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Aspirin, Statins, or Both Drugs for the Primary Prevention of Coronary Heart Disease Events in Men: A Cost–Utility Analysis

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Background: Aspirin and statins are both effective for primary prevention of coronary heart disease (CHD), but their combined use has not been well studied.

Objective: To perform a cost–utility analysis of the effects of aspirin therapy, statin therapy, combination therapy with both drugs, and no pharmacotherapy for the primary prevention of CHD events in men.

Design: Markov model.

Data Sources: Published literature.

Target Population: Middle-aged men without a history of cardiovascular disease at 6 levels of 10-year risk for CHD (2.5%, 5%, 7.5%, 10%, 15%, and 25%).

Time Horizon: Lifetime.

Perspective: Third-party payer.

Interventions: Low-dose aspirin, a statin, both drugs as combination therapy, or no therapy.

Outcome Measure: Cost per quality-adjusted life-year gained.

Results of Base-Case Analysis: For 45-year-old men who do not smoke, are not hypertensive, and have a 10-year risk for CHD of 7.5%, aspirin was more effective and less costly than no treatment. The addition of a statin to aspirin therapy produced an incremental cost–utility ratio of $56 200 per quality-adjusted life-year gained compared with aspirin alone.

Results of Sensitivity Analysis: Excess risk for hemorrhagic stroke and gastrointestinal bleeding with aspirin, risk for CHD, the cost of statins, and the disutility of taking medication had important effects on the cost–utility ratios.

Limitations: Several input parameters, particularly adverse event rates and utility values, are supported by limited empirical data. Results are applicable to middle-aged men only.

Conclusions: Compared with no treatment, aspirin is less costly and more effective for preventing CHD events in middle-aged men whose 10-year risk for CHD is 7.5% or higher. The addition of a statin to aspirin therapy becomes more cost-effective when the patient's 10-year CHD risk before treatment is higher than 10%.

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Aspirin and statin drugs have been shown to be effective for preventing first coronary heart disease (CHD) events (1–3). Systematic reviews and meta-analyses suggest that the relative risk reductions with both forms of therapy are similar in magnitude and seem to be independent and relatively constant across the range of underlying risk for CHD (2–5). The absolute benefit from these treatments seems to be proportional to the patient's underlying risk for CHD.

National treatment guidelines recommend aspirin and statin drugs individually for the primary prevention of cardiovascular events in men who are at increased risk (4, 6, 7). However, no U.S. guidelines have addressed how these drugs should be used together, and we are unaware of any previous analyses that have reported the cost-effectiveness of these drugs when used in combination for CHD prevention.

To help inform clinical and policy decisions about primary CHD prevention, we performed a cost–utility analysis that examined the use of aspirin therapy, statin therapy, or combination therapy with both drugs in men with various underlying levels of risk for CHD.

METHODS

To examine the cost and utility associated with aspirin and with statin use, we used Microsoft Excel 2002 for Windows (Microsoft Corp., Redmond, Washington) to develop a Markov state-transition model. The model was designed to simulate cohorts of initially healthy middle-aged men with no history of cardiovascular events and with various levels of 10-year risk for CHD (**Figure 1**).

Base-Case Scenario

In our base-case scenario, we compared the effectiveness of 10 years of aspirin therapy, statin therapy, combination therapy with both drugs, and no therapy in 45-year-old men with a 10-year risk for CHD of 7.5%. After 10 years, both groups adopted the treatment used in the intervention group. Although the differences in therapy were maintained for only 10 years, we examined the effects of these therapies over a lifetime.

Model Assumptions

All persons were initially healthy and progressed through the model in annual cycles. In each cycle, an in-

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dividual remained healthy, had an initial cardiovascular event (angina, myocardial infarction, or stroke), experienced adverse effects from therapy (gastrointestinal bleeding from aspirin or myopathy from statins), or died. We assumed that those who had cardiovascular events or adverse events stayed in the subacute state for the remainder of that cycle and then entered a postevent state. Adherence to treatment was assumed to be 100% in the absence of adverse effects, although the treatment efficacy data were based on the actual rates of adherence in the clinical trials. Persons who had adverse effects from therapy stopped taking the offending medication; their procession through the model was similar to that of healthy patients after the initial cycle. All costs and outcomes were discounted at 3% in accordance with current consensus recommendations (8).

Model Parameters

Model parameters, including base-case values, ranges, and references, are shown in **Table 1** (1–3, 9–29).

Noncardiovascular Mortality

Age-dependent noncardiovascular mortality rates were estimated from the National Vital Statistics life tables (31). Rates were adjusted as the cohort aged over the time horizon of the analysis.

Cardiovascular Event Rates

Baseline risks for initial cardiovascular events (myocardial infarction, stroke, angina, and death from CHD) were drawn from Framingham risk equations by using hypothetical scenarios of nonsmoking, nonhypertensive, nondiabetic men at different levels of risk for CHD (**Appendix Table**, available at www.annals.org) (32). Assuming an exponential distribution, we translated these 10-year risks into annual event-related transition probabilities. These probabilities were allowed to change over time to reflect increasing risk for CHD over the time horizon of the analysis.

Because we were interested in primary prevention, we did not simulate or examine the details of a patient's course after a primary, nonfatal event. Instead, we assigned them an increased risk for death, increased costs, and decreased utilities by using data from the literature regarding the average experience of patients after an initial event. The increased relative risk for death after an initial event (**Table**

Context

National guidelines recommend aspirin or statin drugs individually to reduce first coronary heart disease (CHD) events, but there are no guidelines about taking both.

Contribution

The authors used a Markov model to estimate the cost-effectiveness of aspirin, statins, both drugs, or neither in men. In patients with a 10-year risk for CHD of 7.5%, aspirin alone reduced costs and lengthened life compared with no treatment. Adding a statin cost $56 200 per additional quality-adjusted life-year at a 7.5% risk but only $42 500 at a 10% risk.

Cautions

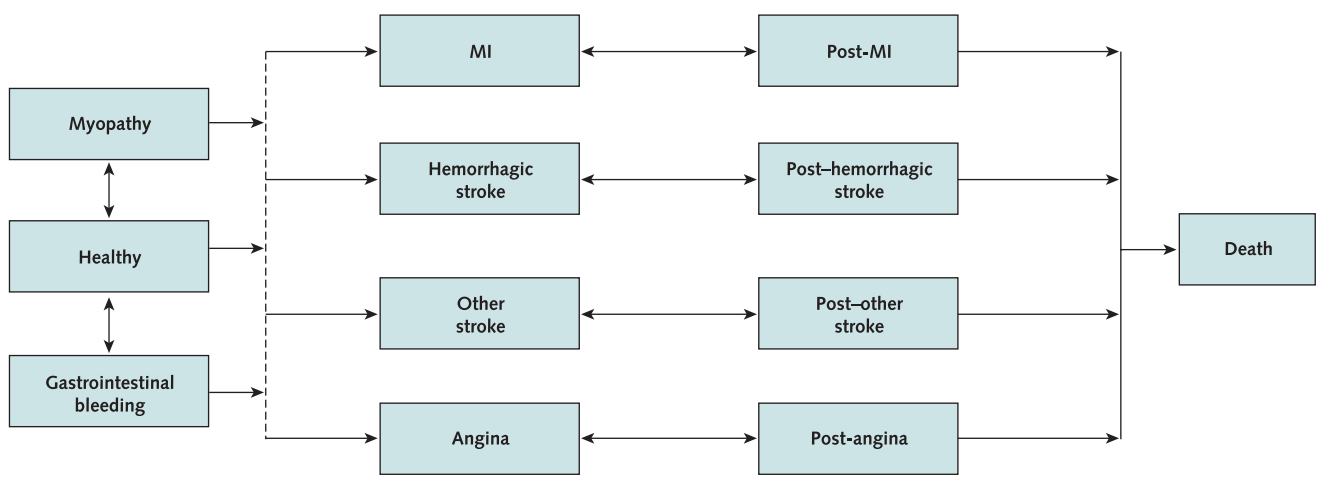
The authors' analysis was limited to men.

