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Decision-making in an era of cancer prevention via aspirin: New Zealand needs updated guidelines and risk calculators

Nick Wilson, Vanessa Selak, Tony Blakely, Josh Knight, Nhung Nghiem, William Leung, Philip Clarke, Rod Jackson

ABSTRACT

Based on new systematic reviews of the evidence, the US Preventive Services Task Force has drafted updated guidelines on the use of low-dose aspirin for the primary prevention of both cardiovascular disease (CVD) and cancer. The Task Force generally recommends consideration of aspirin in adults aged 50–69 years with 10-year CVD risk of at least 10%, in who absolute health gain (reduction of CVD and cancer) is estimated to exceed absolute health loss (increase in bleeds). With the ongoing decline in CVD, current risk calculators for New Zealand are probably outdated, so it is difficult to be precise about what proportion of the population is in this risk category (roughly equivalent to 5-year CVD risk ≥5%). Nevertheless, we suspect that most smokers aged 50–69 years, and some non-smokers, would probably meet the new threshold for taking low-dose aspirin. The country therefore needs updated guidelines and risk calculators that are ideally informed by estimates of absolute net health gain (in quality-adjusted life-years (QALYs) per person) and cost-effectiveness. Other improvements to risk calculators include: epidemiological rigour (eg, by addressing competing mortality); providing enhanced graphical display of risk to enhance risk communication; and possibly capturing the issues of medication disutility and comparison with lifestyle changes.

The United States Preventive Services Task Force (USPSTF) has issued draft recommendations for the use of aspirin for the prevention of cardiovascular disease (CVD) and cancer—with public comment invited by October 2015.1 These recommendations combine the use of low-dose aspirin for the primary prevention of both CVD and colorectal cancer, and give consideration to both life expectancy and addressing potential benefit versus harms depending on personal preferences. The specific text is detailed in Table 1, but in summary the USPSTF generally recommends aspirin in adults aged 50–69 years with 10-year CVD risk of at least 10% (roughly equivalent to 5-year CVD risk ≥5%).

Possible implications for the New Zealand population

To explore the potential implications of the USPSTF recommendations for the New Zealand population, we used an online CVD risk calculator designed specifically for the New Zealand population: “Know Your Numbers”.2 This calculator uses Framingham Risk Equations, modified for the New Zealand setting, to estimate 5-year risk of CVD events. However, the equations currently used almost certainly overestimate CVD risk because of the ongoing downward trend in CVD risk for the whole New Zealand population (and as projected into the future3). However, even if the USPSTF threshold for recommending aspirin in primary prevention is doubled to accommodate this overestimate of CVD risk (ie, to 5-year CVD risk >10%), this is half the threshold of current New Zealand guidelines and, apart from European women, most smokers aged 50–69 years would probably meet the new USPSTF threshold for taking low-dose aspirin (Appendix: Table A).
Table 1: United States Preventive Services Task Force (USPSTF) recommendations on aspirin for the prevention of CVD and cancer (as of September 2015)¹

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults aged 50 to 59 years</td>
<td>“The USPSTF recommends low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer in adults ages 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.”</td>
<td>“The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.”</td>
</tr>
<tr>
<td>Adults aged 60 to 69 years</td>
<td>“The decision to use low-dose aspirin to prevent CVD and colorectal cancer in adults ages 60 to 69 years who have a greater than 10% 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to use low-dose aspirin.”</td>
<td>“The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is at least moderate certainty that the net benefit is small.”</td>
</tr>
<tr>
<td>Adults younger than age 50 years</td>
<td>“The current evidence is insufficient to assess the balance of benefits and harms of aspirin use to prevent CVD and colorectal cancer in adults younger than age 50 years.”</td>
<td>“The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.”</td>
</tr>
<tr>
<td>Adults age 70 years and older</td>
<td>“The current evidence is insufficient to assess the balance of benefits and harms of aspirin use to prevent CVD and colorectal cancer in adults age 70 years and older.”</td>
<td>As above.</td>
</tr>
</tbody>
</table>

