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Primary care

Epidemiological modelling of routine use of low dose aspirin for the primary prevention of coronary heart disease and stroke in those aged ≥70

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Abstract

Objective To investigate the routine use of low dose aspirin in people aged ≥70 without overt cardiovascular disease.
Design Epidemiological modelling in a hypothetical population.
Setting Reference populations of men and women in the year 2000 from the state of Victoria, Australia.
Subjects 10 000 men and 10 000 women aged 70-74 with no cardiovascular disease.
Main outcome measures First ever myocardial infarction or unstable angina, ischaemic or haemorrhagic stroke, and major gastrointestinal haemorrhage. Health adjusted years of life lived.
Results The proportional benefit gained from the use of low dose aspirin by the prevention of myocardial infarctions (−389 in men, −321 in women) and ischaemic stroke (−19 in men and −35 in women) is offset by excess gastrointestinal (499 in men, 572 in women) and intracranial (76 in men, 54 in women) bleeding. The results in health adjusted years of life lived (which take into account length and quality of life) are equivocal for aspirin causing net harm or net benefit.
Conclusion Epidemiological modelling suggests that any benefits of low dose aspirin on risk of cardiovascular disease in people aged ≥70 are offset by adverse events. These findings are tempered by wide confidence intervals, indicating that the overall outcome could be beneficial or adverse.

Introduction

The effects of low dose aspirin for the primary prevention of cardiovascular disease have been investigated in six large scale randomised clinical trials, which have been subjected to meta-analyses.[1–3] On the basis of all but the last of these trials, current US guidelines recommend the use of low dose aspirin (75-150 mg) for people with a five year absolute coronary risk of ≥3% or a 10 year absolute cardiovascular risk of ≥10%.[2 4] If implemented, these recommendations would mean that most elderly people would be prescribed aspirin prophylaxis because age is the greatest determinant of absolute risk. From the Australian diabetes, obesity, and lifestyle (AusDiab) data we estimated that in Australia about two thirds of people aged 70-74 (94% of men and 46% of women) have an estimated 10 year absolute cardiovascular risk of ≥10%.[5 6] Prophylactic use of a potentially toxic agent can be problematic, however, particularly in people in whom comorbidity and polypharmacy are common.

In a prospective observational study in two large UK general hospitals, aspirin was the causal agent in 18% of all admissions for adverse drug reactions and was implicated in 61% of all associated deaths.[7] Importantly, patients admitted with adverse drug reactions were significantly more likely to be older and female than those admitted without adverse drug reactions. In contrast, the primary prevention clinical trials were conducted mostly in middle aged people. The potential health gains of any preventive strategy need to be carefully balanced against their potential risks.

We simulated the broad implications of routine use of aspirin in patients aged ≥70. We used epidemiological modelling, a relatively new research method using evidence from clinical trials, descriptive epidemiology, and demography to critically inform clinical and public health practice.[8]

Methods

Model

We developed an epidemiological model in the configuration of a decision analysis tree, with the main branches representing the treatment options being compared.[9] The progression of hypothetical cohorts of individuals through the decision analysis tree was underpinned by Markov modelling.[10] This enables repeated analyses of the tree, which in essence allows for simulation of a period of follow-up during which multiple events can occur and the risks of these events change with time.

In our model we followed up 10 000 men and 10 000 women from the ages of 70-74 until death or 100. The figure shows the generic framework of the models. The tree is fully displayed only for the baseline arm (no aspirin treatment) but the treatment arm (aspirin treatment) has the same detail. In the baseline year (2000) everyone in the modelled cohort started in the state "alive before incident acute coronary syndrome and stroke." From there, probabilities of fatal and non-fatal disease, specific for age and sex, determined who made transitions to other health states (for example, alive after stroke or death) over time. We assumed that people who suffered episodes of non-fatal major gastrointestinal haemorrhage made full recovery.

To undertake comparative analyses of the two treatment strategies, we applied relative changes to the risks of incident acute coronary syndrome, haemorrhagic stroke, and major gastrointestinal bleeding, as indicated by the meta-analysis by Hayden et al,[2] to the relevant transition probabilities. We derived the relative change to the risk of ischaemic stroke from the meta-analysis by Hart et al.[1]

The consequences of discontinuing treatment (for instance, people who did not comply with treatment or who were taken off aspirin after a major bleeding event) were modelled by stratification of the strategy arm into "on treatment" and "off treatment" branches (see figure). The model was also run assuming complete compliance with treatment therapy.

