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The aspirin in reducing events in the elderly trial: Statistical analysis plan

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Abstract

Rationale: Aspirin has positive and negative effects on a number of age-related chronic conditions and there is uncertainty regarding its role in primary prevention in people aged 70 years and over.

Aims: To assess whether daily active treatment of 100 mg enteric-coated aspirin will extend the duration of disability-free life in healthy older participants.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Design: A double-blind, randomized, placebo-controlled primary prevention trial undertaken in Australia and the United States with careful adjudication of endpoints including stroke.

Study outcome: In Australia 16,703 individuals were recruited through general practices across five states and territories, and in the United States, 2411 participants were recruited through 34 clinical sites across the country. Follow-up of participants will finish at the end of 2017 with average follow-up exceeding 4.25 years per person.

Discussion: The statistical analysis plan for ASPREE, finalized after closure of recruitment but before the end of patient follow-up, outlines the primary analyses and a range of subgroup and sensitivity analyses.

(International Standard Randomized Controlled Trial Number Register ISRCTN83772183 and clinicaltrials.gov Number NCT01038583)

Keywords

Aspirin; clinical trial; ischemic stroke; intracerebral hemorrhage; protocols; statistical analysis plan; disability free survival

Rationale and study aim

A large evidence base exists showing that aspirin has positive and negative effects on a number of age-related chronic conditions. A state of uncertainty and equipoise exists among older people and their treating primary care physicians regarding the role of aspirin as a preventive therapy in the absence of any specific indication for its use such as prior cardiovascular disease.[1–3]

The aspirin in reducing events in the elderly (ASPREE) trial (International Standard Randomized Controlled Trial Number Register ISRCTN83772183 and clinicaltrials.gov Number NCT01038583) is a double-blind, randomized, placebo-controlled primary prevention trial undertaken in Australia and the United States (US) designed to assess whether daily active treatment of 100 mg enteric-coated aspirin will extend the duration of disability-free life in healthy participants aged 70 years and above except for Hispanic and African American minority groups in the US for whom the minimum entry age is 65 years. The study will examine whether the potential benefits of low-dose aspirin, particularly the prevention of heart disease, ischemic stroke, certain cancers and dementia, outweigh the risks, particularly severe gastrointestinal bleeding and hemorrhagic stroke, in this age group.[3–7] The trial's rationale and protocol are published elsewhere.[8,9]

To capture the risk-benefit trade off in terms that are relevant for the elderly population, the primary endpoint in ASPREE is the time from randomization to the first occurrence of incident dementia, persistent physical disability, or death from any cause. This primary endpoint is referred to as "disability-free survival." Dementia is diagnosed using DSM-IV criteria.[10] Briefly, diagnostic features include memory impairment and at least one of the following: aphasia, apraxia, agnosia, disturbances in executive functioning. The cognitive impairments must be severe enough to cause impairment in social and occupational functioning. There must be decline from a previously higher level of functioning. If a

participant does not have evidence of both cognitive and functional impairment, then they are deemed to have mild cognitive impairment. Physical disability is defined as the persistence for at least six months of “a lot of difficulty,” or “inability to perform independently” any one of the 6 Katz basic activities of daily living (ADLs), by self-report.[11] Dementia and cause of death undergo adjudication by a committee to whom key documents including imaging results, death certificates, neurocognitive assessment results, pathology reports, clinical specialist letters and hospital records are presented. Most secondary endpoints also undergo adjudication including for type of cancer, cardiovascular disease, and clinically significant bleeding. Stroke is adjudicated together with intracranial hemorrhage. The study protocol specified sub-classification of ischemic stroke by Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria and specification of site of hemorrhage for hemorrhagic stroke. At the request of the DSMB, stroke and intra-cranial hemorrhage classification was expanded as outlined in Table 1.

The original sample size was for the trial to follow 19,000 participants for 4.25 years on average in order to have 90% power to detect a 10% reduction in the risk of primary endpoint events.[8] In December 2014, the study closed recruitment with 19,114 participants randomized. In Australia, 16,703 individuals were recruited through general practices in Melbourne, regional Victoria, Tasmania, Canberra, Adelaide and Wollongong. In US, 2411 participants were recruited through 34 clinical sites across a number of states.[12] Follow-up of participants will finish at the end of 2017 with average follow-up exceeding 4.25 years per person. The final results of the trial are expected to be submitted in 2018 for publication in a leading medical research journal.

A detailed statistical analysis plan of the primary and secondary outcomes of the ASPREE trial is included in the Supplementary material. Finalization of this SAP prior to the end of follow-up has been undertaken to achieve transparency of the chosen methods that will ultimately be employed to analyze the trial and hence to seek evidence for aspirin’s role as a primary prevention therapeutic intervention in older people. The SAP outlines the primary intention to treat analyses that will use survival analysis methods for time to first event endpoints, i.e. the primary and all secondary endpoints. Sensitivity analyses are also outlined. A range of subgroup analyses are specified with subgroups defined by factors that are considered to convey elevated disease risk such as older age, presence of comorbidities such as diabetes, hypertension, hypercholesterolemia and cancer, and demographics such as participation in Australia or the US, sex, and ethnicity.

