

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.¹⁻³ Current US guidelines recommend the use of low dose aspirin (75-150 mg) for people with a five year absolute coronary risk of $\geq 3\%$ or a 10 year absolute cardiovascular risk of $\geq 10\%$.^{2,4} 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 $\geq 10\%$.^{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.

We simulated the broad implications of routine use of aspirin in patients aged ≥ 70 .

Methods

Model

In our model we followed up 10 000 men and 10 000 women from the ages of 70-74 until death or 100. 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.⁸ 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.⁹

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 simula-



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tion, where for each analysis the progress of a cohort of 10 000 individuals was simulated 2000 times.¹⁰

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 11}

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).¹²⁻¹⁴ The VAED provides a comprehensive record of demographic and clinical information on all admissions to 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.

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 More details of the model, data sources and data inputs can be found on bmj.com.

Results

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 (table). 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 a 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 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.³

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, the balance of harm and benefit could tip either way. 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, with the wide confidence intervals indicating the overall outcome could be beneficial or adverse.

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 also result in possible benefit through its anti-inflammatory action.¹⁵ 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.¹⁶⁻¹⁸ 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.

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.^{19 20}

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Competing interests: MRN has received aspirin and placebo 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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*Endpiece***Satisfaction**

I am never satisfied that I have handled a subject properly until I have contradicted myself at least three times.

John Ruskin