

**Aspirin for the Primary Prevention of Cardiovascular Disease: Technical Report
Prepared for the National Commission on Prevention Priorities**

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PLEASE NOTE: This report reflects estimates based on the 2002 recommendation of the USPSTF and available evidence through August 2004. The estimates in this report reflect the numbers that were used to produce the NCPP ranking published in 2006. Both the USPSTF recommendation and the estimates below primarily reflect evidence of effectiveness in men. Recent evidence indicates that aspirin may have differential effects in men and women with respect to CHD and strokes. In addition, new data have been published that allow more precise estimates of burden in the absence of counseling by stratifying on CHD risk status and using updated estimates of current aspirin counseling and use. See, for example Pignone M et al. Aspirin use among adults aged 40 and older in the United States: results of a national survey. *Am J Prev Med.* 2007 May;32(5):403-407; Ajani UA, et al. Aspirin use among U.S. adults: Behavioral Risk Factor Surveillance System. *Am J Prev Med.* 2006 Jan;30(1):74-7; and Fox CS, et al. Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999: the Framingham Heart Study. *Circulation.* 2004 Aug 3;110(5):522-7. Epub 2004 Jul 19. Daily aspirin use is more common in individuals at risk for CHD, and therefore estimates of the burden of disease in the absence that is based on a stratified analysis will be higher. This would lead to slightly improved CPB and CE estimates but no change of scores. However, if use data stratified on CHD risk were used to estimate the marginal improvement of increasing aspirin above current rates, CPB and CE would be less favorable because those at higher risk for CHD are more likely to already be using daily aspirin. Finally, CHD mortality rates continue to decline. As a result, primary prevention has less impact. Using the most current estimates of CHD burden would make CPB and CE slightly less favorable, but would not reduce their scores in the ranking. In the time since the ranking was released, we have incorporated these new data in secondary analyses to answer specific questions for decision-making, but have not updated the estimate for CPB and CE as used in the preventive services ranking.

A. USPSTF Recommendation

The U.S. Preventive Services Task Force (USPSTF) strongly recommends that clinicians discuss aspirin chemoprevention with adults who are at increased risk for coronary heart disease (CHD). Discussions with patients should address both the potential benefits and harms of aspirin therapy (A recommendation).¹ The USPSTF found good evidence that aspirin decreases the incidence of coronary heart disease in adults who are at increased risk for heart disease. They also found good evidence that aspirin increases the incidence of gastrointestinal bleeding and fair evidence that aspirin increases the incidence of hemorrhagic strokes. The USPSTF concluded that the balance of benefits and harms is most favorable in patients at high risk of CHD (5-year risk of greater than or equal to 3%) but is also influenced by patient preferences.

B. Identification of Population at Risk, Discussion Intervals and Aspirin Dosage

The USPSTF recommends clinicians discuss aspirin chemoprevention for adults at increased risk for coronary heart disease (CHD). This population includes men older than 40 years, postmenopausal women, and younger people with risk factors for heart disease (e.g. smoking, diabetes, or hypertension). The USPSTF determined that the optimal timing for discussion of aspirin therapy, the frequency of these discussions, and the optimal dose of aspirin for chemoprevention are unknown.

C. Literature Search and Abstraction

C.1 Effectiveness Literature

We conducted a Level 1 literature search² for the effectiveness of aspirin in the primary prevention of cardiovascular events. We searched PubMed from January 1992 through August 2004 identifying 1,100 articles. As a result of this search and review of references in these articles, we identified a total of 57 articles for potential abstraction.³⁻⁵⁹

In order for an article to be abstracted, it had to have a control/comparison group, analyze primary prevention of cardiovascular events, and include fatal and/or nonfatal cardiovascular events as outcomes. Fifteen articles, examining the effectiveness of aspirin therapy for the primary prevention of cardiovascular events, met these criteria for abstraction.^{9-11;16;20;29;34;43;45;48;52;54;56-58}