Updated guidelines for New Zealand are needed

Current New Zealand guidelines are that “aspirin and other antiplatelet agents are not generally recommended for people with a risk lower than 20 percent”,¹ a much higher threshold than the draft USPSTF recommendations. However, the New Zealand guidelines are based on older reviews (from the early 2000s) and do not take into account the effect of aspirin on colorectal cancer. Overall, the quality of the draft USPSTF recommendations appears to be high. The recommendations are based on a microsimulation model of the lifetime net benefits of daily use of low-dose aspirin in terms of life-years and quality-adjusted life-years (QALYs). The effects of aspirin on CVD, colorectal cancer and major bleeding outcomes have been taken into account using effect estimates obtained from three recent systematic reviews.⁶⁸ However, the microsimulation model is designed to be representative of the US population and only takes into account two factors (age and sex) in its estimate of (untreated) absolute bleeding rates. This is a limitation because there is considerable variation in absolute bleeding risk according to many of the same risk factors as for absolute CVD risk.⁹ Hence, any updated local guideline development around the use of low-dose aspirin needs to consider the unique aspects of New Zealand’s demography and population health status, and also to adequately consider net health gain and cost-effectiveness as detailed further below.

Determining net QALYs gained

A plausible bottom line with regular use of a preventive pharmacotherapy, such as low-dose aspirin, is the expectation of consumers of gaining extra years of life.
healthy life on average. New guidelines could therefore consider QALYs gained for the use of low-dose aspirin after taking into account: age, sex, ethnicity, CVD risk reduction, colorectal cancer prevention and risk of bleeding (gastric and intracranial).

**Cost-effectiveness**

The issue of cost-effectiveness is relevant for policy-makers who should be striving to get the maximum health gain from the taxpayer-funded public health budget. So guideline development should ideally reflect the intervention costs involved with taking aspirin (supermarket purchase or on-prescription) and the impacts on health system costs from both diseases prevented and adverse effects caused, eg, from gastric bleeding. We suspect, given some existing international literature, that aspirin use in adults aged 50–69 may generally be cost-effective (approximately US$ 5,000 per QALY for 55-year-old men with a 10% CVD risk over 10 years), but ideally such an analysis should be done with New Zealand data (given the very different health system costs in New Zealand versus the US). Furthermore, in an earlier study by the same authors, adding proton pump inhibitor co-therapy versus aspirin alone was found to be not cost-effective, for 55- and 65-year-old men with a 10% CVD risk over 10 years and average gastric bleeding risk, but may be cost-effective for selected men at increased risk for gastric bleeding. A comprehensive economic evaluation of low-dose aspirin, with and without proton pump inhibitor co-therapy, in primary prevention considering the main therapeutic endpoints (CVD and selected cancers) and adverse effects (including medication disutility) is yet to be published.

The cost-effectiveness of enhancing uptake of low-dose aspirin should also be compared with other New Zealand-specific results suggesting the cost-saving nature of additional tobacco control interventions (eg, further raising tobacco tax), and cost-saving dietary salt reduction interventions.

**Considering H. pylori infection**

Really sophisticated New Zealand guidelines would take into account the likelihood that the adverse effects of aspirin may be worse in Māori and Pacific peoples (given higher rates of *H. Pylori* infection and hence higher risk of gastric bleeding). A systematic review has reported that “eradication of *H. pylori* infection before aspirin use could reduce the incidence of upper GI [gastrointestinal] complications by 25–30%.”

**Improving CVD risk calculators for clinical decision-making with patients**

If updated guidelines suggest that low-dose aspirin is a cost-effective intervention for at least some 50–69 year olds in New Zealand, the next step is to consider updated risk calculator development that can inform decision-making by clinicians alongside patients. At present, a large number of online CVD risk calculators currently exist (eg, see these reviews). They do not provide highly precise risk estimates, but their use appears to have some beneficial impact (eg, stimulating lifestyle changes). Nevertheless, some researchers have highlighted the complex responses of users and suggest that such calculators “may best be used in conjunction with health professionals who can guide the user through the calculator.”

