PREVENTION

Time to adjust aspirin dose to body weight

Loss of efficacy can occur if the aspirin dose is too low or too high for body size

Low doses of aspirin are effective for prevention of cardiovascular events only in patients with low body weight and become ineffective as body weight increases; conversely, the efficacy of high-dose aspirin decreases with decreasing body weight. These findings, published in *The Lancet*, suggest that aspirin dosing should be adjusted according to body weight.

Aspirin irreversibly acetylates cyclooxygenase 1 (COX1), which inhibits thromboxane production and platelet aggregation. However, obesity and increased BMI are associated with reduced inhibition of COX1 by low doses of aspirin, probably because of increased platelet activation or turnover.

Researchers identified ten eligible clinical trials of aspirin in primary prevention, involving a total of 117,279 participants. Median body weight ranged from 60.0 kg to 81.2 kg. In an initial meta-analysis of these trials, low-dose aspirin reduced the risk of cardiovascular events in participants weighing <70 kg (OR 0.77, 95% CI 0.68–0.87, $P=0.0001$) but was not effective in those weighing ≥ 70 kg (OR 0.94, 95% CI 0.86–1.04, $P=0.24$).

In a pooled analysis of individual participant data, the efficacy of low-dose aspirin (75–100 mg) to reduce cardiovascular events decreased with increasing weight ($P=0.0072$ for interaction), with the greatest reduction in cardiovascular events in

participant who weighed 50–69 kg (HR 0.75, 95% CI 0.65–0.85, $P<0.001$). Low-dose aspirin prevented stroke in women but not in men, but no significant difference remained after accounting for body weight. The effect of low-dose aspirin on cardiovascular events was not modified by the presence of diabetes mellitus or by age, but was reduced in smokers ($P=0.0026$ for interaction). In participants weighing ≥ 70 kg, low-dose aspirin was associated with an increase in case fatality of first cardiovascular events (OR 1.33, 95% CI 1.08–1.64, $P=0.0082$).

The efficacy of higher doses of aspirin to reduce the risk of cardiovascular events increased with body weight ($P=0.017$ for interaction). In primary prevention, 325 mg of aspirin reduced cardiovascular events in participants weighing ≥ 70 kg (HR 0.83, 95% CI 0.70–0.98, $P=0.028$), and 500 mg of aspirin reduced cardiovascular events or death in those weighing ≥ 90 kg (HR 0.52, 95% CI 0.30–0.89, $P=0.017$).

Of note, low-dose aspirin reduced the risk of colorectal cancer in participants weighing <70 kg (HR 0.64, 95% CI 0.50–0.82, $P=0.0004$) but not in those weighing ≥ 70 kg (HR 0.87, 95% CI 0.71–1.07, $P=0.32$).

“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,” conclude the researchers. “Reductions in cardiovascular events and all-cause death at optimal doses for weight were substantial, highlighting the potential of more tailored aspirin dosing.” The investigators point out that

weight-based dosing is already commonplace for thrombolytics and intravenous antiplatelet treatment, but not for oral antiplatelet drugs.

“The finding that optimal dosing of aspirin for prevention of cardiovascular events (and even cancer) depends on body weight, particularly lean body mass and height, is biologically plausible and argues for more tailored and personalized decision-making about the dose of aspirin,” comments JoAnn Manson (Brigham and Women’s Hospital, USA), who was not involved in the study. “Some of the sexual dimorphism observed in response to aspirin may be due to differences in body size, distribution volumes, and systemic bioavailability,” continues Manson, who was a co-investigator on the Women’s Health Study and US Physicians’ Health Study aspirin trials.

“Despite increasing attention to the importance of precision medicine ... readily available information such as height, weight, body size, age, and sex is often overlooked. Hopefully, this report will help to usher in a new era of personalized medicine that considers readily available clinical factors, as well as molecular data, in clinical decision-making,” concludes Manson.

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ORIGINAL ARTICLE Rothwell, P. M. et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. *Lancet* [https://doi.org/10.1016/S0140-6736\(18\)31133-4](https://doi.org/10.1016/S0140-6736(18)31133-4) (2018)
FURTHER READING Capodanno, D. et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat. Rev. Cardiol.* **15**, 480–496 (2018)