Implications

Therapy with aspirin alone is effective and cost-effective in men with an average level of risk for CHD. The addition of a statin is more cost-effective as risk increases.

—The Editors

Figure 1. **General structure of the Markov model.**



Patients enter the model while taking their specified therapy and can progress from healthy to other states, including death, in each cycle. Patients who have aspirin-related gastrointestinal bleeding or statin-related myopathy stop taking the offending medication. Hemorrhagic stroke is modeled separately in the alternate scenario only. MI = myocardial infarction.

Table 1. **Base-Case Estimates and Ranges Used in Sensitivity Analyses**

Parameter (Reference)	Base-Case Estimate (Range)
Relative risk of primary prevention, %	
Myocardial infarction	
Statin (3)	0.70 (0.62–0.79)
Aspirin (9)	0.70 (0.62–0.79)
Stroke	
Statin (10, 11)	0.85 (0.57–1.28)
Aspirin (9)*	1.06 (0.91–1.24)
Angina	
Statin (12)	0.68 (0.49–0.95)
Aspirin†	1.00 (0.80–1.20)
Death from coronary heart disease	
Statin (3)	0.71 (0.56–0.91)
Aspirin (1)	0.87 (0.70–1.09)
Annual risk for adverse events, %	
Myopathy from statins (2, 13)	0.001 (0.0005–0.05)
Death resulting from myopathy (13)	0.00001 (0.000001–0.0001)
Gastrointestinal bleeding from aspirin (14)	0.0007 (0.0004–0.0100)
Death resulting from gastrointestinal bleeding (15)	0.00001 (0.000001–0.0001)
Increase in relative risk for death, %	
After myocardial infarction (16)	3.7 (3.0–4.7)
After angina (16)	3.0 (2.1–4.2)
After stroke (17)	2.3 (1.6–4.6)
Relative risk for all-cause mortality with secondary prevention, %	
Statin (18)	0.79 (0.72–0.86)
Aspirin (19, 20)	0.85 (0.80–0.90)
Annual cost data, $‡	
Drug cost	
Statin (21)	713
Aspirin (21)	16
Myocardial infarction	
Year 1 care (22)	16 085
Ongoing care (22–24)	2576
Stroke§	
Year 1 care (22)	11 161
Ongoing care (23, 25)	1664
Hemorrhagic stroke	
Year 1 care (23, 25)	27 605
Ongoing care (23, 25)	8013
Angina	
Year 1 care (22)	5662
Ongoing care (22, 24)	2460
Gastrointestinal bleeding	
Nonfatal (22)	6928
Fatal (22)	6928
Myopathy-related death†	10 000
Miscellaneous	
Physician visit (25)‖	36.42
Serum lipid level testing (25)¶	30.90
Hepatic function test (25)¶	11.40
Day institutionalized (25)	43.41
Utility data	
Healthy†	1.0
Death†	0
Myocardial infarction and angina	
Year 1 (26, 27)	0.88 (0.80–0.96)
Subsequent years (26, 27)	0.90 (0.80–0.95)
Stroke	
Nondisabling (28)	0.75 (0.60–0.90)
Disabling (28, 29)	0.5 (0.0–0.75)
Gastrointestinal bleeding (year 1) (15)	0.94 (0.88–1.0)
Myopathy (year 1)†	0.97 (0.94–1.0)
Act of taking aspirin or statin (29)	1.0 (0.99–1.0)

* For the base-case scenario, we modeled the effect on all strokes. In the alternate hemorrhagic stroke scenario, we assumed a relative risk of 1.0 for ischemic stroke and assumed that aspirin was associated with an excess annual risk of 20 hemorrhagic strokes per 100 000 users (14, 19, 30).
† Assumed on the basis of results from individual trials.
‡ All costs were varied by 50% in each direction in sensitivity analysis.
§ To estimate stroke costs in the main analysis, we assumed that 70% of initial strokes were nondisabling, 15% partially disabling, and 15% disabling, based on data from Framingham (23). Disabling strokes were also assumed to lead to 180 days of institutionalization.
‖ Healthy patients receiving aspirin therapy were assumed to have 1 visit per year, whereas patients receiving therapy with a statin (alone or in combination with aspirin) were assumed to have 2 visits per year. After a patient had a cardiovascular event, he was assumed to have 4 additional visits per year. We assumed that patients receiving aspirin therapy did not require the additional monitoring tests that were necessary for patients receiving statin therapy.
¶ Compared with patients who were not receiving treatment, patients receiving therapy with a statin, alone or in combination with aspirin, were assumed to require 2 additional hepatic function tests and 1 additional serum lipid level test each year.

1) was drawn from population-based studies in the United Kingdom (12, 16) and applied to the general mortality rates from the U.S. life tables to generate the estimated postevent mortality rates. We modified these event rates by assuming that all patients received optimal secondary prevention.

Adverse Effects

The excess risks for gastrointestinal bleeding with aspirin use and for myopathy with statin use were drawn from systematic reviews of randomized trials and a recent secondary data analysis (2, 26, 27). Risks for gastrointestinal bleeding and myopathy in untreated patients were assumed to be zero so that only treatment-induced adverse events were counted. Because better data were not available, we estimated the risks for death from aspirin-related gastrointestinal bleeding and statin-induced myopathy and varied them in sensitivity analysis. Patients who had nonfatal adverse effects were not given therapy with alternate agents for primary prevention of CHD.

Modeling Stroke

Because many randomized trials of aspirin prophylaxis did not distinguish by stroke type, we had difficulty estimating the precise effect of aspirin on ischemic and hemorrhagic strokes (30). To account for this limitation, we used 2 approaches to model the effect of aspirin on stroke. In the base-case analysis, we followed the approach that was used in a recent meta-analysis (9) by including hemorrhagic stroke and ischemic stroke together in 1 estimate of the effect of aspirin on total stroke (relative risk for stroke with aspirin, 1.06). In an alternate scenario, 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 on the basis of published meta-analyses and that one third of these hemorrhagic strokes would be fatal (19, 30, 33). We conservatively assumed that aspirin had no effect on ischemic stroke (30). The costs and utilities of ischemic stroke and hemorrhagic stroke were also considered separately.

Treatment Efficacy

We used summary relative risk estimates from existing meta-analyses or relative risks from individual trials to estimate the efficacy of aspirin and statin therapy, either alone or in combination, for preventing CHD events (3, 24, 29). Where data were limited, we made conservative assumptions. The efficacy of the combined use of aspirin and statins was assumed to be independent on the basis of data from secondary prevention trials (5). We did not model the effect of aspirin or statins on initial use of revascularization procedures in the absence of a cardiovascular event.

All patients who survived an initial cardiovascular event were assumed to have received secondary preventive therapy with aspirin and a statin or with an alternate agent if they could not tolerate aspirin or statins. The effect of treatments on all-cause mortality was estimated from meta-analyses of secondary prevention trials (18–20).

Costs

We conducted our analysis from the perspective of a third-party payer. State costs (**Table 1**), which were derived from data from the published literature and several recent national databases, are expressed in 2003 dollars.

To estimate the costs during the year in which an event occurred, we estimated acute care costs by drawing on data regarding hospital charges from the Healthcare Utilization Project database and by converting these values to costs. To convert hospital charges to costs, we used the 1999 cost-to-charge ratio value of 0.4501, which was derived from the Medicare Provider Analysis and Review of short-stay hospitals (28). We then used the Medical Consumer Price Index to generate an inflation factor of 1.195, which was applied to the 1999 cost figure to convert 1999 dollars to 2003 dollars (17). In addition to the acute care costs, we assumed that each patient who survived an acute event would also incur one half of the estimated ongoing annual costs of care for the first year. Costs for subsequent years were based on ongoing costs of care that were drawn from the medical literature (22–25).

