Emerging Aspirin Investigator

Highly Commended Candidate

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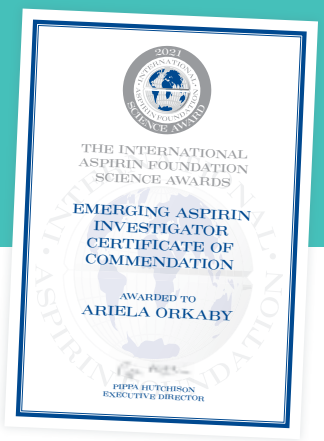
Is aspirin use associated with a decreased risk of frailty and functional limitation in older men?



Dr Orkaby thanked the Scientific Advisory Board for inviting her to share her research investigating whether aspirin use is associated with a decreased risk of frailty and functional limitation in older men. Dr Orkaby choose this research question as a Geriatrician, with the baby boomer generation turning 65 and the world's population aging (PGPF.org). One of the greatest fears among older adults is losing their functional independence and becoming frail.

Dr Orkaby turned to aspirin which at low doses has antithrombotic properties and at high doses analgesic and antipyretic properties and at both high and low doses an anti-inflammatory effect.

Frailty and cardiovascular disease are bidirectionally related and one of the key players in this is inflammation. Dr Orkaby therefore hypothesised that slow gait speed and frailty, which are both interrelated with cardiovascular disease, could potentially be mediated by aspirin

The ASPREE trial showed no benefit for aspirin used for cardiovascular disease (CVD) prevention for participants who are 70 years and older at the start of the trial. However, in a subgroup analysis in the short term of about 5 years low dose aspirin seems to have potentially protected against disability, HR 0.85 (0.70-1.03).

Since decrease in muscle mass is known as a hallmark of frailty, Dr Orkaby investigated some of the basic science and found that salicylates improve muscle regeneration in mice. She then decided to look back at existing trials of aspirin that have followed patients for a decade or longer to see what the relationship is between aspirin, frailty and slow walking speed. She hypothesised that long term aspirin use will lower the risk of frailty and self-reported mobility limitation. Dr Orkaby analysed data from the Physician's Health Study (PHS), a completed randomised trial of aspirin for CVD prevention, from 1982-6 with a continued cohort study from 1987 to 2012. Annual questionnaires assessed cognition, comorbidity, function and mood and there was adjudicated bleeding and CVD outcome data. Aspirin use was self-reported in annual questionnaires, and this was divided by Dr Orkaby into low users (less than or equal to 60 days per year) and regular users (more than 60 days per year) over a mean of 11 years of follow up (Orkaby 2020). The Rockford Frailty Index and Modified Study of Osteoporotic Fractures Scores were used to measure frailty. All covariates were balanced for 12,101 participants after propensity score inverse probability of treatment weighting was applied. The results showed that regular aspirin use, over 15 years of follow up, is associated with 15% lower odds of prevalent frailty, with no statistically significant interactions for age, history of CHD, arthritis, prior GI bleed and significant interaction for exercise (Orkaby 2020). Long term aspirin use is

associated with a lower risk of frailty using the two definitions of frailty.

The second outcome looked at mobility limitation using a self-reported usual walking speed. All covariates were balanced for 14,315 participants after propensity score inverse probability of treatment weighting was applied. The results showed that regular aspirin use was associated with a faster walking speed. Significant interaction for CHD history was found (with added benefit in this group) but not for age, arthritis, exercise or bleeding history. It appears long term aspirin use is associated with a greater probability of faster walking speed according to self-report.

The limitations of the study include an all-male cohort, no direct measure of frailty or function, self-reported walking speed (although this is validated), the possibility of reverse causality in the observational tool and a lack of information on the aspirin dose used. The strengths include a homogeneous cohort which allows for hypothesis generation, the study uses two different definitions of frailty, and has long term aspirin use. It is the first proof of concept study on the role of anti-inflammatory medications in humans on aging.

Another strength of this study is that the average age at the start of aspirin use was 58 years, an age at which bleeding risk is low and there is time to change the inflammatory milieu that leads to frailty.

This contrasts with the Aspirin in Reducing Events in the Elderly (ASPREE) trial which enrolled adults 70 and older and found no benefit for their primary outcome of disability and dementia free survival, with an increased risk of bleeding. It is likely that preventive strategies for frailty must begin earlier in life.

The role of aspirin in healthy aging remains incompletely answered, and while risks and benefits for individual patients must be considered, additional study is needed to understand how aspirin may impact aging physiology. Dr Orkaby plans to study the impact of aspirin on frailty in women and furthermore, to explore mechanisms through which aspirin may slow or prevent the development of frailty she has extracted stored lab samples from the Physicians' Health Study to examine inflammatory biomarkers that may explain the association found between aspirin and lower risk of frailty. The fastest growing segment of the population are those over age 85. Creative approaches are needed to ensure additional life years lived are free of chronic disease and functional decline. Aspirin may play a critical role.

Dr Orkaby hopes this work will help to enlighten the potential role of common medications such as aspirin for the prevention of frailty in older adults.

Discussion

Professor Andrew Chan asked Dr Orkaby if she had looked at the duration of aspirin use and how that compared to the provocative findings in ASPREE that 5 years of use may be enough to being to see a non-significant decrease in disability.

Dr Orkaby: Explained that at the end of the trial, in the PHS, most people switched to going onto aspirin and most people used aspirin for far more than 5 years. Whilst she didn't specifically examine the different duration of use she felt this was a good question to consider. Dr Orkaby also pointed out that the cohort she used was much younger at the start of the study period than those in ASPREE and so one of the thoughts here is that starting in younger individuals and using over a longer duration may be of importance.

Professor Patrono presented Dr Ariela Orkaby with an Emerging Aspirin Investigator certificate of commendation and the book Acetylsalicylic Acid by Karsten Schrör.

References

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