ORIGINAL RESEARCH

Cost-Effectiveness of a Statewide Campaign to Promote Aspirin Use for Primary Prevention of Cardiovascular Disease

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***Background*—**The U.S. Preventive Services Task Force in 2009 recommended increased aspirin use for primary prevention of cardiovascular disease (CVD) in men ages 45 to 79 years and women ages 55 to 79 years for whom benefit outweighs risk. This study estimated the clinical efficacy and cost-effectiveness of a statewide public and health professional awareness campaign to increase regular aspirin use among the target population in Minnesota to reduce first CVD events.

***Methods and Results*—**A state-transition Markov model was developed, adopting a payer perspective and lifetime time horizon. The main outcomes of interest were quality-adjusted life years, costs, and the number of CVD events averted among those without a prior CVD history. The model was based on real-world data about campaign effectiveness from representative state-specific aspirin use and event rates, and estimates from the scholarly literature. Implementation of a campaign was predicted to avert 9874 primary myocardial infarctions in men and 1223 primary ischemic strokes in women in the target population. Increased aspirin use was associated with as many as 7222 more major gastrointestinal bleeding episodes. The cost-effectiveness analysis indicated cost-saving results for both the male and female target populations.

***Conclusions*—**Using current U.S. Preventive Services Task Force recommendations, a state public and health professional awareness campaign would likely provide clinical benefit and be economically attractive. With clinician adjudication of individual benefit and risk, mechanisms can be made available that would facilitate achievement of aspirin's beneficial impact on lowering risk of primary CVD events, with minimization of adverse outcomes. **(*J Am Heart Assoc*. 2015;4:e002321 doi: 10.1161/JAHA.115.002321)**

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Cardiovascular diseases (CVD), including myocardial infarction (MI) and stroke, are the leading causes of disability and death in the United States.[1] In 2010, these 2 conditions accounted for 29.4% of total deaths.[2] The economic consequences of CVD are immense, with estimated annual costs of $315 billion in 2010, including $193 billion in direct medical care spending and $122 billion in lost future productivity.[3] In 2009–2010, about 47% of US adults had at least 1 of 3 risk factors for CVD, including uncontrolled high blood pressure, uncontrolled high cholesterol, or current smoking.[4] Prevalence of CVD risk factors and cardiovascular health also exhibit considerable variation across the United States,[5] suggesting potential value from implementing geographically targeted prevention strategies.

Primary prevention interventions aim to reduce the likelihood of initial cardiovascular ischemic events. Such efforts typically include programs and policies to decrease risk factor exposure. Successful examples include smoking cessation programs and increased use of hypertension and cholesterol-lowering medications.[6,7] One effective evidence-based primary prevention approach is based on use of low-dose aspirin as a targeted pharmacologic risk-reduction intervention. Demonstration of the efficacy of aspirin for primary prevention of CVD was achieved in a series of large randomized clinical trials.[8,9] In a meta-analysis of primary prevention

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Accompanying Figure S1 and Table S1 are available at http://jaha.ahajournals.org/content/4/12/e002321/suppl/DC1

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trials, there was a 12% relative risk (RR) reduction in nonfatal cardiovascular events achieved with aspirin use among healthy adults.[10] A substantial 50% reduction in first myocardial infarctions was documented within the most recent Japanese Primary Prevention Project.[11]

In 2009, the U.S. Preventive Services Task Force (USPSTF) recommended increased aspirin use to improve the primary prevention of CVD events in men 45 to 79 years old and women 55 to 79 years old in whom benefit outweighs risk.[12] The low-dose aspirin recommendation was reinforced by inclusion in the American Heart Association's primary prevention guidelines,[13,14] the Centers for Disease Control and Prevention's Healthy People 2020 plan,[15] and recently, as part of the "Million Hearts" initiative of the Centers for Disease Control and Prevention and the U.S. Department of Health and Human Services.[16] To date, these recommendations have not been actively included in most national or regional prevention efforts. Thus, a major clinical care gap exists in the use of aspirin for primary prevention.[17–19]

Increasing appropriate use of aspirin via population-based interventions has the potential to achieve a substantial benefit in the reduction of first MIs in men and first ischemic strokes in women. From a public health perspective, population-prevalent diseases with high rates of adverse outcomes should ideally be addressed using population-wide approaches. Such approaches have been long been utilized in the State of Minnesota, with considerable success. Minnesota rates of heart attack and stroke are among the lowest in the nation.[20] A multidecade state effort has assured that evidence-based risk reduction interventions are consistently utilized across the entire population. State community CVD prevention efforts are encompassed in the Minnesota Department of Health's "Heart Disease and Stroke Prevention Plan."[21] A commitment to achieve these goals has improved risk factor control and lowered rates of cardiovascular events.[22,23] In 2011, the Minnesota Heart Disease and Stroke Prevention Plan included a goal to lower rates of a first heart attack or stroke by fostering appropriate use of low-dose aspirin in the USPSTF target population (http://www.health.state.mn.us/cvh/cvhplan.html).

Creation of a regionally effective primary prevention dissemination program requires carefully crafted strategies that engage both the public and health professionals. For over 30 years, the Minnesota Heart Health Program has provided such leadership.[24,25] In 2015, in collaboration with the State prevention plan, and supported by private philanthropy as well as a grant from the National Heart, Lung and Blood Institute (1R01HL126041-01), Minnesota Heart Health Program has begun the implementation of a 5-year regional effort to improve use of low-dose aspirin to achieve the USPSTF primary prevention goals. This program is designed to include 2 key strategies. The first strategy provides a public awareness campaign in which media is used to inform the public to consider, with their healthcare professional, the potential benefit of regular low-dose aspirin use for primary prevention. A second strategy utilizes a health system intervention to provide primary care health professionals (family medicine and internal medicine physicians, pharmacists, nurse practitioners, and physician assistants) with a continuing education program to assure maximal efficacy in prescription of low-dose aspirin. This health system strategy also includes use of electronic health record best practice alerts, regional practice facilitators, and process measurements to assure that appropriate aspirin use increases within the clinic population.

