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ASPREE-NEURO study protocol: A randomized controlled trial to determine the effect of low-dose aspirin on cerebral microbleeds, white matter hyperintensities, cognition, and stroke in the healthy elderly

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Abstract

Rationale: Cerebral microbleeds seen on brain magnetic resonance imaging are markers of small vessel disease, linked to cognitive dysfunction and increased ischemic and hemorrhagic stroke

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Authors' contributions

JMcN and GFE were responsible for project inception. JMcN, GFE, SAW, PR, NJF, ES, RLW, AB, PAY, GAD, and MJB were involved in study design, protocol preparation, and acquisition of funding. RW provided input into design for statistical analysis of cognitive data. RT has been involved in data merging with principal ASPREE trial. SAW is responsible for first draft, final revision and PR has prepared MRI protocol details. All authors have reviewed and provided critical revision of the manuscript.

Declaration of conflicting interests

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risk. Observational studies suggest that aspirin use may induce cerebral microbleeds, and associated overt intracranial hemorrhage, but this has not been definitively resolved.

Aims: ASPREE-NEURO will determine the effect of aspirin on cerebral microbleed development over three years in healthy adults aged 70 years and over, participating in the larger 'ASPirin in Reducing Events in the Elderly (ASPREE)' primary prevention study of aspirin.

Sample size: Five hundred and fifty-nine participants provide 75% power (two-sided *p* value of 0.05) to determine an average difference of 0.5 cerebral microbleed per person after three years.

Methods and design: A multi-center, randomized placebo-controlled trial of 100 mg daily aspirin in participants who have brain magnetic resonance imaging at study entry, one and three years after randomization and who undergo cognitive testing at the same time points.

Study outcomes: The primary outcome is the number of new cerebral microbleeds on magnetic resonance imaging after three years. Secondary outcomes are the number of new cerebral microbleeds after one year, change in volume of white matter hyperintensity, cognitive function, and stroke.

Discussion: ASPREE-NEURO will resolve whether aspirin affects the presence and number of cerebral microbleeds, their relationship with cognitive performance, and indicate whether consideration of cerebral microbleeds alters the risk-benefit profile of aspirin in primary prevention for older people.

Trial registration: Australian New Zealand Clinical Trials Registry ACTRN12613001313729.

Keywords

Cerebral microbleeds; small vessel disease; neuroimaging; aspirin; dementia; cognitive decline; healthy aging

Introduction and rationale

Cerebrovascular diseases (CVD) are major contributors to disability and dementia.[1,2] CVD of small vessels (SVD) is associated with risks of ischemic and hemorrhagic stroke, cognitive decline, and dementia.[2] Most SVD markers detected on brain magnetic resonance imaging (MRI) are presumed ischemic in origin, including white matter hyperintensities (WMH) and lacunes. However, SVD markers may also represent hemorrhagic pathologies, such as in cortical siderosis and cerebral microbleeds (CMBs). CMBs are small, hypodense areas <10 mm in diameter, found on T2* gradient-recalled echo (GRE) or susceptibility weighted imaging (SWI) MRI sequences,[3] which are associated on histopathology with blood vessel breakdown and which contain blood products.[4] CMBs are found in high prevalence in populations presenting with intracranial hemorrhage (ICH), ischemic stroke (IS), transient ischemic attack (TIA), and Alzheimer's dementia,[3] and have been associated with cognitive impairment.[5] However, CMBs are also frequently observed in the general population and are strongly linked to aging, with large population-based imaging cohorts reporting prevalence of around 16% for those aged 60–70 years,[6,7] and 30–35% in adults aged >80 years.[6,7]

CMBs in lobar and cortical regions have been associated with older age, amyloid deposition, and the *APOE ε*4 allele, suggesting underlying cerebral amyloid angiopathy, while CMBs in deeper structures are associated with hypertensive microangiopathy. Observational studies suggest CMBs may also be induced by aspirin exposure.[8–10] Furthermore, the increased risk of ICH[11] in the setting of CMBs may be compounded by antithrombotic medications, including aspirin.[12,13] However, the effect of aspirin on CMB development has not been studied in a randomized controlled trial, and observational study data are limited by confounding due to indication. Aspirin may also prevent progression of other markers of SVD and associated cognitive decline,[14] and has an established role in the secondary prevention of large-vessel CVD,[15] which frequently co-exists with SVD, including CMB. Resolving in a randomized controlled study the impact of aspirin on CMB development, associated changes in cognition and risk of stroke is therefore of great importance.

