Aspirin for primary prevention: yes or no?

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ABSTRACT

AIM: To assess benefit versus harm of aspirin for cardiovascular disease (CVD) primary prevention by age group, gender and risk category and to interpret these results in light of current New Zealand CVD risk assessment and management guidelines.

METHODS: Rates of benefit (avoided vascular events) and harm (additional major extracranial bleeds) for each gender and age group were calculated from data from the six randomised controlled trials included in the Anti-Thrombotic Trialists' (ATT) Collaboration meta-analysis. These rates were applied to CVD risk categories to calculate the net benefit or net harm likely to occur from the use of aspirin in primary prevention of CVD as monotherapy and when added to lipid and blood pressure–lowering therapies.

RESULTS: Benefits of aspirin monotherapy outweigh the harms for both men and women aged up to 80 years with calculated five-year CVD risk >15% in primary prevention. Harm may outweigh benefit for primary prevention for those over 80 years. For men 70–79 years the benefit of aspirin in primary prevention is marginal when added to lipid and blood pressure–lowering therapies.

DISCUSSION: The recent ATT Collaboration meta-analysis has raised doubts about the relative safety of aspirin in primary prevention of CVD. However, modelling by risk category and age group suggests that current guidelines are justified in recommending aspirin for primary prevention of CVD in those with five-year CVD risk ≥15% up to the age of 80 years. For men 70–79, consider lipid and blood pressure–lowering therapies first then reassess whether aspirin adds additional net benefit.

KEYWORDS: Aspirin; primary prevention; cardiovascular disease; cardiovascular risk

Introduction

Cardiovascular disease (CVD) is New Zealand's biggest killer and leading cause of loss of healthy life years.[1] Current New Zealand (NZ) CVD risk assessment and management guidelines recommend that CVD preventive management decisions are based on an individual's five-year absolute CVD risk.[2] All people with a five-year CVD risk 15% or greater should be considered for aspirin, lipid-lowering and blood pressure–lowering therapies (unless there are contraindications), in addition to lifestyle interventions, as necessary to reduce their absolute risk. This recommendation was made on the basis that the combination of aspirin, lipid-lowering and blood pressure–lowering therapies is estimated to reduce CVD risk by at least 55% with a much lower risk of harm.[3] While the role of aspirin in the management of people with a prior CVD event remains undisputed, the recently published Anti-Thrombotic Trialists' (ATT) Collaboration meta-analysis has raised doubts about the relative safety of aspirin in the primary prevention of CVD.[4] We sought to model benefit versus harm of aspirin for CVD primary prevention for age group, gender and risk categories using data from the ATT Collaboration meta-analysis and to interpret these results in light of current NZ CVD risk assessment and management guidelines.

J PRIMARY HEALTH CARE 2010;2(2):92–99.

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Methods

Design

Evidence-based modelling of benefit and harm of aspirin for primary prevention of CVD.

Population

This analysis used results from the ATT Collaboration meta-analysis, which included 95 456 individuals without prior CVD who had been randomised to aspirin or no aspirin in six randomised controlled trials of at least 1000 non-diabetic participants each with at least two years of scheduled treatment.[4]

Analysis

Expected CVD events

The expected number of CVD events based on five-year CVD risk for a hypothetical population of 1000 people was calculated. For example, for a hypothetical cohort of 1000 people at 1% five-year CVD risk, 10 CVD events would be expected. The CVD outcomes included in Framingham-based prediction models (such as those used in NZ) are myocardial infarction, angina, stroke, transient ischaemia, congestive heart failure, peripheral vascular disease and CVD-related death.[5]

Benefit

Rates of benefit (avoided vascular events) with aspirin were calculated by applying the proportional reduction in serious vascular events observed in the ATT Collaboration meta-analysis (12%, 99% confidence interval 6–18%) to the number of CVD events expected to be avoided in five years. This reduction was applied to progressively increasing five-year CVD risk groups (from 1% to 20%) for hypothetical populations of 1000 people who were also stratified by gender and 10-year age bands: 50–59, 60–69, 70–79 and 80–89 years. Vascular events in the meta-analysis were defined as myocardial infarction, stroke (haemorrhagic or other), or death from a vascular cause (coronary heart disease death, stroke death, or other vascular death—including sudden death, death from pulmonary embolism, and death from any haemorrhage).