The current study was designed to provide a *pre hoc* evaluation of the potential population impact (clinical and health economic) of the Minnesota Heart Health Program aspirin campaign. Program costs include those required to sustain a public awareness intervention that delivers key aspirin messages through a variety of traditional formats, including television, print, and radio as well as social media. Health system intervention costs include those required to create the educational aspirin use prescriptive informational interventions and their delivery to primary care health professionals. Additional details regarding campaign design are documented elsewhere.[26]

Because the design and implementation of future national CVD preventive campaigns may require significant financial investments by private and/or public sources, we developed a decision analytic model to evaluate the clinical and cost-effectiveness of this Minnesota-based aspirin use primary prevention CVD campaign. Minnesota is ideal for this evaluation as regional CVD clinical event rates are known, baseline aspirin use is well defined, and program costs can be reasonably estimated from real-world study.[27] This analysis was also designed to assess the conditions under which a population-wide campaign may be cost-effective as a CVD primary prevention strategy.

Methods

In a cost-effectiveness analysis (CEA) framework, we developed a state-transition model[28] using a multiple-cohort simulation[29] to evaluate the benefits and costs of an aspirin public awareness campaign linked to a health system intervention, compared to the status quo. This model predicted quality-adjusted life years (QALYs) gained, costs, and the number of CVD events averted under the campaign strategy compared to the status quo from a payer perspective[30–32] and over a lifetime horizon. The annual discount rate for costs and QALYs were set at 3% per US recommendations.[33]

Campaign

For modeling purposes, the campaign design and associated costs for media outreach efforts, health professional education, and prescriptive reinforcement tools were extrapolated from a regional study initiated in February 2012 to test the intervention components and evaluation procedures in a representative Minnesota community (Hibbing, Minnesota) with an estimated population of 16 287.[26,34] This pilot program promoted appropriate aspirin use to achieve the primary prevention goals, and provided an estimated cost of a campaign. The public awareness component included a media campaign that informed adults within the USPSTF sex and age target populations to consider aspirin use if they have known moderate to high cardiovascular risk, excluding individuals who use daily nonsteroidal anti-inflammatory drugs; other antithrombotic medications; who have a history of recent gastrointestinal (GI) bleeding; or aspirin allergy. The health professional awareness component included a mandatory educational module on aspirin primary prevention, linked to an electronic health record–based aspirin primary prevention best practice alert.[26] In the current study, we simply evaluated the impact of the public awareness component.

Model Structure

Figure 1 illustrates the model structure that computed the effect of the public awareness campaign. We simulated the campaign impact on a hypothetical cohort of individuals through distinct health states defined by disease status (with or without CVD) and aspirin use status (yes or no) in the well state. Figure S1 presents the detailed decision tree structure. At the beginning of the simulation, the cohort starts in the well state, with no history of CVD. As the simulation progresses in time, a proportion of this cohort may stay well, die, or develop any of 4 simulated clinical events: MI, ischemic stroke, hemorrhagic stroke, or GI bleeding, based on age- and sex-specific incidence rates. Events were modeled as transient health states such that the maximum duration of staying in any state is 1 cycle and assumed to last for 1 year in the model.[30–32] Moreover, following ischemic or hemorrhagic stroke, we defined long-term complications of these events by 2 health states, post–major stroke and post–minor stroke.[30] For individuals with GI bleeding, we assumed full health could be regained within 1 year,[30–32] whereas other events were assumed to sustain a permanent reduction in quality of life. Given the study's focus on evaluating the costs and benefits