Drug costs were obtained from the 2003 Red Book average wholesale prices (21). For our base-case analysis, we set the annual statin cost to $730 by averaging the Red Book prices of simvastatin ($922 for 10 mg/d) and lovastatin ($503 for 10 mg/d). The base-case cost of aspirin was based on an annual cost of $16 for Bayer aspirin (Bayer Healthcare LLC, Morristown, New Jersey). The annual cost of generic aspirin was estimated at approximately $6 (21). We varied the costs of each drug over wide ranges in sensitivity analysis.

Table 2. **Men between 45 and 54 Years of Age Who Experienced Coronary Heart Disease Events within 10 Years***

Event	Patients Receiving No Treatment, *n*	Patients Receiving Treatment with Aspirin Alone, *n*	Patients Receiving Treatment with Aspirin plus a Statin, *n*
Myocardial infarction	34 177	25 110	17 819
Stroke (ischemic and hemorrhagic)	7174	7579	6524
Angina	35 890	36 069	24 835
Gastrointestinal bleeding	0	6512	6580
Myopathy	0	0	9388
Death	82 365	80 829	77 404

* Results are derived from a hypothetical cohort of 1 000 000 men with a baseline risk for coronary heart disease of 7.5% over 10 years. Values for patients experiencing myocardial infarction, stroke, and angina are based on first events only.

To check our cost estimates, we compared our derived values with other cost estimates from the recent medical literature (14, 23, 24, 34–39). We also performed 1-way sensitivity analyses in which we varied the estimated costs by 50% in each direction.

Utilities

The utilities associated with different health states, measured on a scale from 0.00 to 1.00, were also drawn from the literature and are shown in **Table 1** (26–29). In most cases, they were estimated by using time-tradeoff techniques that were described in the original studies. Where no data existed, we made estimates and examined a wide range of values in sensitivity analysis. The general disutility from taking a medication was included in the model; however, the utility value was set at 1.00 in the base-case analysis (reflecting no disutility) and was varied in the sensitivity analysis.

Outcome Measures

Our main outcome measure was the cost per quality-adjusted life-year (QALY) gained. For each strategy examined, we derived the incremental cost per QALY gained by calculating the difference between the cost of the scenario of interest and the cost of the comparator scenario, which we then divided by the differences in QALYs between each group.

Sensitivity Analyses

We examined the effect of changing several different parameters in 1-way sensitivity analyses, including the effect of different levels of 10-year risk for CHD (2.5%, 5%, 10%, 15%, and 25%) and different starting ages (55, 65, and 75 years). Younger (<45 years) and older (>75 years) starting ages were not examined because insufficient treat-

Table 3. **Effect of Risk for Coronary Heart Disease on Lifetime Cost–Utility Ratio in Base-Case Analysis***

Variable†	Men at Low Risk (2.5%)			Men at Low to Moderate Risk (5.0%)			Men at Moderate Risk (7.5%)		
	Quality-Adjusted Days Gained, *n*	Cost Difference, $	Cost per QALY Gained (95% CI), $	Quality-Adjusted Days Gained, *n*	Cost Difference, $	Cost per QALY Gained (95% CI), $	Quality-Adjusted Days Gained, *n*	Cost Difference, $	Cost per QALY Gained (95% CI), $
Aspirin alone vs. no therapy	3	79	9800‡	8	−17‡	NA	17	−215‡	NA
Combination therapy with aspirin and a statin vs. aspirin alone	13	5760	164 700‡	21	5611	97 900 (46 700 to 288 800)	35	5397	56 200 (26 100 to 246 276)

* Includes 45-year-old men only. NA = not applicable; QALY = quality-adjusted life-year.
† Initial follow-up period of 10 years; after 10 years, both groups received the trial therapy.
‡ In selected cases where it is not possible to estimate confidence intervals, uncertainty is represented as scatter plots in **Figure 4** and the **Appendix Figures**.

ment efficacy data were available. We also examined the effect of varying individual values for all of our main efficacy, adverse event, cost, and utility estimates by using plausible ranges of values from the literature, 95% CIs, or estimates that varied by as much as 50% in each direction.

In addition to 1-way sensitivity analyses, we also performed probabilistic sensitivity analyses (40). The parameters that we varied in these analyses included relative risks for myocardial infarction, angina, stroke, or death from CHD; relative risk for myopathy with statin therapy or for gastrointestinal bleeding with aspirin; mortality rates after an initial cardiovascular event; and utilities for all health states. We assumed that parameter estimates followed a truncated normal distribution for efficacy and harm data, which were presented as means with 95% CIs. We assumed a triangular distribution for utility data that were presented as means with minimum and maximum values. Analyses were run 1000 times for each relevant scenario, using @Risk software, version 4.5 (Palisade Corp., Newfield, New York). When the full range of values fell into the "more costly and more effective" category, 95% CIs were estimated. In other cases, scatter plots were developed to represent uncertainty.

Role of the Funding Source

Bayer 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 were performed solely by the authors. Bayer received a copy of the draft manuscript but had no role in decisions about submission and revision.

RESULTS

Base-Case Analysis

Compared with no treatment, aspirin treatment for 10 years in 45-year-old men with 10-year risk for CHD of 7.5% increased mean QALYs (17.16 vs. 17.20) at a lower mean cost ($6909 vs. $6694). The addition of a statin to aspirin therapy produced more QALYs gained than aspirin alone but at a higher cost. The cost per additional QALY gained was approximately $56 200 for 10 years of combination therapy. A representative table of intermediate out-

Table 4. **Effect of Risk for Coronary Heart Disease on Lifetime Cost–Utility Ratio in Alternate Model for Hemorrhagic Stroke***

Variable†	Men at Low Risk (2.5%)			Men at Low to Moderate Risk (5.0%)			Men at Moderate Risk (7.5%)		
	Quality-Adjusted Days Gained, *n*	Cost Difference, $	Cost per QALY Gained, $	Quality-Adjusted Days Gained, *n*	Cost Difference, $	Cost per QALY Gained, $	Quality-Adjusted Days Gained, *n*	Cost Difference, $	Cost per QALY Gained, $
Aspirin alone vs. no therapy	−5	302	NA‡	−0.35	201	NA‡	10	−8	NA‡
Combination therapy with aspirin and a statin vs. aspirin alone	NA	NA	NA	NA	NA	NA	35	5394	57 100

* Includes 45-year-old men only. NA = not applicable; QALY = quality-adjusted life-year.
† Initial follow-up period of 10 years; after 10 years, both groups received the trial therapy.
‡ Because aspirin was less effective and more costly than no therapy for men at 2.5% risk, we also compared statin vs. no therapy for 10 years, followed by statin in both groups. The cost per QALY was $152 800. The combination of aspirin and statin was less effective and more costly than statin alone. Aspirin was less effective and more costly than no therapy for men at 5% risk. For the comparison of statin vs. no therapy for 10 years, followed by statin in both groups, the cost per QALY was $87 900. The combination of aspirin and a statin was less effective and more costly than statin alone.

Table 3—Continued

Men at Moderate to High Risk (10%)			Men at High Risk (15%)			Men at Very High Risk (25%)		
Quality-Adjusted Days Gained, *n*	Cost Difference, $	Cost per QALY Gained (95% CI), $	Quality-Adjusted Days Gained, *n*	Cost Difference, $	Cost per QALY Gained (95% CI), $	Quality-Adjusted Days Gained, *n*	Cost Difference, $	Cost per QALY Gained (95% CI), $
24	−362‡	NA	41	−731‡	NA	64	−1284‡	NA
45	5256	42 500 (20 600 to 188 000)	58	5297	33 600‡	109	4593	15 300 (7600 to 71 000)

comes is provided in **Table 2**. The cost-effectiveness ratios for aspirin alone and in combination with statin therapy improved as risk for CHD increased (**Table 3**).

Alternate Hemorrhagic Stroke Model

In our alternate model, we used separate health states for hemorrhagic and ischemic strokes. After setting the excess risk for hemorrhagic stroke at 20 per 100 000 per year and the relative risk for ischemic stroke at 1.0, we found that aspirin treatment was less cost-effective for persons at lower risk levels (**Table 4**). In men with a 10-year risk for CHD of 7.5%, aspirin was more cost-effective than no initial therapy; mean costs were lower ($6880 vs. $6888) and QALYs gained were greater (mean, 17.177 vs. 17.150). However, in men at lower risk (2.5% and 5%), aspirin was more costly and less effective than no therapy.

