

# Primary care providers should prescribe aspirin to prevent cardiovascular disease based on benefit–risk ratio, not age

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## ABSTRACT

Recent guidelines restricted aspirin (ASA) in primary prevention of cardiovascular disease (CVD) to patients <70 years old and more recent guidance to <60.

In the most comprehensive prior meta-analysis, the Antithrombotic Trialists Collaboration reported a significant 12% reduction in CVD with similar benefit–risk ratios at older ages. Using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, four trials were added to an updated meta-analysis.

ASA produced a statistically significant 13% reduction in CVD with 95% confidence limits (0.83 to 0.92) with similar benefits at older ages in each of the trials.

Primary care providers should make individual decisions whether to prescribe ASA based on benefit–risk ratio, not simply age. When the absolute risk of CVD is >10%, benefits of ASA will generally outweigh risks of significant bleeding. ASA should be considered only after implementation of therapeutic lifestyle changes and other drugs of proven benefit such as statins, which are, at the very least, additive to ASA. Our perspective is that individual clinical judgements by primary care providers about prescription of ASA in primary prevention of CVD should be based on our evidence-based solution of weighing all the absolute benefits and risks rather than age. This strategy would do far more good for far more patients as well as far more good than harm in both developed and developing countries. This new and novel strategy for primary care providers to consider in prescribing ASA in primary prevention of CVD is the same as the general approach suggested by Professor Geoffrey Rose decades ago.

Recent guidelines from the American Heart Association/American College of Cardiology Task Force restricted aspirin (ASA) in primary prevention of cardiovascular disease (CVD) to patients <70 years old<sup>1</sup> and the most recent guidance from the US Preventive Services Task Force to <60.<sup>2</sup>

Our Perspective to primary care providers is a new and novel evidence-based solution to prescribe ASA based on benefit–risk, not age.

The Antithrombotic Trialists (ATT) Collaboration had published the most

comprehensive meta-analysis of six major trials using individual patient data.<sup>3</sup> These included Physicians' Health Study,<sup>4</sup> British Doctor Study,<sup>5</sup> Thrombosis Prevention Trial,<sup>6</sup> Hypertension Optimal Treatment trial,<sup>7</sup> Primary Prevention Project<sup>8</sup> and Women's Health Study.<sup>9</sup> The point estimate for each of the six was in the direction of a benefit of ASA on CVD (figure 1).

Overall, ASA produced a significant 12% reduction in CVD ( $p=0.0001$ ). The absolute benefits generally outweighed the absolute risks when the 10-year risk of a first CVD event was >10%. The benefits of ASA on CVD in patients over 60 or 70 years were not significantly decreased. These data suggested that the absolute benefit of ASA at older ages would be greater due to the increasing risks of CVD with age.

Using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we conducted PubMed searches for all phase three randomised double-blind placebo-controlled trials of ASA in primary prevention of CVD in English between publication of the ATT meta-analysis on 30 May 2009 and 31 July 2021. Using the PRISMA flow methodology, we identified 142 published manuscripts. We excluded 76 which used other agents, 20 with alternative designs, 16 design manuscripts and 10 not of CVD, 10 of subgroup analyses; 4 of secondary prevention and 2 of observational studies. This search engine yielded four eligible trials, which we added to the six from the ATT to conduct our updated meta-analysis. They are A Study of Cardiovascular Events in Diabetes (ASCEND),<sup>10</sup> ASA to Reduce Risk of Initial Vascular Events (ARRIVE),<sup>11</sup> ASA in Reducing Events in the Elderly (ASPREE)<sup>12</sup> and International Polycap Study (TIPS-3).<sup>13</sup>



