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A randomised controlled trial of low-dose aspirin for the prevention of fractures in healthy older people: protocol for the ASPREE-Fracture substudy

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Abstract

Background—Disability, mortality and healthcare burden from fractures in older people is a growing problem worldwide. Observational studies suggest that aspirin may reduce fracture risk.

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Contributors All authors provided substantial contribution to conception and design of the project; drafted and revised the article critically for important intellectual content; and approved the final manuscript. ALB and JT led the drafting of all sections of the article in consultation with all of the coauthors. KMS, SK, RGC, ES, JAP and PRE provided substantial contributions to the background, critical appraisal of prior studies and rationale for the project. JJM, SAW, RLW and JEL provided substantial contribution to the overall design aspects including refinement of study processes and data collection. ALB, RW and MAB provided substantial contribution to the sample size and statistical analysis section.

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While these studies provide room for optimism, randomised controlled trials are needed. This paper describes the rationale and design of the ASPirin in Reducing Events in the Elderly (ASPREE)-Fracture substudy, which aims to determine whether daily low-dose aspirin decreases fracture risk in healthy older people.

Methods—ASPREE is a double-blind, randomised, placebo-controlled primary prevention trial designed to assess whether daily active treatment using low-dose aspirin extends the duration of disability-free and dementia-free life in 19 000 healthy older people recruited from Australian and US community settings. This substudy extends the ASPREE trial data collection to determine the effect of daily low-dose aspirin on fracture and fall-related hospital presentation risk in the 16 500 ASPREE participants aged ≥70 years recruited in Australia. The intervention is a once daily dose of enteric-coated aspirin (100 mg) versus a matching placebo, randomised on a 1:1 basis. The primary outcome for this substudy is the occurrence of any fracture—vertebral, hip and non-vert-non-hip—occurring post randomisation. Fall-related hospital presentations are a secondary outcome.

Discussion—This substudy will determine whether a widely available, simple and inexpensive health intervention—aspirin—reduces the risk of fractures in older Australians. If it is demonstrated to safely reduce the risk of fractures and serious falls, it is possible that aspirin might provide a means of fracture prevention.

Trial registration number—The protocol for this substudy is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000347561).

BACKGROUND

Fracture prevention in older adults is a major public health priority[1] as fractures cause substantial pain and disability.[2] Approximately 25 000 osteoporotic fractures occur worldwide each day,[3] which is greater than the combined incidence of heart attack, stroke and breast cancer.[4] The financial burden imposed by fractures is large, consisting of hospital treatment, rehabilitation and residential aged care.[5] By 2025, the annual number of fractures in older people in the US is projected to be more than 3 million, representing direct costs of US$25.3 billion.[6]

Studies in Australia and the US suggest a decrease in the incidence of hip fractures over the past decade.[7–9] Despite this decline, the incidence of fractures is expected to increase with the ageing of the population, ranging between 7.3 and 21.3 million fractures worldwide by the year 2050.[10] As the number of fractures in older people increases, so does the demand for prevention strategies.

Fragility fractures are a consequence of structural deterioration produced by age-related bone loss. In women, bone loss accelerates after menopause, while in men reduced exposure to sex steroids also contributes. The loss of bone strength is characterised by thinning and perforation of bone trabeculae and thinning and increased porosity of cortical bone. The latter accounts for about 70% of bone loss. Therapies used to reduce fracture risk have generally been investigated in people with osteoporosis (T-score ≤−2.5) despite well-established evidence suggesting that over half of all fractures occur in people with bone mineral density (BMD) within the osteopenia or normal range.[1112] Antiresorptive agents

such as bisphosphonates reduce the risk of vertebral and hip fractures by about 50% and nonvertebral fractures by about 20–30%;[13] yet they appear not to reduce fracture risk in people without osteoporosis.[14] Hormone therapy reduces the risk of fracture by up to 24% in postmenopausal women with and without osteoporosis.[15] However, this benefit is outweighed by the overall health risks reported for hormone therapy.[16] Other therapies such as vitamin D and calcium supplementation have had mixed results on fracture risk in older populations.[17]