C.2 Cost-effectiveness Literature

We performed Level 1 and Level 2 searches² to identify cost-effectiveness studies and 91 articles were identified in PubMed between January 1, 1992 through March 1, 2005. As a result of this search and review of references in these articles, we identified a total of 13 articles for potential abstraction.⁶⁰⁻⁷² However, none of the cost-effectiveness articles were abstracted because they were either studies that were conducted in non-U.S. populations evaluating costs in non-U.S. dollars,^{60;64-69} or were not cost-effectiveness studies of primary prevention, but rather addressed the secondary prevention of cardiovascular events.^{61-63;70-72}

D. Clinically Preventable Burden Estimate

Conceptually, clinically preventable burden (CPB) is the burden addressed by the service multiplied by the effectiveness of the service. Table 1 shows the summary calculations for CPB. Some of the data points in Table 1 are estimates from the literature and others are calculated based upon other data in the table. The “Data Source” column in Table 1 shows either the reference for the corresponding data point or the formula used to calculate the data point. The letters in the formulas refer to the row labels (leftmost column) for the data on which the calculation is based. The “Base Case” column shows the best available estimate for each variable that was used in our calculation of CPB, and the “Range” column shows the range over which the point estimates were varied in our sensitivity analysis.² We created additional tables (not shown) to summarize the evidence and perform supporting calculations. The contents of these tables are described below.

D.1 Burden of Disease:

D.1.1. Coronary Heart Disease Mortality: Rows a1 – a4.

CPB is based on delivery of the service to a one-year U.S. birth cohort (defined in all of our studies as 4 million live births) over the age range recommended by the USPSTF for the service.

The estimates of CHD mortality and CHD hospitalizations (below) were calculated for all individuals above the age of 20. All women above the age of 50 and all men above age 40 were considered to be at risk for heart disease.¹ The relatively small number of cardiovascular events in younger age groups (men younger than 40 years and premenopausal women) is likely to occur in individual that are at high risk of cardiovascular events. For example, Khot and colleagues⁷³ reported that 80% to 90% of patients with CHD have one of four conventional risk factors, namely cigarette smoking, diabetes, hyperlipidemia or hypertension. Thus including CHD

mortality and hospitalization for all individuals above the age of 20 year is an acceptable approximation of the disease burden for all individuals at higher risk.

CHD mortality was estimated from 1998 death rates data using the CDC Wonder engine⁷⁴ and ICD-9 codes 410 to 414. Whenever U.S. population estimates were needed for calculations, the 2000 census data were used.⁷⁵ The number of CHD deaths in a birth cohort of 4 million individuals was estimated for persons 20 years and older, stratified by 5 or 10-year age groups, as available in the mortality data tables. By applying the age-specific death rate to the birth cohort of 4 million, the total CHD mortality was estimated to be 817,949 (row a1).

This estimate reflects cumulative (lifetime risk) CHD deaths among persons at increased risk in a birth cohort given current aspirin counseling practices. To estimate the total value of aspirin counseling, we first predicted what the burden would have been in the absence of aspirin counseling by adjusting for current aspirin use rates. We used an analysis of the 1999 Behavioral Risk Factor Surveillance System (BRFSS) survey in people over the age of 40 years for their use of aspirin, which found that 24.5% (row a2) are currently using aspirin either daily or every-other-day.⁷⁶ Because data on the delivery rates of aspirin counseling are not available, we assumed that all aspirin use of this frequency was attributable to physician counseling. As a result, we may have slightly overstated burden of disease in the absence of counseling.

The efficacy estimate used in the calculation shown for row a3 is explained below in section D.2. Using this calculation, we obtained an estimate of the predicted mortality from CHD among individuals in a birth cohort in the absence of aspirin counseling of 882,838 deaths (row a4).

D.1.2. Coronary Heart Disease Events: Rows a5 and a6.

As a measure of acute CHD events, we used hospitalizations with a first listed diagnosis for CHD from the 2001 National Hospital Discharge Survey.⁷⁷ As with mortality, events were estimated by age group over the lifetime of a birth cohort of 4 million. The nonfatal CHD events (row a5) were adjusted for current aspirin counseling in the same manner as CHD mortality above. The result is predicted lifetime hospitalizations among individuals in the absence of aspirin counseling: 3,361,255 events in a birth cohort of 4 million (row a6).

D.1.3. Congestive Heart Failure Cases: Rows a7 – a9.

