Title

Aspirin Use in Older People Highlights the Need for Improved Inclusion of Older People in Clinical Trials.

Journal

The Senior Care Pharmacist, 39(6)

ISSN

2639-9636

Authors

Watanabe, Jonathan H

Zajac, Dagmara

Publication Date

2024-06-01

DOI

10.4140/tcp.n.2024.209

Peer reviewed

Title

Aspirin Use in Older Adults Highlights the need for improved inclusion of older adults in clinical trials

The Senior Care Pharmacist Journal
Guest Editorial

Jonathan H. Watanabe PharmD, MS, PhD, BCGP, Dagmara Zajac, PharmD

Cite as: *Watanabe JH, Zajac D. Aspirin Use in Older People Highlights the Need for Improved Inclusion of Older People in Clinical Trials. Sr Care Pharm. 2024 Jun 1;39(6):209-211. doi: 10.4140/TCP.n.2024.209. PMID: 38803025.*

The Aspirin in Reducing Events in the Elderly (ASPREE) trial[1] was performed in order to assess whether the daily use of aspirin by older patients was effective for primary prevention and would lead to improved disability-free survival. Community-dwelling individuals from Australia and the United States were enrolled in this trial that included more than 19,000 people randomized to aspirin or placebo. Half of the study population were between the ages of 65 and 73 years old with the other half being 74 years and older. The researchers combined the outcomes of death, dementia, and persistent physical disability into a composite endpoint of disability-free survival. After a median 4.7 years of follow up time, the study was halted after a determination was made that there would be no benefit with continued aspirin for the primary end point. The team reported no statistically significant difference for prolonged disability-free survival. However, a statistically significant increased major hemorrhage rate for the aspirin group was observed. The rate of the composite of death, dementia, or persistent physical disability was 21.5 events per 1000 person-years in the aspirin group and 21.2 per 1000 person-years in the placebo group (hazard ratio, 1.01; 95% confidence interval [CI], 0.92 to 1.11; P=0.79). Differences between the aspirin group and the placebo group were not substantial for the secondary end points of death from any cause (12.7 events per 1000 person-years in the aspirin group and 11.1 events per 1000 person-years in the placebo group), dementia, or persistent physical disability. While the rate of major hemorrhage was higher in the aspirin group than in the placebo group (3.8% vs. 2.8%; hazard ratio, 1.38; 95% CI, 1.18 to 1.62; P<0.001).[1] As described in recent efforts of the National Academies of Sciences, Engineering, and Medicine,[2] prophylactic aspirin in healthy older adults opens the door for potential serious harm with indeterminate clinical benefit. While the Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) trial and the A Study of Cardiovascular Events in Diabetes (ASCEND) trial both also found increased bleed risk for older patient study sub-groups that used aspirin,[3,4] consumption of aspirin in older people continues to remain high with a 2021 estimate that nearly 10 million older adults in the US who took aspirin for primary prevention would no longer be recommended to continue.[5] In the absence of robust clinical trial data that included older adults to moderate the estimated benefits extended from clinical trials in younger populations, the overutilization of aspirin in seniors rapidly and durably took hold to this day.

The manuscripts in this special issue serve not only to inform senior care pharmacists on the importance of evidence-based approaches to reduce unnecessary aspirin use, but also underscores the urgent need for the large and rapid increase in older adult representation in clinical trials and clinical research in general. A striking analysis performed in the United States that examined the trial populations used for Medicare coverage determinations found that while that average age of a Medicare enrollees was 70.8 years old (74.7 years old for older Medicare participants), the average age of the clinical trial population patients used in technology assessments for Medicare coverage determinations was 60.1 years old.[6] Hence, the US Medicare system, one of the largest national health care purchasers for older adults in the world,[7] has relied on non-representative data to inform medical coverage decisions.