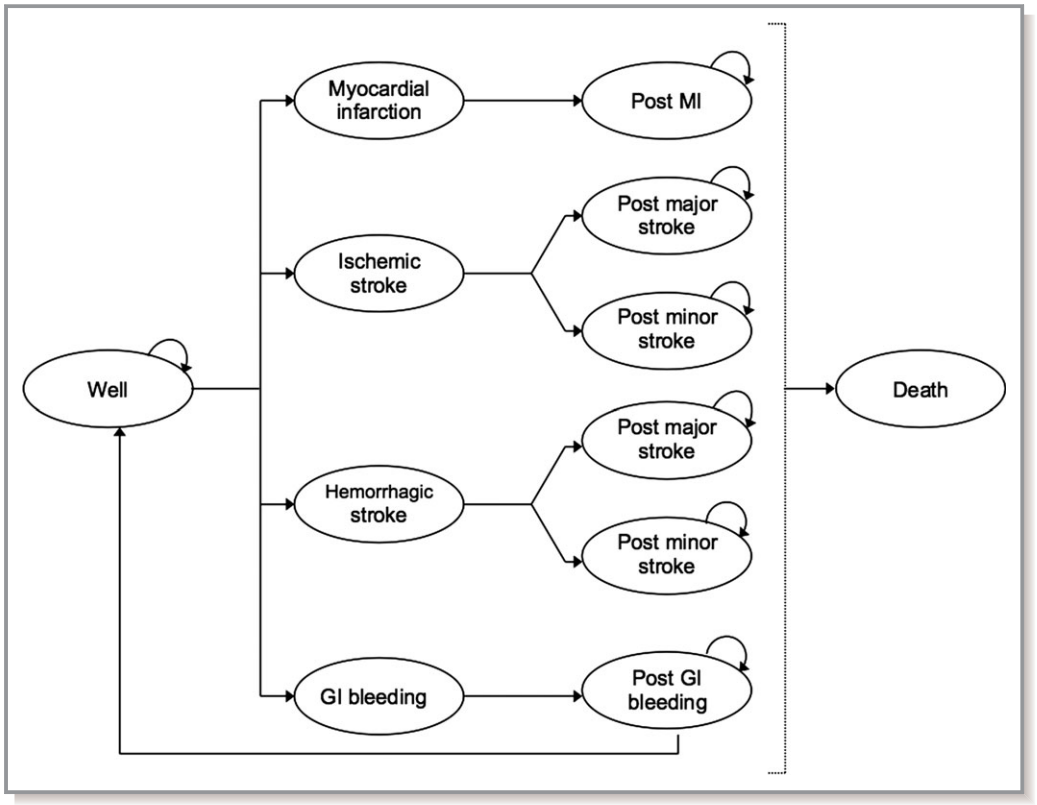

Figure 1. State-transition model structure. The hypothetical cohort starts in the well state and can transition to the other states in a model cycle according to corresponding transition probabilities in Table 1. Transition to the death state is allowed from any state. GI indicates gastrointestinal; MI, myocardial infarction.

of primary CVD prevention resulting from increased aspirin use due to the campaign, the benefits associated with secondary prevention of recurrent CVD events were not included. Table S1 summarizes all relevant assumptions used in the model.

Parameters and Sources

Table 1 summarizes the parameter estimates and their distributions. We used Minnesota-specific estimates for the model parameters where available, and published estimates for those for which state-specific estimates were not available. These published parameters are unlikely to be significantly different from national estimates (eg, health-state utilities).

Aspirin use

We derived population-based aspirin use data from the primary prevention, self-reported, and biochemically validated aspirin use survey administered as part of a contemporary Minnesota regional aspirin use study.[26,42] At baseline, 36% of primary prevention candidates reported regular use of aspirin,

Table 1. Parameter Values Used in the Base-Case Analysis

Parameter*	Men	Women	Distribution	Reference
Treatment effectiveness of aspirin (relative risk)				
Myocardial infarction	0.68 (0.54–0.86)	1.01 (0.84–1.21)	Lognormal	10
Ischemic stroke	1 (0.72–1.41)	0.76 (0.63–0.93)	Lognormal	10
Treatment-associated adverse events				
Hemorrhagic stroke	1.69 (1.04–2.73)	1.07 (0.42–2.69)	Lognormal	10
Gastrointestinal bleeding	1.56 (1.13–2.15)	1.52 (1.11–2.03)	Lognormal	35
Health utility				
Well	1			
Myocardial infarction				
Year 1	0.88 (0.80–0.96)		Beta	31,36,37
Subsequent year	0.90 (0.80–0.95)		Beta	31,36,37
Major stroke	0.50 (0.10–0.75)		Beta	31,38
Minor stroke	0.75 (0.60–0.9)		Beta	31,38
Gastrointestinal bleeding (year 1)	0.94 (0.88–1.0)		Beta	31,39
Taking aspirin	0.999 (0.99–1)		Beta	30,32,39
Annual cost (per person or patient)†				
Campaign	6.75 (5–15)		Gamma	Assumed
Aspirin	5.75 (5–15)		Gamma	31
Myocardial infarction				
During first year	20 737 (1069–31 106)		Gamma	31,40
During subsequent year	3109 (1555–4664)		Gamma	31,40
Major stroke				
During first year	32 233 (16 117–48 350)		Gamma	30,41
During subsequent year	18 821 (9411–28 232)		Gamma	30,41
Minor stroke				
During first year	5652 (2826–8478)		Gamma	30,41
During subsequent year	967 (484–1451)		Gamma	30,41
Gastrointestinal bleeding	7538 (3769–11 307)		Gamma	30,31
Death	2404 (1202–3606)		Gamma	39,41
Discount rate	3% (2%–5%)			33

*Values in parentheses represent 95% CIs, which also indicate ranges used in the Tornado diagram in Figure 2, and were applied to derive the parameters used in the distribution.
†Costs were inflated to 2012, using Minnesota medical consumer price index.

defined as taking aspirin daily or every other day. At 4 months after initiation of the campaign, regular aspirin use increased to 54%. This increase was sustained at 18 months and was greater than nonintervention temporal trends. In the current study, the campaign's main impact was through increased aspirin use. We used a conservative assumption that aspirin use would increase annually by 5 percentage points for 3 years from 36% to 51% in both the male and female cohorts. In the sensitivity analysis, we further examined the contribution from the length of campaign impact by assuming the campaign effect would continue for 8 years and would increase the total aspirin use population from 36% to 81%. We assumed the adherence to aspirin is 100%[31,32] and varied it (50%–100%) in the sensitivity analysis.

Transition probabilities

We derived Minnesota age- and sex-specific incidence estimates of MI, hemorrhagic stroke, and upper GI bleeding from the 2011 Minnesota Hospital Association discharge records[43] and the 2011 National Inpatient Sample[35] (Minnesota hospitals only) as well as state-based population estimates (Table 2). Because the data that described the impact of aspirin on CVD mortality or all-cause mortality in either men or women were less robust than the associated benefits on nonfatal events,[45] we assumed CVD mortality for aspirin users to be the same as non-users. In general, for patients who experienced an event, the mortality risk from that event (case fatality) should be different from the risk of dying after 1-year survival. Thus, we extracted case fatality rates of MI, ischemic stroke, and hemorrhagic stroke from the published literature (Table 2), with the exception that GI bleeding was fixed at 3% annual risk.[30] We assumed that all-cause mortality in subsequent years following a MI, major stroke, or minor stroke remains twice as high compared to individuals who do not experience such events.[30] The post-GI bleeding mortality rate was assumed to be identical to all-cause mortality. Age- and sex-specific all-cause mortality rates were derived from the 2011 Minnesota Health Statistics life table.[46] All rates applied in the model were converted to probabilities.[47]

Health utilities

Our health outcome measure was QALYs, as recommended by the Panel on Cost-Effectiveness in Health and Medicine.[48] QALYs are a composite measure of survival (longevity) and quality of life, where survival time is weighted by individuals' health-related quality of life, as measured by health utilities.[49] Individuals in perfect health are assigned a health utility value of 1, with lower values representing worse quality of life and a value of 0 representing death. We assigned health utilities by disease status. We also assigned a disutility for taking aspirin due to the inconvenience and varied it in the sensitivity analysis.

