Cardiovascular Drugs and Therapy
https://doi.org/10.1007/s10557-020-07093-8

LETTER TO THE EDITOR

Aspirin for Primary Cardiovascular Prevention in Patients with Family History of Cardiovascular Disease: Meta-analysis

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Accepted: 8 October 2020

Letter to the Editor:

The use of aspirin, while well established in the secondary prevention of cardiovascular events, remains controversial in the primary prevention of these events in the general adult population [1]. In this setting, aspirin showed a significant but modest decrease of cardiovascular event incidence at the cost of a significantly increased risk of bleeding, a pattern that is also seen in higher risk patients, such as diabetics [2]. It becomes exceedingly important to identify other patient clusters that would benefit from cardiovascular risk reduction at the best benefit/risk ratio.

One significant group that is missing from landmark analyses is the one with family history of early cardiovascular disease, which is known to be an independent risk factor for the occurrence of cardiovascular events according to the American Heart Association (AHA)/American College of Cardiology (ACC) [3].

We proposed to systematically evaluate the impact of aspirin vs placebo/no aspirin in randomized controlled trials enrolling patients with family history of cardiovascular disease. MEDLINE, CENTRAL, and Embase were comprehensively searched for aspirin trials in primary prevention (Supplementary Online) [2]. There were no language or time restrictions.

In order to quantify the effect of aspirin, we performed a random effects model meta-analysis, using RevMan 5.3 and based on the raw data from the three included studies. Estimates were reported as risk ratio [RR] and 95% confidence interval [95% CI]. Statistical heterogeneity was assessed through I^2 statistics.

After removal of duplicates, 14 studies were yielded, three of which presented data referring to our population of interest—Japanese Primary Prevention Project (JPPP), Women's Health Study (WHS), and Physicians' Health Study (PHS) [4–6]. Any cardiovascular event related to family history of cardiovascular disease was considered.

The three studies had heterogeneous populations gender-wise, with an age average > 50. Only one study separately defined family history of cardiovascular disease, clearly establishing age/gender thresholds [5]. Regarding outcomes, no trial reported data for all-cause mortality or bleeding events. Only two outcomes were reported by more than one study: major adverse cardiovascular events (MACE) and myocardial infarction (MI). MACE is defined as a composite outcome of myocardial infarction, stroke, and death from cardiovascular causes. Other individual outcomes included stroke and ischemic stroke. The intervention regimes, types of control, and follow-up time differed among studies—WHS had a higher dose of aspirin than the other two studies (325 mg vs 100), and JPPP had a "no-aspirin" control while others compared to placebo.

The incidence of MACE was 2.9% in a total of 8622 participants and of MI 1.7% in a total of 7511 patients (Fig. 1). Compared to no aspirin or placebo, primary prevention with aspirin did not reduce the incidence of MACE in patients with family history of cardiovascular disease, RR of 1.00 (95% CI 0.74–1.35) (Fig. 1), and comparing to placebo primary prevention with aspirin did not significantly reduce the incidence of MI, RR of 0.73 (95% CI 0.50–1.07) (Fig. 1).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10557-020-07093-8) contains supplementary material, which is available to authorized users.

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Published online: 16 October 2020

