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Original article

Potential economic impact of increasing low dose aspirin usage on CVD in the US

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Abstract

Background:
Cardiovascular disease (CVD) is a leading cause of death in the US and Western Europe, but regular use of preventive low-dose aspirin has proven effective in preventing CVD events. The purpose of this study was to explore the potential economic impact in the US if preventive aspirin usage were to be increased in line with clinical guidelines for primary and secondary prevention.

Methods:
The risk profile of the US population was characterized using NHANES data, and Framingham cardiovascular risk equations were applied to calculate risk for myocardial infarction, angina and ischemic stroke according to age and gender. Primary and secondary patients were considered separately. Using publicly available unit costs, a budget impact model calculated the annual impact of increased preventive aspirin usage considering gastrointestinal bleeding and hemorrhagic stroke adverse events and diminishing aspirin adherence over a 10-year time horizon.

Results:
In a base population of 1,000,000 patients, full implementation of clinical guidelines would potentially prevent an additional 1273 myocardial infarctions, 2184 angina episodes and 565 ischemic strokes in primary prevention patients and an additional 578 myocardial infarctions, and 607 ischemic strokes in secondary prevention patients. This represents a total savings of $79.6 million for primary prevention and $32.2 million for secondary and additional out-of-pocket expense to patients of $29.0 million for primary prevention and $2.6 million for secondary prevention for the cost of aspirin.

Conclusions:
This budgetary model suggests that there is a strong economic case, both for payers and society, to encourage aspirin use for patients at appropriate risk and per clinical guidelines. It also provides an example of how minimizing costs do not necessarily have to imply a rationing of care. Limitations include the exclusion of other CVD interventions in the analysis.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States, accounting for 36.3% of all deaths[1]. Aspirin offers the unique combination of being highly efficacious in preventing CVD events including MI and angina as well as stroke[2–5], has a reasonable adverse event profile compared to other anti-coagulants[6], and is highly affordable at only $18.23 per year[7]. A total of 80 million American adults are experiencing one or more kinds of CVD[8], but preventive aspirin use is suboptimal[9,10] both in patients who have CVD and in patients at risk of developing CVD.

The purpose of this economic model was to determine the potential budget impact of increasing adherence to the guidelines for preventive aspirin use for primary and secondary CVD prevention[11,12] for a population representative of the US, building on previous economic evaluations that have been performed in the US and around the world[13–19]. The estimated economic impact of aspirin is assessed in terms of specific direct and indirect costs.

Methods

Model flow

A cohort model was developed to simulate the events and costs of primary and secondary prevention cohorts for up to 10 years. In both primary and secondary prevention groups, patients at high risk according to guidelines (3% risk over 5 years for primary prevention[12]; all patients experiencing previous CV event or stroke for secondary prevention[11] but not currently taking aspirin) are identified as eligible patients.

Events considered include myocardial infarction, ischemic stroke, angina (primary prevention only), hemorrhagic stroke and gastrointestinal bleeding. Persistence of patients on aspirin was followed. After patients experience events, they are tracked for medical care, institutionalization and mortality. Patients may only experience one event throughout the model time horizon. The model estimates the cost implications of improving aspirin use among high risk CVD patients from the perspective of health care payers. The base case analysis includes direct costs only. The additional out-of-pocket cost to patients for aspirin as well as indirect costs attributable to morbidity and mortality are considered as secondary analyses.

Cumulative costs are considered over a time horizon ranging from one to ten years with ten years considered as the base case.

Primary data inputs are summarized in Table 1 including references.

Risk equations

Risk for CVD was estimated by using the Framingham risk equations[20–23]. The most recent data from the Framingham studies were used wherever possible. The equations for primary prevention risk for CVD events, including both CHD and stroke were derived from the most recent Framingham equations[20]. To separate CHD events into MI, angina and CHD death, the distribution of different types of CHD events[23] was applied to the predicted CHD risks[20]. The risk of secondary events were estimated using published equations for secondary CHD risk estimation[21] and secondary stroke events[22]. Because secondary MI was not reported separately from CHD, sample descriptive statistics were used to determine the ratio of MI over total secondary CHD. Tables A1–A4, published at the *CMRO* website as Electronic Supplementary Data (ESD), present the risk equations used in the model.

