Are the benefits of aspirin likely to exceed the risk of major bleeds among people in whom aspirin is recommended for the primary prevention of cardiovascular disease?

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ABSTRACT

AIM: The 2018 New Zealand Consensus Statement on cardiovascular disease (CVD) risk assessment and management recommends the use of aspirin in people aged less than 70 years with a five-year CVD risk ≥15% but without prior CVD. We determined whether the estimated number of CVD events avoided by taking aspirin is likely to exceed the number of additional major bleeds caused by aspirin in this patient population.

METHOD: Major bleeding rates were obtained from the PREDICT primary care study, a large New Zealand cohort of people eligible for CVD risk assessment, after excluding those with no other indications for (eg, established CVD) or contraindications/cautions (eg, prior major bleed) to aspirin use. We modelled the benefits (CVD events avoided) and harms (additional major bleeds) of aspirin for primary prevention of CVD over five years using hypothetical populations aged 40 to 79 years, stratified by sex, age-group and estimated five-year CVD risk. Two clinical scenarios were modelled, according to whether or not optimisation of lipid- and blood pressure-lowering therapy was required prior to aspirin initiation.

RESULTS: In both clinical scenarios the number of CVD events prevented by aspirin over five years was estimated to be, on average, more than the number of bleeds caused by aspirin among people aged less than 70 years with estimated five-year CVD risk of ≥15%. However, the magnitude of the net benefit of aspirin was modest among people aged 60–69 years, particularly if lipid- and blood pressure-lowering therapy had not already been optimised.

CONCLUSION: The benefits of aspirin are likely to exceed the risk of major bleeds among people in whom aspirin is recommended for the primary prevention of CVD. A more cautious approach to the use of aspirin is appropriate for people aged 60–69 years who are likely to have a smaller net benefit from aspirin, particularly those in whom lipid- and blood pressure-lowering therapy has not already been optimised or who have other bleeding risk factors, such as diabetes or smoking. More specific recommendations will be possible when bleeding risk equations are developed to complement the recently developed New Zealand CVD risk equations.

Cardiovascular risk assessment has been an integral component of New Zealand efforts to prevent cardiovascular disease (CVD) for over a decade.[1] Nationally, about 90% of eligible people have had their CVD risk assessed in the last five years. Decisions about the use of medicines known to prevent CVD in New Zealand are therefore able to be based on CVD risk, rather than simply dichotomising people according to whether or not they have had a prior CVD event or using levels of individual risk factors.[2]

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Aspirin reduces the risk of CVD, but is also associated with an increased risk of bleeding.[3,4] For people who have already had a cardiovascular event, the benefits of aspirin generally outweigh its harms, but the balance of benefits and risks is less clear in the case of primary prevention.[5]

The 2018 Ministry of Health Consensus Statement on the assessment and management of CVD in primary care recommends that aspirin be considered in people under 70 years with a five-year CVD risk of ≥15%.[2] The Statement notes that the potential benefits and harms of aspirin "must be carefully assessed and discussed during shared decision-making" but do not offer resources to support decision-making regarding the harms of aspirin.[2]

The purpose of this study is to determine whether the estimated number of CVD events avoided is likely to exceed the number of additional major bleeds caused by aspirin among people in whom aspirin is recommended for primary prevention, using data on bleeding rates from a large New Zealand cohort of people in whom aspirin for primary prevention may be considered.[6]

Method

We estimated the benefits (CVD events avoided) and harms (additional major bleeds) of aspirin for the primary prevention of CVD over five years among hypothetical populations of 1,000 people in whom aspirin for primary prevention may be considered, stratified by sex, 10-year age-groups between 40 and 79 years and estimated five-year CVD risk. Two clinical scenarios were modelled to take into account the strong New Zealand recommendations for lipid-lowering therapy and blood pressure-lowering therapy for people with five-year CVD risk of ≥15%.[2] In clinical scenario 1, people were assumed to already be receiving optimal lipid-lowering therapy (ie, achieving low density lipoprotein cholesterol of <1.8mmol/L[2]) and blood pressure-lowering therapy (below 130/80mmHg[2]). In clinical scenario 2, people were assumed to be on no or suboptimal lipid-lowering therapy and blood pressure-lowering therapy.