Discussion

For primary prevention with no overt disease present nor current treatment indicated, pharmacological preventive therapies need to be evaluated in terms of their risk to benefit trade-off. Aspirin is a relatively cheap, widely available and widely used therapy that has been shown to have protective effects against cardiovascular disease including ischemic stroke. But in an elderly population, the risk of known side-effects such as gastrointestinal bleeding and hemorrhagic stroke is elevated. The ASPREE trial will provide definitive evidence about the role, if any, of low-dose daily aspirin as a primary prevention agent in older people using a composite endpoint of disability-free survival that integrates aspirin’s

benefits and risks. The trial's results will influence clinical guidelines and will inform primary care physicians and general practitioners around the world in addressing the difficult question of how best to advise their patients for extending a healthy lifespan free of disability.

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References

1. Patrono C, Garcia Rodriguez LA, Landolfi R and Baigent C. Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med 2005; 353: 2373–2383. [PubMed: 16319386]
2. Hennekens CH, Hollar D and Baigent C. Sex-related differences in response to aspirin in cardiovascular disease: an untested hypothesis. Nat Clin Pract Cardiovasc Med 2006; 3: 4–5. [PubMed: 16391594]
3. Eikelboom JW and O'Donnell M. Using aspirin to prevent cognitive decline. Br Med J 2008; 337: a958. [PubMed: 18762478]
4. Antithrombotic Trialists (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009; 373: 1849–1860. [PubMed: 19482214]
5. Flossmann E and Rothwell PM. Effect of aspirin on longterm risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet 2007; 369: 1603–1613. [PubMed: 17499602]
6. He J, Whelton PK, Vu B and Klag MJ. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials. J Am Med Assoc 1998; 280: 1930–1935.
7. Nelson MR, Liew D, Bertram M and Vos T. Epidemiological modelling of routine use of low dose aspirin for the primary prevention of coronary heart disease and stroke in those aged > or =70. Br Med J 2005; 330: 1306–1311. [PubMed: 15908442]
8. ASPREE Protocol Version 9, https://aspree.org/aus/wpcontent/uploads/sites/2/2014/04/ASPREE-Protocol-AUS-Version-9-Nov-2014-Monash-approved.pdf (accessed 23 May 2017).
9. ASPREE Investigator Group. Study design of ASPirin in reducing events in the elderly (ASPREE): a randomized, controlled trial. Contemp Clin Trials 2014; 36: 555–564.
10. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994.
11. Katz S and Apkon CA. A measure of primary sociobiological functions. Int J Health Serv 1976; 6: 493–507. [PubMed: 133997]
12. McNeil JJ, Woods RL, Nelson MR, et al. Baseline characteristics of participants in the ASPREE (ASPirin in Reducing Events in the Elderly) study. J Gerontol A Biol Sci Med Sci 2017; 72: 1586–1593. [PubMed: 28329340]

Table 1.

Adjudication criteria for ischemic stroke and intracranial hemorrhages in the ASPREE randomized trial

Adjudication outcome[a]	Endpoint description and subclassification
A	Ischemic stroke
	No hemorrhagic transformation
	Hemorrhagic transformation
	Small petechiae, no mass effect
	Confluent petechiae, no mass effect
	Hematoma <30% of infarcted tissue, no mass effect
	Hematoma >30% of infarcted tissue with obvious mass effect
B	Hemorrhagic stroke
	Lobar
	Basal ganglionic
	Brain Stem
	Other
C	Subarachnoid hemorrhage stroke
D	Stroke type uncertain
E	Non-stroke intracranial bleeds
	Parenchymal hemorrhage (includes parenchymal hemorrhages excluded from the WHO stroke definition e.g. hemorrhages from cerebral metastasis, primary cerebral tumor or brain trauma)
	Intraventricular bleed
	Subarachnoid hemorrhage
	Sub-dural hemorrhage
	Extra-dural hemorrhage
	Site not determined

[a]Participants report stroke/TIA at annual visits and six month phone calls, and medical records are reviewed annually. Supporting documentation is sought from hospitals, specialists and General Practitioners/Primary Care Providers and sent to the stroke endpoint adjudication committee. Hemorrhagic intracerebral events are also adjudicated by the committee. Two adjudicators give the case summary an adjudication outcome of A, B, C, D, E or as not a stroke endpoint with no intra-cerebral bleed. One of the adjudicators subclassifies the event using Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria for ischemic stroke and giving site of hemorrhage for hemorrhagic stroke. If the two adjudicators do not agree the case is sent to the adjudication chair to provide an adjudication outcome and subclassification. Events adjudicated to be non-stroke intracranial bleeds are subject to assessment by the clinically significant bleeding (CSB) committee. If the CSB endpoint criteria are satisfied, the bleed is sub-classified by anatomical location by the committee neurologist.

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ASPREE: ASPirin in reducing events in the elderly.