Epidemiological data

In the base case, epidemiological data were derived from NHANES (National Health and Nutrition Examination Survey), a national US survey obtained yearly through interview and a physical examination of approximately 5000 subjects selected to be representative of the US population. Variables of interest that were captured include percentage of patients experiencing a previous CVD event, total cholesterol, HDL cholesterol, smoking status, diabetes, systolic blood pressure, and antihypertensive medication. For risk factors required in the Framingham risk equations but not measured in the NHANES data (electrocardiogram, atrial fibrillation, alcohol consumption), the sample means from the Framingham studies were used.

Patients in the NHANES database were stratified according to gender and age groups with the following age categories:18–34, 35–44, 45–54, 55–64, 65–74, and 75+. Risk variables for each age and gender group were estimated using SAS Systems 9.0. The population for the base case was assumed to be a hypothetical cohort of 1,000,000 patients. Limiting the budget impact to specific subpopulations based on USPSF guidelines and other subpopulations based on age, gender and presence of diabetes was tested in a sensitivity analyses.

Risk calculation

The annual risks are calculated for each age and gender cohort from the first to tenth year. Patients age over the 10 year time horizon increasing CVD risk with corresponding increases in mortality, but other cardiovascular risk factors are assumed to be constant within the population. Because the guidelines suggest all patients in the secondary prevention population should consider using aspirin, the mean risks for each age and gender cohort were directly calculated from the NHANES values of the risk factors and Framingham equations. For the primary prevention cohort, however, only a fraction of the population is recommended aspirin based upon risk factors. To simulate this population in the model, means and distributions were calculated for each age and gender cohort using individual level NHANES data. Then for each age/gender cohort, 1000 patients were simulated using a Monte Carlo simulator. The risk of these simulated populations was used to determine the percentage of each cohort that had risk above guideline levels and should be treated with aspirin for primary CVD prevention. This number was corrected

Table 1. Clinical model inputs.

Clinical Input	Mean	Source
Primary Prevention – Male	Efficacy of Aspirin (Relative Risk)	
MI	0.74	Hayden *et al.*, 2002[4]
Angina	0.82	de Gaetano, 2001[5]
Ischemic Stroke	0.97	Eidelman *et al.*, 2003[3]
Primary Prevention – Female	Efficacy of Aspirin (Relative Risk)	
MI	1.02	Ridker *et al.*, 2005[24]
Angina	0.82	de Gaetano, 2001[5]
Ischemic Stroke	0.83	Ridker *et al.*, 2005[24]
Secondary Prevention	Efficacy of Aspirin (Relative Risk)	
Non-fatal MI	0.74	Berger *et al.*, 2008[2]
Non-fatal Stroke	0.75	Berger *et al.*, 2008[2]
All-cause Mortality	0.87	Berger *et al.*, 2008[2]
Primary Prevention	Baseline Aspirin Use (%)	
18–44	13	Stafford *et al.*, 2005[25]
45+	36	Pignone *et al.*, 2007[10]
Of pts taking aspirin, at increased CVD risk	59	Bayer Data on File[26]
Secondary Prevention	Baseline Aspirin Use (%)	
Men and Women	69	Pignone *et al.*, 2007[10]
GI Bleeding		
Age Groups	Incidence (%)	
18–34	0.18	Saini *et al.*, 2008[27]; Laine, 2006[28]; Hernandez-Diaz and Garcia Rodriguez, 2006[29]
35–44	0.20	
45–54	0.25	
55–64	0.38	
65–74	0.60	
75+	0.90	
Hemorrhagic Stroke AEs	0.02	Hart *et al.*, 2000[30]; He *et al.*, 1998[31]
Year	Persistence (%)	
0	100	Shaya *et al.*, 2006[32]; WHO, 2003[33], assumption on functional form
1	90	
2	82	
3	76	
4	71	
5	67	
6	64	
7	61	
8	59	
9	57	
10	56	
CVD Event	Institutionalization Rate Following CVD Event (%)	
Stroke	14	Portelli *et al.*, 2005[34]
MI, Angina	12	Jones, 2002[35]

to account for the high risk individuals who were already taking aspirin.

Clinical data

Efficacy of aspirin for primary MI and stroke prevention was based on meta-analyses of the major aspirin trials by Hayden and Eidelmann with the Women's Health Study used to evaluate efficacy of aspirin specifically in women[3,4,24]. Gender-specific results of a recent meta-analysis by the Antithrombotic Trialists' Collaboration was tested in a sensitivity analysis[36]. The Primary Prevention Project specified the efficacy of aspirin in primary prevention of angina, with no differentiation between genders[5]. Efficacy of aspirin for secondary prevention was evaluated by a meta-analysis with no gender differentiation[2]. Efficacy of angina prevention due to preventive aspirin in secondary prevention patients was not reported. Hence, angina was not included as a possible event in secondary prevention patients.