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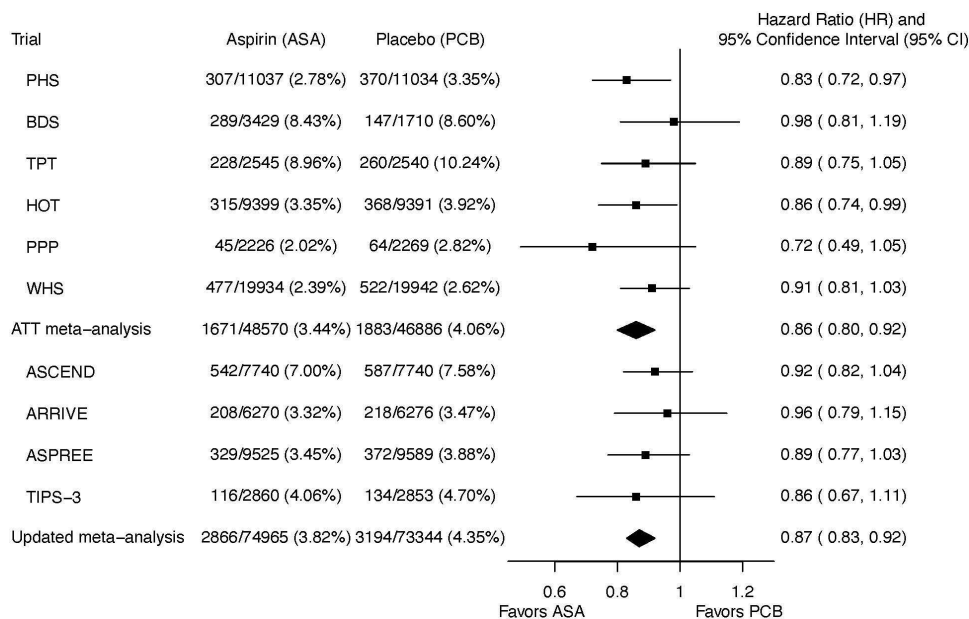
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**Figure 1** Point estimates using HRs and 95% CIs for each of the six individual trials included in the ATT meta-analysis as well as the four individual trials added to the updated meta-analysis. ASCEND, A Study of Cardiovascular Events in Diabetes; ARRIVE, ASA to Reduce Risk of Initial Vascular Events; ASPREE, ASA in Reducing Events in the Elderly; BDS, British Doctor Study; HOT, Hypertension Optimal Treatment; PHS, Physicians' Health Study; PPP, Primary Prevention Project; TIPS-3, International Polycap Study; TPT, Thrombosis Prevention Trial; WHS, Women's Health Study.

The point estimate for each of the four was in the direction of a benefit of ASA on CVD (figure 1).

ASCEND<sup>10</sup> randomised 15 480 subjects with diabetes mellitus without prior CVD aged 40 to 85 years who were treated at entry and followed for 7.2 years. ASA produced a significant 12% benefit on CVD (HR=0.88, 95% CI: 0.79 to 0.97,  $p=0.010$ ) and a significant increased risk of major bleeding (HR=1.29, 95% CI: 1.09 to 1.52,  $p=0.003$ ). Older patients had the same apparent benefit from ASA than those at younger and middle ages. ARRIVE<sup>11</sup> randomised 12 546 subjects, >55 years of age for men and 60 years for women, with a 10-year risk of a first event of 10% to 20%. There was no significant reduction in CVD (HR=0.96, 95% CI: 0.81 to 1.13). ASPREE<sup>11</sup> randomised 19 104 subjects >70 years and showed no significant reduction in the primary combined endpoint (HR=0.95, 95% CI: 0.83 to 1.08). In those above age 70 years, there was a possible but not significant 11% reduction in their prespecified tertiary endpoint of CVD, which closely resembled that used in other trials and meta-analyses. TIPS-3<sup>13</sup> randomised 5713 subjects to a polypill and/or ASA and reported HRs on CVD of 0.79 (0.63 to 1.00) and 0.86 (0.67 to 1.10), respectively. For the combined treatment, the HR was 0.69 (0.50 to 0.97). Older patients had the same apparent benefit from ASA as those at younger and middle ages.

To conduct our updated meta-analysis, we defined a composite endpoint comparable to that of the ATT meta-analysis of myocardial infarction, stroke and CVD death. Each individual randomised trial was included in a 2x2 contingency table of the subjects on ASA (ASA) or placebo (PCB) with CVD. A weighted analysis of these

2x2 contingency tables was performed using inverse variance meta-analytic methods. From these aggregate data, we calculated HRs and 95% CIs.<sup>14</sup>

ASA produced a statistically significant 13% (0.83 to 0.92) reduction in CVD. This point estimate is virtually identical to that reported in the ATT meta-analysis of 0.88 but has greater precision (figure 1).

For any randomised trial, the ability to detect any benefit depends on the maintenance of high adherence rates.<sup>14</sup> As duration increases, adherence rates decrease during the same time that the majority of events are accruing. Further, the effect of ASA on CVD is acute as the half-life of the platelet is about 8 days. Thus, ASA non-adherence after only 1 week produces risks as high as those assigned PCB. At trial termination, reported overall adherence rates in ARRIVE, ASPREE and TIPS-3 were about 60%, a weighted average over 5 years. For other drugs such as statins, benefits are far more prolonged after cessation. Non-adherence may have contributed to a failure to detect significant benefits in ARRIVE, ASPREE and TIPS-3 that were reported in older adults in previous individual trials as well as the ATT meta-analysis.<sup>3-9</sup>

In the trials of ASA in primary prevention, the doses ranged from 75 mg to 500 mg<sup>1</sup> without significant effect modification. In three trials directly comparing 75-150 mg with 160-325 mg daily, there were no significant differences in efficacy or safety and no modifications by age. A recently published large-scale randomised trial directly compared 81 mg with 325 mg and found no significant differences in efficacy or safety of ASA.<sup>15</sup>

The previous guideline used age 70<sup>1</sup> as the upper age limit and the recent guidance used age 60.<sup>2</sup> Guidelines and guidance based on age are intrinsically contradictory because ASA is recommended, on the one hand, only for higher risk primary prevention subjects, but on the other, not over age 60 or 70 where the absolute risks of CVD are much higher than at younger or middle ages. Our Perspective to primary care providers is a new and novel evidence-based solution to prescribe ASA based on benefit–risk, not age.