One-Way Sensitivity Analyses

Starting Age

Differences in the starting age had only a modest effect on cost–utility ratios after the level of risk for CHD was specified (data not shown).

Drug Costs

Model results were sensitive to the costs of statin drugs (**Figure 2**). For the addition of a statin to aspirin therapy, the cost–utility ratio was less than $50 000 per QALY when the annual cost of the statin was less than $632. Statin drugs accounted for more than 70% of the total costs that accrued in this scenario. In comparison, aspirin cost had little effect on the model over its plausible range.

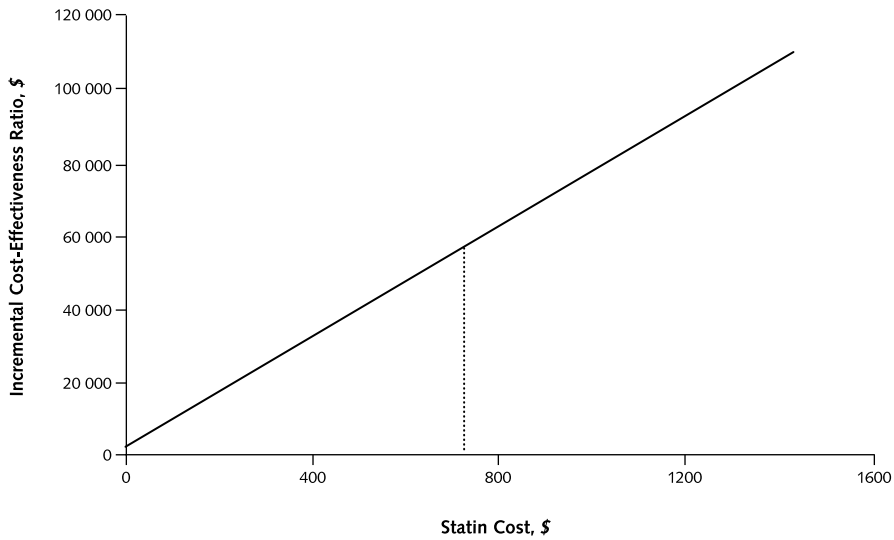
Gastrointestinal Bleeding

The excess rate of gastrointestinal bleeding with aspirin also had an important effect on the cost-effectiveness ratio for aspirin therapy. **Figure 3** shows the effect of varying the annual excess incidence of gastrointestinal bleeding for moderate-risk patients (10-year risk for CHD of 7.5%) who were taking aspirin. Aspirin remained more effective than no therapy until the annual risk for gastrointestinal bleeding exceeded 4.9%.

Table 4—Continued

Men at Moderate to High Risk (10%)			Men at High Risk (15%)			Men at Very High Risk (25%)		
Quality-Adjusted Days Gained, *n*	Cost Difference, $	Cost per QALY Gained, $	Quality-Adjusted Days Gained, *n*	Cost Difference, $	Cost per QALY Gained, $	Quality-Adjusted Days Gained, *n*	Cost Difference, $	Cost per QALY Gained, $
17	−161	NA‡	34	−533	NA‡	58	−1125	NA‡
45	5252	43 100	57	5294	33 900	109	4592	15 500

Figure 2. **Effect of annual statin cost on cost-effectiveness for the combination of aspirin and a statin versus aspirin alone.**



Statin cost is expressed in 2003 dollars. Base-case value is shown with the dotted vertical line.

Hemorrhagic Stroke

With our alternate model, we varied the excess risk for hemorrhagic stroke with aspirin therapy for patients with a 10-year risk for CHD of 7.5%. We found that aspirin became less effective than no therapy when the annual risk for hemorrhagic stroke was greater than 45 per 100 000 (0.045%).

Disutility of Taking Medication

In our base-case analysis, we did not attribute reduced utility to the act of taking a medication daily. If persons with a 10-year risk for CHD of 7.5% who take aspirin are assumed to have even small reductions in utility (<0.9975) from the burden of taking a pill each day, aspirin becomes less effective, but remains less costly, than no therapy.

Other Variables

Our 1-way sensitivity analyses found only small changes in cost-effectiveness ratios when other factors (including treatment efficacy, risks for myopathy or for death after an initial event, and other costs and utilities, as shown in **Table 1**) were varied across plausible ranges.

Probabilistic Sensitivity Analysis

Figure 4 depicts the results of a probabilistic sensitivity analysis of the cost-effectiveness of aspirin compared with no treatment for patients with a 10-year risk for CHD of 7.5%. In the base case, 91% of the results fall within the cost-saving quadrant (aspirin is less costly and more effective). Additional scatter plots and selected cost-effectiveness acceptability curves for different risk levels are provided (**Appendix Figures 1** to 7, available at www.annals.org).

DISCUSSION

We found that initial use of aspirin for 10 years was both more effective and less costly than no treatment for primary prevention of CHD events in middle-aged men with a 10-year risk for CHD of 7.5% or greater. In the base case, the addition of a statin to aspirin therapy had a cost per QALY gained of $56 200 when the 10-year risk was 7.5% and $33 600 when the 10-year risk was 15%. The results of our analysis were sensitive to the costs of statins; when the annual cost of the statin is less than $633, its addition to aspirin therapy has a cost per QALY of less than $50 000 for men with a 10-year risk of 7.5%.

Although aspirin was both more effective and less costly than no therapy in the base case, the discounted mean QALYs gained (about 15 days) and dollars saved ($215) were small in magnitude. It is important to consider the effect of uncertainty in key parameters in the model. Increasing the excess risk for gastrointestinal bleeding with aspirin use above base-case values or modeling an excess risk for hemorrhagic stroke separately reduced the cost-effectiveness of aspirin. For example, when we modeled hemorrhagic stroke separately, aspirin was less effective and more costly than no therapy for men with a 10-year CHD risk of 5% or less.

Assuming a modest or greater disutility from taking a pill each day also made aspirin or statins less effective than no treatment. In the case of aspirin, if the patient had a utility level of less than 0.9975 for taking the pill, aspirin became less effective than no treatment but remained less costly. Such a level would be similar to a patient's willingness to give up 3.6 minutes per day to avoid taking aspirin. To date, little empirical evidence is available to help pa-

tients determine their disutility for routine preventive care tasks.

Our analysis was robust to reasonable variation of most other variables during 1-way sensitivity analysis, including variation in the efficacy of the drugs used to prevent CHD events. Our probabilistic sensitivity analysis suggested that the collective uncertainty around our base-case utility, adverse event, and efficacy estimates did not threaten the validity of the results for the effect of aspirin compared with no therapy; the CIs for the same estimates for the addition of statins were wider, particularly at lower risk ranges.

The U.S. Preventive Services Task Force and the American Heart Association advise physicians to consider aspirin therapy for patients with a 10-year risk for CHD of greater than 6% and 10%, respectively (4, 7). Our results provide support for these recommendations in men. For middle-aged men with a 10-year risk of 7.5% or greater, aspirin was more effective and less costly than no therapy and can be recommended. At lower risk levels, however, we found that the effectiveness of aspirin was dependent on how the risk for stroke was modeled. In our alternate scenario that modeled hemorrhagic stroke explicitly, aspirin appeared less effective and more costly than no therapy for men with a 10-year risk for CHD of 5% or less. Consequently, we believe that aspirin should not be routinely recommended for men at or below these risk levels.