Adverse events were considered to be GI bleeding and hemorrhagic stroke; incidence and mortality rates were considered for both events. Excess GI bleeding risk due to aspirin use was estimated by a dynamic risk equation of GI bleeding by age[27–29]. A secondary analysis examined the effect of using an alternative non-dynamic estimate[37].

Overall mortality rates by age and gender were taken from the National Center for Health Statistics preliminary data for 2005. Post-stroke mortality over ten years was estimated using survival curve data[38] and was specific to gender but not to age. Gender-specific mortality for MI and angina was also estimated but only for a five year time period[39]. Mortality for years 6–10 was assumed to be in line with year five mortality. Institutionalization rates were estimated specific to stroke, MI and angina[34,35,40]. A summary of mortality data can be found in Table A5, ESD at the *CMRO* website.

Aspirin use and compliance

The study by Pignone *et al.*[10] was the primary source for determining the proportion of patients age 40+ currently taking aspirin, with aspirin usage in patients under 40 being estimated by a study by Stafford *et al.*[25].

Persistence – defined as the accumulation of time from initiation to discontinuation of therapy – was considered in the model. Three years following commencement of aspirin treatment, a persistence rate of 76% has been reported[32], and WHO data suggest that long-term persistence in the developed world for chronic treatments, irrespective of disease area, is approximately 50%[33]. An exponential equation was fitted with patients starting at 100% persistence and was fitted to these data points with 50% being the equation limit. As soon as patients became non-persistent, all clinical benefit of aspirin ceased.

Costs

The yearly cost of Bayer aspirin at a dose of 81 mg (the standard low dose aspirin) was $18.23 not considering reduced compliance or persistence (Red Book 2008, average wholesale price). Gender-specific annual costs for treatment of the first year of GI bleeding, MI, angina, ischemic stroke, and hemorrhagic stroke were estimated according to 2005 H-CUPnet data[41] and were inflated to 2007/08 costs. Annual follow-up costs for specific CVD events were adapted from costs provided by Pignone *et al.*[13] and H-CUP 2007/08[41] costs.

The episode cost of patients who experienced a fatal CVD event was estimated using a formula suggested by Pignone *et al.*[13]. All cost estimates were tested in sensitivity analyses and costs were discounted at a yearly rate of 5%.

Results

In the base case with a total of 1,000,000 patients, a total of 474,109 patients (57% male, 43% female) were eligible for aspirin use. Of these 301,658 patients (61% male, 39% female) were not currently taking aspirin and were considered to be the target population for calculating the budget impact. The model assumed that for compliance with guideline use, all target patients started aspirin therapy, but numbers of patients included in this population were reduced annually in accordance with mortality and non-persistence with aspirin. In this population, implementation of clinical guidelines would prevent an additional 1273 (17% of total) myocardial infarctions, 2184 (18%) angina episodes and 565 (8%) strokes in primary prevention patients and an additional 610 (26%) myocardial infarctions, and 660 (25%) strokes in secondary prevention patients.

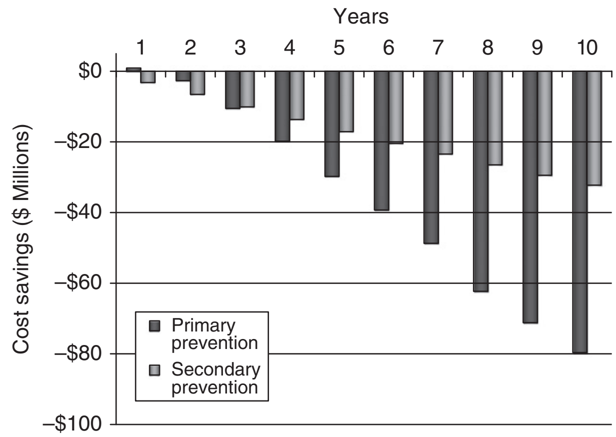


Figure 1. Cost impact by year – direct costs.

