Journal Club
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Title: Effect of Aspirin on All-Cause Mortality in the Healthy Elderly

Authors: McNeil JJ, Nelson MR, Woods RL, et al

Source: *N Engl J Med*. 2018;379(16):1519-1528.

Background: The history of aspirin can be traced back centuries to natural remedies.[2] Aspirin has several chemical properties that allow it to function as an anti-platelet, anti-pyretic, analgesic, and anti-inflammatory agent.[2] In more modern times, the use of aspirin for secondary prevention for cardiovascular disease is backed by several trials, however, its use in primary prevention is not as defined.[3] Previous use of aspirin has also shown decreased colon cancer risks. The ASPREE (Aspirin in Reducing Events in the Elderly) trial looked to establish if low-dose aspirin should be used in healthy, elderly patients for disability-free survival. Ultimately, this study showed that aspirin was not proficient as a primary prevention measure. This article aims to examine secondary outcomes of the ASPREE trial, specifically, all-cause mortality, and mortality due to cancer.

Primary Objective: The ASPREE trial looked o determine if daily use of 100 mg of enteric-coated aspirin would prolong the healthy life span of older adults. This article looked to evaluate secondary endpoints of all-cause mortality and mortality due to cancer.

Primary Efficacy Measure: Time to death from any cause.

Study Design: This was a randomized, multi-center, double-blinded, placebo-controlled study that took place in Australia and the United States. Patients were screened and began a 4-week run-in period where they were instructed to take a placebo to check for compliance before beginning the trial. Patients were instructed to take their study medication 30 minutes prior to other medications to avoid drug interactions, specifically with non-steroidal anti-inflammatory drugs (NSAIDs). To analyze death, first notification of death required confirmation from two independent sources. Next, clinical details were obtained to determine the cause. Details were presented to two adjudicators who were unaware of the group assignments. The adjudicators examined both the underlying and proximal cause of death, or the terminal event that led to death.

Subjects: Randomization of patients produced groups that were similar in age, sex, country, race, smoking status, diabetes, hypertension, dyslipidemia, personal cancer history, previous use of aspirin, and frailty.[3] IN this trial, blacks and Hispanics were allowed in the trial if they were 65 or older. Groups were stratified by study center and age.

Inclusion Criteria:

- Men and Women 70 years of age and older

- Willing and able to provide informed consent, and willing to accept the study requirements

Exclusion Criteria:

- A history of a diagnosed cardiovascular event defined as MI, heart failure, peripheral arterial disease, angina pectoris, stroke, transient ischemic attack, >50% carotid stenosis or previous carotid endarterectomy or stenting, coronary artery angioplasty or stenting, coronary artery bypass grafting, or abdominal aortic aneurysm.
- A clinical diagnosis of atrial fibrillation.
- A serious intercurrent illness likely to cause death within the next 5 years, such as terminal cancer or obstructive airways disease.
- A current or recurrent condition with a high risk of major bleeding, e.g. cerebral aneurysm or cerebral AV malformation, any bleeding diathesis, gastrointestinal malignancy, recent peptic ulcer, liver disease, esophageal varicosities, uremia, aortic aneurysm or any other condition known to be associated with a high risk of serious bleeding.
- Anemia, i.e. hemoglobin level below the normal value for the gender of the participant (males: 12 g/dL, females: 11 g/dL) (Note: Hemoglobin levels within the normal range in a participant taking therapy for anemia will not be an exclusion criterion).
- Absolute contraindication or allergy to aspirin.
- Current participation in a clinical trial.
- Current continuous use of aspirin for secondary prevention.
- Current continuous use of other anti-platelet drug or anticoagulant.
- A systolic blood pressure ≥180 mmHg and / or a diastolic blood pressure ≥105 mmHg
- A history of dementia or a Modified Mini-Mental State Examination (3MS) score ≤ 77 as measured at Visit 1: Lifestyle Profile and Screening.
- Severe difficulty or an inability to perform any one of the 6 Katz ADLs, as determined at Visit 1: Lifestyle Profile and Screening.
- Pill-taking compliance below 80% during the placebo run-in phase.

Study Period: This study occurred from March 2010 until June 12th, 2017, when it was stopped at the request of the National Institute of Aging. Patients participated in a 4-week run-in where they were instructed to take a daily placebo tablet to check for compliance. Patients who were above 80% complaint where randomized into either the aspirin or placebo treatment group.

Monitoring: Patients were monitored through annual visits and phone calls between visits. Deaths were identified during routine trial activity, review of health records, or when next of kin notified the trial center.

Data Analysis: Analysis of an intent-to-treat population was performed with 9,525 assigned to receive aspirin and 9,589 assigned to receive placebo (19,114 total). Power was set at 90% with 19,000 patients total required to detect a hazard ratio of 0.90. Alpha was set at 0.05.

