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Weight-Adjusted Aspirin Dosing: Evidence Builds in Primary Prevention

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Low-dose aspirin intended for primary prevention, typically 75 to 100 mg once daily, doesn't protect against cardiovascular events in persons who weigh at least 70 kg (about 154 pounds), suggests a patient-level analysis of randomized trials that included more than 100,000 patients.

But daily aspirin at higher dosages, usually at least 300 mg, was cardioprotective in that group, as was low-dose aspirin in people who weighed less than 70 kg.

What constitutes a "low" or "high" aspirin dosage tends to vary somewhat by world region; regardless, the current findings challenge the common practice of prescribing a "one-size-fits-all" aspirin dosage in primary cardiovascular (CV) prevention, and possibly in secondary prevention.

That low-dose aspirin seems protective only in lighter adults has major implications for the primary prevention strategy. About half of women and 80% of the men weighed at least 70 kg in the meta-analysis of mostly older trials of primary prevention aspirin. The study was published July 12 in the *Lancet*, with lead author Peter M. Rothwell, MD, PhD, University of Oxford John Radcliffe Hospital, United Kingdom.

"We showed fairly convincingly that in the trials done 10 or 20 years ago, there was weight dependence, and those on the right dose per weight seemed to benefit quite a lot in primary prevention," Rothwell told *theheart.org* | *Medscape Cardiology*.

Weight dependence was also seen for aspirin's associated bleeding risk and its potential for protecting against some forms of cancer.

"Best Estimate at the Moment"

Low-dose aspirin was associated with a 12% drop in risk for CV events (vascular death, myocardial infarction, or stroke) overall in the primary prevention population ($P = .0008$) but a decrease of 23% for people weighing less than 70 kg ($P < .0001$). The risk edged nonsignificantly lower in the remaining people 70 kg or heavier ($P = .24$).

"It's the best estimate that we've got at the moment: You'd have to say that the low-dose aspirin does seem to work in people under 70 kg," Rothwell said.

He acknowledged, however, that the degree of CV protection seen in the analysis "might well be smaller now than it was 10 to 20 years ago" given the rise of statins and other treatment advances in the intervening years.

Although any of the conventional low aspirin doses appear protective in people who weigh less than 70 kg, "there is a question mark about the need for higher doses at higher weights," he said.

The CV risk reduction was about 17% for persons 70 kg or heavier at a daily aspirin dose of 325 mg ($P = .028$), which should be weighed against the possibility of bleeding and other attendant risks.

Even with low-dose aspirin, the risk for bleeding complications was weight-dependent, dissipating with increasing weight to about 90 kg (about 198 pounds). That a bleeding risk was observed in people weighing 70 to 90 kg "is not good news," Rothwell said. "Then you're probably not getting much benefit at all, and possibly harm, if you're talking the low dose."

Fodder for Future Trials

Because half the women and most of the men in the analysis weighed more than 70 kg, authors of an accompanying editorial point out, "weight-adjusted dosing would result in increased daily doses of aspirin in the majority of patients."

That would be expected to increase the risk for bleeding, but perhaps not in a linear fashion, write Katherine N. Theken, PharmD, PhD, and Tilo Grosser, MD, from the University of Pennsylvania, Philadelphia.

"Bodyweight should be considered in ongoing and future randomized clinical trials that address aspirin dosing in cardiovascular prevention to clarify how weight-adjusted dosing will affect both benefit and risk," they concluded.

The current analysis has "major implications for clinical practice," JoAnn E. Manson, MD, DrPH, Brigham and Women's Hospital, Boston, Massachusetts, told *theheart.org* | *Medscape Cardiology*.

"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," she wrote in an email.

Manson, not connected with the current report, was a coinvestigator on the Women's Health Study and the Physicians' Health Study. Both studies helped define the field of aspirin for primary CV prevention and were included in the meta-analysis.

The new report's findings indeed "are very plausible," agreed Adrian Hernandez, MD, MHS, Duke Clinical Research Institute, Durham, North Carolina, also not a coauthor. "Why would one dosage have the same effect in all? Especially if you have someone who is aged 40 vs 80, and has a different risk for bleeding, and a different risk for having an MI?"

No contemporary trial has been large enough to answer those questions, he said when interviewed, "so a meta-analysis can be very useful."

For the time being, the current analysis is a good way to summary the state of evidence so far, "and it does help emphasize that there's some need to personalize treatment here," Hernandez said.