Treatment efficacy

We obtained estimates of treatment efficacy of aspirin as the RR for reducing each CVD event, as well as the relative harm of hemorrhagic stroke and GI bleeding using findings from a meta-analysis of 6 randomized controlled trials.[10] This meta-analysis stratified the risk of CVD and hemorrhagic stroke by

Table 2. Summary of Base-Case Incidence Rates and Case Fatality Rates of Myocardial Infarction, Stroke and GI, Bleeding by Sex and Age

	Men				Women			
Parameters/Age Groups	45 to 54	55 to 64	65 to 74	75 to 79	55 to 64	65 to 74	75 to 79	Source
Incidence rate (per 100 000 person-years)*								
Myocardial infarction	270	520	1040	1040	210	590	590	43
Ischemic stroke	53	139	353	775	73	198	566	30
Hemorrhagic stroke	30	60	120	120	50	100	100	43
Upper GI bleeding	100	160	228	479	87	203	375	35
1-year case fatality rate†								
Myocardial infarction	0.06	0.11	0.21	0.36	0.13	0.23	0.41	44
Ischemic stroke	0.07	0.12	0.18	0.34	0.11	0.17	0.32	30
Hemorrhagic stroke	0.38	0.44	0.53	0.66	0.45	0.51	0.72	30
Upper GI bleeding	0.03	0.03	0.03	0.03	0.03	0.03	0.03	Assumed

GI indicates gastrointestinal.
*Incidence data were from 2011 Minnesota Hospital Association and 2011 Nationwide Inpatient Sample (MN facilities; weighted).
†The risk of dying in the year that an event occurs.

sex and event type.[10] We also obtained estimates for the RR of aspirin use on major upper GI bleeding using estimates from a meta-analysis performed by the Antithrombotic Trialists' Collaboration.[50]

Costs

Associated costs for event-specific medical utilization were estimated from published literature.[31,41] Statewide aspirin use campaign costs were measured on a per person-year basis using aggregate, projected annual campaign expenses divided by the total target population from the Hibbing study. Average campaign costs were estimated at $6.75 per person-year. Furthermore, the campaign was assumed to run for 3 years only. All costs were inflation-adjusted to 2012 dollars using the Minnesota medical consumer price index.[51]

Analysis

Base case analysis

In the base-case analysis, the target population reflected USPSTF recommendations. Within the recommended USPSTF target cohort, we defined 3 age cohorts for men: 45 to 54 (42% of the target population), 55 to 64 (34%), and 65 to 79 years old (24%). Among women, we defined 2 age cohorts, including those 55 to 64 (56%) and 65 to 79 years old (44%).[52] Costs and QALYs saved in each cohort were aggregated and weighted by their relative size in the target population based on 2011 Minnesota Vital Statistics.[52] We calculated expected discounted lifetime costs and QALYs for the campaign strategy and the status quo.

Sensitivity analysis

The clinical efficacy and cost-effectiveness of a population-based aspirin use campaign would be anticipated to be highly dependent on the efficacy of the campaign and the benefit and harms of aspirin use. The historical rates of efficacy and harm may, or may not, apply to a contemporary population intervention. Thus, a preplanned series of sensitivity analyses were performed. We conducted deterministic and probabilistic sensitivity analyses to evaluate uncertainty with respect to the parameter assumptions. In the deterministic sensitivity analysis, we varied 1 parameter at a time (1-way) to recalculate lifetime costs and QALYs for each strategy, and then determined the influence of each parameter on the CEA results (e.g., the range of recalculated net QALYs). We drew upper and lower bound values of each parameter based on published 95% CI estimates or used values 50% lower or higher than the mean[53] if not available (Table 1). The model outcome here was presented as net QALYs gained from adopting the campaign compared to no campaign. We used the tornado diagrams to summarize the effects of varying key model parameters one at a time on the model outcome. The parameters were sorted in descending order by their importance for both males and females, respectively. The longer bars indicated the most important parameters, giving the diagram its classic "tornado" appearance. The cost savings were converted to QALYs gained using the willingness-to-pay (WTP) threshold value of $50 000 per QALY.

Additionally, we conducted probabilistic sensitivity analyses using second-order Monte Carlo simulation in which values of all input parameters were randomly drawn from their assumed distributions simultaneously to account for uncertainty. We used a beta distribution to represent uncertainty in the probability and utility parameters because such estimates are constrained on the interval [0, 1]. We characterized uncertainty in RR estimates using the log-normal distribution, and we used gamma distributions to reflect uncertainty in costs that have a lower bound at 0 and are generally skewed.[54] We conducted 10 000 probabilistic sensitivity analyses iterations. The probabilistic sensitivity analyses results are presented using a cost-effectiveness acceptability curve,[55] which depicts the percentage of times that a strategy is cost-effective in the probabilistic sensitivity analyses iterations at different WTP thresholds (up to $100 000 per QALY).

All analyses were executed using TreeAge Pro 2014 (TreeAge Software Inc, Williamstown, MA) and Microsoft Excel (Microsoft Corp, Redmond, WA).