The free, online New Zealand CVD risk calculator (“Know Your Numbers”) has a number of desirable features (see Appendix: Table B). However, to optimally make use of such calculators (including in the light of the new USPSTF recommendations on aspirin), they could benefit from the following improvements.

**Background epidemiological refinements**

As discussed above, there is a need for upgraded risk calculators to be adjusted for the latest CVD risk information given the ongoing downward trend in CVD risk in New Zealand (and as projected into the future). Socioeconomic status is another possible refinement, eg, derived using the latest NZDep scores for small-area level deprivation, based on a person’s residential address. Although not so relevant to the aspirin issue in the 50–69 year age range, extending the age range of CVD calculators is generally desirable. For example, the current New Zealand calculators are only designed for the <75 year age group. New versions of such calculators could also take into
account “competing mortality” in terms of the increased risk of death from other causes at older ages. This particular issue probably starts to matter quite a lot for older people in their 80s and 90s.20

Incorporating cancer and bleeding risks
Ideally, absolute bleeding risk (gastric and intracranial) and colorectal cancer risk would be estimated alongside absolute CVD risk, with integrated results being produced (eg, net QALYs gained or lost). While CVD risk calculators are abundant, there is a paucity of bleeding and cancer-risk equations that would be suitable for use in primary prevention populations (but some work in this area is proceeding21).

Graphical display of risk
To assist with understanding risk by patients, it is probably desirable to show graphically how many cases of CVD events plus colorectal cancer events are prevented “in 100 people like me” who adopt risk reduction efforts, such as aspirin use. This is already being done for non-specific CVD risk reduction in some such calculators (eg, for QRisk2,22 and a Mayo Clinic calculator for statin use23). The JBS3 risk calculator24 graphically displays the average survival time that is free of a CVD event, and how this can be extended with reductions in blood pressure etc. Again, these estimates should ideally be upgraded to allow for competing mortality risk.

Medication disutility
Some people simply don’t like the idea of taking daily preventive medications, as described in the literature on “medication disutility”.25-27 This issue is likely to apply to low-dose aspirin, particularly when it is the only daily medication being taken. So really sophisticated calculators could allow users to incorporate various levels of such medication disutility. For example, a threshold analysis result could be a possible output: “to outweigh the health benefit of taking daily aspirin for a year, you would have to regard taking daily aspirin as worse than losing ‘x’ days of life per year”.

Lifestyle change comparisons
Other than quitting smoking, it may be difficult for individuals to adopt the dietary and physical activity changes that would equate to the benefit of taking low-dose aspirin. Nevertheless, a really sophisticated calculator would provide information on how the health gain from low-dose aspirin might compare with that from quitting smoking, increasing physical activity, adopting a Mediterranean diet28-30 and reducing consumption of processed meat or red meat (given the association with colorectal cancer31).

Conclusions
Based on the USPSTF draft recommendations, it seems likely that some (albeit a still unclear) proportion of New Zealanders aged 50–69 years might obtain net benefit from the use of low-dose aspirin for the prevention of CVD and cancer. This group is especially likely to include smokers. But to inform appropriate New Zealand guidelines, updated risk estimates are needed to account for the ongoing decline in CVD risk. Good decision-making also requires data on absolute net health gain (in QALYs per person) and cost-effectiveness. Along with this, improvements could be made to New Zealand-specific risk calculators to improve their epidemiological rigour (eg, by addressing competing mortality), capture other important aspirin-related aspects (cancer prevention and risk of bleeding), provide enhanced graphical display of risk to enhance risk communication, and possibly capture the issues of medication disutility and comparison with lifestyle changes.
## Appendix

Table A: The probably out-of-date (over-estimated) 5-year risk of a CVD event in different demographic groups estimated using the current New Zealand specific risk calculator “Know Your Numbers”.