Methods

Design

ASPREE-NEURO is a neuroimaging sub-study of the ASPirin in Reducing Events in the Elderly (ASPREE)[16] trial. We will image a subset of 559 participants using 3 Tesla (3T) brain MRI, at baseline, one and three years to determine the impact of low-dose aspirin compared with placebo on MRI markers of SVD, in particular CMB and WMH. We will relate the impacts of aspirin on these markers to cognitive function, over three years. We will also relate the impacts of aspirin to stroke risk and cognitive impairment in exploratory analyses.

Patient population

Participants were recruited from the ASPREE trial, a multi-center, randomized, double-blinded, placebo-controlled trial of daily 100 mg aspirin in 19,000 healthy community dwelling older adults in Australia and the USA. Inclusion and exclusion criteria for ASPREE have been published elsewhere.[16] In brief, participants are eligible in Australia if aged 70 years and over, have no history of occlusive vascular disease, atrial fibrillation, cognitive impairment, or disability, are not currently taking antithrombotic therapy, and do not have anemia or a diagnosis likely to cause death within five years.

ASPREE participants enrolling at each Melbourne study center from December 2013 to December 2014 were offered the opportunity to volunteer for ASPREE-NEURO.

Additional exclusion criteria specific to ASPREE-NEURO included the presence of contraindications to MRI, such as certain foreign bodies and metallic or electronic implants not known to be safe at 3T, and claustrophobia.

Randomization

Block randomization was used for ASPREE and, along with procedures for concealment of allocation, is described in detail elsewhere.[16]

Intervention

The intervention is 100 mg enteric-coated aspirin or an identical placebo medication in a 1:1 ratio, dispensed after a four-week placebo run in and compliance check. Study medication is dispensed at baseline and thereafter annually.

Primary outcome

Number of CMBs on brain MRI at three years after randomization.

Secondary outcomes

1. Number of CMBs on brain MRI at one year after randomization.
2. Change in volume of white matter hyperintensity on MRI after one and three years.
3. Cognitive function and cognitive decline after three years.
4. Ischemic and hemorrhagic stroke.

Brain MRI (see Supplementary Material 1 for full MRI protocol)

All MRIs are performed on a 3T Skyra scanner (Siemens, Erlangen, Germany), located at the Monash Biomedical Imaging (MBI) facility, Blackburn Road, Clayton (Melbourne, Australia).

The MRI examination takes 38 min to complete and comprises standardized sequences used for analysis of brain morphometry, microstructure, and function including:

1. T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) (gray and white matter morphometry, anatomical reference);
2. Fluid-attenuated inversion recovery (FLAIR; white matter abnormalities including WMH);
3. Susceptibility weighted imaging (SWI; CMB, cortical siderosis, and venous vasculature);
4. Diffusion-weighted imaging (white matter microstructure); Resting state Functional MRI (rs-fMRI)
5. Multiple inversion arterial spin-labeling (ASL; cerebral blood flow); and
6. A gradient-echo-based field map to enable distortion corrections.

Processing and interpretation of neuroimaging data are done blind to participant information and treatment allocation

CMB will be reported based on the microbleed anatomical scale (MARS)[3] including numbers and sites of lesions.

A quantitative susceptibility map (QSM) will be generated from the SWI acquisition to help distinguish CMB from calcifications.[17]

Clinical notification.—All scans are reported by a neuroradiologist. Participants and their doctors are notified of incidental findings of clinical significance (see supplementary material 2).

Cognitive function testing

Cognitive function tests are performed in ASPREE at baseline, and 1, 3, and 5 years after randomization. These include:

1. Modified mini-mental state examination (3MS). Participants are required to score >77/100 for entry into the ASPREE Trial;[18]
2. Single-letter controlled oral word association test (COWAT);[19]
3. Hopkins verbal learning test-revised;[20]
4. Symbol digit modalities test.[21]

Two additional tests are used in the ASPREE-NEURO study, at baseline, one and three years:

1. Stroop test (Victoria version)[22]
2. The Color Trails test[23]

The test assessors undergo standard training and assessment, and are re-certified annually, or if the number of assessments conducted falls below three in a three-month period.