Results

Base Case Analysis

The CEA results indicate that the statewide campaign to promote aspirin use was more effective and less costly than a no-campaign strategy (i.e., the campaign was cost-saving) for both the male and female target populations. The lifetime benefits of the campaign, as defined by the prevention of first heart attacks and strokes and improved quality of life, outweighed the short-term costs associated with aspirin use. Although the cost savings at the individual level were small, the projected cost savings for the Minnesota population were quite high. For men between ages 45 to 79 years, the mean lifetime effectiveness of the campaign was 16.653 QALYs per individual with a mean cost of $11 385, while the mean effectiveness of the status quo was 16.652 QALYs with a mean cost of $11 545. For women between ages 55 to 79 years, the campaign and the status quo generated 14.950 and 14.949 QALYs, respectively. The mean cost for the campaign strategy was $6 491 per capita over lifetime, while the status quo had a mean cost of ≈$6 519 (Table 3). Given the cost-saving results, which suggest more QALYs and fewer costs for the intervention, we do not present the CEA results using incremental cost-effectiveness ratios.[57]

Table 3. Cost-Effectiveness of the Statewide Campaign for the Primary Prevention of CVD Events in the Base-Case Analysis

	Men		Women	
Strategy	Costs	QALYs	Costs	QALYs
Campaign	$11 385	16.653	$6 491	14.950
Status quo	$11 545	16.652	$6 519	14.949
Difference*	−$160	0.001	−$28	0.001

CVD indicates cardiovascular disease; QALYs, quality-adjusted life years.
*According to the theory of cost-effective resource allocation,[56] the intervention would be preferred when the result of the intervention is less costly but more effective compared with the status quo.

Simulated Outcomes for CVD Cases Averted and GI Bleeding Cases Incurred

Table 4 shows the statewide primary CVD events averted as a result of increased aspirin use attributed to the campaign compared to the status quo. In the target population of 1 598 690 individuals in Minnesota (men=987 355 and women=611 335, respectively), implementation of the campaign was predicted to avert 9874 primary MIs in men ages 45 to 79, and 1223 primary ischemic strokes in women ages 55 to 79 years. However, increased aspirin use resulting from the campaign was also estimated to generate 7222 more major upper GI bleeding episodes and 2849 additional hemorrhagic strokes.

Sensitivity Analysis

The tornado diagram in Figure 2 shows the results of 1-way sensitivity analyses for the examined parameters in Tables 1 and 2. CEA results were most sensitive to the RR of hemorrhagic stroke and ischemic stroke, the incidence rate of MI or ischemic stroke, and the disutility of taking aspirin in both the male and female target populations. The effects of changes in other parameters, such as the RR of GI bleeding, per capita campaign costs, and the utility of MI were less pronounced. We also considered the proportional increase in aspirin use in the current non-aspirin-use population (the campaign effect), campaign costs per person, the aspirin adherence rate (50%–100%), and the campaign effect duration. For these parameters, no significant changes in the CEA result were documented. Furthermore, we performed an analysis to identify the threshold of campaign costs such that the most cost-effective strategy would switch from the campaign to the status quo (no campaign) at a WTP of $50 000/QALY. Threshold analyses indicated that the no-campaign strategy would become cost-effective if the per person campaign costs of the campaign were greater than $95 and $32 for the male and female target populations, respectively. These threshold costs are in ranges that are substantially higher than what was documented for costs in the pilot study.[26]

Figure 3 presents the probability that the campaign is cost-effective for varying values of WTP (i.e., the cost-effectiveness acceptability curve) for both males and females. The probability of the campaign being cost-effective remained above the indifference line (P=0.5) for the entire range of examined WTP thresholds, indicating that regardless of the payer's WTP threshold, the campaign was cost-effective for both males and females compared to the no-campaign strategy after taking into account all relevant parameters.

Discussion

The 2009 USPSTF recommendation for CVD primary prevention aspirin use and other aspirin CVD primary prevention guidelines (e.g., the American Heart Association primary prevention guidelines) offer a promising potential approach to improve population health. These data demonstrate that beneficial clinical outcomes can be achieved with a net cost-saving (less costly but more effective) impact when aspirin use for primary prevention of CVD events is promoted according to current USPSTF guidelines and supported by an investment in a regional (ideally state-based) public and health professional intervention. It would be anticipated that this

Table 4. Projected Number of Cardiovascular and GI Bleeding Events Over the Lifetime Horizon From the Minnesota Heart Health Program (Regional Aspirin Primary Prevention Program) Compared With the Status Quo in the Statewide Target Population

	Men			Women		
Primary Events	Campaign	No Campaign	Difference	Campaign	No Campaign	Difference
Myocardial infarction	165 184	175 058	−9874	64 863	64 740	123
Ischemic stroke	72 077	71 682	395	26 776	27 999	−1223
Hemorrhagic stroke	29 621	26 955	2666	14 183	14 000	183
GI bleeding events	64 277	59 439	4838	34 235	31 851	2384

GI indicates gastrointestinal.