A review of National Institutes of Health (NIH)-funded phase 3 clinical trials that focused on the leading 10 causes of hospitalization and/or disability adjusted life years in older adults found that for virtually all of the conditions reviewed, the populations skewed younger than the real-world population. Moreover, it was reported that several excluded older adults entirely. When the rationale for exclusion was further probed, other challenges surfaced. While many patients with these conditions had comorbid conditions such as diabetes or hypertension or use multiple medications, these were often the precise factor for excluding them. In essence, ensuring the real world older adult population would not be present in these studies.[2] Informed with this data, NIH held a workshop in 2017 titled "Inclusion Across the Lifespan".[8] The participants examined the challenges and barriers to including older adults in medical research with the goal of distilling strategies to generate age-relevant research studies. Based on the conversations at the workshop, along with other deliberations across NIH, a new policy was announced in December 2017 by NIH. The policy required that clinical study applications submitted to NIH must include a plan for enrolling individuals across the lifespan. The policy further outlined that if researchers propose to exclude study patients predicated on age, a justification must be provided. It may not be appropriate, for example, to include older people in a measles research project. The policy now requires investigators to generate progress reports with anonymized, data about enrollees' age, sex/gender, and race/ethnicity. All efforts to bolster inclusion of older patients, women, and minorities.

Additionally, research funding agencies such as NIH, the Agency for Healthcare Research and Quality (AHRQ), and the Advanced Research Projects Agency for Health (ARPA-H) in the US can better leverage their roles to incentivize improved inclusiveness of older adults. The score-driving criteria that measure the scientific integrity and overall impact of a NIH grant proposal should formally include participant representativeness data. Patient age representativeness data should be components of the assessment of the scientific approach, including whether it is appropriate for concluding insights for the populations to whom the results are intended to generalize. In prior federally supported proceedings in the US, Alzheimer's Disease research was referenced as an area in which representation of older adults would be expected. The concept of requiring a justification for not including older adults was frequently described. The NIH should also assess in its annual review of progress reports of funded studies whether a given study has met the proposed enrollment goals of representativeness by race/ethnicity, sex, and

gender, and should consider establishing a plan for remediation that includes criteria for pausing funding that has not met predefined recruitment goals.[2] With a rapidly aging population in much of the developed and developing world, bold policy actions are urgently needed to ensure relevant, appropriate, robust, and timely evidence is available for clinical decision making in older people. The benefits are well defined. The risks, several of which are articulated clearly in this special issue, are explicit. Now is the time to marshal our efforts to improve research and care.

References

1. McNeil John J., Woods Robyn L., Nelson Mark R., et al. Effect of Aspirin on Disability-free Survival in the Healthy Elderly. *New England Journal of Medicine*. 2018;379(16):1499-1508. doi:10.1056/NEJMoa1800722

2. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division;Board on Health Sciences Policy; Board on Health Care Services; National Cancer Policy Forum; Forum on Drug Discovery, Development, and Translation; Forum on Aging, Disability, and Independence. *Drug Research and Development for Adults Across the Older Age Span: Proceedings of a Workshop*. (Forstag HE, Shore C, eds.). National Academies Press (US); 2021. Accessed April 3, 2024. http://www.ncbi.nlm.nih.gov/books/NBK566857/

3. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *New England Journal of Medicine*. 2018;379(16):1529-1539. doi:10.1056/NEJMoa1804988

4. Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *The Lancet*. 2018;392(10152):1036-1046. doi:10.1016/S0140-6736(18)31924-X

5. Liu EY, Al-Sofiani ME, Yeh HC, Echouffo-Tcheugui JB, Joseph JJ, Kalyani RR. Use of Preventive Aspirin Among Older US Adults With and Without Diabetes. *JAMA Network Open*. 2021;4(6):e2112210. doi:10.1001/jamanetworkopen.2021.12210

6. Dhruva SS, Redberg RF. Variations Between Clinical Trial Participants and Medicare Beneficiaries in Evidence Used for Medicare National Coverage Decisions. *Archives of Internal Medicine*. 2008;168(2):136-140. doi:10.1001/archinternmed.2007.56

7. cms-financial-report-fiscal-year-2021.pdf. Accessed April 2, 2024. https://www.cms.gov/files/document/cms-financial-report-fiscal-year-2021.pdf

8. Inclusion Across the Lifespan | grants.nih.gov. Accessed April 3, 2024. https://grants.nih.gov/policy/inclusion/lifespan.htm