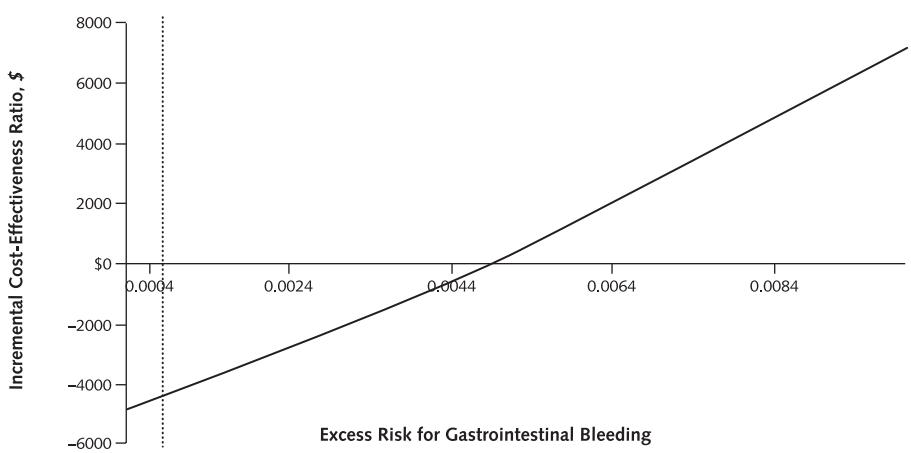
Previous analyses, including our own, that examined the proper threshold for recommending aspirin relied on relatively crude analyses to balance benefits and harms because better information was not available (1, 9). For example, Sanmuganathan and colleagues (9) suggested that aspirin was warranted for patients with a 10-year risk for CHD of greater than 15%; this recommendation appeared to be based on the level at which the number of myocardial infarctions prevented exceeded the number of serious bleeding events induced. However, the short- and long-term consequences of hemorrhagic stroke, myocardial infarction, and gastrointestinal bleeding are not equal at this level. Our analysis accounts for these differences and has identified a lower threshold.

Our results for the comparison of aspirin with no treatment are generally consistent with published decision analyses (15, 41), a cost-effectiveness analysis of aspirin (42), and a recent economic analysis that reported cost per event prevented but not cost-effectiveness (43). Troche and colleagues (44) considered the cost-effectiveness of aspirin and statin therapy but did not report a specific cost-effectiveness ratio. To our knowledge, this analysis is the first to report explicitly the cost-effectiveness of the combined use of statin and aspirin for primary CHD prevention.

Our analysis has several limitations. Although our model is based on the best available clinical information, several of the parameters that we used had only limited empirical supporting data and are therefore subject to error. We attempted to control for this possibility, which is inherent in modeling studies, by performing extensive sensitivity analyses (including probabilistic sensitivity analyses) to test our assumptions. In some cases, particularly in the case of patients at low risk, additional empirical research is needed to better measure such important parameters as the risk for hemorrhagic stroke and the disutility of daily medication use.

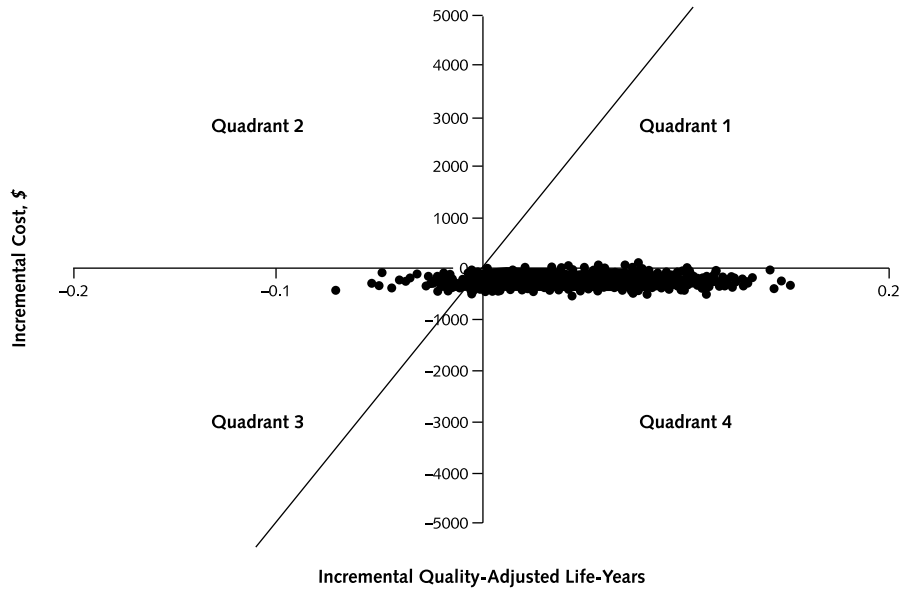
We chose to use a Markov model instead of a more complex simulation model to improve transparency and interpretability and because it is not clear that more complex models necessarily yield more informative results. Because we are interested in primary prevention, we did not

Figure 3. **Effect of the annual excess risk for gastrointestinal bleeding with aspirin on the cost–utility ratio for aspirin versus no treatment.**



Base-case value is shown with the dotted vertical line. Cost–utility ratios below $0 per quality-adjusted life-year represent the range over which aspirin is more effective and less costly.

Figure 4. **Results of probabilistic sensitivity analysis for men with a 10-year risk for CHD of 7.5% (base case): aspirin versus no treatment.**



Plot of incremental costs versus incremental quality-adjusted life-years for aspirin versus no treatment; the diagonal line represents the incremental cost-effectiveness ratio of $50 000. Individual dots represent results for each of 1000 iterations of the model; quadrant 1 contains 1.80% of iterations, quadrant 2 contains 0.00%, quadrant 3 contains 7.20%, and quadrant 4 contains 91.00%.

model the detailed course of patients after their initial events. Instead, we used mean estimates of cost, survival, and utility after cardiovascular events and applied optimal secondary prevention to all patients.

Our model does not capture all of the possible beneficial or harmful effects of each drug. For example, we chose not to attempt to model the effect of aspirin or statins on cancer risk, dementia, or osteoporosis because the data supporting such effects are not as strong as the data for the main outcomes we chose to model. In the case of beneficial effects, the effect on CHD is likely to be a much more important determinant of cost-effectiveness than the effect on such outcomes as colon cancer (45). We did not model peptic ulcers separately, choosing instead to incorporate their consequences within the outcome of gastrointestinal bleeding. We also did not include dyspepsia or minor bleeding as outcomes or headache prevention or pain relief as benefits. We used a fixed risk for gastrointestinal bleeding with aspirin that was drawn from mostly middle-aged trial participants. Risk for bleeding increases with age; therefore, the aspirin treatment threshold may be higher for older patients at any given level of risk for CHD (41). We did not model a discontinuation rate for statins related to elevated liver enzymes; doing so would slightly decrease the cost-effectiveness of statins depending on the threshold for withdrawing the drug and on whether a rechallenge was used (46).

We did not examine other effective options for reducing risk for CHD, such as smoking cessation, hypertension treatment, and counseling to increase physical activity. Because these treatments have benefits that go beyond reducing the risk for CHD, they should be considered independently of the decision to prescribe aspirin or statins for patients in whom they are applicable. Such modeling is beyond the scope of this analysis, although our results should apply generally to patients who have treated hypertension, those who smoke, and those who have CHD risk levels that are similar to those we examined in our analysis. Patients older than 40 years of age who have diabetes are generally at higher risk for CHD and, in most cases, should receive combination therapy with aspirin and a statin (47).

We did not model incomplete adherence for either aspirin or statin use, although we used efficacy estimates that came from studies that used intention-to-treat analyses and therefore incorporated some of the effect of incomplete adherence. The actual benefits of therapy with aspirin and statins will be lower if adherence to prescribed therapies is less than the high levels seen in the trials.

We have presented results for men only in this analysis because less high-quality data are available regarding the efficacy of aspirin and statin therapy for primary prevention of CHD events in women. We plan to conduct separate analyses for women because the estimates of treatment efficacy are different and the amount of uncertainty is greater (48). The recent publication of the Women's Health Study (49), which identified a different pattern of effect for women who take low-dose aspirin for prevention of CHD events, will help inform such an analysis.