The most significant chronic sequela of acute CHD events is congestive heart failure (CHF) as a sequel to acute myocardial infarctions (MIs). Approximately 34% of MIs result in disabling CHF within 6 years (row a9).⁷⁸ To apply this estimate, we first calculated the lifetime MIs in the absence of aspirin counseling in the same manner as lifetime CHD hospitalizations. This estimate is built upon an estimate of 565,000 annual incident MIs in the current U.S. population.⁷⁹ From this estimate, we calculated an incidence rate that we applied to the years of life lived by a birth cohort of 4 million.⁸⁰ The resulting number of CHF cases as sequela to MIs is 235,472 (row a10). The number of incident MIs was not available by age group. Applying the population average incidence rate for MIs rather than age-specific rates results in an understatement of cases because the age-distribution of years of life lived in the birth cohort is older than the current cross-section.

D.2 Effectiveness of Screening:

The primary distinction we make between efficacy and effectiveness is that effectiveness reflects the level of patient adherence that can be expected in every-day practice, while efficacy

reflects 100% patient adherence.² CPB is based on effectiveness, where patient adherence includes the percent who accept the service once offered and adhere with follow-up treatment or advice to change behavior.

D.2.1 Effectiveness Literature:

We abstracted 15 articles that examined the effectiveness of aspirin in the prevention of fatal and/or nonfatal CHD events.^{9-11;16;20;29;34;43;45;48;52;54;56-58} Seven articles were not included in the calculation of our estimate of effectiveness for the following reasons.^{9;10;16;34;48;52;54} Both Cook et al. articles^{9;10} and the Glynn et al. article¹⁶ were additional analyses of the Physicians' Health Study which is represented in our calculation by an earlier paper.⁵⁸ MacCallum et al. was not used in our calculations because it primarily analyzed the relationship of the international normalized ratio to coronary events in the Thrombosis Prevention Trial.³⁴ Zanchetti and colleagues⁵⁴ performed an analysis of subgroups from the Hypertension Optimal Treatment (HOT) Study. The results were excluded as not generalizable and instead we used the main HOT study results in our calculation.²⁰ Also Waeber et al. examined compliance with aspirin in the HOT study and therefore was not included in our estimate of effectiveness.⁵² The Prevention with low-dose Aspirin of Cardiovascular Disease in the Elderly (PACE) pilot was excluded as it only reported 12 month results.⁴⁸ The remaining 8 articles reported estimates for fatal and/or nonfatal CHD events.^{11;20;29;43;45;56-58} The mean for these estimates was 30% (median is 31%). The mean and median were almost identical for fatal events, non-fatal events, and fatal or nonfatal events. Therefore we used the combined mean of 30% for all events (rows a3 and a12), and also used this estimate in predicting burden of disease in the absence of physician counseling (rows a4,a6, and a8).

D.2.2. Patient Adherence: Row a11.

In the CPB calculation, we differentiated two types of medication non-adherence. First, not all patients will accept treatment when recommended by their physicians. In aspirin chemoprevention, patients need to balance risks and benefits of treatment based on their understanding of the information provided by their physicians and their individual preferences. However, among patients at high risk for CHD, risks of aspirin treatment are outweighed by benefits.⁸¹ Even among those who are allergic to aspirin, desensitization should be considered so that these high risk patients may take advantage of low-dose aspirin.⁸²

A second type of patient non-adherence involves taking less of the medication than directed. Two abstracted articles reported adherence measures.^{48;52} Waeber and colleagues reported results of a sub-study of the HOT study that utilized a Medication Event Monitoring System or MEMS device to record opening and closing of the prescription vial as a measure of medication adherence. The one-year adherence rate was 78.3% for the aspirin group and it was not significantly different from the placebo group (78.5%).⁵² Silagy and colleagues conducted a pilot study with 400 subjects 70 years and older and found that their adherence to aspirin therapy was 87% by pill count.⁴⁸ These results reflect adherence levels of the participants of the aspirin trials, which have employed methods to approximate real life conditions. For example, in the HOT study, participants were provided a 1-year supply of aspirin or placebo and follow-up interactions were minimal at every 6 months. However, participants in the randomized controlled trials (RCTs) that are included in the estimated 30% clinical trial effectiveness were volunteers and, in at least in some trials, were selected by the investigators for high probability of adherence. Therefore, we make a moderate adjustment to trial effectiveness to create an estimate