Budget impact results

The overall budget impact for primary prevention patients was found to be an overall savings of $79.6 million and the budget impact for secondary prevention patients was a savings of $32.2 million. Figure 1 displays the cumulative budget impact by year for both primary prevention and secondary prevention patients. In these results, negative figures represent a savings and positive figures represent additional costs. In addition to these MCO costs, the total out of pocket drug cost for aspirin over 10 yrs was $29.0 million in the primary prevention population and $2.6 million in the secondary prevention population.

If full compliance with guidelines was not achieved, the budget impact was still positive overall but was reduced linearly, assuming an equal distribution in risk between those patients that were and were not using aspirin (Figure 2). However, this is likely to be a conservative assumption due to an expectation that patients with higher risk could be more likely to follow guidelines than patients with lower risk, therefore underestimating the budget impact. Patients with higher risk are also likely to have a higher cost if they are not on a preventive regimen.

Indirect costs added substantially to the overall cost implications of aspirin with a ten year budget impact considering both direct and indirect costs producing savings of $137.9 million for primary prevention patients and $74.8 million for secondary prevention patients (Figure 3).

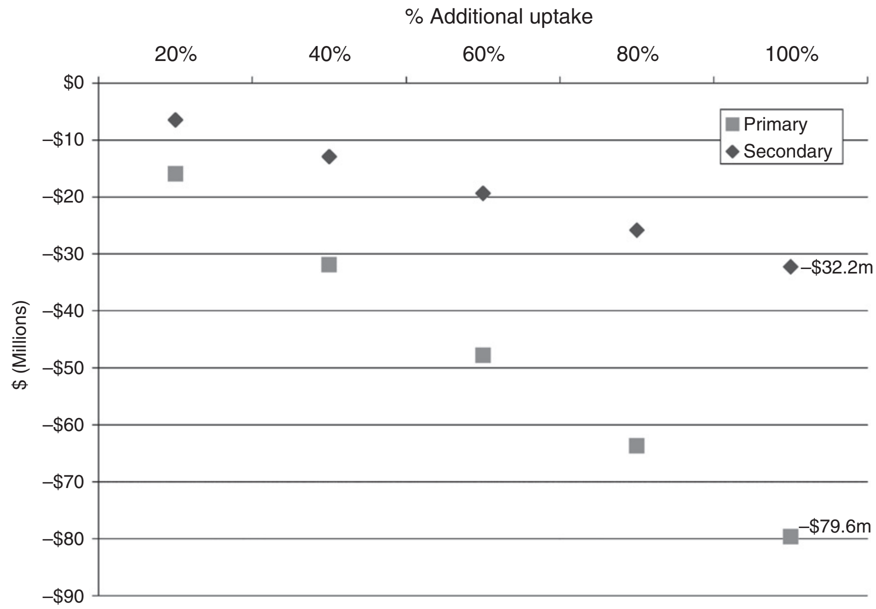


Figure 2. Ten year direct cost savings considering variable aspirin uptake rates in accordance with guidelines.

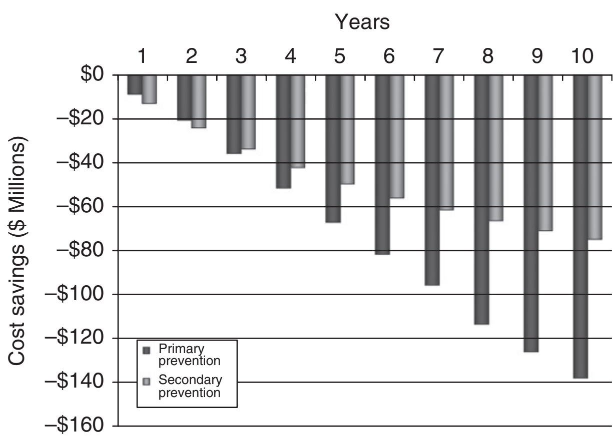


Figure 3. Cost impact by year – direct and indirect costs.