When the absolute risk of CVD is >10%, the benefits are generally likely to outweigh the risks as shown in the ATT meta-analysis,<sup>3</sup> ASCEND,<sup>10</sup> ASPREE,<sup>12</sup> TIPS-3<sup>13</sup> and our updated meta-analysis.

For long-term use of ASA or any over-the-counter drug, patients should consult their primary care provider. Primary care providers have the most insight and knowledge to decide. ASA should be prescribed only on an individual patient basis after weighing all benefits and risks, not just age. These include additional challenges of patients with prior gastrointestinal bleeding, having upper gastrointestinal symptoms or using non-steroidal anti-inflammatory drugs, all of whom have higher absolute bleeding risks.<sup>16 17</sup>

Drug therapies should always be adjunctive to therapeutic lifestyle changes. Nonetheless, in many developed countries, adjunctive drug therapies will be necessary for many high-risk primary prevention subjects.<sup>18</sup> For example, in the USA, 40% of adults over age 40 have metabolic syndrome, which includes overweight and obesity, hypertension, dyslipidaemia and insulin resistance, a precursor to diabetes mellitus. Such primary prevention patients have a 16%–18% ten-year risk of a first CVD event, which is similar to the absolute risk of a recurrent event in secondary prevention patients.<sup>19</sup> ASA should be considered only after implementation of therapeutic lifestyle changes and other drugs of proven benefit such as statins which are, at the very least, additive to ASA.<sup>20</sup> Further, the increased prescription by primary care providers of evidence-based doses of high potency statins will be sufficient for the vast majority of patients. In contrast, for the effective management of blood pressure, multiple drugs may be necessary adjuncts to therapeutic lifestyle changes. These may render residual risks below 10% in which cases ASA would not be indicated.

The clinical decisions by primary care providers about ASA should be based on a totality of evidence including age but also other data not routinely available in most risk calculators. These include overweight and obesity, physical inactivity and family history of premature CVD. When the magnitude of absolute benefits and risks is similar, individual patient preference assumes increasing importance but should only be one factor in clinical decision making. This may include consideration of whether the prevention of a first myocardial infarction or stroke is more important to an individual patient than the development of a significant gastrointestinal bleed. Individual

randomised trials and their meta-analyses should also be only one component of the totality of evidence. Finally, guidelines should only provide guidance to primary care providers.<sup>18</sup>

In summary, our Perspective is that individual clinical judgements by primary care providers about the prescription of ASA in primary prevention of CVD should be based on our evidence-based approach of weighing absolute benefits and risks rather than a decision based solely on age. This strategy would do far more good for far more patients as well as far more good than harm in both developed and developing countries. This new and novel strategy for ASA for primary care providers to consider in prescribing ASA in primary prevention of CVD is the same as the general approach previously suggested by Professor Geoffrey Rose.<sup>21</sup>

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**Competing interests** CHH reports that he serves as an independent scientist in an advisory role to investigators and sponsors as Chair of data monitoring committees for Amgen, British Heart Foundation, Cadila, Canadian Institutes of Health Research, DalCor, and Regeneron; to the US FDA and UpToDate; receives royalties for authorship or editorship of three textbooks and as co-inventor on patents for inflammatory markers and cardiovascular disease that are held by Brigham and Women's Hospital; has an investment management relationship with the West-Bacon Group within SunTrust Investment Services, which has discretionary investment authority; does not own any common or preferred stock in any pharmaceutical or medical device company. JMG reports that he serves as a consultant to Bayer. MAP reports that he receives research support from Novartis. He serves as an independent scientist in an advisory role to AstraZeneca, Boehringer-Ingelheim and Eli Lilly Alliance, Corvidia, DalCor, GlaxoSmithKline, NHLBI CONNECTs (Master Protocol Committee), Novartis, Novo Nordisk, Peerbridge and Sanofi; and has equity in DalCor and Peerbridge. DLD reports that he serves as an independent scientist in an advisory role to the National Institutes of Health, the US Food and Drug Administration (FDA) and the pharmaceutical and medical device industry on the design, monitoring and analysis of trials. He serves on data monitoring committees for Astra Zeneca, Amgen, Action, DalCor, GSK, Merck, Sanofi, Boehringer Ingelheim, Teva and AbbVie. He holds no stock in any pharmaceutical or device company. SKW reports that she serves as an independent scientist in an advisory role to investigators and sponsors as member of three data monitoring committees for Amgen.

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