of adherence in usual practice. We found no long-term observational studies of adherence on which to base this adjustment. We assumed usual practice effectiveness would be 60% of that observed in clinical trials due to lower adherence (row a11). This adjustment is meant to account for both initial refusals to begin aspirin therapy and any difference in continuance between study volunteers and the general population. If aspirin adherence in trials (and reflected in our efficacy estimate) is 80%, then the implicit long-term adherence in our CPB estimate for aspirin is 48% (= 80% x 60%). For comparison purposes, the best available evidence for anti-hypertensives and statins for which costs of medication may be a larger barrier to adherence, indicates that long term adherence is about 40% (see corresponding technical reports of hypertension screening and cholesterol screening).

D.3 Clinically Preventable Burden Estimate:

D.3.1. Years of Life Saved Through Prevented Mortality: Rows a14-a16.

The total number of deaths prevented is equal to the predicted CHD deaths among individuals multiplied by the effectiveness of aspirin counseling. Aspirin counseling would prevent 158,911 deaths (row a14) if periodically offered to individuals at increased risk for coronary heart disease in a birth cohort of 4 million. For each death prevented, we tabulated the years of life saved as the life expectancy for each age⁷⁵ at which the CHD death would have occurred.⁸³ In Table 1 we show the average life-expectancy weighted by the number of deaths per age group (row a15). Multiplying this estimate by the number of deaths prevented yields the same result as the age-by age calculation: 1,448,913 life years saved (row a16).

D.3.2. Quality Adjusted Life Years (QALYs) Saved Through Reduced Morbidity: Rows a17-a23.

Making the same calculation as for CHD deaths prevented, 605,026 hospitalizations with primary discharge diagnosis of CHD would be prevented over the lifetime of the birth cohort (row a17) along with 42,385 cases of CHF due to prevented MIs (row a20). Quality Adjusted Life Years (QALYs) saved were tabulated by multiplying each case by the duration of morbidity and the reduction in quality of life that would have occurred. We assumed an average duration of 3 weeks (.058 years) for hospitalizations (row a19), which is roughly based on reported days of restricted activity for acute conditions.⁸⁴ We applied the CHF duration of 2.3 years (row a22) reported for 'established market economies' in the Global Burden of Disease study.⁸⁵ We used the quality of life reductions of 0.30 and 0.20 for CHD hospitalization and CHF, respectively (rows a18 and a21). These are the standard QALY weights for acute and chronic conditions in the prevention priorities study that are used for all conditions unless available utility scales indicate that quality of life reductions are substantially different.^{80;86} The tabulations yielded 29,969 QALYs saved from reduced morbidity (row a23).

D.3.3. Clinically Preventable Burden Result: Row a24.

CPB is the total of quality adjusted life years saved from mortality and morbidity prevented by offering aspirin counseling for individuals at increased risk for coronary heart disease over the lifetimes in a birth cohort of 4 million individuals: 1,478,881 QALYS saved (row a24).

D.4 Sensitivity Analysis for Clinically Preventable Burden:

In single variable sensitivity analysis, CPB was most sensitive to two variables: the effectiveness of aspirin therapy, and adherence with aspirin therapy in usual practice (rows a3 and a11). For these variables, changing to the levels shown in the 'Range' column in Table 1 increased and decreased CPB by 33%-50%. CPB was moderately sensitive to two other variables: total CHD mortality in the birth cohort, and the average years of life gained per CHD death prevented (rows a1 and a15). Changing these variables to the levels shown in the 'Range' column in Table 1 increased and decreased CPB by 20% in single variable sensitivity analysis.

In multivariate sensitivity analysis, we varied three variables at a time to identify a range of CPB estimates that demonstrates the uncertainty of the base case estimate.^{80:86} Simultaneously changing the three variables to which CPB was the most sensitive (effectiveness of aspirin therapy, adherence with aspirin therapy in usual practice, and the average years of life gained per CHD death prevented) produced the widest range of CPB estimates: 381,900 to 3,205,500 QALYs saved.