One-way sensitivity analyses

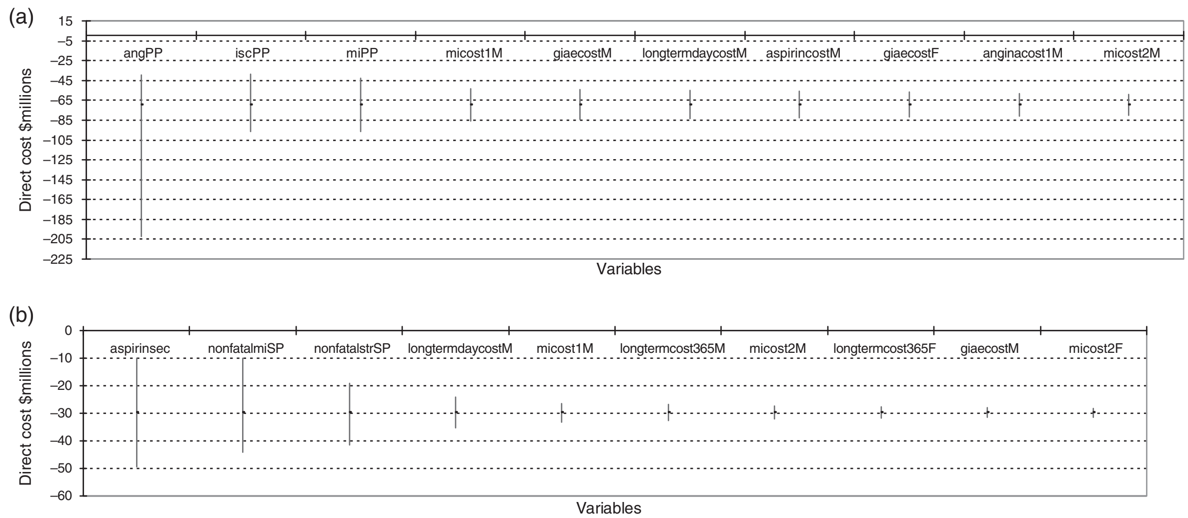
One-way sensitivity analysis was performed to determine to which variables the model is most sensitive. Figure 4a displays an influence diagram describing the relative impact of individual variables on the model's outcome for primary prevention. The influence diagram for secondary prevention is displayed in Figure 4b. The most influential variable for primary prevention patients was aspirin efficacy for the prevention of angina followed by the efficacy of aspirin to prevent stroke and MI respectively. For secondary prevention patients, the most influential variable was the baseline use of aspirin. This was followed by efficacy of aspirin in reducing the risk of MI and stroke respectively.

Budget impact with alternative population scenarios

In addition to the basecase scenario, several different scenarios were tested to determine the impact on budget of using an alternative non-age dependent GI bleeding risk estimate[37]. The largest changes in the estimated budget impact were obtained when considering only subpopulations including patients identified in the USPSTF 2009 primary prevention guidelines[42], age 65+ Medicare-eligible patients, population below 65 years only, females, males and diabetics (Table 2) with the most efficient group being secondary prevention in Medicare-eligible patients (270% additional cost savings) and the least efficient group being primary prevention in females (73% reduction in cost savings). Application of alternative aspirin efficacy values for primary prevention using a recent patient-level meta-analysis resulted in a minimal 1% reduction in the estimated budget impact[36].

Discussion

In a base population of 1,000,000 patients, implementation of clinical guidelines is predicted to prevent an additional 1273 myocardial infarctions, 2184 angina episodes and 565 ischemic strokes in primary prevention patients and an additional 578 myocardial infarctions, and 607 ischemic strokes in secondary prevention patients over ten years. The budget impact of preventing these events was an overall savings of $79.6 million for primary prevention patients and $32.2 million for secondary prevention



Variable name	*Description*
anginacost1M	Angina annual costs – yr 1 for males
angPP	Relative risk of reducing angina with aspirin in primary prevention
aspirincostM	Aspirin annual costs
aspirinsec	Baseline aspirin use for secondary prevention
giaecostF	Annual GI AE costs for females
giaecostM	Annual GI AE costs for males
iscPP	Relative risk of reducing ischemic stroke with aspirin in primary prevention
longtermcost365F	Long-term care costs (per 365 days) for females
longtermcost365M	Long-term care costs (per 365 days) for males
longtermdaycostM	Long-term care costs (per day) for males
micost1M	MI annual costs – yr 1 for males
micost2F	MI annual costs – yr 2+ for females
micost2M	MI annual costs – yr 2+ for males
miPP	Relative risk of reducing MI with aspirin in primary prevention
nonfatalmiSP	Relative risk of reducing non-fatal MI with aspirin in secondary prevention
nonfatalstrSP	Relative risk of reducing non-fatal stroke with aspirin in secondary prevention

Figure 4. Tornado diagram. (a) Primary prevention. (b) Secondary prevention.

Table 2. Cost impact with alternative scenarios ($ millions).