Outcomes of interest were lifetime differences between the treatment groups in terms of:

- Fatal and non-fatal myocardial infarction/unstable angina
- Fatal and non-fatal ischaemic stroke
- Fatal and non-fatal haemorrhagic stroke
- Fatal and non-fatal major gastrointestinal haemorrhage
- Total years of life lived
- Years of life lived adjusted for health.

We calculated health adjusted years of life lived by adjusting the years of life lived by a "disability weight" to reflect the disability associated with (non-fatal) health states.[11] Future health gains were discounted to reflect society's preference for immediate rather than future health. The discount rate applied was 3% as recommended by the US Panel on Cost-effectiveness in Health and Medicine.[12]

To reflect uncertainty surrounding data inputs (and hence outputs) for the model, we entered these as ranges rather than single values. Each range was described by a probability distribution to reflect the nature of uncertainty. We used Monte Carlo simulation, with 2000 simulations for each analysis (that is, for each analysis, the progress of a cohort of 10 000 individuals was simulated 2000 times).[13] During each simulation, we sampled a value from every input range according to its probability distribution. For each outcome of interest, the model generated 2000 results, and we derived uncertainty ranges from the distributions of these. Sensitivity analyses were also undertaken to determine which of the input ranges most influenced the modelled outputs.

The models were developed in Microsoft Excel with the software macro @Risk (Palisade Corporation, NY, USA) for Monte Carlo micro-simulation.

Data sources

The reference populations were men and women aged 70-74 in the year 2000 from Victoria, Australia. We used baseline population data from the Australian Bureau of Statistics and data on the prevalence of coronary heart disease and stroke, specific for age and sex, from the AusDiab study.[5 14] The AusDiab study (1999-2001) collected representative cross sectional data on major chronic diseases and their risk factors in 11 427 Australians aged ≥ 25.

Incident rates of the outcomes of interest were derived from combined data from the Victorian admitted episodes database (VAED), the World Health Organization's monitoring trends and determinants of cardiovascular disease (MONICA) studies (two Australian sites), and the north east Melbourne stroke incidence study (NEMESIS).[15–17] The VAED provides a comprehensive record of demographic and clinical information on all admissions to all public and private healthcare institutions across Victoria, and the NEMESIS study maintained a register of strokes occurring in a defined area of Melbourne (the capital city of Victoria) from the mid to the late 1990s.

Admissions for acute coronary syndrome were defined by ICD-10 (international classification of diseases, 10th edition) codes I20 (angina pectoris), I21 (acute myocardial infarction), I23 (certain current complications after acute myocardial infarction), and I24 (other acute ischaemic heart diseases). Admissions for stroke were defined by ICD-10 codes I61 (intracerebral haemorrhage), I62 (other non-traumatic intracranial haemorrhage), I63 (cerebral infarction), and I66 (stroke not specified as haemorrhagic or infarction). These codes had to have been nominated as one of the primary causes of admission.

We applied decreasing trends to transition probabilities underlying acute coronary syndrome and ischaemic and haemorrhagic stroke to reflect probable ongoing falls in the incidence and case fatality. These trends were extrapolated from those observed in Victoria from 1979 to 2000.[18] Between 1981 and 2000 in the UK, mortality from coronary heart disease fell by 62% in men and 45% in women; 42% of the fall was attributed to individual treatment (including 11% to secondary prevention, 13% to heart failure treatment, 8% due to initial treatment of acute myocardial infarction, and 3% to blood pressure treatments) and 58% to reductions in population risk factors.[19] On the basis of this finding, we apportioned 58% and 42% of the overall decreasing mortality trend to incidence and case fatality, respectively, in the model.

