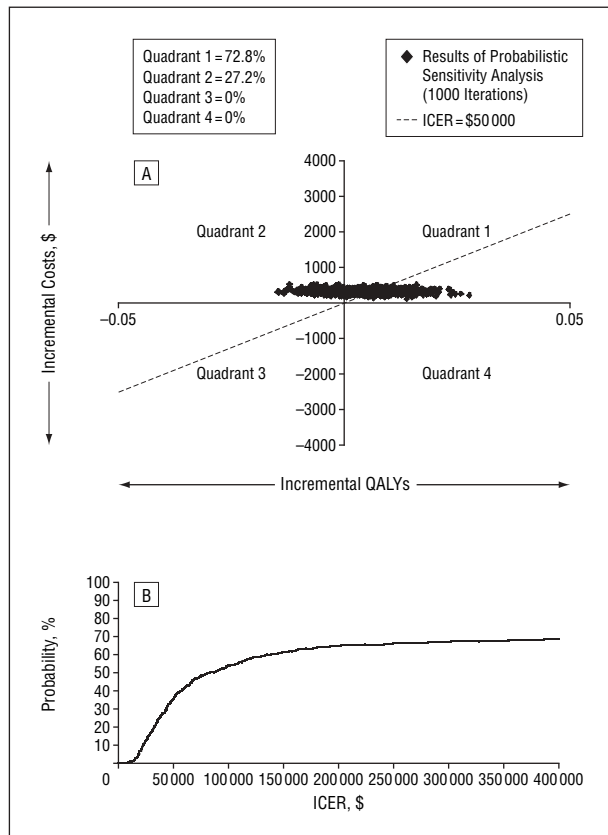


Figure 6. Probabilistic sensitivity analysis and cost-effectiveness acceptability curve. A, Results of the probabilistic sensitivity analysis for the base case of 65-year-old women at moderate cardiovascular risk. Each dot represents 1 iteration of the model. The y-axis represents incremental costs of aspirin compared with no therapy. The x-axis represents net quality-adjusted life-years (QALYs) with aspirin compared with no therapy. The diagonal line represents a cost per QALY gained of \$50 000 in quadrant 1. B, The y-axis represents the probability that the cost per QALY gained is less than or equal to the values listed on the x-axis. ICER indicates incremental cost-effectiveness ratio.

tiveness of aspirin at this risk level difficult. For women at higher risk for stroke, the benefits of aspirin appear more clear and aspirin use can be recommended for those not at increased risk for adverse effects. For lower-risk women, including women 55 years and younger without additional stroke risk factors, aspirin does not appear beneficial and cannot be recommended based on the available evidence.

Our results are consistent with 1 previously published decision analysis that examined the threshold for use of aspirin in women¹⁵ but differ somewhat from a recent modeling study conducted in Australia.³³ The threshold for prescribing aspirin depends mainly on the balance between its benefits (reduction in ischemic stroke) and its adverse effects (gastrointestinal bleeding and hemorrhagic stroke). As seen in our sensitivity analyses, if the risk of ischemic stroke is greater, the potential benefits are greater and the cost-effectiveness of aspirin improves considerably.

The excess risk of gastrointestinal bleeding for adults older than 65 years may be higher than the base case estimate (0.7 per 1000 per year), which was derived from the trials of aspirin conducted mainly in middle-aged adults. Hernandez-Diaz and Rodriguez³⁴ performed a sys-

tematic review and estimated a background rate of upper gastrointestinal tract bleeding of approximately 2 per 1000 per year at the age of 65 years and 4 per 1000 at the age of 75 years. Using a relative risk with aspirin of 1.4, we would anticipate an excess rate of upper gastrointestinal tract bleeding of approximately 0.8 per 1000 per year at the age of 65 years and 1.6 per 1000 in 75-year-olds, levels that still produce favorable costs per QALY gained with aspirin therapy. However, given this uncertainty, further trials in older women are required to better define the true net effects.

If the act of taking a pill daily reduces one's quality of life, then the net value of aspirin for primary prevention is diminished. Alternate-day therapy, as used in the WHS, may have less disutility, but this topic has not been well studied and requires further research.