	Primary Prevention (% difference from base case)	Secondary Prevention (% difference from base case)
Base case Cost Impact	−$79.6	−$32.2
Alternative Fixed GI Bleeding Estimates	−$125.5 (+58%)	−$38.0 (+18%)
USPSTF 2009 Guidelines	−$37.0 (−54%)	n/a
Age 65+ Medicare Population	−$188.4 (+137%)	−$119.0 (+270%)
Age 18–64	−$57.9 (−27%)	−$14.9 (−54%)
Female	−$21.6 (−73%)	−$21.8 (−32%)
Male	−$144.1 (+81%)	−$43.8 (+36%)
Diabetic	−$82.7 (+4%)	−$42.7 (+33%)
ATTC 2009 Aspirin Efficacy	−$78.8 (−1%)	n/a*

*Secondary prevention data was not available in the ATTC 2009 meta-analysis in a form that is compatible with the model.

patients, or the equivalent of $289 per patient for primary prevention and $1246 per patient for secondary prevention. Savings per patient are higher in secondary progression due to aspirin's efficacy for the prevention of CVD events and the high risk profile in this population.

To the best of the authors' knowledge, this is the first time that the US budget impact of preventive aspirin has been evaluated. However, there have been several other economic analyses of aspirin for the use of CVD prevention, particularly cost-effectiveness analyses. In a series of recent studies, aspirin was found to be the economically dominant strategy compared to not using aspirin in the UK, Germany, Spain and Japan[14–16]. For aspirin to be dominant in a cost-effectiveness analysis, the overall treatment costs with aspirin must be found to be less than treatment costs without aspirin, implying that the budget impact in these countries would be cost-saving. In Italy, cost-effectiveness analysis did not show aspirin to be dominant, but instead demonstrated a small cost-effectiveness ratio of €1030/QALY[14]. In a US cost-effectiveness analysis of men only[17], cost savings of $215 per patient were identified over a lifetime horizon. However, in a cost-effectiveness analysis of females[13], aspirin resulted in an additional cost of $76 per patient over a lifetime horizon. A broader range of results has been reported in a Dutch study including patients with increased risk for CVD events with males having a cost-effectiveness ratio ranging from €34/QALY to €141,160/QALY and females ranging from −€4,465/QALY (dominant) to €114,356 depending on risk level and age[18]. An analysis of aspirin cost-effectiveness in the setting of developing nations demonstrated low cost per QALY results for both primary and secondary prevention ranging from $306/QALY to $1221/QALY depending on region and risk level[19]. In all, these results are broadly in line with our findings, although variations in cost savings would be expected based upon differences in the health care cost structure. These results are also expected to be influenced by the scope of different cardiovascular events considered in the evaluation.

There were several assumptions in the model that might have influenced results. In the baseline risk estimation, the number of events occurring in a high risk population (3% five year risk) was based upon the Framingham risk equations. However, some patients in Framingham population were taking aspirin. Therefore, applying this risk profile will potentially underestimate the risk in the aspirin naïve patients and hence the number of events avoided. There was incomplete information about the efficacy of aspirin according to gender and it was necessary to use efficacy data that was not gender specific for angina efficacy in primary prevention and for MI and stroke efficacy in the secondary prevention populations. This in turn might have led to reduced specificity in estimating the differences in male and female budget impact. Need for primary prevention was considered based upon USPSTF 2002 guidelines. More recent guidelines[38] recommend the use of aspirin only in those with the greatest benefit from among males between ages of 45–79 for MI prevention, and females between 55–79 for stroke prevention. By selecting patients with a five-year risk above 3%, the model is also implementing the individual discretion required by these guidelines to be used in making aspirin prescribing judgments. Limiting the patient population strictly according to USPSTF 2009 guidelines to males 45–74 for MI and angina prevention, and females 55–74 for stroke prevention, the primary prevention budget impact remains highly impactful at $37.0 million, despite a 54% reduction from the reported budget impact of $79.6 million based upon USPSTF 2002 guidelines. It should also be considered that based on individual risk profiles, there are patients outside these age groups who are likely to benefit clinically both in the long and short term from aspirin treatment.

