ESC European Society of Cardiology
European Heart Journal (2019) **40**, 2922–2923
doi:10.1093/eurheartj/ehz223

Aspirin for primary cardiovascular prevention: is there a need for risk stratification?

Alberto Aimo and Raffaele De Caterina*

Cardiology Division, University Hospital of Pisa, Via Paradisa 2, 56126 Pisa, Italy

Online publish-ahead-of-print 21 April 2019

This commentary refers to 'Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials', by A.N. Mahmoud *et al.*, 2019;40: 607–617.

The meta-analysis by Mahmoud *et al.*[1] shows that aspirin for primary cardiovascular prevention does not reduce mortality, while increasing bleeding. On behalf of the ESC Working Group on Thrombosis in 2014, we attempted a comprehensive evaluation of evidence from published studies[2]: for each trial we plotted the risk differences

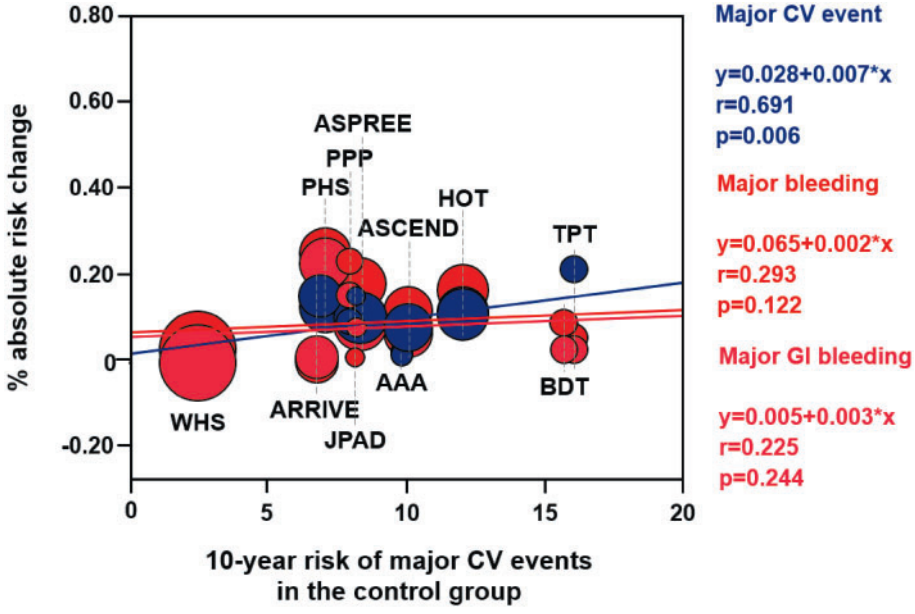

Figure 1 Relationships between magnitude of antithrombotic benefit vs. bleeding risk and cardiovascular risk in trials of aspirin for primary prevention. We fitted a univariate linear regression between the 10-year risk of major cardiovascular events (vascular death, non-fatal myocardial infarction, and non-fatal stroke) in the control group of each primary prevention trial included in the meta-analysis[1] (*independent variable*), and the percent absolute risk reduction for outcome events (major cardiovascular events, major bleeding, and major gastrointestinal bleeding) (*dependent variable*). The percent absolute risk reduction was calculated as: annual incidence in the control group - the annual incidence in the aspirin group × 100. We used the sample size of each trial as the weight (as in Ref.[1]). ARRIVE, Aspirin to Reduce Risk of Initial Vascular Events; ASCEND, A Study of Cardiovascular Events iN Diabetes; ASPREE, Aspirin in Reducing Events in the Elderly; BDT, British Doctors Trial; HOT, hypertension optimal treatment; JPAD, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; PHS, US Physicians Health Study; PPP, primary prevention project; TPT, thrombosis prevention trial; WHS, Women's Health Study.

* Corresponding author. Tel: +50 315 2683, Email: raffaele.decaterina@unipi.it

between aspirin and placebo for major cardiovascular events (MACE) major bleeding and major gastrointestinal bleeding against the 10-year MACE risk in controls. In linear regression analysis, the reduction of MACE greatly outweighed the increase in bleeding risk when the 10-year MACE risk was ≥20%; there was an 'uncertainty area' between 10% and 20%, and no net benefit for a risk <10%. Aspirin was then recommended for subjects with >20% risk and suggested for those with a 10–20% risk.[2]

When re-assessing the 11 studies assessed in the meta-analysis by Mahmoud *et al.*, we may note that the authors excluded all trials enrolling patients with even indirect signs of atherosclerotic disease, such as reduced ankle-brachial index, thus evaluating only patients in the lower range of the cardiovascular risk.[1] Still, a separation of regression lines depicting the risk vs. benefit could be observed, with a limited increase in bleeding risk, and a more prominent reduction in thromboembolic events (*Figure 1*). Although the regressions did not achieve statistical significance, there is still—apparently—a risk range where the use of aspirin could be worthy. We had previously emphasized that 'lack of (statistical) evidence is not evidence against' treatment: as in many areas of medicine, even Class I recommendations can be given despite level C supporting evidence. After completion of the recent ARRIVE, ASCEND, and ASPREE trials,[1] now with 157 248 subjects included in trials with a mean follow-up of 6.6 years,[1] we are still in no better position than before[2] in exploring areas of risk where we were predicting benefit, i.e. >10%/year risk of MACE, also as a consequence of the fact that older tools for 10-year risk prediction now tend to overestimate risk in contemporary patients.[2]

For these reasons, we think that any sensible recommendation on aspirin use should be based on the consideration that primary prevention is an extremely heterogeneous conundrum, ranging from young healthy individuals to subjects who will experience their first cardiovascular event within days. Albeit imperfect, our tools for risk stratification can support clinicians to identify the patients in whom the benefits from aspirin outweigh the risks, even irrespective of the possible impact of aspirin on gastrointestinal cancer.

Conflict of interest: none declared.

References

1. Mahmoud AN, Gad MM, Elgendy AY, Elgendy IY, Bavry AA. 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**: 2924–2925.
2. Halvorsen S, Andreotti F, ten Berg JM, Cattaneo M, Coccheri S, Marchioli R, Morais J, Verheugt FW, De Caterina R. Aspirin therapy in primary cardiovascular disease prevention: a position paper of the European Society of Cardiology working group on thrombosis. *J Am Coll Cardiol* 2014; **64**:319–327.