WHAT GAP THIS FILLS

What we already know: The benefits of aspirin outweigh the risks in people with a history of cardiovascular disease.

What this study adds: The benefits of aspirin outweigh the risks in primary prevention of CVD in those with five-year CVD risk ≥15%, up to the age of 80 years, although in men 70–79 consider lipid and blood pressure–lowering therapies first then reassess whether aspirin adds additional net benefit.

Harm

Rates of harm (i.e. the difference between rates of non-fatal major extracranial bleeds in the aspirin and control groups) were provided by the ATT Collaboration meta-analysis for men and women aged 50–59 years (0.2% and 0.1%, respectively). Non-fatal major extracranial bleeds were mainly gastrointestinal and usually defined as a bleed requiring transfusion. Rates of harm were estimated for other age groups (60–69, 70–79 and 80–89 years) by multiplying the rate for those aged 50–59 years by the rate ratio associated with age (per decade) identified by the ATT Collaboration meta-analysis for each additional decade (2.15, 95% confidence interval 1.93–2.39). Haemorrhagic stroke and fatal extracranial haemorrhage were included in vascular events (see above).

Aspirin monotherapy

Rates of benefit and harm were compared in CVD risk / sex / age categories to assess the net benefit or net harm likely from the use of aspirin in primary prevention of CVD and depicted in table format.[6]

Adding aspirin to lipid and blood pressure–lowering therapy

The effect of adding aspirin to a regime of lipid and blood pressure–lowering therapy among those with five-year CVD risk ≥15% was assessed for each sex / age category. The benefit of lipid-lowering therapy (statin) and blood pressure–lowering therapy was estimated from recent meta-analyses of randomised controlled trials.[7,8] Proportional reductions in the risk of coronary and cerebrovascular events associated with treat-

ment in people without a history of CVD were combined using the ratio of these events from the ATT Collaboration meta-analysis to produce a proportional reduction in the risk of CVD events. Rates of harm from the most serious adverse events associated with statins (rhabdomyolysis) and antihypertensives (adverse events serious enough to warrant discontinuation of antihypertensive therapy) were also estimated from meta-analyses of randomised controlled trials.[9,10]

Results

Aspirin monotherapy

The benefits of aspirin are estimated to exceed the harms at least fourfold among men 60–69 years and women 70–79 who have a calculated five-year CVD risk ≥15% in primary prevention (see Table 1). In people one decade older (men 70–79 and women 80–89) with the same CVD risk, the number of vascular events avoided by aspirin are still close to twice the harms. From the age of 80 years the harms of aspirin are likely to outweigh the benefits in primary prevention among men with five-year CVD risk at or just over 15%.

Adding aspirin to lipid and blood pressure–lowering therapy

For people with a five-year CVD risk of 15%, statin and antihypertensive therapy are estimated to reduce absolute CVD risk by 6.6% (relative risk reduction (RRR) of 26% and 24% for statin and antihypertensive therapy respectively applied in a stepwise fashion to produce an overall RRR of 44%) and increase absolute risk of serious side effects by 0.15% over a five-year period (see Figure 1). The balance of benefits and risks varies by sex and age when aspirin is added to the regime. Aspirin is estimated to reduce absolute CVD risk by a further 1% (12% RRR), but absolute risk of additional serious side effects (extracranial bleeding) is estimated to increase by 0.20% in men aged 50–59 years, 0.43% in men 60–69, 0.92% in men 70–79 and 1.99% in men 80–89. Absolute risk of additional serious side effects is estimated to increase by 0.10% in women aged 50–59 years, 0.22% in women 60–69, 0.46% in women 70–79 and 0.99% in women 80–89 (see Figure 2).

Discussion

This analysis found that the benefits of aspirin monotherapy outweigh the harms for both men and women aged up to 80 years with five-year CVD risk ≥15% in primary prevention. However, harm may outweigh benefit for primary prevention for those over 80 years, particularly for men. The proportional reduction in CVD risk is greater and the risk of serious adverse events is lower with statin and antihypertensive therapies than with aspirin. For men 70–79 years the benefit of aspirin in primary prevention is marginal when added to lipid and blood pressure–lowering therapies. Therefore, current New Zealand CVD risk assessment and management guidelines are justified in recommending aspirin for primary prevention of CVD in those with five-year CVD risk ≥15%, up to the age of 80 years, although in men 70–79, lipid and blood pressure–lowering therapies should be considered first and additional net benefit of aspirin assessed.