The median weight for people in the included randomized trials ranged from 60 kg to 81 kg. The association between low-dose aspirin (75 to 100 mg/day) and risk for CV events in the overall cohort was driven by a significant benefit in those weighing less than 70 kg and declined with increasing body weight. That was also true for the female and male subgroups separately.

Table. Hazard Ratios for CV Events on Low-Dose Aspirin by Weight and Sex: Patient-Level Analysis of Primary Prevention Trials

Endpoints	Total Cohort	Women	Men
Body weight <70 kg	0.77 (0.68 - 0.87)[a]	0.80 (0.69 - 0.92)	0.70 (0.54 - 0.91)
Body weight ≥ 70 kg	0.95 (0.86 - 1.04)[b]	0.97 (0.83 - 1.12)	0.92 (0.81 - 1.05)
Any weight	0.88 (0.81 - 0.95)[c]	0.88 (0.79 - 0.97)	0.87 (0.77 - 0.98)

Values in parentheses are 95% confidence intervals.
[a] $P < .0001$.
[b] $P = .24$.

[c] $P = .0008$.

The risk for a fatal first CV event in people weighing at least 70 kg on low-dose aspirin was elevated, with an odds ratio (OR) of 1.33 (95% confidence interval [CI], 1.08 - 1.64; $P = .008$).

The trend in heavier people reversed for those taking high-dose aspirin. For people 70 kg or heavier, the HR for CV

events was 0.83 (95% CI, 0.70 - 0.98; *P* = .028).

Low-dose aspirin was also associated with a reduced risk for colorectal cancer in the patients weighing less than 70 kg (HR, 0.64; 95% CI, 0.50 - 0.82; *P* = .0004), but not in heavier people (HR, 0.87; 95% CI, 0.71 - 1.07).

A similar pattern but with a different weight cutoff was observed for high-dose aspirin, which was associated with an HR for colorectal cancer of 0.69 (95% CI, 0.55 - 0.87; *P* = .0014) for persons weighing less than 80 kg (about 176 pounds) but 1.08 (95% CI, 0.83 - 1.39) for those weighing 80 kg or more.

Sex Differences in Aspirin Effect Explained?

"Interactions between dose and weight probably explain previously reported sex differences in the effects of aspirin on risks of stroke and myocardial infarction," write Rothwell and colleagues.

"Widespread use of 325 mg aspirin once a day in the USA and elsewhere is questionable in low-weight individuals given the effectiveness of lower doses and the apparent hazards of excess dosing."

Manson agreed that the meta-analysis may "be highly relevant to findings of sex differences in effects of aspirin and other therapeutic agents that have been found to have different benefit-risk profiles in men and women and require different dosing strategies."

Many of those differences by sex and weight "may be due to differences in body size, distribution volumes, and systemic bioavailability," she said.

"It is ironic that, despite increasing attention to the importance of precision medicine and consideration of complex genomic and molecular factors in optimal targeting of treatments," Manson said, "readily available information such as height, weight, body size, age, and sex is often overlooked."

The published report points to an abundance of upcoming large randomized trials aimed at clarifying the role of aspirin in primary CV prevention.

They include ARRIVE with more than 12,000 people at moderate CV risk assigned to aspirin 100 mg/day or placebo; ASPREE, testing the same dosage in an estimated 19,000 people age 65 or older; and ASCEND, also comparing aspirin 100 mg/day, in more than 15,000 adults with diabetes but no history of CV events.

ARRIVE and ASCEND are both scheduled for presentation and coverage by *theheart.org* | *Medscape Cardiology* at the upcoming European Society of Cardiology 2018 scientific sessions.

Even the ongoing ADAPTABLE trial comparing aspirin 81 mg/day to 325 mg/day for secondary CV prevention in a projected 15,000 patients could inform the use of aspirin for primary prevention.

In its prespecified subgroup analysis, "we should be able to shed some light on whether there are differences in terms of outcomes based on age, sex, and body weight," said Hernandez, who is a co-principal investigator on the trial.

The current meta-analysis "lays out a pretty strong argument that dose does matter," he said. "If ADAPTABLE indeed shows in secondary prevention that dose matters, then you start seeing consistency across the spectrum from primary to secondary prevention."

Rothwell declares receiving personal fees from Bayer "outside the submitted work." Disclosures for the other authors are in the report. Disclosures for Hernandez can be found here. Manson has disclosed no relevant financial relationships.

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