Our analysis has several limitations. Our results are dependent on a single trial, the WHS, which examined a low dose (100 mg every other day) of aspirin in a low-risk population. The WHS reached a conclusion regarding the effect of aspirin on stroke and myocardial infarction that stands in contrast to its effect in preventing cardiovascular events in men (for whom aspirin reduced myocardial infarction but not ischemic stroke) and in contrast to data in men and women from secondary prevention studies that suggest little or no difference in aspirin's effects by sex. In a subanalysis of the WHS, aspirin reduced myocardial infarction in older women, but this finding needs to be interpreted with caution.⁴ If aspirin is effective for reducing myocardial infarction in women, aspirin's benefits and cost-effectiveness will be greater. Further trial evidence in women, using conventional dosages of at least 75 mg/d, is needed to produce more robust estimates of the true effect of aspirin.

In addition to the limited data on efficacy and adverse effects of aspirin, we did not have female-specific data on utilities and costs. If such parameters differ in women compared with men, our results could also differ. We have attempted to account for limitations in our input by performing extensive sensitivity analyses to test our assumptions, including probabilistic sensitivity analyses.

We chose to use the perspective of a third-party payer because we did not have estimates of the patient time costs that would be required to conduct an analysis from the societal perspective. Such costs can have important effects, and further research is required to better measure them for cardiovascular prevention.³⁵

We chose to use a Markov model rather than a more complex simulation model to improve its transparency and interpretability and because it is not clear that more complex models necessarily yield different or more informative results. Because we are interested in primary prevention, we did not model in detail the course of patients after their initial events. Instead, we used mean estimates of cost, survival, and utility and applied projections of the benefit from secondary prevention to all patients. We did not model patients with other cardiovascular risk factors, such as diabetes, hypertension, or smoking, and we did not examine other effective cardiovascular risk-reducing options, such as hypertension treatment or smoking cessation, or potentially effective ones, such as counseling to increase physical activity or to change diet.

Despite these limitations, we believe that our analysis has important implications for clinical practice and policy decisions. Aspirin may be indicated for middle-aged and older women with moderate cardiovascular risk who are not at increased risk for complications, but better data about aspirin's efficacy (particularly for myocardial infarction) and harm (particularly the risk of gastrointestinal bleeding and disutility from taking a pill) are needed to reach a definitive conclusion. Aspirin is likely beneficial for women at higher risk for ischemic stroke; low-risk women probably should not use aspirin prophylaxis because the risk of harm exceeds potential benefits.

Accepted for Publication: October 24, 2006.

Correspondence: Michael Pignone, MD, MPH, Division of General Medicine, University of North Carolina, 5039 Old Clinic Bldg, Campus Box 7110, Chapel Hill, NC 27599 (pignone@med.unc.edu).

Author Contributions: *Study concept and design:* Pignone, Earnshaw, Pletcher, and Tice. *Acquisition of data:* Earnshaw. *Analysis and interpretation of data:* Pignone, Earnshaw, Pletcher, and Tice. *Drafting of the manuscript:* Pignone and Earnshaw. *Critical revision of the manuscript for important intellectual content:* Pignone, Earnshaw, Pletcher, and Tice. *Statistical analysis:* Earnshaw. *Obtained funding:* Pignone. *Administrative, technical, and material support:* Pignone. *Study supervision:* Pignone.

Financial Disclosure: Dr Pignone has received consulting fees and honoraria from Bayer Inc and has provided expert testimony. His institution has received licensing fees from Bayer for use of the Web-based cardiovascular risk calculator "Heart to Heart." Dr Pignone has also received grant support from grant 1P30CD000138-01 from the Centers for Disease Control and Prevention for the RTI Health Solutions and University of North Carolina (RTI-UNC) Center for Health Promotion Economics.

Funding/Support: The work was supported by a grant from Bayer Inc. Dr Pignone's work was also supported by grant 1P30CD000138-01 for the RTI-UNC Center for Health Promotion Economics.

Role of the Sponsor: Bayer had no role in the design, analysis, or interpretation of the results.

Acknowledgment: We acknowledge Evan Sloan, BA, for his assistance in preparation of the manuscript and Su-meet Patil, MS, and Jon Graham, BS, for their assistance with developing the figures and table.