The use of aspirin and statins for primary prevention is currently far below optimal levels, despite the proven efficacy of these drugs. One recent study found that only 30% of patients with intermediate CHD risk (2 or more risk factors but no history of diabetes or previous cardiovascular event) reported regular aspirin use (50). Consequently, providers and payers should consider promoting the use of these preventive therapies among moderate- and high-risk populations. Rational use of these therapies can be improved if providers assess risk for CHD in all middle-aged and older adults and in younger adults with additional risk factors, as recommended by the American Heart Association (4). Several tools are available to perform such calculations in routine practice; one such tool, Heart to Heart, is available at www.med-decisions.com. The risk levels used in this tool and in our current analysis are for total CHD events; some risk calculators, such as the one found at the National Heart, Lung, and Blood Institute Web site, present only risk for myocardial infarction and death and therefore cannot be applied directly to our findings (51). Because we used total risk for CHD, we believe our findings support aspirin use in men with a 10-year risk for CHD of 7.5% or greater and combination therapy with aspirin and a statin when the risk is greater than 10%.

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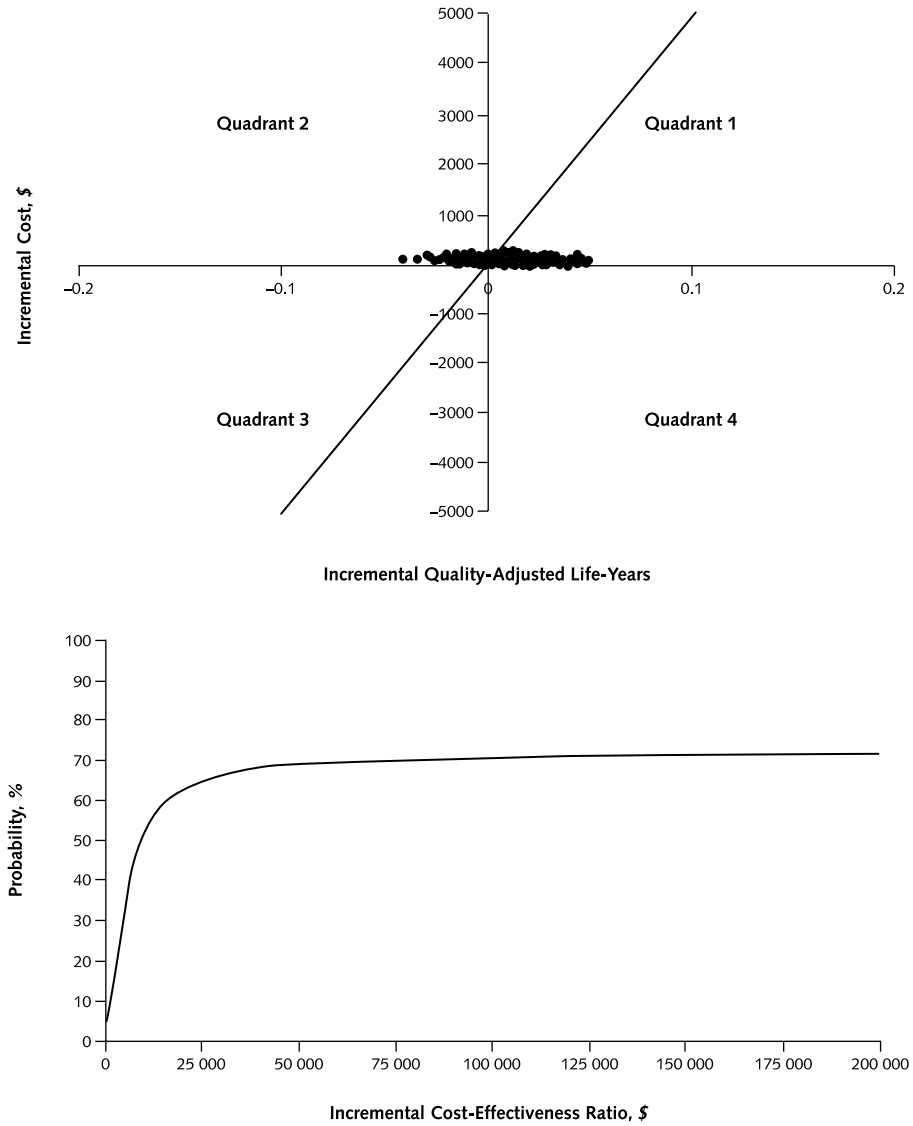
Collection and assembly of data: S. Earnshaw.

Appendix Table. **Sample Baseline Characteristics of 45-Year-Old Men by Risk Level***

10-Year Risk for Coronary Heart Disease, %	Systolic Blood Pressure, *mm Hg*	Serum Total Cholesterol Level, *mmol/L (mg/dL)*	Serum High-Density Lipoprotein Cholesterol Level, *mmol/L (mg/dL)*
2.5	120	3.5 (135)	1.2 (45)
5	120	4.4 (170)	1.0 (40)
7.5	120	6.2 (240)	1.0 (40)
10	120	5.7 (220)	0.8 (30)
15	120	8.1 (313)	0.8 (30)
25	140	9.0 (350)	0.6 (25)

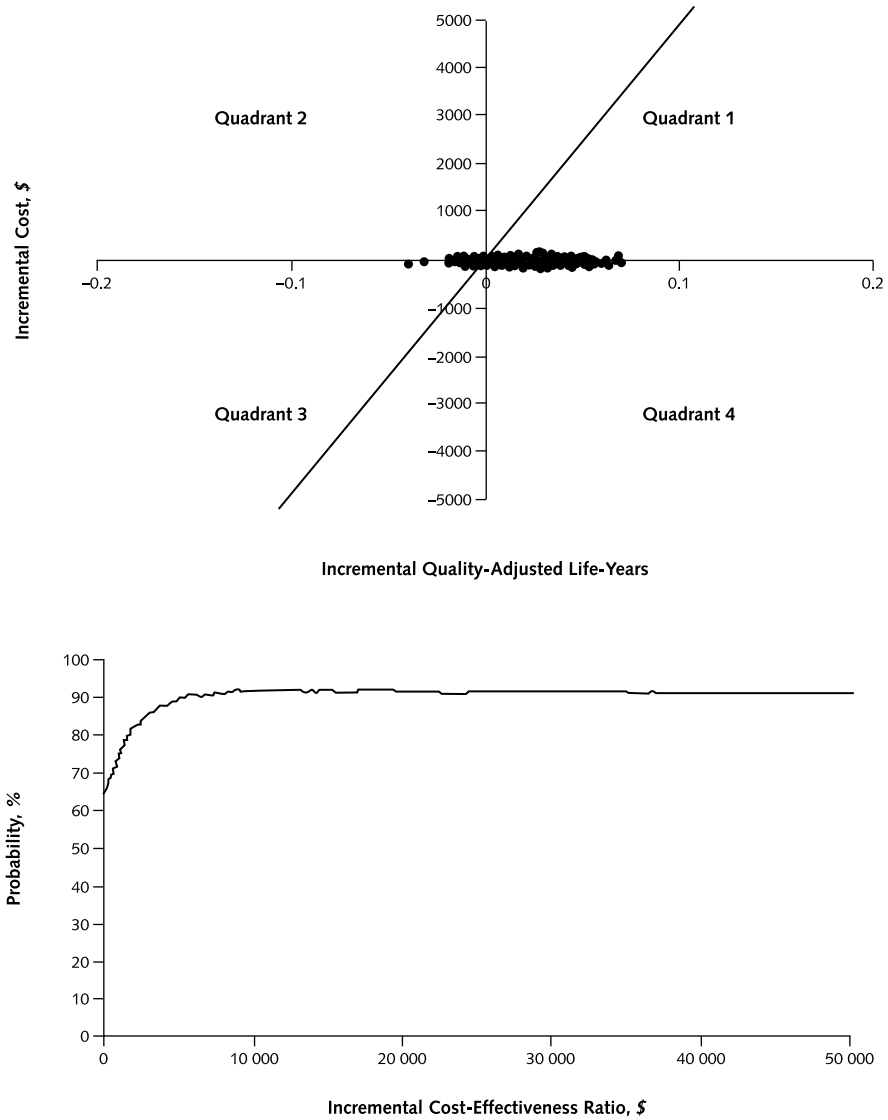
* All patients were nonsmokers with no history of diabetes.

