Aspirin prophylaxis: No magical single dose

Rothwell PM, Cook NR, Gaziano JM, Price JF, Belch JFF, Roncaglioni MC, Morimoto T, Mehta Z. (Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neuroscience, University of Oxford, Oxford, UK; Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; Harvard Medical School, Boston, Massachusetts, USA; Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK; Institute of Cardiovascular Research, Vascular and Inflammatory Diseases Research Unit, University Division of Medicine and Therapeutics, Ninewells Hospital and Medical School, Dundee, UK; Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy; Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Japan.) Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: Analysis of individual patient data from randomised trials. *Lancet* 2018;**392:**387–99.

SUMMARY

In this study, the authors sought to assess whether the weight, height, body mass index (BMI) and other measures of body size of patients had any bearing on the effectiveness of low and higher doses of aspirin for prophylaxis against coronary heart disease and cancer.

Ten trials (involving 117 279 participants) were identified from the Antithrombotic Trialists' Collaboration, the Cochrane Collaboration Database of Systematic Reviews and previous systematic reviews. Trials were analysed separately according to whether they were investigating aspirin for primary or secondary prevention and whether they used low doses (≤100 mg, seven trials) or higher doses (≥300 mg, two trials). Participants were dichotomized by body weight: those weighing <70 kg versus those weighing ≥70 kg. For each outcome, hazard ratios were calculated for aspirin versus control in each trial. Effect modification by other measures of body size (including lean body mass, BMI, fat mass and body surface area) and by vascular risk factors was also assessed. In the trials with follow-up for cancer, the effect of aspirin on the 20-year risk of colorectal cancer was stratified by weight in the same way, with additional stratification by age (<70 years *v*. ≥70 years) and dose of aspirin (75–100 mg *v*. ≥300 mg).

Low-dose aspirin reduced cardiovascular events by 23% (hazard ratio 0.77, 95% CI 0.68–0.87; p<0.0001) in those weighing <70 kg, compared with a reduction of only 12% (hazard ratio 0.88, CI 0.81–0.95; p=0.0008) in the overall primary prevention population when weight was not considered. The greatest effect, to an extent more than previously thought, was in participants weighing 50–69 kg, particularly

with daily use. However, this reduction was not seen in people weighing <50 kg, who also had an increased risk of all-cause death. Low-dose aspirin prevented stroke in women but not in men, but no difference remained after accounting for weight. Weight remained a considerable effect modifier after inclusion of age, sex and smoking interactions in the model. Weight dependence was observed for all tablet formulations, but loss of effect was more evident for enteric-coated or delayed-release aspirin. In participants weighing ≥70 kg, low-dose aspirin was ineffective in the primary prevention of cardiovascular events in 80% of men and nearly 50% of women, even increasing the case fatality of first events. The ability of higher doses to reduce the risk of cardiovascular events increased with weight, 325 mg aspirin reduced cardiovascular events in participants weighing ≥70 kg and 500 mg aspirin for those weighing ≥90 kg. Weight-dependent dosing (75–100 mg for people weighing 50–69 kg, 300–325 mg for 70–89 kg and ≥500 mg for ≥90 kg) suggested that primary prevention might be improved for cardiovascular events, stroke, cardiovascular-related death and all-cause death. Risk of sudden cardiac death was increased when the dose of aspirin exceeded this weight-dependent dosing.

Low-dose aspirin reduced the risk of colorectal cancer in participants weighing <70 kg but not in people weighing ≥70 kg. Higher doses extended this benefit for weight up to 80 kg. Aspirin had no effect on the overall incidence of first cancer. However, it appeared to increase the incidence of cancer in participants aged ≥70 years in the first 3 years of follow-up, reflecting an apparent age-related hazard. This increased risk was greatest in those with smaller body size, particularly in those weighing <70 kg and, consequently, in women. This was followed by a reduced incidence of cancer after 5 years.

The findings suggest the existence of a therapeutic window related to body size within which a given daily dose is most effective. Specifically, loss of efficacy can occur if the aspirin dose is too low or too high for body size, and other harms appear to result from excess dosing. Reductions in cardiovascular events and all-cause death at optimal doses for weight were substantial, highlighting the potential for a more tailored dosing of aspirin. Use of a low dose of aspirin twice a day might also reduce any hazards resulting from excess dosing.