The use of evidence from trials for estimating gastrointestinal bleeding was problematic because most trials studied younger age groups, and results probably underestimate the risk in elderly people. To estimate rates of "aspirin modifiable" gastrointestinal bleeding, we first determined the rates of hospital admissions for gastrointestinal bleeding where there was no mention of cancer, cirrhosis/portal hypertension, vascular malformations in the gastrointestinal tract, or inflammatory bowel disease as underlying causes. These were then reduced proportionally by the number of people with existing coronary heart disease or stroke on low dose aspirin (using age and sex specific data on the prevalence of coronary heart disease and stroke reported in the AusDiab study) and by the greater share of risk for gastrointestinal bleeding (relative risk as indicated by the meta-analysis by Hayden et al) that they would have contributed.[2]

We used disability weights for coronary heart disease, stroke, and major gastrointestinal haemorrhage—ranging from 0 (perfect health) to 1 (worst possible health)—from the Australian burden of disease study.[11] Projected years lived were further adjusted for other causes of ill health, with estimated prevalence and age specific weighted probabilities of disability from all other diseases apart from coronary heart disease and stroke. The contemporary publication of the women's health study (WHS) allowed us to recalculate outcomes for women using these data.

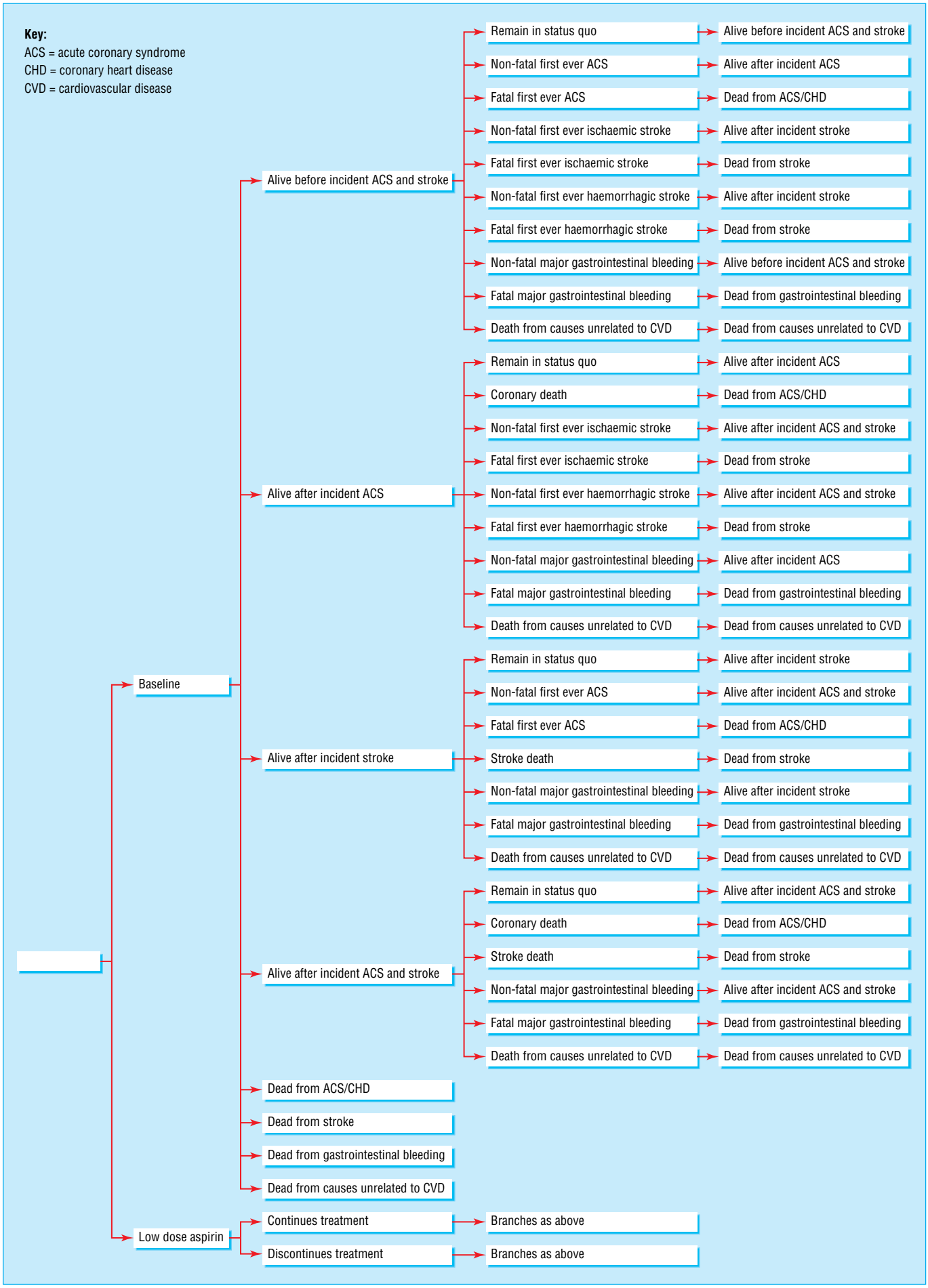
Inputs for the analysis

Tables 1 to 3 list all data inputs in the analyses.

