

Aspirin for Primary Prevention in Adults Older than 70 Years is Not Supported by High-Quality Trial Data and May Cause Harm



To the Editor:

We read with interest the commentary on aspirin in primary prevention by Gitin et al.¹ As ASPirin in Reducing Events in the Elderly (ASPREE) investigators, 1 of 3 key aspirin primary prevention trials referenced in this paper, we write to reiterate the unambiguous message from the ASPREE trial.²

The authors state that “considerable confusion has arisen from recently reported results of three large scale, randomized trials of aspirin in primary prevention.” On the contrary, these 3 methodologically robust trials show consistent results: a lack of net benefit for aspirin. Further, net harm with aspirin use in older adults was seen in ASPREE, with a 38% increase in bleeding risk, an increased mortality in the aspirin arm, and a lack of benefit for the primary outcome of disability-free survival. The compelling evidence provided by ASPREE, Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE), and A Study of Cardiovascular Events in Diabetes (ASCEND) has prompted a revision of guideline recommendations for aspirin primary prevention in older individuals, with recommendations against aspirin use.³

Of note, the authors state that the negative findings of ASPREE may have been due to the adherence rates of approximately 62% by trial completion. Our use of an intention-to-treat analysis estimates aspirin effects as the impact of assignment to treatment. While 62% of participants were still taking study medication after a median 4.7 years of follow-up, when calculated as a proportion of time in study, participants in the aspirin arm took study medication for on average 73% of their time under study (75% in the placebo arm).² Gitin et al¹ also assert that adherence rates “must have

been far lower”; this is unsupported, because in ASPREE we took the rigorous step of asking patients to bring bottles back for pill counts by staff.

We note the authors’ comment that the “current uncertainties may be clarified” by the results of the forthcoming International Polycap Study-3.⁴ This trial has randomized 5713 people, only 10% of the combined total of the ARRIVE, ASCEND, and ASPREE trials. Even if a net benefit result for aspirin is seen in this study, it would be unlikely to achieve a magnitude of benefit many times higher, which is what would be required to influence the collective findings of the 3 trials. We agree that an updated individual patient data meta-analysis holds value in improving the precision of findings, both benefits and harms, and propose that research into how patients value thrombotic events avoided, compared with bleeding events incurred, would greatly assist clinical decision-making.

Suzanne E. Mahady, PhD^a

Robyn L. Woods, PhD^a

Rory Wolfe, PhD^a

Mark R. Nelson, PhD^b

Anne M. Murray, MD^c

John J. McNeil, PhD^a

^aSchool of Public Health and Preventive Medicine, Monash University, Clayton, Victoria, Australia

^bMenzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia

^cBerman Center for Outcomes and Clinical Research, Hennepin Healthcare Research Institute, Hennepin Healthcare & Division of Geriatrics, Department of Medicine, Hennepin Healthcare and the University of Minnesota, Minneapolis, Minn USA

<https://doi.org/10.1016/j.amjmed.2020.02.031>

Funding: None.

Conflict of Interest: All authors declare no conflict of interest relevant to this manuscript.

Authorship: All authors had access to the data, were involved in writing the manuscript, and approved the final version.

Requests for reprints should be addressed to Suzanne Mahady, MBBS, MClin Epi, FRACP, PhD, School of Public Health and Preventive Medicine, Monash University, 553 St Kilda Road, Melbourne 3004, Australia.

E-mail address: suzanne.mahady@monash.edu

References

- Gitin A, Pfeffer MA, DeMets DL, Hennekens CH. Aspirin in primary prevention: needs individual clinical judgments. *Am J Med* 2020: Available at: <https://doi.org/10.1016/j.amjmed.2020.01.006>. Accessed April 10, 2020 .
- McNeil JJ, Woods RL, Nelson MR, et al. Effect of aspirin on disability-free survival in the healthy elderly. *N Engl J Med* 2018;379(16):1499–508.

3. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;140(11):e596–646.
4. Pais JP, Dans AL, Bosch J, et al. The International Polycap Study-3 (TIPS-3): design, baseline characteristics and challenges in conduct. *Am Heart J* 2018;206:72–9.