Aspirin, via generalised cyclooxygenase (COX) inhibition, may inhibit inflammatory mediators and reduce bone resorption attributable to low-grade inflammation. Inflammatory cytokines stimulate bone resorption and inhibit bone formation.[18] Several studies provide evidence that low-grade inflammatory processes in older adults are associated with bone loss and fracture risk. An observational study by Ding et al reported that higher levels of tumour necrosis factor (TNF)-α, interleukin (IL)-6 and C reactive protein (CRP) were associated with increased bone loss over 3 years in older adults.[19] Pasco et al[20] reported that fracture risk increased by 24–32% for each SD increase in CRP levels in older women. Cauley et al[21] reported that in addition to CRP levels, high serum levels of inflammatory markers, IL-6, TNF-α and TNF receptors predict a higher incidence of fractures. Prostaglandins, important inflammatory mediators, particularly prostaglandin E2 produced by bone, also influence bone remodelling.[22] As summarised by Raisz,[23] prostaglandins transiently inhibit osteoclast function. However, their long-term effect is to stimulate bone resorption by increasing formation, replication and differentiation of osteoclasts leading to increased bone removal, remodelling, loss and structural decay. At low concentrations, prostaglandins stimulate osteoblast replication and differentiation and bone formation increases. At high concentrations, they inhibit collagen synthesis.

Effective fracture prevention drugs should optimally target both bone fragility and the risk of falling. More than 90% of hip fractures result from a fall.[424] Therefore, reducing the risk of falls is likely to have a substantial impact on fracture risk. Falls result from a complex interaction of risk factors that are both extrinsic (relating to the environment such as a slippery floor) and intrinsic (e.g. sensory impairment or comorbidities).[25] Aspirin may reduce falls risk by slowing physical decline attributable to reduced cardiovascular risk and cerebrovascular events through its antiplatelet effects. Aspirin also may reduce cognitive decline—an important falls risk factor[26]—by protecting against stroke, subclinical cerebrovascular disease and dementia through its antiplatelet and anti-inflammatory effects.[27] The role of aspirin in the prevention of dementia and cognitive decline is currently being investigated by the ASPirin in Reducing Events in the Elderly (ASPREE) principal trial[33] and the ASPREE neurovascular imaging substudy (ENVIS-ion).[28] If aspirin is demonstrated to positively influence either bone fragility or the likelihood of falling, it might provide a population-wide fracture prevention intervention.

The effect of aspirin on fracture risk in older people remains unclear, with prior observational studies showing conflicting results.[29–32] To date, no prospective randomised, placebo-controlled trials on the effects of aspirin on fracture or fall risk have been published. The ASPREE-Fracture substudy will address this evidence gap by investigating whether daily low-dose aspirin (100 mg) is associated with decreased risk of vertebral, hip and non-

vert-non-hip fractures in healthy men and women aged ≥70 years and whether the reduced fracture risk is explained, in part, by reducing the risk of fall-related hospital presentations.

METHODS

Design

ASPREE-Fracture is a double-blind, randomised, placebo-controlled trial and substudy of the ASPREE clinical trial.[33]

The ASPREE principal trial

ASPREE is a double-blind, randomised, placebo-controlled primary prevention trial that examines the benefits and risks of low-dose aspirin in 19 000 healthy people (16 500 aged ≥70 years from Australia and 2500 people aged ≥65 years from the US) without overt cardiovascular disease or dementia. The primary aim of ASPREE is to determine whether low-dose aspirin (100 mg enteric-coated, daily) will prolong disability and dementia-free survival and provide a net benefit for older adults in a primary prevention setting.

Setting and participants

The ASPREE-Fracture substudy will be conducted in all participants recruited to the ASPREE principal trial within Australia. This substudy mirrors the design of the ASPREE principal trial. Therefore, participant recruitment and inclusion and exclusion criteria for the principal trial will apply to this substudy. In brief, the majority of participants are recruited through general medical practices (approximately 2000) and through community advertising. At the general practice, a list of potentially eligible patients is derived and each of them is sent a letter from their general practitioner (GP) inviting them to participate in the trial. The letter advises participants to call a toll-free number to discuss participation in the study. Upon calling the number, interested participants are checked for self-reported eligibility, and suitable persons are invited to attend a screening visit (week 0) where baseline examination and testing is organised and run-in medication (placebo) is provided for 4 weeks. If entry testing and compliance with run-in medication are deemed satisfactory at a second visit (week 4) and the GP has authorised participation, participants who meet the inclusion criteria (box 1) are randomised into the study.

Randomisation

Eligible participants are randomly assigned into one of the two groups. A computer-generated randomisation schedule via the ASPREE web portal is used, in a ratio of 1:1 to active or placebo therapy, with permuted block randomisation stratified by recruitment site and for age (< or ≥80 years).

Intervention

The intervention group participants receive a once daily dose of 100 mg enteric-coated aspirin. The control (placebo) group receives a once daily dose of a placebo enteric-coated un-scored white tablet with identical appearance to aspirin. Participants, study staff and GPs are blinded to participants group allocation. After randomisation, compliance and retention

is maintained through direct phone contact by research staff every 3 months, interspersed with annual face-to-face visits.

