

## Aspirin for primary prevention

**To the Editor:** I greatly appreciated the review by Drs. Schenone and Lincoff about aspirin for primary prevention in your May 2020 issue.<sup>1</sup> I wanted to note that the statement in green on page 303, “Statins may dilute the potential benefit of aspirin,” conflicts with what I have read regarding statins’ ability to improve aspirin resistance.<sup>2</sup>

Moreover, as I interpret a meta-analysis performed by the Antithrombotic Trialists’ Collaboration,<sup>3</sup> statins may halve the risk of coronary heart disease, but when aspirin is added, hypothetically the added benefit of the aspirin is marginal, given the increased risk of bleeding. Ultimately it would be the aspirin theoretically diluting the benefit of the statin because of bleeding risk. The authors of the meta-analysis note: “If the risk of occlusive vascular disease is already approximately halved by statins or other measures, then the further absolute benefit of adding aspirin could well be only about half as large as was suggested by these primary prevention trials, but the main bleeding hazards could well remain. In that case, the benefits and hazards of adding long-term aspirin in people

without preexisting disease might be of approximately similar magnitude.”

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### REFERENCES

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3. Antithrombotic Trialists’ (ATT) Collaboration; Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; 373(9678):1849–1860. doi:10.1016/S0140-6736(09)60503-1

doi:10.3949/ccjm.87c.08005

**In Reply:** We appreciate the comments made by Dr. Henning about our statement that statins may dilute the benefit of aspirin.<sup>1</sup> She alludes to interesting data on the potential interaction between aspirin and statins from a small study that enrolled patients with coronary artery disease and aspirin resistance (defined as closure time < 186 seconds with Col/Epi cartridges despite a regular aspirin regimen).

In that study, statin therapy was associated with a resolution of in vitro aspirin resistance in up to two-thirds of patients.<sup>2</sup> Notably, however, that study did not assess the impact of this reported interaction on cardiovascular or bleeding outcomes.

Dr. Henning then provides her interpretation of available data proposing that aspirin therapy would dilute the benefit of statin therapy rather than vice versa. We respectfully disagree with this interpretation. The statement in our review that “statins may dilute the benefit of aspirin” refers to the impact of statin therapy on the risk-benefit profile of aspirin on cardiovascular and bleeding outcomes, rather than to drug-drug interactions.

Our statement is also supported by evidence that the relative risk reduction in atherosclerotic cardiovascular events provided by aspirin is about the same across different levels of risk, and thus the absolute risk reduction by aspirin is primarily dictated by the baseline risk of the patient.<sup>3</sup> As the risk of cardiovascular events is reduced by guideline-directed statin therapy, the absolute risk reduction of cardiovascular events provided by aspirin is also reduced by the same magnitude with no anticipated change in the bleeding hazard. Thus, the number needed to treat to prevent 1 cardiovascular event when aspirin is prescribed as add-on therapy to a guideline-directed statin regimen would be expected to increase compared with an aspirin regimen without a statin, while the number needed to harm would likely remain the same. As a consequence, one could expect a dilution of the net overall benefit of aspirin (absolute

risk reduction in cardiovascular events minus absolute increase in bleeding risk) reported by initial primary prevention trials, when statins were infrequently used, compared with aspirin added to a background regimen of statin. This has been hypothesized to be a potential reason for the dissipation of benefit in the contemporary aspirin primary prevention trials.<sup>4</sup>

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4. **Mahmoud AN, Gad MM, Elgendy AY, et al.** Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials. *Eur Heart J* 2019; 40(7):607–617. doi:10.1093/eurheartj/ehy813

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