This analysis used the most recently published meta-analysis of randomised controlled trials of aspirin for the primary prevention of CVD to model the benefit and harm of aspirin.[4] The proportional reduction of CVD (and increase in haemorrhagic stroke) with aspirin was assumed to be constant across sex and age groups. Aspirin has been shown to reduce CVD primarily by reducing myocardial infarctions in men and ischaemic strokes in women.[11] Modelling could be improved by updating the ATT Collaboration with more recent trials,[12] obtaining nationally representative data to provide more up-to-date and generalisable estimates for rates of serious adverse events and assessing the treatment effect of aspirin by sex and age groups.

There are differences in the way outcomes are defined that should be considered when interpreting results. Firstly, haemorrhagic strokes and fatal extracranial bleeds were included in the ATT Collaboration's estimate of the proportional reduction in serious vascular events. This may explain why their estimate of the benefit of aspirin was lower than those previously reported.[2] Secondly, the number of estimated CVD events and those avoided may be slightly overestimated by the NZ CVD risk assessment and management guidelines, which use the Framingham equation, because while the ATT Collaboration

Table 1. Estimated vascular events avoided and estimated additional extracranial bleeds associated with using aspirin for five years in hypothetical cohorts of 1000 people

5-year risk of CVD event	CVD events expected, *n	Estimated vascular events avoided† in 5 years,‡n							
		Men				Women			
		Age 50–59 years	Age 60–69 years	Age 70–79 years	Age 80–89 years	Age 50–59 years	Age 60–69 years	Age 70–79 years	Age 80–89 years
1%	10	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
2%	20	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
3%	30	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
4%	40	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
5%	50	6	6	6	6	6	6	6	6
6%	60	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
7%	70	8.4	8.4	8.4	8.4	8.4	8.4	8.4	8.4
8%	80	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6
9%	90	10.8	10.8	10.8	10.8	10.8	10.8	10.8	10.8
10%	100	12	12	12	12	12	12	12	12
11%	110	13.2	13.2	13.2	13.2	13.2	13.2	13.2	13.2
12%	120	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4
13%	130	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6
14%	140	16.8	16.8	16.8	16.8	16.8	16.8	16.8	16.8
15%	150	18	18	18	18	18	18	18	18
16%	160	19.2	19.2	19.2	19.2	19.2	19.2	19.2	19.2
17%	170	20.4	20.4	20.4	20.4	20.4	20.4	20.4	20.4
18%	180	21.6	21.6	21.6	21.6	21.6	21.6	21.6	21.6
19%	190	22.8	22.8	22.8	22.8	22.8	22.8	22.8	22.8
20%	200	24	24	24	24	24	24	24	24
		Estimated additional non-fatal extracranial bleeds§ in 5 years, n							
		2.0	4.3	9.2	19.9	1.0	2.2	4.6	9.9

Areas shaded light grey indicate combinations of five-year CVD risk, sex and age for which the estimated number of additional extracranial bleeds are greater than or equal to the estimated number of vascular events avoided[6]