Results

Table 4 summarises the results from the simulations. The model suggests that the benefit gained from routinely prescribing low dose aspirin to patients aged ≥ 70 in terms of preventing first ever coronary heart disease events would be offset by a greater occurrence of gastrointestinal and intracerebral bleeding. On balance, there was no indication of a net benefit or harm in terms of deaths, years of life saved, or years of healthy life saved. The last measure takes into account both length and quality of life and is therefore the most comprehensive measure of health effect.

Sensitivity analyses indicated dominance of the relative risks for disease associated with aspirin on the modelled outputs. For each of the disease related outcomes, whether incident events or deaths, the input variable that singularly dominated the modelled output was the relative risk of that particular outcome associated with aspirin. For example, the relative risk associated with coronary heart disease was the input variable which most



Basic structure of model for cardiovascular disease prediction and estimation of the effects of low dose aspirin

Table 1 Baseline incidence rates (per person per year) of first ever events

Age group (years)	Non-fatal acute coronary syndrome	Non-fatal ischaemic stroke	Non-fatal haemorrhagic stroke	Major gastrointestinal haemorrhage	
				Non-fatal	Fatal
Men					
70-74	0.0122	0.0056	0.0008	0.0045	0.0003
75-79	0.0190	0.0093	0.0014	0.0047	0.0006
80-84	0.0261	0.0140	0.0021	0.0056	0.0008
≥85	0.0298	0.0193	0.0029	0.0047	0.0021
Women					
70-74	0.0085	0.0036	0.0004	0.0038	0.0002
75-79	0.0119	0.0068	0.0008	0.0045	0.0002
80-84	0.0161	0.0111	0.0012	0.0051	0.0005
≥85	0.0205	0.0150	0.0017	0.0063	0.0014

influenced the predicted number of coronary heart disease events or deaths prevented. For the combined outcomes (years of life saved and health adjusted years of life saved), the relative risks associated with each of coronary heart disease, ischaemic stroke, and haemorrhagic stroke were the three most influential variables on the modelled outputs (to roughly equal extents), but the relative risk associated with major gastrointestinal haemorrhage was less influential.

When we assumed 100% compliance and used data from the women's health study, the outcomes were altered but not the overall uncertainty of the balance of events prevented versus adverse events (numbers not shown).

Discussion

Our modelling suggests that the routine use of low dose aspirin from the age of 70 in those without overt cardiovascular disease is as likely to be associated with benefit as harm. Because of the uncertainty in the assumptions, indicated by the wide confidence intervals, the balance of harm and benefit could tip either way. These findings reinforce the need for a clinical trial in elderly people to establish the true benefit or harm of aspirin in the primary prevention of cardiovascular disease.[20] They also underscore the importance of targeting preventive treatment (especially primary preventive treatment) to those for whom the potential balance of benefit versus harm is optimal.

Comparison with previous data

The earliest of the primary prevention trials for aspirin—the British male doctors trial and the physicians' health study—were conducted in men, had conflicting results for risk of myocardial infarction, and had insufficient power to allow firm estimates of serious adverse events such as gastrointestinal bleeding and haemorrhagic stroke.[21 22] This is particularly relevant in elderly people, in whom the risk of fatal and non-fatal stroke is greater than in any other section of the community, and the cost of caring for patients with stroke is a major concern. Meta-analyses of these and three more recent trials—the primary prevention project, the hypertension optimal treatment study, and the thrombosis prevention trial—concluded that aspirin reduces the combined risk of non-fatal myocardial infarction and fatal coronary heart disease and increases the risk for haemorrhagic stroke and major gastrointestinal bleeding.[1 2 23–25] The women's health study had a non-significant 9% reduction in the first major cardiovascular event (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular mortality).[3] Subgroup analyses in those aged ≥65 (10% of the cohort), however, did show a significant reduction in major cardiovascular events, ischaemic stroke, and myocardial infarction. The risk of gastrointestinal bleeding for which patients required transfusion was significantly higher in the aspirin group (relative risk 1.40, 95% confidence interval 1.07 to 1.83, P = 0.02), and thus the 44 fewer coronary heart disease events in those aged ≥65 years taking aspirin needs to be offset by the 16 more gastrointestinal haemorrhages that resulted in a need for transfusion.[3]

The primary prevention trials present estimates of gastric bleed across all ages, although only 24% of the cohort and none of the thrombosis prevention trial cohort were ≥70 at baseline. Our routine hospital data indicate a dramatic increase in incidence with age and, to a greater extent, the case fatality of gastric bleeding. This applies to all aspirin dosage regimens, however, and therefore there is a need for observational data on low dose aspirin.