Outcomes

The primary outcome of the ASPREE-Fracture substudy is the occurrence of any fracture in the 5 years post randomisation. Fractures are defined as any type of vertebral, hip and non-vert-non-hip fractures (including traumatic and pathological) confirmed by medical imaging (eg, X-ray). A Fall-related hospital presentation post randomisation is a secondary outcome. Fall events are defined as 'an event which results in a person coming to rest inadvertently on the ground or floor or other lower level'[34] that results in hospital presentation. Hospital presentations include emergency department (ED) presentations (without admission to hospital) and hospital admissions.

Data collection—The ASPREE principal trial captures data from several sources including annual face-to-face visits with study participants, 6-monthly interviewer-administered questionnaires through telephone contact, review of general practice and hospital records and death certificates. Demographic data including age, sex, height and weight, comorbidities, smoking history, alcohol intake and concomitant medications are available from the ASPREE principal trial data and will be accessed for this substudy for the purpose of describing study participants. Physical and cognitive function data collected by the principal ASPREE trial will be retrieved for this substudy to perform risk-adjusted analyses of primary and secondary outcomes (table 1).

During each annual visit and 6-month telephone follow-up, participants will be questioned on the occurrence of fractures or fall-related hospital presentations in the previous 6 months. Notification of any potential fracture or fall-related hospital presentation event will trigger the collection of information for outcome confirmation. Verification and confirmation of outcomes will be ascertained by collecting information from hospital, general practice and specialist medical records—including hospital admission notes, hospital discharge summaries, medical imaging reports (eg, X-ray, magnetic resonance imaging (MRI), CT and bone scans), ED progress notes and death certificates. Medical records will be obtained from the usual treating physician, other treating specialist physicians or secondary/tertiary medical care centres.

Outcome ascertainment—All outcomes will be adjudicated by an endpoint adjudication committee (EAC) consisting of clinicians and research personnel who are blinded to group allocation. This adjudication process is web based. ASPREE trial staff will prepare all documentation on possible fracture and fall-related hospital presentation events and send this information to the EAC for review. Two members of the EAC will adjudicate each event with discordant results going to a third reviewer. For fracture events, information relating to time of fracture event (date of medical imaging that confirms the fracture); type of fracture (eg, avulsion, burst, communited); bone affected (classified according to International Classification of Diseases (ICD)-10 codes); location of fracture (left or right) and cause of fracture (motor vehicle accident, fall-related, metastatic/cancer-related, crush, spontaneous, periprosthetic) will be recorded by the EAC. For fall-related hospital

presentation events, information relating to the time of the fall event (date of fall-related hospital/ED presentation) and fall mechanism (fall from motorcycle, scooter, pushbike or similar, fall from greater than standing height, fall from less than or equal to standing height) will be recorded.

Statistical analysis

Outcome analyses will be undertaken on an intention to treat basis by a statistician blinded to group allocation. Fracture endpoints will be analysed without Bonferroni correction using a survival time method and the proportional hazards assumption which will be tested. This analysis will compare time to first fracture between aspirin and placebo groups. Primary analysis will be unadjusted. Secondary analysis will adjust for a number of covariates including osteoarthritis, rheumatoid arthritis, use of medications that affect BMD, cognitive impairment, age, malignancy, alcohol intake and smoking. This will increase the efficiency of the analysis and allow for any imbalance between groups in these baseline variables. We will also perform an unadjusted log-rank test on the final results. Secondary analysis using recurrent events survival models will also be conducted including all fracture events (not just the first fracture) to compare the overall fracture risk between aspirin and placebo groups over the follow-up.

Fall events will be analysed using negative binomial regression models, where the dependent variable will be the total number of fall-related hospital presentations for each participant during the follow-up and group allocation will be the independent variable. The rate of fall-related hospital presentations in the aspirin group compared with those in the placebo group will be expressed as an IRR. Use of a negative binomial regression model will allow for the fact that fall-related hospitalisations can be recurrent events with a non-normal distribution and that individual participants may have different follow-up times. It will also allow investigation of the treatment effect to be adjusted for known confounding variables. Secondary analysis that adjusts for covariates (cognitive impairment and age) will be undertaken if found to be significant when added to the model. This will increase the efficiency of the analysis.

Sample size

Approximately 16 500 participants from Australia will be enrolled in the ASPREE principal trial. The ASPREE principal trial aims for 5 years follow-up per participant and for the primary endpoint this ‘at risk’ time for occurrence of a first primary endpoint event will be reduced to an average of 4.25 years per participant. The reasons for this reduction include censoring due to the occurrence of a primary endpoint, loss to follow-up for death (which is expected to be extremely low due to access to mortality statistics through National Death Index records in Australia), non-completion of dementia screen or diagnosis, and non-completion of activities of daily living. In total, we assume that 5% of participants per year will have an occurrence of the primary endpoint or have insufficient follow-up to enable assessment of their primary endpoint status.