E. Cost-effectiveness Estimate

We estimated the cost effectiveness (CE) of screening by adding service costs, cost-savings, and discounting to the estimate of CPB. We estimated CE for the recommended screening ages over the lifetime of a birth cohort of 4 million. We followed our methods for producing consistent estimates of CE across preventive services.^{80:86} These methods are consistent with the 'reference case' of the Panel on Cost-Effectiveness in Health and Medicine.⁸⁷ The methods include use of a 3% discount rate for both costs and health benefits, the exclusion of productivity losses from disease costs, and the exclusion of medical costs that are not related to the conditions prevented by the service. We adjusted all costs to year 2000 dollars.

E.1. Lifetime Costs of Aspirin Use: Rows b2 – b7.

Table 2 is, in effect, a continuation of Table 1 and therefore, we continue with a similar row numbering as Table 1 in Table 2. Row b1 is the number of years of life lived in the target population in a birth cohort of 4 million computed from U.S. life tables.⁷⁵ This estimate was used to simplify calculations using annual costs over the cohort's lifetime.

The costs of aspirin use include physician time to discuss CHD risk factors and the potential benefits and harms from aspirin chemoprophylaxis; the cost of patient time for travel and medical appointment, and the cost of aspirin. We measured the cost of physician time in 10 minute increments based upon a 10-minute evaluation and management office visit for an established patient (CPT4 99219). The cost of this visit was estimated as the average of Medicare reimbursement and the median private sector charges.⁸⁸ However, in the base case we assumed that only 25% of this office visit time is spent on the discussion of aspirin (row b4). We also assumed, in the base case, that annual discussions are needed to maintain the level of adherence that generates the health benefits estimated for CPB. Therefore the estimate of 25% of visit costs was chosen to represent a long term average, not the cost of an initial discussion which may require substantially more time.

To improve consistency across the preventive services included in our study, we used our standard method of valuing time for patients to travel to the clinic and receive the service. We assumed that it takes 2 hours for travel and clinic appointment and we used average hourly earnings plus benefits in 2000⁸⁹ to estimate the value of patient time. The resulting estimate was \$42.32 per office visit in year 2000 dollars (row b3). However, as with the cost of the physician

visit, we assumed that only 25% of this time is attributable to the discussion of aspirin chemoprophylaxis.

The cost of low-dose aspirin can vary widely depending on the choice of brand-name or store-brand and the pill count. In the base case we used an estimate of \$15 per year to represent the average of the choices patients will make (row b6).

The lifetime costs of aspirin chemoprophylaxis (undiscounted) for the entire birth cohort were then simply computed by adding these annual costs and multiplying by the number of years of life in the birth cohort and by adherence as shown in the equation for row b7.

E.2. Treatment Costs of Prevented Illness: Rows b8 – b11.

We estimated the costs of events with hospitalizations using the first year and follow-up disease costs for CHD reported by Russell et al.⁹⁰ We used the first-year costs for non-fatal MIs and unstable angina (both of which include a hospitalization in the first year for 100% of patients), and we weighted these estimates using the relative frequency of inpatient discharges with a first listed diagnosis of MI or angina.⁷⁷ To these costs, we added four years of follow-up costs less the costs of hospital readmissions as estimated by Russell et al. Using this method, the total cost savings assigned to each hospitalization is \$19,931 (row b8), of which \$18,029 occurs in the year of the hospitalization.

Both the first year costs and the follow-up costs include outpatient costs, emergency department costs, and pharmaceuticals. Therefore, applying the first year costs with additional years of follow-up costs to each hospitalization approximates the total costs of care for individuals with CHD. This approximation is accurate if individuals with CHD have a CHD related hospitalization once every 5 years. We have no data to support that frequency.

To estimate the lifetime costs of treatment for CHF, we calculated an average from two cost-effectiveness models of beta-blocker therapy for CHF patients that reported long-term costs in U.S. dollars.^{91;92} Delea et al. reported the predicted lifetime costs of CHF with and without beta-blocker therapy⁹¹ and Cowper et al. reported the predicted 5-year costs with and without beta-blocker therapy.⁹² We use the average of the two rather than the lifetime costs from Delea et al. alone because the 5-year estimates estimated by Cowper et al. are higher than the life-time costs estimated by Delea et al. Both studies reported long-term costs discounted at 3%. For both studies we calculated the average of costs for patients using and not using beta-blockers. For both studies, we ‘took-out’ the 3% discount factor (assuming a median of 3 years discounting) so that we could readily discount costs back to the age of initial cholesterol screening in our CE calculation. Adjusted to year 2000 dollars, the resulting average was \$46,814 (row b9).