<table>
<thead>
<tr>
<th>Demographic group</th>
<th>5-year CVD event risk using the online calculator (range generated by using each year of age)**</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smokers</td>
<td>Non-smokers</td>
</tr>
<tr>
<td><strong>European men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–54 years</td>
<td>9–11</td>
<td>4–6</td>
</tr>
<tr>
<td>55–59 years</td>
<td>12–15</td>
<td>6–8</td>
</tr>
<tr>
<td>60–64 years</td>
<td>16–19</td>
<td>9–11</td>
</tr>
<tr>
<td>65–69 years</td>
<td>20–22</td>
<td>11–13</td>
</tr>
<tr>
<td><strong>Māori men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–54 years</td>
<td>14–16</td>
<td>9–11</td>
</tr>
<tr>
<td>55–59 years</td>
<td>17–19</td>
<td>11–13</td>
</tr>
<tr>
<td>60–64 years</td>
<td>21–24</td>
<td>14–15</td>
</tr>
<tr>
<td>65–69 years</td>
<td>24–27</td>
<td>16–18</td>
</tr>
<tr>
<td><strong>European women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–54 years</td>
<td>5–6</td>
<td>2–3</td>
</tr>
<tr>
<td>55–59 years</td>
<td>6–7</td>
<td>3</td>
</tr>
<tr>
<td>60–64 years</td>
<td>8–10</td>
<td>4–5</td>
</tr>
<tr>
<td>65–69 years</td>
<td>10–12</td>
<td>5–6</td>
</tr>
<tr>
<td><strong>Māori women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–54 years</td>
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<tr>
<td>65–69 years</td>
<td>16–18</td>
<td>10–11</td>
</tr>
</tbody>
</table>

* Dark shading indicates overall >20% 5-year risk of a CVD event; lighter shading indicates 10–20% risk; font in bold and italics indicates 5–9% risk.

** Using average blood pressure data (systolic/diastolic) from the 2008/2009 Adult Nutrition Survey and the total cholesterol (TC) to HDL ratio from the same survey. All risks calculated assuming “no diabetes” and “no family history” of CVD, which will result in some under-estimation of the true risk. On the other hand, this particular risk calculator is very likely to over-estimate the risks given the on-going decline in CVD incidence in New Zealand since it was designed, and because competing mortality is not built into the calculator (a common design limitation of such calculators).
Table B: Comment on selected features of the online “Know Your Numbers” CVD risk calculator designed for the New Zealand setting.*

<table>
<thead>
<tr>
<th>Domain</th>
<th>Further detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time horizon</td>
<td>This New Zealand-specific calculator provides 5-year risk—which seems to us to be more relevant for clinical decision-making than the 10-year timeframe used by most such CVD risk calculators (for more details see this article by Jackson, et al34).</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Relatively detailed ethnicity input options are available (ie, Māori, various Pacific and Asian populations). Nevertheless, adding in the New Zealand-based Chinese population could be a good addition.</td>
</tr>
<tr>
<td>Graphical features</td>
<td>The output provides projections in a graphic form and there are also dynamic graphic options that show current risk and future risk at different settings. Furthermore, there is also a comparison with an ‘ideal trajectory and also what the likely trajectory is for the person if no CVD risk reduction efforts are made. But further improvements are possible in graphical display (see main text).</td>
</tr>
<tr>
<td>Calculator tools</td>
<td>The calculator has sliding scales to allow the user to see the implications of reductions in blood pressure (BP) and cholesterol ratio (TC/HDL) changes on their CVD risk. This can be used to demonstrate visually the relatively large importance of high BP in influencing CVD risk.</td>
</tr>
<tr>
<td>‘Heart age’</td>
<td>The calculator estimates the person’s ‘heart age’. It is possible that this might help motivate some people, but more research on this is probably needed on this issue. For example, one study found that participants told that they had an older heart age found it ‘confronting’.18</td>
</tr>
<tr>
<td>Recommendations</td>
<td>For those at high CVD risk, the calculator provides information about seeing a doctor about CVD medications. The user can also proceed to creating a somewhat personalised “heart health plan”. There is also discussion of the importance of stopping smoking and making dietary changes.</td>
</tr>
</tbody>
</table>

* An earlier version of this table along with some of the ideas in the main text were previously included in a blog that some of the authors wrote.35 We note that one of the authors (RJ) was involved in epidemiological aspects of developing this “Know Your Numbers” calculator.

Competing interests: Nil

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