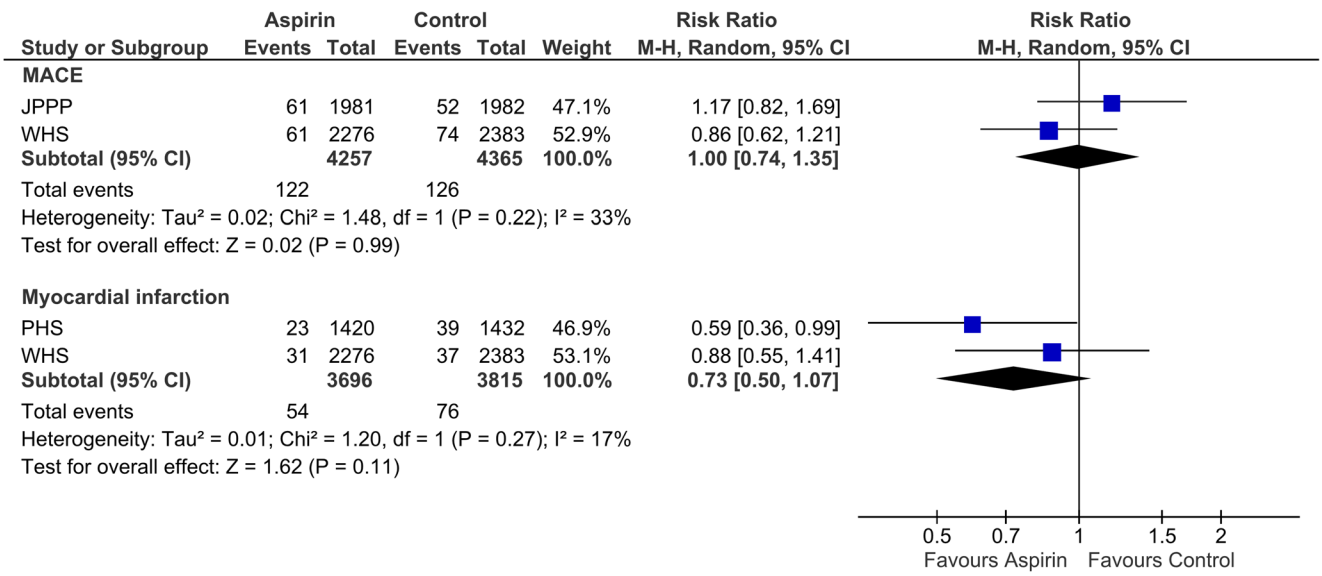

Fig. 1 Forest plot with pooled results for MACE and MI

This evaluation has limitations which include the fact that gender-wise the populations are heterogeneous, the dosing and posology of aspirin also differ among studies, and that the control in the MACE subgroup also differs among studies. One limitation that is particularly striking is the lack of a standardized and unequivocal definition of family history of cardiovascular disease in the trials—which may be due to a difficulty to clearly elicit this information from patients in the first place, but needs to be tackled nonetheless.

Given the studies that were found, and the pooled results, our conclusions are as follows:

(a) Few trials report the impact of aspirin as primary prevention in individuals with a family history of early cardiovascular disease.
(b) Based on these data, patients with family history of early cardiovascular disease do not benefit from aspirin in the primary prevention of cardiovascular events. This contrasts with mounting data suggesting that clinicians are prone to prescribe aspirin to this subset [7].
(c) The absence of any data regarding all-cause mortality or bleeding events renders any risk-benefit assessment impossible in this evaluation.
(d) We propose that the standardized definition of early cardiovascular disease in a family member—cardiovascular disease/atherosclerotic < 55 years in men and < 60 years in women—should be used in all clinical trials [3].
(e) As current data does not exclude a potential clinically relevant MI risk reduction, we challenge investigators for individual patient data meta-analysis of existing trials in order to investigate the remaining doubts and unanswered questions. If not feasible, there might be still an open road for further studies in this setting.

Compliance with Ethical Standards

Conflict of Interest The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: DC has participated in educational meetings and/or attended a conferences or symposia (including travel, accommodation) with Daiichi Sankyo, Menarini, Merck Serono and Roche, in the last 3 years . MA has participated in conferences with Boehringer-Ingelheim, AstraZeneca, Bayer, Bristol-Myers-Squibb- Grünenthal, Tecnimede, and Merk Sharp & Dohme. FJP had consultant and speaker fees with AstraZeneca, Bayer, BMS, Boehringer Ingelheim, and Daiichi Sankyo. JJF had speaker and consultant fees with Grunenthal, Fundação MSD (Portugal), TEVA, MSD, Allergan, Medtronic, GlaxoSmithKline, Novartis, Lundbeck, Solvay, BIAL, Merck-Serono, Merz, Ipsen, Biogen, Acadia, Allergan, Abbvie, Sunovion-Pharmaceuticals. MMA has nothing to declare.

Ethics Approval The ethical approval and patient informed consent were not required because no patient-level data is involved for this systematic review and meta-analysis.

References

1. Baigent C, 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):1849–60.
2. Caldeira D, et al. Aspirin in the primary prevention of cardiovascular disease on diabetic patients: systematic review and meta-analysis. Prim Care Diabetes. 2019.
3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, 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. Ikeda Y, Shimada K, Teramoto T, Uchiyama S, Yamazaki T, Oikawa S, et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. Jama. 2014;312(23):2510–20.
5. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JAE, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005;352(13):1293–304.
6. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med. 1989;321(3):129–35.
7. Rivera CM, Song J, Copeland L, Buirge C, Ory M, McNeal CJ. Underuse of aspirin for primary and secondary prevention of cardiovascular disease events in women. J Women's Health (Larchmt). 2012;21(4):379–87.