Contrary to other published economic models of aspirin that have used a fixed risk for GI bleeding due to aspirin for all age groups[13–17,37], a dynamic risk according to age was used according to a recently developed model[27]. Using static risk estimates for GI bleeding[37] resulted in an increased savings of $45.9 million in primary prevention patients (58% increase) and $5.8 million in secondary prevention patients (18% increase). The difference in budget impact based on these two GI bleeding risk estimates indicates the important role that GI adverse events plays in the economic impact of preventive aspirin use. In other scenario analyses, the influence of age and gender was tested. In a Medicare-eligible patient group aged 65+ of 1,000,000 patients, budget impact was more substantial at $188 m and $119 m due to the increased risk profile in these patients (increase of 137% and 270% respectively), whereas in the patient group aged 18–64, the risk of exposure to AEs in a larger population tempered the savings achieved through event prevention[43]. Similarly, the higher overall CVD risk profile of men in the US population led to higher potential budget savings ($152 m primary prevention/$45 m secondary prevention; 81%/36% increase) than in females ($26 m primary prevention/$23 m secondary prevention; 73%/32% decrease). This finding is in line with the more favorable cost effectiveness of aspirin use in males[17] compared to the cost effectiveness of aspirin use in females[13]. Considering an all-diabetic population, there were no major changes in the overall budget impact; however, it should be noted that while the risk equations used considered the influence of diabetes, they were not specific for diabetic patients[44] and therefore might have lacked sensitivity. Combined with findings that aspirin might have a differential efficacy profile in diabetic patients[45], further investigation is required as to whether this patient group requires separate consideration.

The cost of adverse events played a substantial role in the model reducing the potential cost savings of aspirin. The occurrence of hemorrhagic stroke might be relatively unavoidable, but GI bleeding can feasibly be countered by proton pump inhibitor (PPI) treatments, therefore further improving the clinical profile and patient acceptability of preventive aspirin treatment. However, this would impact the overall cost savings suggested by the model.

Sensitivity analysis found that when holding the patient numbers and age distribution constant, efficacy of aspirin was the most important determining factor for both primary prevention and secondary prevention patients, followed by treatment costs. Because of the likely relationship between improved adherence and greater efficacy, it suggests the importance of patient education about the need to closely adhere to a preventive aspirin regime and also to monitor and preventively treat AEs such as GI bleeds that are likely to encourage poor adherence to treatment.

Limitations

There were several limitations within the model. Prevention of angina, which had a large impact on the cost savings in a primary prevention population, could not be considered in a secondary prevention population due to lack of appropriate aspirin efficacy data regarding angina. Because the model considered several different types of cardiovascular and cerebrovascular outcomes, there was a necessity to utilize risk equations derived from different sources to characterize the risk. The most up-to-date equations available were used in each case, but this implies a certain amount of heterogeneity in the risk estimates.

Although we attempted to be comprehensive in scope, the model is simplified in that it only considers the influence of aspirin on CVD risk. There are several other interventions that impact CVD risk that were not considered in the analysis including statins, ACE-inhibitors, aggrenox, the polypill, clopidogrel, smoking cessation, exercise and dietary programs that could all potentially alter the risk profile of the base case population as well as change the cost structure. There are other population dynamics that likewise might influence the risk profile such as the increasing trend in obesity, socioeconomic differences, differences in race and lifestyle patterns and comorbidities. Further detailed study into these clinical and cultural differences is necessary before these dimensions can be considered within a modeling framework.

This model supports US treatment guidelines for primary and secondary prevention with aspirin[11,12]. However, the high cumulative costs of AEs mean that use of aspirin in lower risk populations would likely have less favorable results.

Conclusions

Preventive aspirin use in high-risk patients in the US is currently suboptimal[10]. The analysis presented here demonstrates that there are potential savings from a health care payer perspective if better adherence to guidelines can be encouraged. These results were most sensitive to aspirin efficacy parameters – but robust regarding most other parameters, including the assumptions about mortality, persistence, and risk equation parameters.

Transparency

Declaration of funding

Bayer Schering Pharma conceived and funded this research; technical work was carried out by United BioSource Corporation (UBC).

Declaration of financial/other relationships

K.W.J. has disclosed that she reviewed the model as an active collaborator. In order to avoid any potential for bias this might cause, care was made to consistently select conservative values throughout the model. S.M., A.B. and F.P. have disclosed that they are employed by UBC, which provides consulting and other research services to pharmaceutical, device, government and non-government organizations. In this salaried position, S.M., A.B. and F.P. work with a variety of companies and organizations. They receive no payment or honoraria directly from these organizations for services rendered. A.M.F. has disclosed that he has received research support from Bayer and is a consultant to Bayer. The manuscript was developed entirely by the authors.

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