Appendix Figure 1. **Results of probabilistic sensitivity analysis for men with a 10-year risk for CHD of 2.5%: aspirin versus no treatment.**



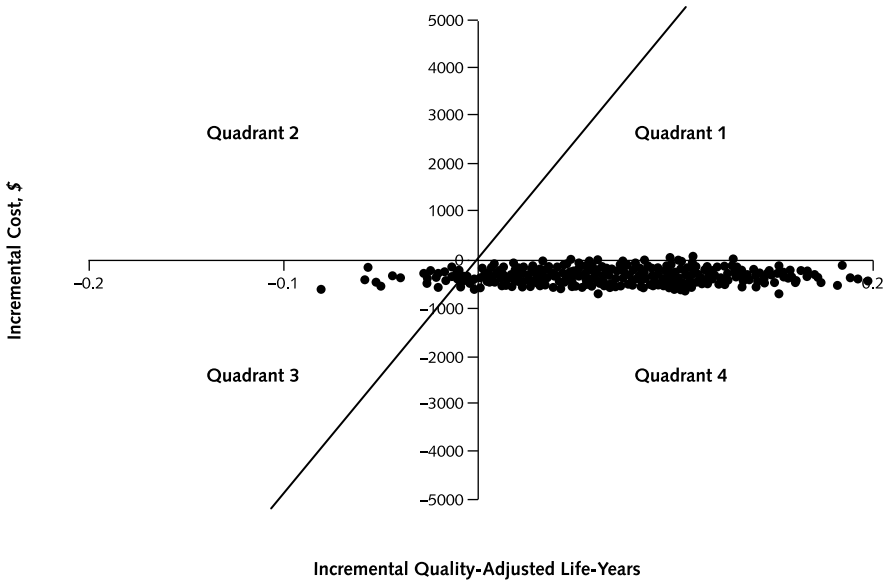
Top. Plot of incremental costs versus incremental quality-adjusted life-years for aspirin versus no treatment; the diagonal line represents the incremental cost-effectiveness ratio of $50 000. Individual dots represent results for each of 1000 iterations of the model; quadrant 1 contains 69.80% of iterations, quadrant 2 contains 25.10%, quadrant 3 contains 1.20%, and quadrant 4 contains 3.90%. **Bottom.** Cost-effectiveness acceptability curve for aspirin versus no treatment.

Appendix Figure 2. **Results of probabilistic sensitivity analysis for men with a 10-year risk for CHD of 5%: aspirin versus no treatment.**



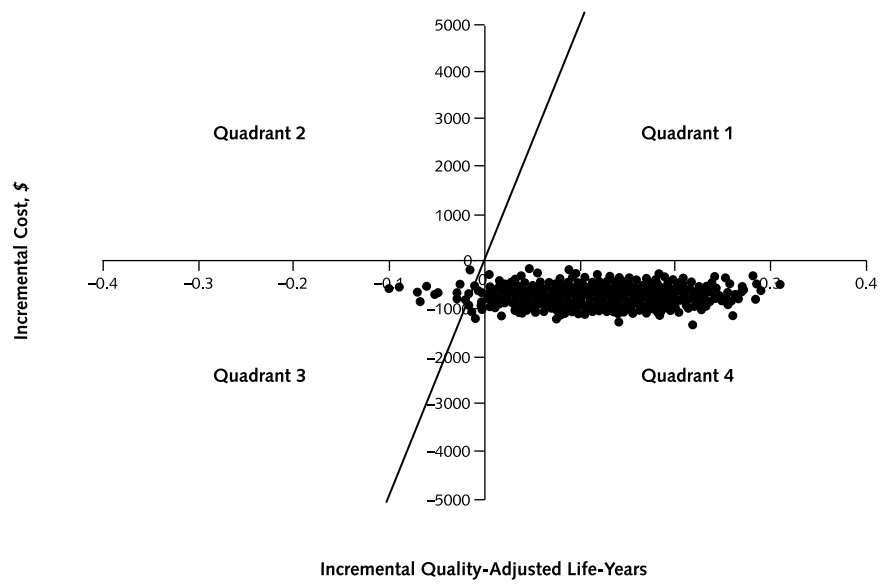
Top. Plot of incremental costs versus incremental quality-adjusted life-years for aspirin versus no treatment; the diagonal line represents the incremental cost-effectiveness ratio of $50 000. Individual dots represent results for each of 1000 iterations of the model; quadrant 1 contains 32.80% of iterations, quadrant 2 contains 3.40%, quadrant 3 contains 6.50%, and quadrant 4 contains 57.30%. **Bottom.** Cost-effectiveness acceptability curve for aspirin versus no treatment.

Appendix Figure 3. **Results of probabilistic sensitivity analysis for men with a 10-year risk for CHD of 10%: aspirin versus no treatment.**



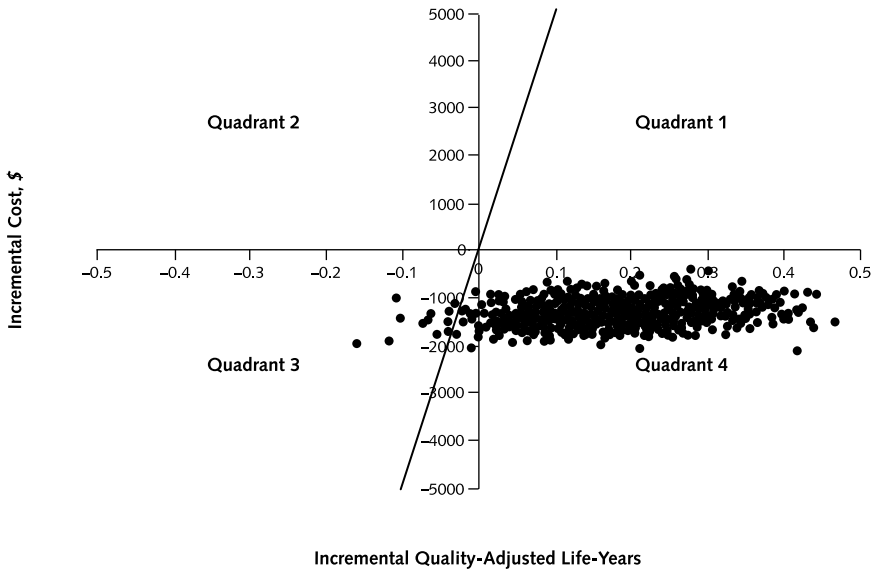
Plot of incremental costs versus incremental quality-adjusted life-years for aspirin versus no treatment; the diagonal line represents the incremental cost-effectiveness ratio of $50 000. Individual dots represent results for each of 1000 iterations of the model; quadrant 1 contains 0.3% of iterations, quadrant 2 contains 0.0%, quadrant 3 contains 4.6%, and quadrant 4 contains 95.1%.