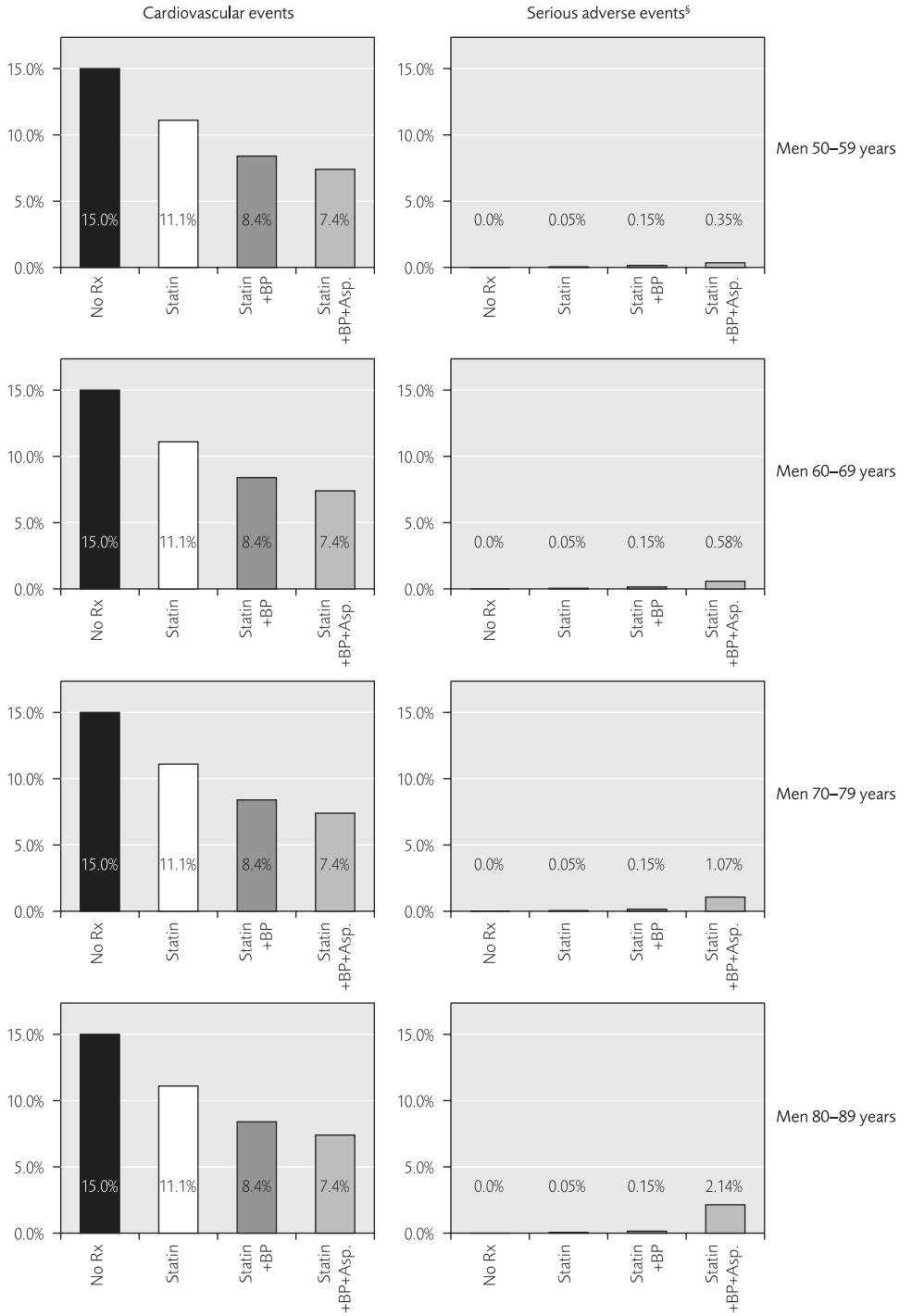
* Based on Framingham equation, i.e. including myocardial infarction, angina, stroke, transient ischaemia, congestive heart failure, peripheral vascular disease and CVD-related death[5]

† Vascular events avoided defined as myocardial infarction, stroke (ischaemic, haemorrhagic or other), or vascular death (coronary heart disease death, stroke death, or other vascular death [which includes sudden death, death from pulmonary embolism, and death from any haemorrhage])[4]

‡ Assuming 12% proportional net reduction in vascular events[4]

§ Calculated from number of excess non-fatal gastrointestinal or other extracranial bleeds (usually defined as a bleed requiring a transfusion) among those aged 50–59 years and allocated to aspirin. Extrapolated to older age groups using rate ratio associated with age (2.15 per decade). Haemorrhagic stroke and fatal extracranial haemorrhage counted in vascular events (see above).[4]

Figure 1. Cardiovascular events and serious side effects with addition of aspirin to a regime of statin† and antihypertensive therapy‡ over a five-year period in men with calculated five-year CVD risk ≥15%*