REFERENCES

- American Heart Association. *Heart Disease and Stroke Statistics—2002*. Chicago, Ill: American Heart Association; 2002.
- American Heart Association. *Women and Cardiovascular Disease*. Chicago, Ill: American Heart Association; 2004.
- Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2000;136:161-172.
- Ridker PM, Cook NR, Lee JM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005;352:1293-1304.
- Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet*. 1998;351:1755-1762.
- de Gaetano G. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. *Lancet*. 2001;357:89-95.
- Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA*. 2006;295:306-313.
- Pignone M, Earnshaw S, Tice JA, Pletcher MJ. Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. *Ann Intern Med*. 2006;144:326-336.
- Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. *JAMA*. 1996;276:1339-1341.
- Minino AM, Smith BL. Death: preliminary data for 2001. *Natl Vital Stat Rep*. 2001;49:1-40.
- Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J*. 1991;121:293-298.
- Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1991;22:312-318.
- D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication: the Framingham Study. *Stroke*. 1994;25:40-43.
- Murphy M, Foster C, Sudlow C, et al. Cardiovascular disorders: primary prevention. *Clin Evid*. June 2002:91-123.
- Augustovski FA, Cantor SB, Thach CT, Spann SJ. Aspirin for primary prevention of cardiovascular events. *J Gen Intern Med*. 1998;13:824-835.
- Hart RG, Halperin J, McBride R, Benavente O, Man-Son-Hing M, Kronmal R. Aspirin for the primary prevention of stroke and other major vascular events. *Arch Neurol*. 2000;57:326-332.
- He J, Whelton PK, Vu B, Klag MJ. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials. *JAMA*. 1998;280:1930-1935.
- Benderly M, Behar S, Reicher-Reiss H, Boyko V, Goldbourt U; SPRINT Study Group. Long-term prognosis of women after myocardial infarction. *Am J Epidemiol*. 1997;146:153-160.
- Dennis MS, Burn JP, Sandercock PA, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke*. 1993;24:796-800.
- Walsh JM, Pignone M. Drug treatment of hyperlipidemia in women. *JAMA*. 2004;291:2243-2252.
- LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA*. 1999;282:2340-2346.
- Medical Economics Co. *RedBook for Windows Version 5.0*. Greenwood Village, Colo: Thomson PDR Publishing; 2003.
- Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project. <http://www.hcup-us.ahrq.gov/overview.jsp>. Accessed November 17, 2006.
- Russell MW, Huse DM, Drowns S, Hamel EC, Hartz SC. Direct medical costs of coronary artery disease in the United States. *Am J Cardiol*. 1998;81:1110-1115.
- Ingenix Inc. *The Essential RBRVS: A Comprehensive Listing of RBRVS Values for CPT and HCPCS Codes*. Eden Prairie, Minn: St. Anthony/Ingenix Publishing Group; 2005.
- Nease RF Jr, Kneeland T, O'Connor GT, et al. Variation in patient utilities for outcomes of the management of chronic stable angina: implications for clinical practice guidelines: Ischemic Heart Disease Patient Outcomes Research Team. *JAMA*. 1995;273:1185-1190.
- Tsevat J, Goldman L, Soukup JR, et al. Stability of time-tradeoff utilities in survivors of myocardial infarction. *Med Decis Making*. 1993;13:161-165.
- Gage BF, Cardinali AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA*. 1995;274:1839-1845.
- Naglie IG, Detsky AS. Treatment of chronic nonvalvular atrial fibrillation in the elderly: a decision analysis. *Med Decis Making*. 1992;12:239-249.
- Centers for Medicare and Medicaid Services. 100% MEDPAR Inpatient Hospital Fiscal Year 2002. <http://www.cms.hhs.gov/MedicareFeeForSvcPartsAB/Downloads/DRG02.pdf>. Accessed November 17, 2006.
- US Department of Labor, Bureau of Labor Statistics. Consumer Price Index: All Urban Consumers (Current Series). <http://data.bls.gov/PDQ/outside.jsp?survey=cu>. Accessed November 17, 2006.
- Briggs AH, Goeree R, Blackhouse G, O'Brien BJ. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. *Med Decis Making*. 2002;22:290-308.
- Nelson MR, Liew D, Bertram M, Vos T. Epidemiological modelling of routine use of low dose aspirin for the primary prevention of coronary heart disease and stroke in those aged > or =70. *BMJ*. 2005;330:1306.
- Hernandez-Diaz S, Rodriguez LA. Incidence of serious upper gastrointestinal bleeding/perforation in the general population: review of epidemiologic studies. *J Clin Epidemiol*. 2002;55:157-163.
- Yabroff KR, Warren JL, Knopf K, Davis WW, Brown ML. Estimating patient time costs associated with colorectal cancer care. *Med Care*. 2005;43:640-648.