Data Analyzed	Type of Data	Statistical Test Used	Appropriate/Not Appropriate
Time to death from any cause and Time to death from cancer	Survival	Cox proportional hazards	Appropriate

Results: The use of low-dose aspirin was shown to increase the risk of mortality when compared to placebo. This is shown by the lower bound of the 95% CI not crossing the absolute equivalency of 1.

Cause of Death	Overall (n=19,114)	Aspirin (n=9,525)	Placebo (n=9,589)	Hazard Ratio (95% CI)	NNH
Any	1052	558 (5.9)	494 (5.2)	1.14 (1.01-1.29)	142
Cancer	522	295 (3.1)	227 (2.3)	1.31 (1.10-1.56)	125
Cardiovascular disease, including ischemic stroke	203	91 (1.0)	112 (1.2)	0.82 (0.62-1.08)	n/a
Major hemorrhage, including hemorrhagic stroke	53	28 (0.3)	25 (0.3)	1.13 (0.66-1.94)	n/a
Other	262	140 (1.5)	122 (1.3)	1.16 (0.91-1.48)	n/a

Confidence intervals and P values were not adjusted for multiple comparisons

Tolerability: As shown, more deaths occurred in the aspirin group (558 vs 494). This was mostly attributed to the higher cancer-related mortality in the aspirin group. This mortality was not attributed to any specific cancer and was observed in patients within the aspirin treatment group in both the United States and Australian patients. Overall, cancer was the underlying cause in 49.6% of the deaths, cardiovascular disease accounted for 19.3%, and major hemorrhage counted towards 5%.

Author's Conclusion: The use of low-dose aspirin could increase the risk of mortality from any cause from 1-29% in healthy, elderly patients.

Strengths:

- Power was set and met for the primary outcome
- Treatment was appropriate, however, 100 mg aspirin is not readily available within the United States
- Study period allowed adequate time for the primary outcome to occur
- Inclusion and exclusion criteria were appropriate
- Blinding was present
- Randomization produced similar groups and were stratified based on country and age
- Biostatistical test was appropriate
- Author's conclusion supported by results

- Study was ended when it was shown to be unlikely to show a benefit for the primary outcome
- Researchers were able to determine cause of death for all but 12 deaths

Limitations:

- P values and confidence intervals were not adjusted for multiple comparisons which increases the risk of type I error
- Limited follow-up period, which may have ended before the possible emergence of a preventive effect on cancer (1526-1527)[1]
- Trial focused on a specific age group and had a limited statistical power to base conclusions about the effect of aspirin on mortality in subgroups of the United States population (1527)[1]

Level of Evidence: Level I – interventional, placebo-controlled, randomized trial that met power with minor limitations

Recommendation: I do not recommend the use of low-dose aspirin in healthy, elderly patients without an indication for aspirin due to the concern of an increased risk of all-cause mortality and cancer mortality and based on ASPREE not showing a benefit with regards to the primary outcome of disability-free survival.

- Efficacy
  - All-cause mortality was shown to be higher among patients within the low-dose aspirin treatment group.
- Safety
  - The mortality rate of patients was higher within the aspirin treatment group.
  - The number of patient deaths due to cancer was higher in the aspirin treatment group.
- Cost
  - According to LexiComp, the cost of 81 mg enteric coated aspirin ranges from $0.01 – $0.12 per tablet[3]
    - Could not find pricing data for 100 mg aspirin
- Special Considerations/Populations
  - This study included a wide variety of patients that did not have an indication for aspirin and applied to mostly healthy, elderly patients
  - Aspirin should still be considered for situations where there is a true indication, such as secondary prevention.
  - This study consisted of a predominantly white population.[3]
  - The benefit of aspirin in younger patients (< 70 years old) is not known based on this trial
  - This study consisted of mostly Australian patients
  - 100 mg of aspirin is not used in the United States
  - Previous studies show the benefit of aspirin with certain cancers and this trial may have been stopped to soon to show a benefit

Grade of Recommendation: A

References:

1. McNeil JJ, Nelson MR, Woods RL, et al. Effect of Aspirin on All-Cause Mortality in the Healthy Elderly. *N Engl J Med*. 2018;379(16):1519-1528. doi:10.1056/NEJMoa1803955
2. The Story of Aspirin | The International Aspirin Foundation. Aspirin Foundation. Accessed August 6, 2021. https://www.aspirin-foundation.com/history/the-aspirin-story/
3. McNeil JJ, Woods RL, Nelson MR, et al. Effect of Aspirin on Disability-free Survival in the Healthy Elderly. *N Engl J Med*. 2018;379(16):1499-1508. doi:10.1056/NEJMoa1800722
4. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed August 5, 2021.