E.3. Discounting and Cost Effectiveness Calculation: Rows b12 – b24.

We discounted all costs and benefits to their present value at the age of 20 using a 3% discount rate. Because building year-by-year Markov models for each service in the prevention priorities study is beyond the study scope, we developed alternate discounting techniques as described in our methods technical report.⁸⁰ We used the median year of life lived after age 20 (row b12) to approximate the discount factor for future costs of aspirin and associated physician and patient time.⁷⁵ Using this median year, we applied an appropriate discount factor based upon an annual discount rate of 3% (row b13) from present value tables. Similarly, we used the age distribution of the year of death from CHD and remaining life-expectancy at the age of death to determine a discount factor for years of life saved. We used the age distribution of hospitalizations to determine a discount factor for QALYs saved from hospitalizations and

associated costs. The discount factor for QALYs saved from CHF cases prevented and associated costs was calculated relative to that of hospitalizations in order to reflect the fact that the CHF cases included in the model are sequelae of MIs.

These discounted factors were applied to the relevant cost or health benefit to tabulate discounted costs and QALYs (rows b20 – b22). The CE ratio was calculated as the net discounted costs divided by the discounted QALYs saved (row b24). However, because net costs are negative in the base case, the CE ratio is not defined. Instead, we expressed the base case results as the cost-savings per person in the target population at age 20 (row b23). The model predicted that brief discussions regarding aspirin prophylaxis would generate a discounted lifetime savings of \$514 per person engaged.

E.4. Sensitivity Analysis for Cost Effectiveness

For the purposes of sensitivity analysis, we treated the set of variables that address the discount factors as a single variable (changing the value of each at the same time) to test for the effects of systematic error in measurement. In single-variable sensitivity analysis, CE was found to be most sensitive to two variables – the effectiveness of aspirin therapy and adherence with aspirin therapy in usual practice (rows a3 and a11). For these variables, changing to the levels shown in the ‘Range’ column in Table 1 increased and decreased CE by 60%-90%.

Other variables to which CE was moderately sensitive (19% to 41% change in CE with changes to variables inside their sensitivity analysis ranges) included the number of nonfatal CHD events in a birth cohort, the portion of a 10-minute office visit used for aspirin discussion, the frequency of aspirin discussions, the average annual cost of aspirin, and the corresponding discount factors.

In multivariate sensitivity analysis, several combinations of three of these variables led to changes in CE of over 200% in the positive direction and a single combination led the largest change in the negative direction (-184%). In the positive direction, the largest change (228%) resulted from simultaneously changing the adherence to aspirin therapy in usual practice, the effectiveness of aspirin therapy, and the number of nonfatal CHD events in a birth cohort. In the negative direction, the largest change resulted from simultaneously changing the portion of a 10-minute office visit used for aspirin discussion, frequency of aspirin discussions, and adherence to aspirin therapy in usual practice. These combinations produced our overall range from multiple variable sensitivity analysis that we use as our key indicator of uncertainty of CE in comparing services: net savings of \$1,600 per person counseled to a positive net cost of 11,800 \$/QALYs saved.

F. Scoring

We ranked services in the Prevention Priorities Project based upon scores for CPB and CE rather than point estimates.^{2:80} For each measure, we assigned scores according to the quintile in which the service’s CPB and CE estimates fall among all services included in the study scope. Services having the highest CPB or best cost-effectiveness received a score of 5.

The base-case estimate of 1,478,881 QALYs saved resulted in a CPB score of 5. Sensitivity analysis revealed no scenarios in which CPB would have received a score of anything lower than a 5.

The base-case estimate of lifetime savings of \$514 per person resulted in a CE score of 5. Sensitivity analysis reveals scenarios in which CE would have received a score of 4. At the same time, no scenarios produced CE estimates that were consistent with scores of 3, 2 or 1.

The base case estimates for CPB and CE produced a total score of 10, and the multivariate sensitivity analysis indicated that a total score of 9 is also possible.