In clinical scenario 1, no adjustments were made to account for either the effect of lipid lowering or blood pressure reduction because the New Zealand CVD risk equation includes variables for each medication type as well as the level of lipids (ratio of total cholesterol to high-density lipoprotein cholesterol) and blood pressure (systolic blood pressure).[7]

New Zealand recommendations on the use of lipid- and blood pressure-lowering therapy are stronger than those for the use of aspirin in people with five-year CVD risk of ≥15% for the primary prevention of CVD. Therefore, in clinical scenario 2, adjustments were first made for the effect of optimising lipid-lowering and blood pressure-lowering therapies before considering the effect of adding aspirin. The proportional benefit of a statin on CVD events was based on the estimate obtained by an individual participant data meta-analysis of randomised controlled trials by the Cholesterol Treatment Trialists Collaboration, which was a 21% proportional reduction in CVD events with a 1mmol/L reduction in low density lipoprotein with a statin.[8] The proportional effect of blood pressure-lowering therapy on CVD events was based on the estimate obtained by a meta-analysis of randomised controlled trials by Ettehad and colleagues, which was a 20% proportional reduction in CVD events with a 10mmHg reduction in blood pressure with blood pressure-lowering therapy.[9]

The number of CVD events likely to be avoided with aspirin within each sex/10-year age-group/five-year CVD risk stratum over five years was estimated by multiplying the number of expected CVD events (based on five-year CVD risk, estimated by the 2018 New Zealand CVD risk equation[7]) by the proportional benefit of aspirin on CVD events.[10] CVD events included in the New Zealand CVD risk equation are admissions or deaths from ischaemic heart disease (including unstable angina), ischaemic or haemorrhagic cerebrovascular events (including transient ischaemic attacks), peripheral vascular disease or congestive heart failure, or other ischaemic cardiovascular disease death.[7] The New Zealand CVD risk equation was developed from the New Zealand PREDICT cohort, which included 401,752 people of whom 15,386 (4%) had a first CVD event, 1,507 (10%) of which were fatal. CVD events included myocardial infarction (34%), unstable angina (15%), ischaemic stroke

(15%), haemorrhagic stroke (4%), transient ischaemic attack (7%), peripheral vascular disease (6%) and congestive heart failure (12%). The proportional effect of aspirin on CVD events was based on the estimate obtained by the Antithrombotic Trialists' Collaboration individual participant data meta-analysis of six primary prevention trials (n=95,000; 660,000 person-years), which found a 12% proportional net reduction in CVD events (including haemorrhagic stroke) with aspirin.[3]

The likely number of additional major bleeds with aspirin within each sex/10-year age-group/five-year CVD risk stratum over five years was estimated by multiplying the number of expected major bleeds by the proportional effect of aspirin on major bleeds.[10] The annual expected rate of major bleeds was obtained from a subset of the PREDICT cohort study that followed 240,254 people for a median of 2.8 years (interquartile range 1.8 to 5 years) after cardiovascular risk assessment in primary care.[6] People had been excluded from that cohort if they were already receiving aspirin (or other antiplatelet/ anticoagulant medication), if they had an indication for aspirin (or other antiplatelet/anticoagulant medication) (ie, prior CVD, congestive heart failure, atrial fibrillation, chronic kidney disease, diabetes with renal disease) or if they had any contraindications/cautions to the use of aspirin (ie, prior major bleed, peptic ulcer disease, chronic liver disease, chronic pancreatitis, chronic alcohol-related disease, thrombocytopaenia; receiving nonsteroidal anti-inflammatory, corticosteroid or selective serotonin reuptake inhibitor medication).[6] Major bleeds were defined as hospital admissions or deaths associated with a significant non-cerebral bleed. Admissions were only included if a bleed was the principal diagnosis (ie, the main reason for the admission) or, if the bleed was not the principal diagnosis, when there was also a blood transfusion of whole blood or a transfusion of packed cells.[6] Bleeds associated with trauma and procedures were excluded. Intracerebral bleeds were excluded from this analysis because haemorrhagic stroke was included as an outcome within the New Zealand CVD risk equation, and the proportional effect of aspirin on CVD events incorporates the net effect of aspirin on haemorrhagic strokes. A total of 1,768 first major bleeding events (1,473 gastrointestinal, 295 other—respiratory, ocular or bleeding into a joint, the pericardium or peritoneum) were identified during follow-up, of which 62 (4%) were fatal. The expected number of major bleeds over five years was obtained by multiplying these annual rates by five as there was no statistically significant difference in the annual risk of bleeding over a five-year period in that study.[6] The proportional effect of aspirin on major bleeds was based on the estimate obtained by the Antithrombotic Trialists' Collaboration meta-analysis, which found a 54% proportional increase in major extracranial bleeds with aspirin.[3]

Results

Among people aged less than 70 years with estimated five-year CVD risk of ≥15%, the estimated number of CVD events prevented by aspirin exceeded, on average, the number of additional bleeds caused by aspirin among those already receiving optimal lipid-lowering therapy and blood pressure-lowering therapy (clinical scenario 1, Table 1) and among those in whom lipid-lowering and blood pressure-lowering therapy would need to be optimised prior to adding aspirin (clinical scenario 2, Table 2). The magnitude of the net benefit of aspirin was however minimal among people aged 60–69 years around the 15% five-year risk threshold, particularly those in whom lipid- and blood pressure-lowering therapy had not already been optimised. The number of estimated CVD events averted was more than twice the number of estimated major bleeds caused by aspirin among all people recommended for aspirin therapy in clinical scenario 1, but was as little as 40–50% more than the number of estimated major bleeds among people aged 60–69 years in clinical scenario 2. In men aged 70–79 years there were more events caused by aspirin than prevented by aspirin in those with a CVD risk below 20% and minimal benefit in women in scenario 2 (Table 2).