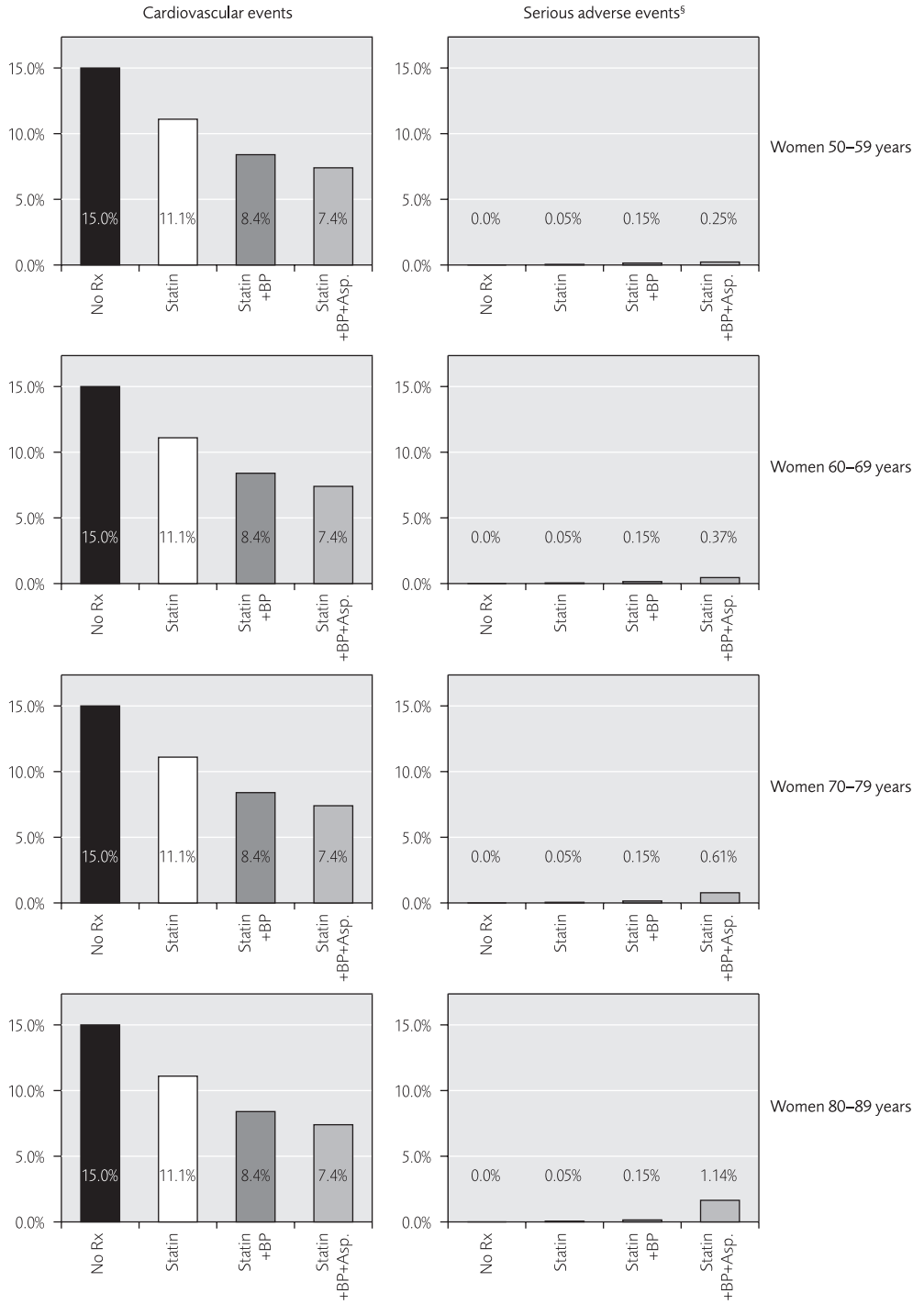
* Assuming 12% proportional reduction in CVD events with aspirin[4]

† Assuming 26% proportional reduction in CVD events with statin[7]

‡ Assuming 24% proportional reduction in CVD events with antihypertensive[8]

§ Assuming 0.05% rhabdomyolysis with statins, 0.1% experience adverse events serious enough to warrant discontinuation of antihypertensive therapy (as demonstrated with thiazides and ACE [angiotensin converting enzyme] inhibitors)[9] and extracranial bleeds as outlined in Table 1

Figure 2. Cardiovascular events and serious side effects with addition of aspirin to a regime of statin† and antihypertensive therapy‡ over a five-year period in women with calculated five-year CVD risk ≥15%*



* Assuming 12% proportional reduction in CVD events with aspirin[4]

† Assuming 26% proportional reduction in CVD events with statin[7]

‡ Assuming 24% proportional reduction in CVD events with antihypertensive[8]