Cognitive decline occurs when the 3MS falls below 78 or there is an age-adjusted fall of 10 points or more on the 3MS, after adjustment for repeated long-interval administration, or when the combined averaged z score for any domain falls by >1 SD across the study period when compared with age/education-adjusted norms, and/or an adjudicated diagnosis of dementia occurs through the ASPREE study within three years from randomization (see ASPREE Clinical Protocol for details).[24]

Cerebrovascular events:

Ischemic and hemorrhagic stroke.: Fatal and non-fatal stroke are secondary end-points of the principal ASPREE trial, adjudicated by the ASPREE Stroke Endpoint Committee. Descriptions of relevant processes in the definition of these clinical strokes are available on the ASPREE study protocol.[24]

Data monitoring body

The ASPREE Data and Safety Monitoring Board (DSMB) oversees the study.[24]

Sample size

A target sample size of 606 subjects was calculated to detect an average difference in the number of CMBs per person between aspirin and placebo groups of 0.5 at 12 months (95% power) and 36 months (80% power). These calculations were based on standard deviations in CMBs of 1.5 and 2 at 12 and 36 months, respectively, and included a 20% inflation for non-normality, dropout, cross-over, and loss to follow-up.

Following final recruitment of 559 participants, this study now has 94% power to detect an average difference of 0.5 CMB per person between groups at 12 months and 75% power at 36 months (two-sided *p* value of 0.05). With approximately 280 patients per group, this will equate to a total difference of 140 CMBs between aspirin and placebo. These calculations included a 15% inflation for a lack of normality[22] and a further 5% for dropout, loss to follow-up, and crossover. As multiple measurements per participant will further increase the power of the study, these calculations are conservative; however, without knowledge of the within-person correlation between data points, it is impossible to know by how much power would be increased.

Statistical analyses

At the ASPREE study completion in 2018, the ASPREE-NEURO sub-study will be analyzed on an intention-to-treat basis. Continuous-scale outcomes will initially be assessed for normality and log-transformed where appropriate. Changes in outcomes over time will be determined using mixed linear (or non-linear) longitudinal modeling with main effects fitted for treatment and time and an interaction between the two to determine if the groups behaved differently over time. Additional sensitivity analyses will be performed adjusting for known predictors of outcome (age, sex, cardiovascular risk factors) and any baseline imbalances between groups. Where missing data are found to exceed 5%, additional analysis will be conducted using multiple imputation. Subgroup analysis will be performed by presence or absence of CMB at baseline. A two-sided *p* value of 0.05 or less will be considered to be statistically significant.

The relationship between changing CMB number and cognitive function will also be determined using the mixed linear longitudinal model for 3MS measurements over time.

Discussion

The ASPREE-NEURO trial is to our knowledge the first randomized controlled trial to assess the impact of daily, low-dose aspirin on the number of CMBs (primary outcome measure). This is important as a higher number of CMBs has previously been shown to increase the risk of clinically significant outcomes.[25,26] This study will also ascertain the clinical significance of change in CMB count by measuring associations with cognitive outcomes, and quantifying the relationship between CMB count and cerebrovascular outcomes and cognitive function in an exploratory analysis. The MRI measurement at three time points will enable illustration of the time course of any aspirin effect in older people over three years of aspirin usage for primary prevention.

Summary and conclusions

Aspirin is widely used by older adults.[27] While aspirin is well evidenced for the secondary prevention of cardiovascular disease, it is also prescribed for primary prevention, despite conflicting guidelines. The ASPREE-NEURO findings will augment the outcomes of the principal ASPREE trial, by showing whether low-dose aspirin affects CMB development, in the healthy elderly. Secondly, it will determine whether any aspirin-associated changes in CMBs are associated with changes in cognitive function, and whether low-dose aspirin

limits changes in WMH volume. Thirdly, it will determine whether CMB presence identifies a subgroup for whom the risk:benefit ratio for primary prevention with low-dose aspirin is altered. Our findings may be applicable to populations beyond the healthy elderly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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