

# Which people should take aspirin for primary prevention of cardiovascular disease?

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## Dear editor

A single trial, ISIS-2,<sup>1</sup> in 1988, demonstrated the utility of daily aspirin in the setting of acute myocardial infarction, reducing the risk of vascular death by 23%. In addition, aspirin has also proven effective in the setting of acute ischemic stroke.<sup>2</sup> Thus, for a subset of the general population, aspirin may help to prevent heart attacks and strokes. In fact, at low doses, in the range of 75 to 100 mg per day, aspirin prevents the progression of existing cardiovascular disease (CVD), including coronary heart disease, stroke and peripheral arterial disease, and reduces the frequency of cardiovascular events in patients with history of CVD,<sup>3,4</sup> referred to as secondary prevention. Although the benefits of aspirin for secondary prevention of CVD are well known, its use in primary prevention of CVD, defined as prevention of the first occurrence of CVD for all patients without clinical CVD, including those with diabetes mellitus and those without clinical evidence of atherosclerotic disease who are at higher CVD risk, is less clear and controversial results have been obtained. In fact, the results of several studies using aspirin for primary prevention of CVD have generally shown more modest reductions of major vascular events compared with secondary prevention (12% vs 23%).<sup>3,5</sup>

In this regard, the health study of women,<sup>6</sup> the hypertension optimal treatment (HOT) study,<sup>7,8</sup> the primary prevention project,<sup>9,10</sup> the health study research group,<sup>11</sup> the British doctors' trial,<sup>12</sup> and the thrombosis prevention trial,<sup>13</sup> indicate that aspirin therapy is associated with a significant reduction of 19% in the risk of stroke and no reduction in the risk of myocardial infarction in women; and a significant reduction of 32% in the risk of myocardial infarction and a non-significant increase in the risk of stroke in men. However, in all cases, aspirin significantly increased the risk of bleeding, as the main important side effect.<sup>14</sup>

In this context, because fatal and non-fatal thrombotic events (eg, stroke and/or myocardial infarction events) are usually prevented by aspirin, in an order of magnitude lower than in secondary prevention, and overall risk for bleeding events (eg, intracranial and/or subarachnoid hemorrhage events) are generally increased by aspirin, in an order of magnitude equal to secondary prevention, aspirin appears to offer little benefit for the primary prevention of CVD.

Moreover, in the vast majority of primary prevention studies, the overall risk level for CVD events was very low<sup>5</sup> and the events rate was much lower than expected, leading to studies with less power to detect differences in the primary prevention of CVD. In addition to this, it must add a greater use in general population of preventive medications for different atherosclerotic risk factors, such as antihypertensive and lipid-lowering drugs, and other preventive measures, which together result in fewer events than expected.<sup>15</sup>

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Accordingly, it was more difficult to achieve an overall risk reduction of cardiovascular events than in secondary prevention,<sup>2,3,5</sup> and most studies concluded that low-dose aspirin does not significantly reduce the risk of cardiovascular death, non-fatal stroke (ischemic or hemorrhagic) or non-fatal myocardial infarction in subjects without prior CVD.<sup>16</sup>

Thus, using aspirin, in a cost-effective manner and with a good risk–benefit balance, for primary prevention of CVD, we must consider that patients are affected by different atherosclerotic risk factors (eg, hypertension, dyslipidemia, and diabetes mellitus) and, therefore, the preventive effects of aspirin on CVD will be heterogeneous. So, it will be necessary to study these preventive effects, for each type of individual cardiovascular event (eg, ischemic or hemorrhagic stroke, fatal or non-fatal myocardial infarction) among the different subgroups of patients, stratified according to cardiovascular risk factors studied, eg, hypertension, dyslipidemia, diabetes mellitus, sex, age, smoking, family history of premature CVD, blood pressure (<120/75 mmHg, 120–129/75–84 mmHg, 130–139/85–89 mmHg, and  $\geq 140/\geq 90$  mmHg), body mass index (<25.0, 25.0–29.9, and  $\geq 30.0$ ) and/or 10-year cardiovascular risk of 6%–10%.<sup>16</sup> This would be the case for the following ongoing clinical trials: the ASCEND study, involving aspirin for patients 40 years and older with type 1 or type 2 diabetes;<sup>17</sup> the ARRIVE study, testing aspirin in middle aged and older patients who are at moderate risk based on the presence of multiple risk factors for CVD;<sup>18</sup> and the ASPREE study, testing aspirin in individuals older than 70 years.<sup>19</sup>

With these data, it will be possible to demonstrate the presence or absence of a preventive effect of low-dose aspirin and, consequently, the benefit of aspirin treatment for primary prevention in certain types of patients. However, so long as clinical trials are conducted and until completion, the use of aspirin for primary prevention of CVD should target patients at high cardiovascular risk: physicians should evaluate the risks and benefits of aspirin therapy for primary prevention and incorporate patient preferences.

## Disclosure

The authors have no conflicts of interest to disclose in this work.

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