Table 1: Estimated number of CVD events prevented by and additional major bleeds caused by aspirin over five years in hypothetical populations of 1,000 people in sex-specific 10-year age groups already receiving optimal lipid- and blood pressure-lowering therapy (clinical scenario 1).

Five-year risk of CVD	Expected number of CVD events		Estimated number of CVD events prevented by aspirin per 1,000 people treated							
	Additional medication		Men				Women			
	None	+ Aspirin	40–49 years	50–59 years	60–69 years	70–79 years	40–49 years	50–59 years	60–69 years	70–79 years
1–4%	10–40	9–35	1.2–4.8	1.2–4.8	1.2–4.8	1.2–4.8	1.2–4.8	1.2–4.8	1.2–4.8	1.2–4.8
5–9%	50–90	44–79	6.0–10.8	6.0–10.8	6.0–10.8	6.0–10.8	6.0–10.8	6.0–10.8	6.0–10.8	6.0–10.8
10–14%	100–140	88–123	12.0–16.8	12.0–16.8	12.0–16.8	12.0–16.8	12.0–16.8	12.0–16.8	12.0–16.8	12.0–16.8
15–19%	150–190	132	18.0–22.8	18.0–22.8	18.0–22.8	18.0–22.8	18.0–22.8	18.0–22.8	18.0–22.8	18.0–22.8
20–29%	200–290	176–255	24.0–34.8	24.0–34.8	24.0–34.8	24.0–34.8	24.0–34.8	24.0–34.8	24.0–34.8	24.0–34.8
			Estimated number of additional major bleeds caused by aspirin per 1,000 people treated							
			4.3	5.6	8.1	11.4	3.5	4.6	6.8	10.0

The grey shaded areas represent sex/age-group/five-year CVD risk group strata in which the estimated number of additional major bleeds is equal to or greater than the estimated number of CVD events averted with aspirin. The black horizontal bar is the level at which aspirin is recommended for the primary prevention of CVD among people aged less than 70 years.

Table 2: Estimated number of CVD events prevented by and additional major bleeds caused by aspirin over five years in hypothetical populations of 1,000 people in sex-specific 10-year age groups on no or suboptimal lipid- and blood pressure-lowering therapy (clinical scenario 2).

Five-year risk of CVD	Expected number of CVD events				Estimated number of CVD events prevented by aspirin per 1,000 people treated							
	Additional medication				Men				Women			
	None	+ Statin (1mmol/L reduction in LDL)	+ BP-lowering treatment (10mmHg reduction in systolic BP)	+ Aspirin	40–49 years	50–59 years	60–69 years	70–79 years	40–49 years	50–59 years	60–69 years	70–79 years
1–4%	10–40	8–32	6–25	6–22	0.8–3.0	0.8–3.0	0.8–3.0	0.8–3.0	0.8–3.0	0.8–3.0	0.8–3.0	0.8–3.0
5–9%	50–90	40–71	32–57	28–50	3.8–6.8	3.8–6.8	3.8–6.8	3.8–6.8	3.8–6.8	3.8–6.8	3.8–6.8	3.8–6.8
10–14%	100–140	79–111	63–88	56–78	7.6–10.6	7.6–10.6	7.6–10.6	7.6–10.6	7.6–10.6	7.6–10.6	7.6–10.6	7.6–10.6
15–19%	150–190	119–150	95–120	83–106	11.4–14.4	11.4–14.4	11.4–14.4	11.4–14.4	11.4–14.4	11.4–14.4	11.4–14.4	11.4–14.4
20–29%	200–290	158–229	126–183	111–161	15.2–22.0	15.2–22.0	15.2–22.0	15.2–22.0	15.2–22.0	15.2–22.0	15.2–22.0	15.2–22.0
					Estimated number of additional major bleeds caused by aspirin per 1,000 people treated							
					4.3	5.6	8.1	11.4	3.5	4.6	6.8	10.0

The grey shaded areas represent sex/age-group/five-year CVD risk group strata in which the estimated number of additional major bleeds is equal to or greater than the estimated number of CVD events averted with aspirin. The black horizontal bar is the level at which aspirin is recommended for the primary prevention of CVD among people aged less than 70 years.