This study has some limitations. Some older trials were included and temporal changes in risk factors or medication could alter findings. Only one primary prevention trial used standard-release, low-dose aspirin. Some trials were conducted only among men and some only among women. The authors validated findings in trials in the secondary prevention of stroke and mention that they cannot be certain of the generalizability of the results to other secondary prevention settings. Body weight might have changed during trial follow-up.

In conclusion, the optimal dose of aspirin to prevent cardiovascular events depends on body weight, driven more by lean body mass and height than by BMI. Low-dose aspirin once a day was ineffective in people weighing 70 kg or more, particularly in those who smoked or were treated with enteric-coated formulations, whereas higher doses became more effective with increasing weight. Given that the effects on sudden cardiac death and cancer also showed dose–weight interactions, the one-dose-fits-all strategy for daily aspirin use is unlikely to be optimal.

COMMENT

Aspirin is the most important drug used in the primary and secondary prophylaxis of coronary artery disease and ischaemic stroke. It reduces the risk of serious vascular events in high-risk patients by 20%–25%.[1] It is also known to reduce the risk of several gastrointestinal malignancies, particularly gastric, oesophageal, pancreatic, hepatic and colorectal cancers.[2,3] Use of aspirin is not without its risks. There is an increased risk of major bleeding events, particularly from the gastrointestinal tract and in the brain.

Due to the unusual and variable metabolism and elimination kinetics of salicylate, there is person-to-person variation in the response to salicylate therapy. Women frequently exhibit higher plasma concentrations. Salicylate clearance is reduced and exposure is considerably increased in the elderly. In case of obesity and increased BMI, low doses of aspirin result in reduced inhibition of cyclo-oxygenase 1, probably because of increased platelet activation or turnover. Intravenous antiplatelet drugs and thrombolytics are already used in weight-based dosages. It is intriguing that, given the implications, there has been little focus so far on whether pharmacokinetics and dynamics of aspirin are affected by body weight.

Available formulations of aspirin are of 75, 81, 150 and 325 mg. There is no consensus, however, on the dose to be used for prophylaxis. The situation is further complicated by the issue whether to use enteric-coated preparations or standard-release ones, the bioavailability of the former having been shown to be lower than that of the latter.[4] It is agreed that for secondary prevention of cardiovascular disease, benefits of aspirin use outweigh the risks. However, for primary prophylaxis, there is ambiguity. Prevention of myocardial infarction by aspirin is numerically balanced by the serious gastrointestinal bleeds it precipitates.[5] Therefore, it is largely the discretion of the treating physician as to what dose should be prescribed. In practice, this decision is made after considering the pros and cons of aspirin therapy by assessing risk factors for individual patients, presence of comorbid conditions, risk of bleeding, age of the patient, other drugs being taken, etc. However, it is well known that despite aspirin prophylaxis, cardiovascular events still occur.[6]

In this meta-analysis, low-dose aspirin (≤100 mg/day) prevented cardiovascular events only in individuals with low body weight (<70 kg). For those with higher weights, there was no benefit in 80% of men and nearly 50% of all women. The problem is, for those with weights >70 kg, only doses of ≥300 mg were effective, which are likely to increase the risk of gastrointestinal bleeding. A single 325-mg dose of aspirin approximately doubles the mean bleeding time of normal persons for 4–7 days.[1] Even the so-called low doses of 75–100 mg per day were found to have some detrimental effects for people with low body weight (≤50 kg), like accelerating growths of gastrointestinal cancers and increasing risk of bleeding. Twice-a-day dosing was also found to be better for individuals with higher weights. No data exist for doses between 100 and 325 mg.

To summarize, for the prevention of cardiovascular events, an aspirin dose of ≤100 mg/day is practically useless for patients weighing over 70 kg and might be harmful for those weighing <50 kg. For those weighing >70 kg, the dose must be ≥300 mg. Therefore, weight-based dosing is likely to be more appropriate.

Since this was a retrospective analysis of older trials, the authors have acknowledged that these findings need to be confirmed by larger studies. Randomized controlled trials are needed and outcomes of existing trials have to be seen in this new light of importance of weight or other parameters of body size.

This study suggests that the approach of one-dose-fits-all needs to be discarded. Precision medicine seems to be the next evolutionary step in clinical practice and this study could be the harbinger of radical changes in the way drugs, even other than aspirin, are prescribed in the future.

Conflicts of interest. None declared

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