Our findings highlight the limitations of assessing clinical effectiveness with single disease states as outcomes. Consideration needs to be given to possible adverse effects, especially for special risk groups such as elderly people and for conditions of high prevalence. The model predicts no changes in years lived free from heart disease, stroke, and major gastrointestinal bleeding. Indeed there seems to be equal likelihood that extra life is lost as it is gained.

Table 2 Baseline case fatality of first ever events. Figures represent triangular distributions specified as minimum, most likely value, maximum

Age group (years)	Acute coronary syndrome		≤28 days for ischaemic stroke	≤28 days for haemorrhagic stroke	>28 days for ischaemic and haemorrhagic stroke
	≤28 days	>28 days			
Men					
70-74	0.09, 0.10, 0.12	0.02, 0.02, 0.02	0.07, 0.12, 0.16	0.30, 0.46, 0.60	0.03, 0.03, 0.03
75-79	0.10, 0.11, 0.13	0.02, 0.03, 0.03	0.07, 0.12, 0.16	0.30, 0.46, 0.60	0.04, 0.05, 0.05
80-84	0.10, 0.12, 0.14	0.04, 0.05, 0.05	0.07, 0.12, 0.16	0.30, 0.46, 0.60	0.07, 0.08, 0.08
≥85	0.11, 0.14, 0.16	0.12, 0.12, 0.13	0.07, 0.12, 0.16	0.30, 0.46, 0.60	0.18, 0.19, 0.21
Women					
70-74	0.05, 0.06, 0.07	0.02, 0.02, 0.02	0.07, 0.12, 0.16	0.30, 0.46, 0.60	0.02, 0.02, 0.02
75-79	0.06, 0.07, 0.08	0.02, 0.02, 0.03	0.07, 0.12, 0.16	0.30, 0.46, 0.60	0.03, 0.03, 0.03
80-84	0.06, 0.08, 0.09	0.04, 0.04, 0.04	0.07, 0.12, 0.16	0.30, 0.46, 0.60	0.05, 0.05, 0.05
≥85	0.06, 0.09, 0.11	0.11, 0.12, 0.12	0.07, 0.12, 0.16	0.30, 0.46, 0.60	0.13, 0.14, 0.15

Table 3 Other data inputs for modelling of effects of aspirin

Variable	Value and uncertainty distribution
Disability weights	
Acute coronary syndrome (incident coronary heart disease)	0.395 for 6 weeks*
Chronic coronary heart disease:	
70-74	0.057*
≥75	0.086*
Incident ischaemic stroke and haemorrhagic stroke:	
70-74 men	0.520 for 6 months*
70-74 women	0.510 for 6 months*
≥75 men	0.620 for 6 months*
≥75 women	0.590 for 6 months*
Chronic ischaemic stroke and haemorrhagic stroke†:	
70-74 men	0.520 applied for 55% of population*
70-74 women	0.510 applied for 57% of population*
≥75 men	0.620 applied for 71% of population*
≥75 women	0.590 applied for 71% of population*
Major gastrointestinal haemorrhage	0.400 for 6 weeks*
Relative risks associated with low dose aspirin	
Acute coronary syndrome	0.60, 0.72, 0.87‡
Ischaemic stroke	0.87, 1.03, 1.21‡
Haemorrhagic stroke	0.90, 1.40, 2.00‡
Major gastrointestinal haemorrhage	1.40, 1.70, 2.10‡
First year discontinuation of low dose aspirin	30%-50%§

*With ±25% uniform uncertainty distribution.
†Disability weights applied only to estimated proportions with ongoing disability beyond six months, estimated from Bonita et al.[31]
‡Triangular uncertainty distributions: lower 95% confidence limit, point estimate, upper confidence limit.[1 2]
§Uniform uncertainty distribution.