§ Assuming 0.05% rhabdomyolysis with statins, 0.1% experience adverse events serious enough to warrant discontinuation of antihypertensive therapy (as demonstrated with thiazides and ACE [angiotensin converting enzyme] inhibitors)[9] and extracranial bleeds as outlined in Table 1

meta-analysis included only serious events such as myocardial infarction, stroke and death from CVD (or haemorrhage), the Framingham equation includes 'softer' CVD events such as angina, transient ischaemia and peripheral vascular disease.[5]

New Zealand CVD risk management guidelines use an adjusted Framingham equation.[2] Certain groups (on the basis of family history, ethnicity, diabetes status) are moved up one risk category (5%) during risk assessment and people with isolated high blood pressure or high cholesterol are categorised as being at ≥15% five-year CVD risk. The implications of this adjustment to the absolute benefit likely from medications such as aspirin in people who have been 'upgraded' are not fully known, but there is no obvious reason to believe that the benefit gained would be different. However, one study has suggested that the risk assessment strategy currently used in New Zealand for ethnicity adjustment may be over-estimating risk,[13] while another suggests that for people who have diabetes with microalbuminuria, the Framingham equation underestimates risk substantially, and still underestimates risk with current adjustments.[14]

The ATT Collaboration found that the main risk factors for coronary disease were also risk factors for bleeding associated with aspirin.[4] Whilst our analysis accounted for the risk factors with the greatest effect on bleeds (age and male sex), diabetes, smoking, mean blood pressure and body mass index have not been adjusted for.

On the other hand, the ATT Collaboration meta-analysis is likely to overestimate current gastrointestinal bleeding rates with aspirin. There has been an increase in the use of triple eradication therapy (for H. Pylori) and proton pump inhibitors, along with a reduction in the use of non-steroidal anti-inflammatory agents. Further, while efforts were made to balance the severity of benefit and harm events, side effects of comparable severity to ischaemic stroke or a coronary heart disease event are very rare.

Our findings and recommendations are broadly consistent with, and if anything more conservative than, British and United States (US) guidelines. British guidelines advise that the benefit of aspirin in primary prevention outweighs harm in people aged over 50 years and with 10-year CVD risk ≥20% (equivalent to five-year CVD risk ≥10%[15]).[16] US guidelines recommend that aspirin is offered to men 45–79 years and women 55–79 years when the potential benefit (reduction in myocardial infarction (MI) in men and ischaemic stroke in women) outweighs the potential harm of an increase in gastrointestinal haemorrhage.[6] They estimate that the number of MIs prevented is closely balanced to the number of serious bleeding events when 10-year coronary heart disease risk is 4% for men 45–69, 9% for men 60–69 and 12% for men 70–79 years (equivalent to five-year CVD risk 3, 6.75 and 9%, respectively[15]) . For women, the number of ischaemic strokes prevented is estimated to be closely balanced to the number of serious bleeding events when 10-year stroke risk is 3% for women 55–59, 8% for women 60–69 and 11% for women 70–79 years.

The proportional reduction with aspirin in the ATT Collaboration meta-analysis is comparable across 'primary' and 'secondary' prevention settings in cause-specific outcomes: major coronary events (Rate Ratio 0.82 in primary prevention vs 0.80 in secondary prevention), ischaemic stroke (0.86 vs 0.78) and serious vascular event (0.88 vs 0.81),[4] which questions the rationale for dichotomising CVD prevention. It is more likely that CVD risk and benefit from aspirin are on a continuum.

In conclusion, the findings of this analysis reinforce the importance of basing preventive management decisions on CVD risk. CVD risk assessment is recommended prior to commencing aspirin, lipid-lowering and blood pressure–lowering therapy, and management decisions should generally be made on the basis of this assessment, according to current guidelines. From these analyses, aspirin should still be considered for primary prevention of CVD in those with five-year CVD risk ≥15%, up to the age of 80 years, although in men 70–79 consider lipid and blood pressure–lowering therapies first and then reassess whether aspirin adds additional net benefit.

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ACKNOWLEDGEMENTS
Colin Baigent provided helpful comments during the preparation of this article.

FUNDING
Vanessa Selak is the recipient of a National Heart Foundation Research Fellowship.

COMPETING INTERESTS
VS, CE and AR are undertaking research into a cardiovascular polypill that includes aspirin, but have no financial interest in this product.