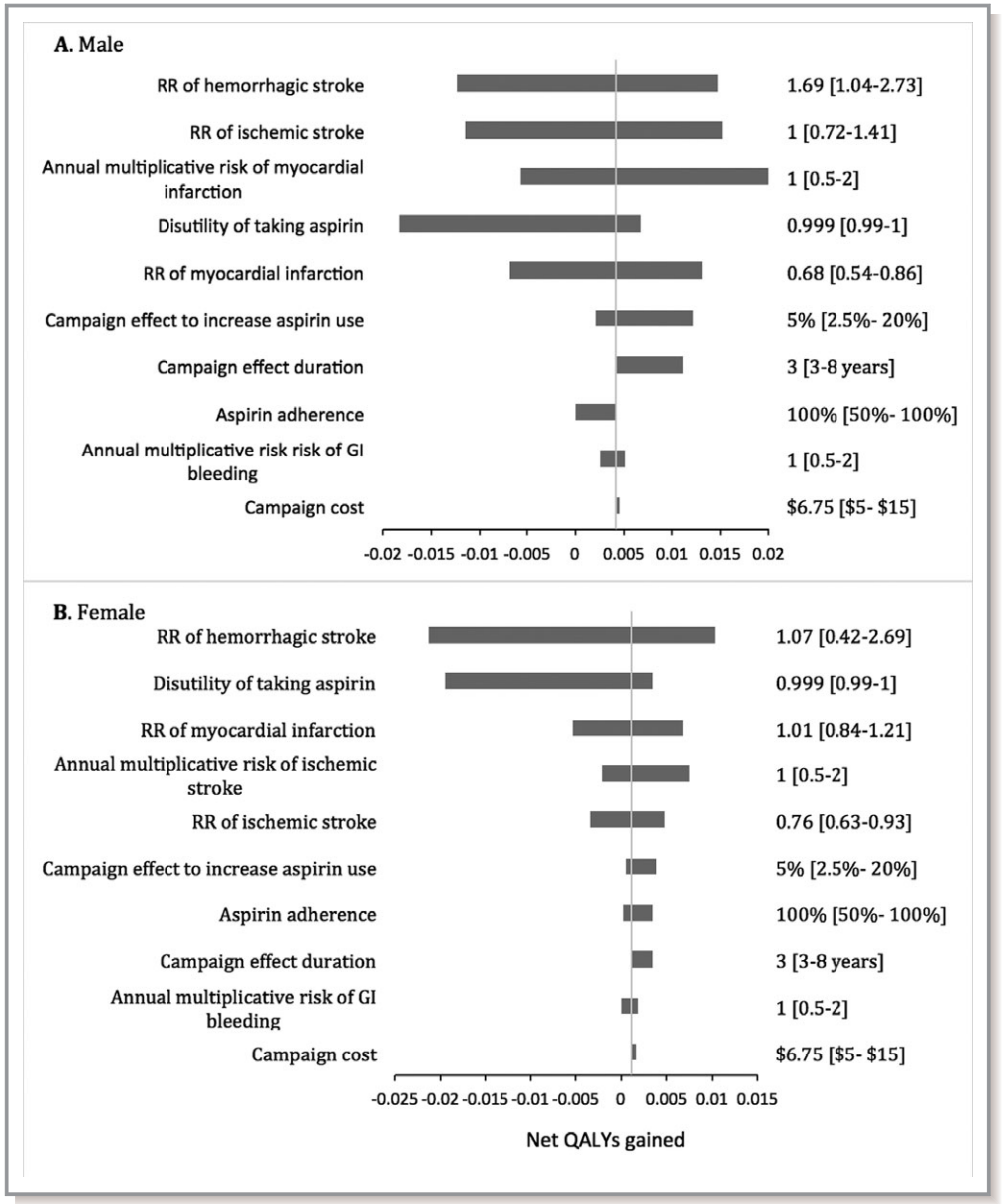

Figure 2. One-way sensitivity analysis tornado diagram that summarizes the effect of variation in key model parameters one at a time on the model outcome. The parameters are sorted in descending order by their outcome impact for both (A) males and (B) females, respectively. Longer bars indicate the most important parameters, giving the diagram its "tornado" appearance. The vertical line in both figures represents the base-case results for both males and females. GI indicates gastrointestinal; QALYs, quality-adjusted life years; RR, relative risk.

benefit could be achieved in states spanning low to high cardiovascular risk.

Using state-specific data from Minnesota, our state-transition Markov model results suggest that a campaign to promote aspirin use within the overall age- and sex-specific target population would likely be both clinically effective and cost-effective in both the male and female target populations over a lifetime time horizon. This model, by design, focuses on a general age- and sex-specific target population without explicitly distinguishing individuals by their specific cardiovascular risk.[30,31] Sensitivity analyses suggest that the cost-effectiveness of such a campaign is sensitive to the incidence of CVD events and RRs of hemorrhagic stroke, MI, and ischemic stroke and to the disutility of taking aspirin.

While it is possible that the campaign could have positive spillover effects by improving aspirin use (and clinical benefit) for individuals who should receive cardiovascular secondary prevention, we did not explicitly model this outcome. Such spillover effects were neither the focus of this investigation, nor were the current data adequate to reliably calculate the