While aspirin's beneficial vascular effect is probably through its antiplatelet action, because inflammation may have a role in both the pathogenesis of atherosclerosis and in the precipitation of ischaemic events, aspirin may result in possible benefit through its anti-inflammatory action.[26] Aspirin may be beneficial in other diseases. The onset of dementia may be delayed through both anti-inflammatory and antiplatelet actions, and aspirin has anticarcinogenic effects on the gastrointestinal tract and elsewhere.[27–29] Thus it is possible that the US guidelines, being based on a single disease state, may underestimate the benefits and risks of the use of aspirin for the primary prevention of manifestations of cardiovascular disease in elderly people.

Table 4 Simulated lifetime effects of low dose aspirin compared with no aspirin on cohorts of 10 000 men and 10 000 women in Australia, initially aged 70-74 years and free from cardiovascular disease. Figures are point estimates with 95% uncertainty intervals

Lifetime effects (≥70)	Men	Women
Cases prevented:		
Coronary heart disease	389 (213 to 581)	321 (170 to 484)
Ischaemic stroke	19 (–107 to 146)	35 (–99 to 168)
Haemorrhagic stroke	–76 (–195 to 28)	–54 (–136 to 22)
Major gastrointestinal haemorrhage	–499 (–740 to –266)	–572 (–849 to –308)
Deaths prevented:		
Coronary heart disease	186 (92 to 287)	153 (73 to 241)
Ischaemic stroke	–14 (–94 to 64)	7 (–69 to 83)
Haemorrhagic stroke	–62 (–163 to 23)	–44 (–121 to 20)
Major gastrointestinal haemorrhage	–89 (–133 to –48)	–70 (–105 to –38)
Other causes	–17 (–139 to 108)	–40 (–154 to 72)
Total deaths	3 (–9 to 16)	6 (–8 to 20)
Years of life saved	20 (–784 to 774)	145 (–496 to 780)
Health adjusted years of life saved	3 (–654 to 623)	106 (–488 to 678)

What is already known on this topic

Current US guidelines recommend the use of low dose aspirin in people with a raised risk of cardiovascular and coronary disease

Implementation of these guidelines would mean that most elderly people would be prescribed aspirin

What this study adds

Epidemiological modelling suggests that the reduction in incident myocardial infarction and ischaemic stroke with routine use of low dose aspirin in elderly people may be offset by increased cases of serious bleeding

These findings are tempered by wide confidence intervals, indicating that the overall outcome could be beneficial or adverse

Limitations of the study

The main limitation of our study stems from potential unreliability of data sources, especially for rates of "aspirin modifiable" gastrointestinal haemorrhage as these were not directly available and had to be extrapolated. Some elderly people, especially the very infirm or institutionalised, may not have been admitted to hospital after disease events of interest and therefore were not captured by the Victorian admitted episodes database. In the case of stroke, we established that we did not miss many cases by using those admitted to hospital as the incidence of admission to hospital with first ever stroke was almost identical to that measured in the north east Melbourne stroke incidence study. We did not have a similar comparator for coronary heart disease.

The initial five primary prevention trials were dominated by middle aged men. Publication of the women's health study allowed us to recalculate event rates (data not shown). The results for women were also equivocal.

Input data regarding the underlying rates of disease were drawn from the Victorian admitted episodes database, and therefore the results are at least directly applicable to elderly people in Victoria. There are no indications that these people differ significantly from those in the rest of Australia and other developed countries.

Conclusion

Despite sound evidence for efficacy, the temptation to blindly implement low dose aspirin treatment for the primary prevention of thromboembolic cardiovascular disease in elderly people must be resisted. Epidemiological modelling suggests that the benefits of this strategy (a reduction of incident myocardial infarction and ischaemic stroke) may be offset by increased cases of serious bleeding.

The contrast of a 1.02 relative risk for ischaemic stroke in primary prevention with a 0.7 relative risk in secondary prevention shows that the true balance of risks and benefits for these and other outcomes in elderly people needs to be established by a randomised clinical trial in enough participants to accurately weigh these possibilities and to investigate impacts on other diseases prevalent in elderly people.[20 30]

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Competing interest: MRN has received aspirin and placebo tablets for an investigator driven trial and travel support from Bayer, a manufacturer of aspirin.

Ethical approval: Monash University standing committee on ethics in research involving humans (SCERH).

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