Appendix Figure 4. **Results of probabilistic sensitivity analysis for men with a 10-year risk for CHD of 15%: aspirin versus no treatment.**



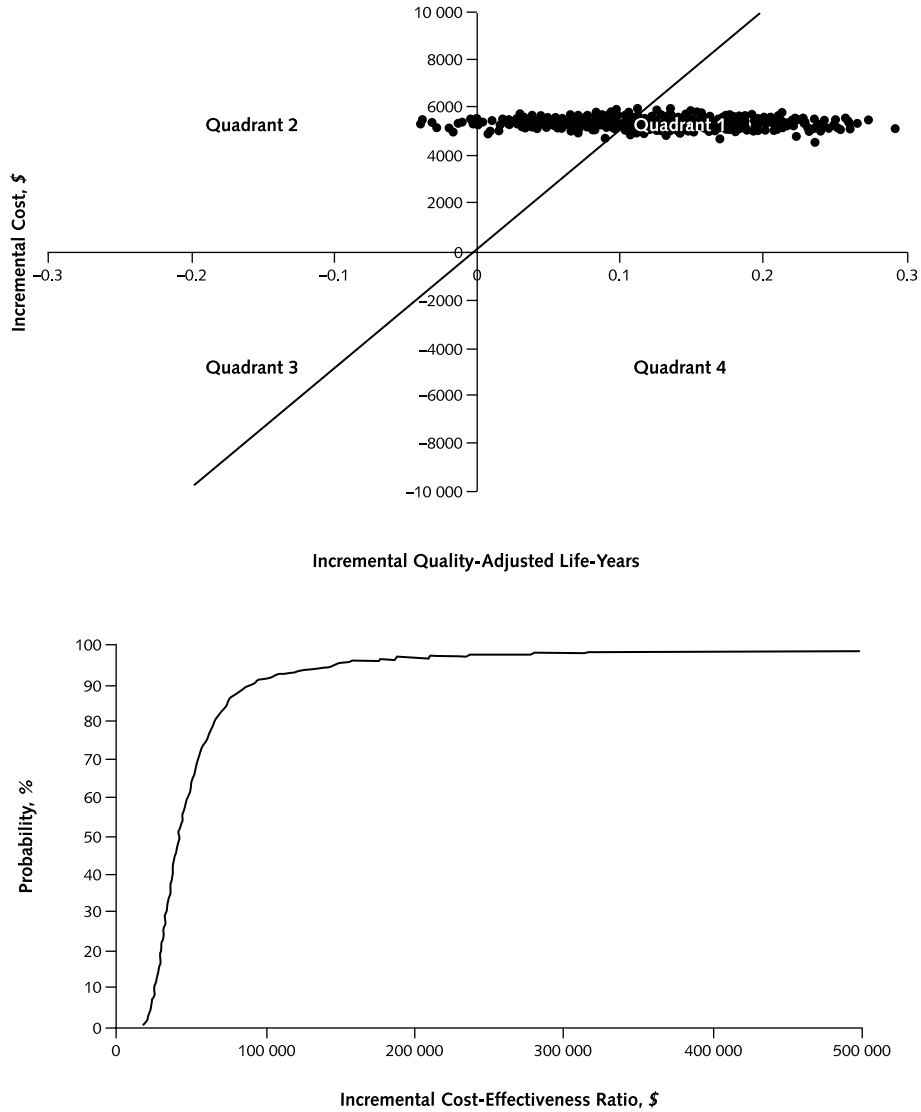
Plot of incremental costs versus incremental quality-adjusted life-years for aspirin versus no treatment; the diagonal line represents the incremental cost-effectiveness ratio of $50 000. Individual dots represent results for each of 1000 iterations of the model; quadrant 1 contains 0.0% of iterations, quadrant 2 contains 0.0%, quadrant 3 contains 2.8%, and quadrant 4 contains 97.2%.

Appendix Figure 5. **Results of probabilistic sensitivity analysis for men with a 10-year risk for CHD of 25%: aspirin versus no treatment.**



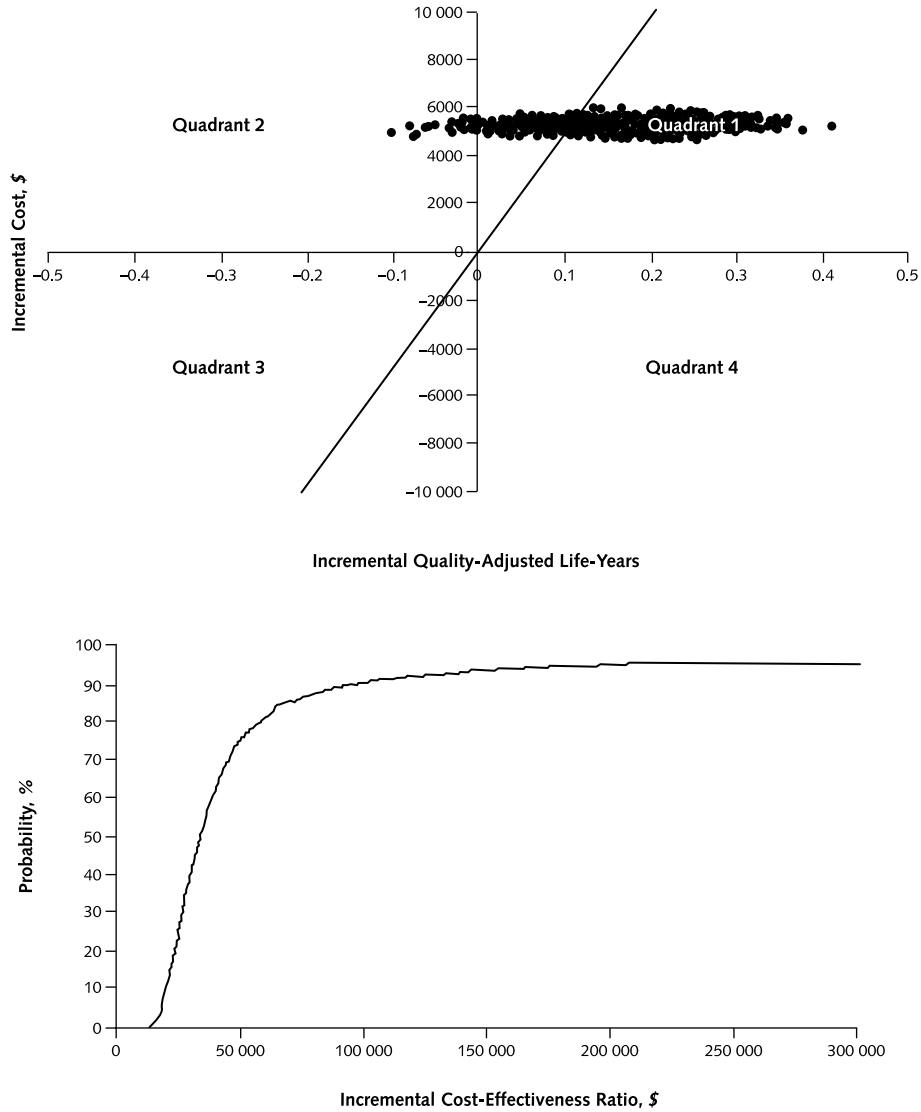
Plot of incremental costs versus incremental quality-adjusted life-years for aspirin versus no treatment; the diagonal line represents the incremental cost-effectiveness ratio of $50 000. Individual dots represent results for each of 1000 iterations of the model; quadrant 1 contains 0.0% of iterations, quadrant 2 contains 0.0%, quadrant 3 contains 2.8%, and quadrant 4 contains 97.2%.

Appendix Figure 6. **Results of probabilistic sensitivity analysis for men with a 10-year risk for CHD of 10%: aspirin plus statin versus aspirin alone.**



Top. Plot of incremental costs versus incremental quality-adjusted life-years for combination therapy with aspirin and a statin versus aspirin alone; the diagonal line represents the incremental cost-effectiveness ratio of $50 000. Individual dots represent results for each of 1000 iterations of the model; quadrant 1 contains 98.9% of iterations, quadrant 2 contains 1.1%, quadrant 3 contains 0.0%, and quadrant 4 contains 0.0%. **Bottom.** Cost-effectiveness acceptability curve for combination therapy with aspirin and a statin versus aspirin alone.

Appendix Figure 7. **Results of probabilistic sensitivity analysis for men with a 10-year risk for CHD of 15%: aspirin plus statin versus aspirin alone.**



Top. Plot of incremental costs versus incremental quality-adjusted life-years for combination therapy with aspirin and a statin versus aspirin alone; the diagonal line represents the incremental cost-effectiveness ratio of $50 000. Individual dots represent results for each of 1000 iterations of the model; quadrant 1 contains 97% of iterations, quadrant 2 contains 3%, quadrant 3 contains 0%, and quadrant 4 contains 0%. **Bottom.** Cost-effectiveness acceptability curve for combination therapy with aspirin and a statin versus aspirin alone.