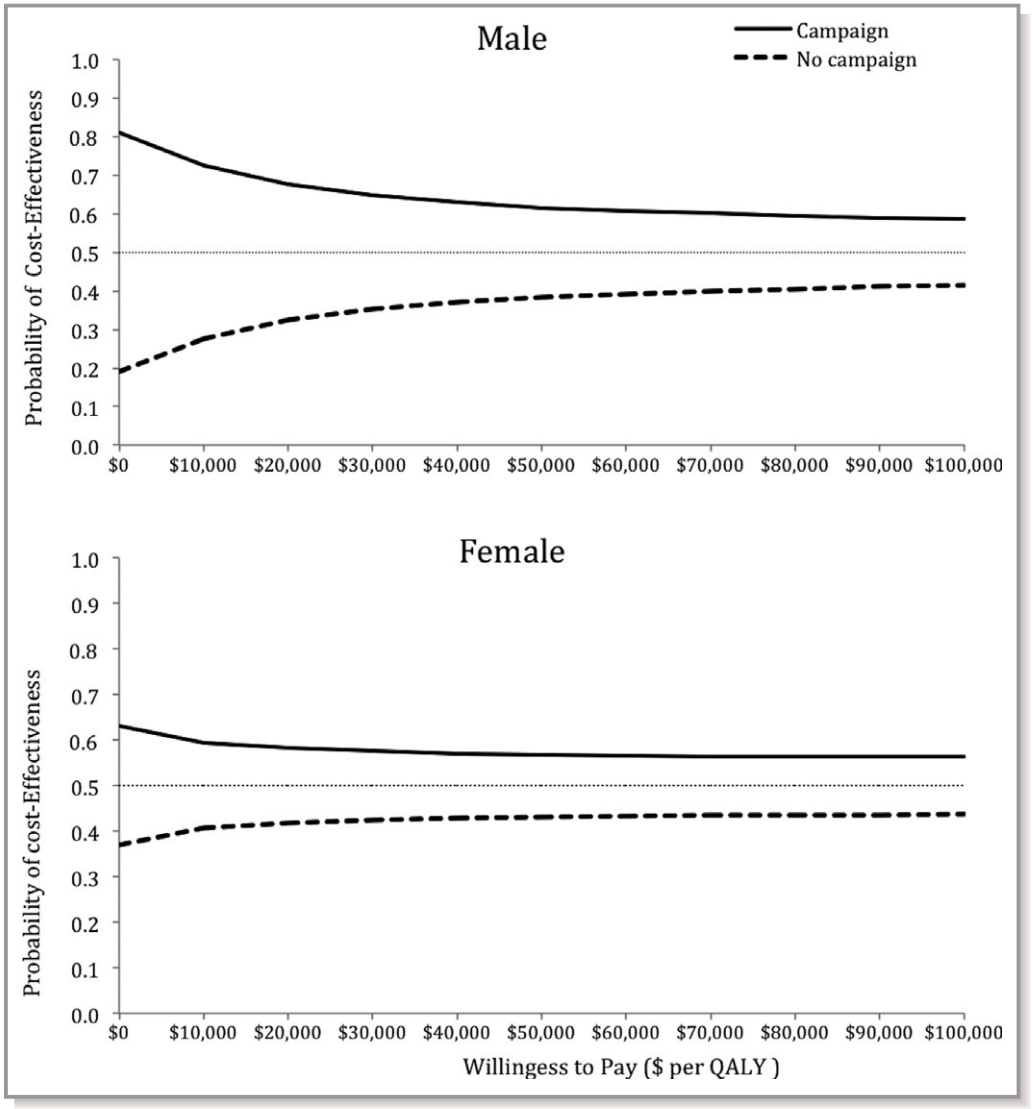

Figure 3. Cost-effectiveness acceptability curve. The probability that the campaign is cost-effective (solid line) is greater than that of no campaign (dashed line) at various willingness-to-pay thresholds for both males and females. QALYs indicates quality-adjusted life years.

magnitude of this spillover benefit. Since the current primary prevention campaign produces a cost-saving result, any beneficial secondary prevention spillover effect would likely be more favorable to the campaign strategy by producing more QALYs without incurring additional costs.

The campaign considered in this analysis was designed to include a public awareness intervention and a health system intervention. The public awareness campaign would provide the "at risk" target population with information regarding the benefits and harms of aspirin therapy. The health system intervention was designed to assure that primary care health professionals would be capable of effectively identifying the "aspirin appropriate" target population in order to evaluate both cardiovascular risk and associated bleeding risk (as well as other aspirin contraindications, such as aspirin allergies and use of other antithrombotic medications). Studies completed by Manson and colleagues demonstrated, for example, that the greatest potential aspirin benefit was gained when this antithrombotic intervention was applied in the higher CVD risk cohort.[58] Such individualized risk assessment would be anticipated to mitigate aspirin-related hemorrhagic stroke or upper GI bleeding by withholding a new aspirin prescription from individuals with a history of recent GI bleeding, daily use of nonsteroidal anti-inflammatory drugs, or other medical comorbidities that are associated with bleeding.

The potential extrapolation of these results to other states or international populations offers additional public health opportunities. While the data applied in the current analysis were derived from a robust database from Minnesota, most of these assumptions (informed by the sensitivity analysis) would permit a similar outcomes analysis to be generated in

other regions. For example, current aspirin use in the primary prevention candidate population has been measured, and now ranges between 20% and 50%. These rates demonstrate that a "prevention gap" is widespread and that a primary prevention campaign would be likely to increase aspirin use. Second, while Minnesota is characterized by low incident rates of both first and subsequent MIs and ischemic strokes, our cost-saving results of an aspirin use public campaign suggest that the preventive benefit would likely be magnified in higher risk states. Finally, the most frequent adverse bleeding events (GI bleeding)—a risk that now lowers enthusiasm for aspirin use in primary prevention populations—can be mitigated in any region by careful selection of aspirin candidates and use of generic proton pump inhibitors. Thus, these data should be informative as primary prevention campaigns are developed in other regions. We note that despite the documented temporal trends of increasing use of aspirin, other antiplatelet, and other anti-thrombotic medications, there has been no associated increase in population rates of major GI bleeding events. These data should help to lower contemporary concerns that bleeding risks would inevitably blunt any net benefit derived from careful primary prevention use of aspirin.

Limitations

All prospective models that evaluate cardiovascular risk interventions are associated with limitations. First, the incidence rates of CVD events and GI bleeding used in the study cannot separately reflect first events from second events. This may overestimate the risk of first MIs and strokes when overall incidence rates from the hospitalization data are applied in the model. Second, we simplified our classification of post-stroke events, combining ischemic and hemorrhagic strokes, and designating major and minor stroke severity levels. In fact, these events may have different post-event outcomes due to the different treatment efficacy of aspirin and prevalence associated with ischemic stroke and hemorrhagic stroke. Third, we did not assign different per capita campaign costs based on Minnesota regional geography. We believe that our pilot data campaign costs are high; economies of scale associated with a statewide campaign, versus a geographically targeted pilot study, would be associated with lower per capita costs. Also, our analysis demonstrates that such cost variation would not likely impact the CEA results significantly. Finally, the proposed aspirin campaign utilized in our analysis consisted of 2 components: a public and a health professional campaign. The effects of these 2 interventions were not designed to be individually distinguished and therefore, we cannot ascertain the separate contribution of each component. If, for example, the health professional component leads to better recognition by physicians of individuals' bleeding risk, this could reduce potential harms within the target population and improve the cost-efficacy outcomes. As well, the adherence to aspirin use over the lifetime of the model is unknown. Yet, as for all pharmacologic interventions, methods to sustain adherence are well-defined and are known to be improved by both public and health professional educational interventions. We have attempted to account for many of these limitations by performing sensitivity analyses to assess the robustness of the findings.