Discussion

Among people aged less than 70 years with estimated five-year CVD risk of ≥15% and no other indications for or contraindications/cautions to aspirin use, the number of CVD events avoided are estimated to exceed the number of additional major bleeds, whether or not lipid- and blood pressure-lowering therapy need to be added and/or optimised. However, in the 60–69 year age group, the net benefit was small, emphasising the need to be cautious about prescribing aspirin in this age group if they are smokers or have other risk factors associated with increased bleeding rates.

Bleeding rates were obtained from a large, contemporary New Zealand cohort of people who were likely to be considered for aspirin for the primary prevention of CVD as they did not already have CVD (or congestive heart failure, atrial fibrillation, chronic kidney disease, diabetes with renal disease), were not already receiving aspirin, anti-platelet or anticoagulant medication and did not have contraindications/cautions to the use of aspirin (ie, prior major bleed, peptic ulcer disease, chronic liver disease, chronic pancreatitis, chronic alcohol-related disease, thrombocytopaenia; receiving nonsteroidal anti-inflammatory, corticosteroid or selective serotonin reuptake inhibitor medication).[6]

While it is not possible to directly equate experiencing a CVD and a bleeding event, the severity of the events in this study are reasonably comparable. CVD events included in the New Zealand CVD risk equation are admissions or deaths from ischaemic heart disease (including angina), ischaemic or haemorrhagic cerebrovascular events (including transient ischaemic attacks), peripheral vascular disease or congestive heart failure, or other ischaemic cardiovascular disease death.[7] Major bleeding events included in this study were admissions or deaths associated with a non-cerebral bleed. Admissions were only included if a bleed was the main reason for the admission or, if not the main reason, there was also a transfusion of whole blood or packed cells during the admission.[6] Fatal events comprised 10% of the total number of CVD events used to develop the New Zealand CVD risk equation, and 4% of the total number of major non-cerebral bleeds from the bleeding study.

The United States Preventive Services Task Force (USPSTF) recommends aspirin for people aged 50 to 59 years (Grade B recommendation) and those aged 60 to 69 years (Grade C recommendation) for the primary prevention of CVD and colorectal cancer among people with 10-year CVD risk of ≥10% (equivalent to a five-year CVD risk of ≥5%).[11] Although the USPSTF guideline CVD risk threshold for recommending aspirin is lower than that used in the New Zealand Consensus Statement (five-year CVD risk of ≥15%), the USPSTF guidelines take into account the beneficial effect of aspirin on colorectal cancer.[11]

This study did not take into account the growing body of evidence indicating that aspirin is also associated with a reduction in the risk of cancer,[12–14] in particular colorectal cancer. Appropriate synthesis of the effects of aspirin on CVD, bleeding as well as cancer outcomes is particularly challenging given that the time course of these effects vary from several years for bleeding and CVD to over a decade for cancer.[15] We were able to use more appropriate bleeding risk data than was available to the USPSTF. The USPSTF, noting the paucity of absolute bleeding risk data from community cohorts, used an indirect measure of bleeding risk from people not taking aspirin who had been identified by propensity matching to people who were taking aspirin. Instead, we used data that directly measured bleeding risk in people not receiving aspirin and who also had no other indications for aspirin and no contraindications or cautions to the use of aspirin.[6]

The main limitation of this study is the implicit assumption that bleeding risk is homogeneous within a sex and 10-year age-group stratum, irrespective of CVD risk. The individual participant data meta-analysis of randomised controlled trials of aspirin for the primary prevention of CVD has demonstrated, however, that many of the same risk factors that are associated with an increase in the absolute risk of CVD (eg, diabetes, smoking) are also associated with an increase in the absolute risk of a major bleed, and may not contribute the same weight to each outcome.[3] A clinical prediction model that estimates absolute bleeding risk by taking into account multiple risk factors at the same time, as with CVD,

is required in order to optimise the individualised assessment of the balance of absolute benefits and harms of aspirin for the primary prevention of CVD, and such a model is currently in development.[6]

Conclusion

These data provide assurance to clinicians and patients regarding the use of aspirin for primary prevention as recommended by the New Zealand Consensus Statement, as the estimated number of CVD events averted was more than twice the estimated number of major bleeds caused by aspirin among all people recommended for aspirin therapy in whom lipid- and blood pressure-lowering therapy is optimised, and those aged less than 60 years in whom lipid- and blood pressure-lowering therapy needs to be optimised before considering aspirin. A more cautious approach to the use of aspirin should be taken among those with a smaller estimated net benefit from aspirin (ie, those aged 60–69 years and in whom lipid- and blood pressure-lowering therapy has not already been optimised), particularly if they have other bleeding risk factors, such as diabetes or smoking, as these have not been taken into account when estimating bleeding risk in the present analysis.

Competing interests:
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