G. Limitations

The primary limitation of these estimates is the lack of data on usual adherence with aspirin chemoprophylaxis. For every one percentage point change in adherence, CPB changes one percentage point.

Another limitation of the CPB estimate is that the QALY loss due to disability from CHD events may be an underestimate. CHD event survivors suffer other types of disability in addition to CHF, including arrhythmia and angina pectoris. Only acute episodes of these conditions that result in hospitalizations are captured in our estimate of CPB. CHD event survivors are also more likely to have a stroke and consequently be disabled. Outcomes data for these patients are not well documented and hence the current analysis only included CHF in the calculation. The CHF calculations themselves may be dated due to developments in disease management. In recent years, several landmark clinical trials have provided evidence supporting use of angiotensin-converting enzyme inhibitors, beta-blockers, angiotensin-receptor blockers, and aldosterone blockers in the management of CHF patients.⁹³ Survival rates have improved significantly in the past decade, and the improvement may continue as the evidence disseminates.⁹⁴⁻⁹⁶

The CPB calculation did not include effectiveness of primary prevention of stroke because the effect of aspirin on ischemic stroke versus hemorrhagic stroke appeared to be offsetting. A meta-analysis based on 4 primary prevention aspirin trials showed a non-significant increase in risk of stroke (6%) among aspirin users.⁴⁶ The four studies included in the meta-analysis are the thrombosis prevention trial,⁵⁶ the HOT study,²⁰ British male doctors study,⁴³ and the physicians' health study.⁵⁸ The stroke end point included definite and probable cerebral infarction, cerebral hemorrhage, and stroke of uncertain cause, but not transient ischemic attacks. The authors of the meta-analysis pointed out that the available data only accounted for strokes by the number of events, not severity; hence, we are not able to discern whether aspirin increases risk to hemorrhagic strokes that are more severe than the ischemic strokes it prevents.

Most available data, including the impact of aspirin on strokes, is based on male research subjects. Some research suggests effects may be different for females.

Risk of major gastrointestinal (GI) bleed is not included in the CPB calculation due to low incidence (3 per 1000 over 5 years),⁹⁷ very low mortality (2% of severe bleeds) and short quality of life (QOL) loss from acute phase of internal bleeds.⁴ Aspirin causes higher incidence of moderate and minor bleeds (such as bruising, hematemesis, and melena), but QALY loss due to these bleeding events are minimal relative to QALY loss gained by preventing CHD mortality and events. An estimate of QALY loss due to major GI bleeds (not shown) resulted in less than 1% of the calculated CPB. We calculated that net savings would fall by about \$50 per person if GI complications are included. Because these adjustments do not affect the priority scores or conclusions regarding the value of counseling about aspirin use, we chose to simplify model presentation by excluding them from the base case estimates of CPB and CE.