Conclusions

This analysis provides the economic case for a 3-year statewide public awareness campaign to promote aspirin use for primary prevention of CVD. Results from this study can inform policy recommendations and public health investments for promoting primary prevention of CVD. This analysis indicates that a campaign promoting targeted low-dose aspirin use is less costly and more beneficial than the current standard of practice. With clinician adjudication of individual benefit and risk, mechanisms can be made available that would facilitate achievement of aspirin's beneficial impact on lowering risk of CVD events, with minimization of adverse events. These data demonstrate that a population-based CVD primary prevention strategy may lead to a positive health and economic benefit, particularly for Medicare and other secondary payers.

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Disclosures

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SUPPLEMENTAL MATERIAL

Figure S1. Model flow depicted by the decision tree.

Abbreviations: MI: myocardial infarction; GI: gastrointestinal.

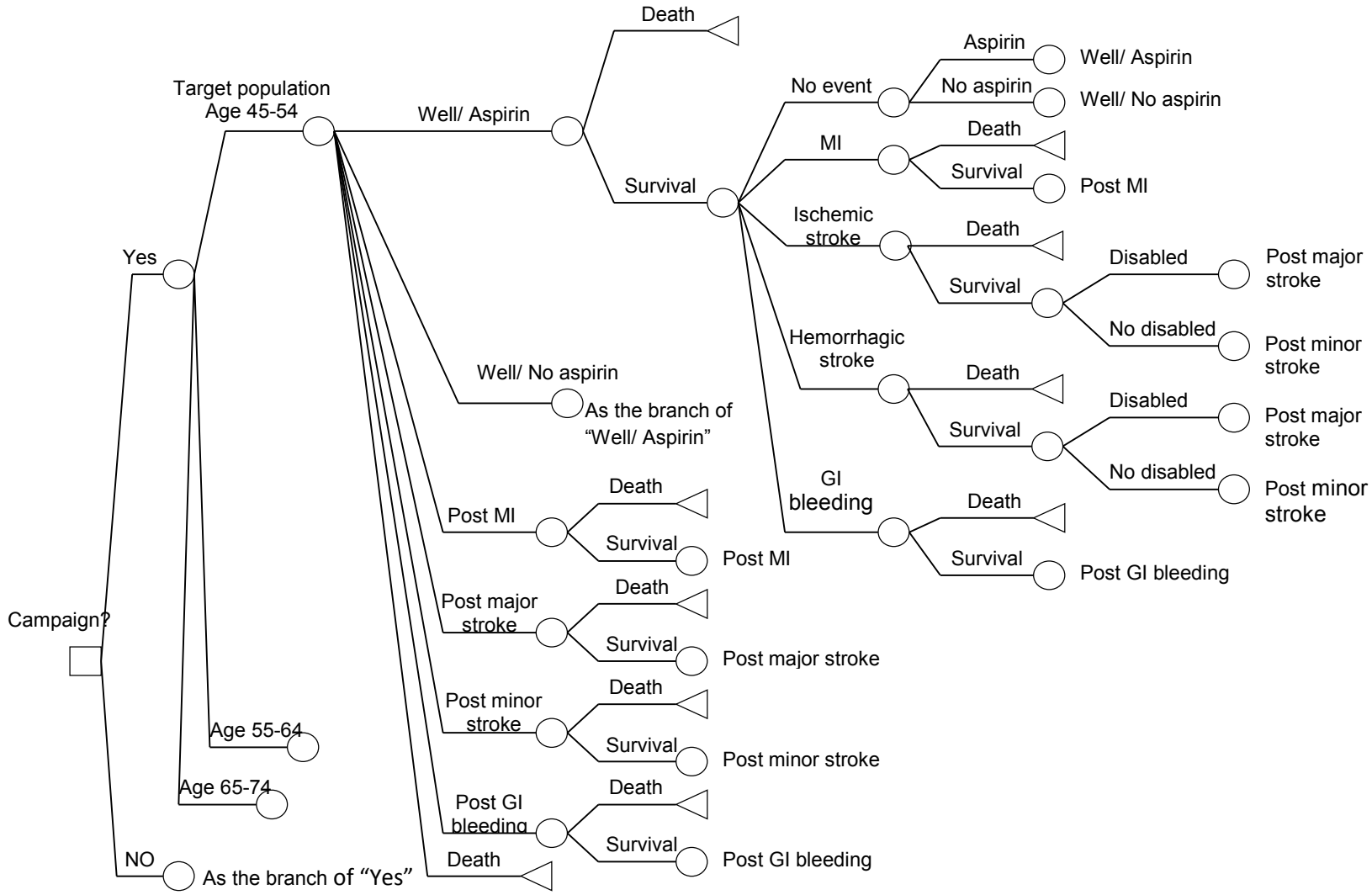

Table S1. Summary of assumptions used in the model.

Assumption	Source
Recovery to full health for individuals with GI bleeding	1-3
Post-major stroke and post-minor stroke represented the health states after the first ischemic stroke or hemorrhagic stroke event	1
Aspirin use would increase annually by 5 percentage points for 3 years from 36% to 51% in both the male and female cohorts.	4
CVD mortality for aspirin users to be the same as non-users	5
Fatality rate of GI bleeding was fixed at 3% annual risk	1
All-cause mortality in subsequent years following a MI, major stroke or minor stroke remains twice as high compared to individuals who do not experience such events	1
The post-GI bleeding mortality rate was assumed to be identical to all-cause mortality	1
Adherence to aspirin was assumed 100%	2,3

Abbreviations: GI, gastrointestinal; CVD, cardiovascular disease.

Supplemental References

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