Table 1. Summary of Clinically Preventable Burden Estimate for Aspirin Chemoprevention				
Row	Variable	Base Case	Data Source	Range for Sensitivity Analysis
	Coronary heart disease deaths in target population			
a1	Total CHD mortality in the birth cohort	817,949	^{74;75}	+/- 20%
a2	% used aspirin regularly	24.5%	⁷⁶	20% to 30%
a3	Efficacy/RRR of drug treatment on CHD deaths	30%	^{11;20;29;43;45;56-58}	20% to 30%
a4	Predicted CHD deaths in absence of aspirin chemoprevention	882,838	a1/(1-a2*a3)	
	Acute coronary heart disease events in target population			
a5	Total nonfatal CHD events in the birth cohort	3,114,203	⁷⁷	+/- 20%
a6	Predicted number of nonfatal CHD events in absence of aspirin chemoprevention	3,361,255	a5/(1-a2*a3)	
	Congestive heart failure cases in target population			
a7	Incident myocardial infarctions in birth cohort	641,661	⁹⁸	+/- 20%
a8	Predicted incident MIs in the absence of aspirin chemoprevention	692,565	a7/(1-a2*a3)	
a9	% nonfatal MI survivors with disabled with CHF	34%	⁷⁸	15% to 55%
a10	CHF cases subsequent to MIs	235,472	a8*a9	
	Effectiveness of aspirin counseling in preventing deaths and events			
a11	Adjustment for usual practice adherence	60%	Assumed	30% to 80%
a12	Efficacy/RRR of drug treatment on CHD deaths	30%	^{11;20;29;43;45;56-58}	20% to 40%
a13	Effectiveness of drug treatment	18%	a11*a12	
	Quality adjusted life years (QALYs) saved mortality			
a14	Number of CHD deaths prevented	158,911	a4*a13	
a15	Average life year gained per of CHD death prevented	9.1		+/- 20%
a16	Number of life years saved	1,448,913	a14*a15	
	Quality adjusted life years (QALYs) saved, morbidity			
a17	Number of nonfatal CHD events prevented	605,026	a6*a13	
a18	Acute QOL reduction per year (CHD) (Acute=0.3, chronic=0.2)	0.3	Assumed	.2 to .4
a19	Average duration of acute illness (nonfatal CHD event) in years	0.058	Assumed	2 to 5 weeks
a20	Number of CHF cases prevented	42,385	a10*a13	
a21	CHF disability QOL reduction per year (CHD) (Acute=0.3, chronic=0.2)	0.2	Assumed	0.1 to 0.3
a22	Average duration of CHF (nonfatal CHD event) in years	2.3	⁸⁵	+/-30%
a23	QALY saved from acute and chronic disease prevented	29,969	a17*a18*a19+a20*a21*a22	
a24	Total QALYs saved (CPB estimate)	1,478,881	a16+a23	

Table 2. Summary of Cost Effectiveness of Aspirin Chemoprevention				
Row	Variable	Base Case	Data Source	Range for Sensitivity

				Analysis
b1	Years of life in target population age range	155,259,280	75	
Costs of aspirin counseling and use				
b2	Cost of office visit	\$43.63	88	+/- 33%
b3	Cost of patient time and travel for office visit	\$42.32	89	+/- 50%
b4	Portion of 10-minute office visit used for aspirin discussion	25%	Assumed	10% to 40%
b5	Frequency of discussions about aspirin (times per year)	1	Assumed	.25 to 2.0
b6	Average annual cost of aspirin taken to prevent heart disease	\$15	Assumed	\$5 to \$25
b7	Life time costs of physician time, patient time, and aspirin, undiscounted	\$4,733,591,854	$b1*((b2+b3)*b4*$ $b5+b6*a11)$	
Cost savings from prevented disease				
b8	Costs of CHD hospitalizations and subsequent care	\$19,931	90	+/- 50%
b9	Lifetime costs of CHF	\$46,814	91;92	+/- 50%
b10	CHD costs prevented	\$12,058,998,860	$a17*b8$	
b11	CHF costs prevented	\$1,984,206,234	$a20*b9$	
Discounting (all discounting to present value at age 20)				
b12	Median year of physician discussion and aspirin use	30	75;99	
b13	Corresponding discount factor for lipid screening and associated office visit	0.41	Present value tables	.36 to .46
b14	Median year of year of life prevented from age 20	55	74;75	
b15	Corresponding discount factor for years of life saved	0.20	Present value tables	.15 to .25
B16	Median year of acute event prevented from age 20	40	75;77	
b17	Corresponding discount factor for CHD morbidity QALYs and costs	0.31	Present value tables	.26 to .36
b18	Median year of chronic disease morbidity prevented from age 20	46	$b16 + 5 +$ $a22*0.5$	
b19	Corresponding discount factor for CHF morbidity QALYs and costs	0.26	Present value tables	.21 to .31
Cost effectiveness calculation				
b20	Discounted costs of physician time, patient time, and aspirin	\$ 1,950,177,169	$b7*b13$	
b21	Discounted savings from prevented events and sequelae	\$ 4,206,186,813	$b10*b17+b11*$ $b19$	
b22	Discounted QALYs	293,314	$a16*b15+(a17*$ $a18*a19)*$ $a15+(a20*a21*$ $a22)*a17$	
b23	Discounted net costs per person at alive at age 20	(\$514)	$(b20-$ $b21+sequelae$ $costs)/$ $(4,000,000*$	

			0.98654)	
b24	Discounted \$/QALY (CE estimate)	(\$7,691)	(b20-b21)/b22	

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