Data from the Geelong Osteoporosis Study[24] and a national report on fall-related hospital presentations[35] were applied to the expected age distribution of Australian participants on

recruitment to the ASPREE principal trial of 50%, 30%, 15% and 5% in the age groups 70–74 years, 75–79 years, 80–84 years and 85 years and above, respectively, to estimate outcome event rates in the placebo group. Based on an average follow-up of 4.25 years per participant and the assumption that 14% of participants in the placebo group will sustain a fracture during the follow-up period, a sample size of 16 500 provides 80% power to detect a HR of 0.88 comparing the intervention group with the placebo group in an intention to treat analysis (p=0.05; two tailed). The underlying true effect for all fractures is assumed to be a HR of 0.85 on the basis that we expect 5% per annum of placebo-group participants to initiate aspirin use or vice versa.

Based on an average follow-up of 4.25 years per participant and an expected event rate of 53 fall-related hospital presentations per 1000 person-years in the placebo group, a sample size of 16 500 provides 80% power to detect an IRR of 0.88 comparing the intervention group with the placebo group in an intention to treat analysis (over-dispersion parameter=1.3; p=0.05; two tailed). The underlying true effect for fall-related hospital presentations is assumed to be an IRR of 0.85 on the basis that we expect 5% per annum of placebo-group participants to initiate aspirin use or vice versa.

DISCUSSION

While the use of aspirin is accepted for the secondary prevention of cardiovascular disease through its antiplatelet action, its broader anti-inflammatory properties via generalised COX inhibition may confer other benefits. Several reviews suggest that daily low-dose aspirin can reduce all-cause mortality, and not just cardiovascular mortality.[3637] However, previous studies suggest that aspirin's benefits in older people may be offset by adverse effects.[38] The balance of risks and benefits of daily low-dose aspirin has not been established in older people.[37] The ASPREE principal trial will address this unmet need by determining whether daily low-dose aspirin can prolong life or prolong the duration of 'disability-free life' in older people. The ASPREE-Fracture substudy will add to the current fracture prevention evidence base to determine if regular low-dose aspirin is associated with decreased fracture and serious falls risk.

It is possible that aspirin may increase fracture risk. Four observational studies[29–32] have examined the effect of aspirin on fracture risk in older adults, demonstrating conflicting results. Two studies observed a decrease in fracture risk[3031] with aspirin use, while two found no association.[2932] The most recent case–control study of middle-aged men and women by Vestergaard et al found a small decrease in fracture risk associated with the use of low-dose aspirin (<1 defined daily dose/day). Despite a reduced risk being observed in the entire sample taking aspirin, those recorded as receiving >1 defined daily dose/day of aspirin had an increased fracture risk compared with non-users.[31] An earlier case–control study by Vestergaard et al[30] also reported a reduction in fracture risk in aspirin users compared with that in non-users. A third case–control study by Vestergaard et al investigating effects of higher aspirin doses (mean dose=352±26 mg/day) in perimenopausal women reported no association between aspirin use and fracture risk.[29] The fourth study was a cohort study of postmenopausal women by Bauer et al, which found no association between fracture risk and daily aspirin use (undefined dosage) in the 2-year follow-up period.[32] While these

studies provide room for optimism, three of the four studies were performed in people predominantly aged <60 years and were likely to be underpowered, which may account for the conflicting results.[29–31] A large-scale controlled trial, with the inclusion of estimates of the net benefit/risk ratio is required to provide more credible estimates of the effect of daily low-dose aspirin on fracture risk in older people. In addition, no previous randomised controlled trials have investigated whether the risk of fall events is increased or decreased with aspirin administration. If this study finds that aspirin increases fracture or serious falls risk, these important observations will require inclusion in estimates of the net benefit/risk ratio when public health recommendations regarding the use of aspirin are made.

Furthermore, current fracture prevention therapies are targeted at people with osteoporosis who represent only a small proportion of the total population fracture burden.[1124] If the burden of fractures is to be reduced significantly, interventions must be applied across the population, and not just to those with osteoporosis. The availability of a simple preventative intervention that can reduce the population burden of fractures and has other benefits, such as reduced risk of cardiovascular disease, cancer and dementia, represents an important contribution to public health. Even if small impacts are observed, the net benefits of aspirin in terms of reduced fracture risk at a population level may be substantial.

A potential limitation of this substudy is the exclusion of people with cardiovascular disease, cognitive impairment and disability, making generalisability of study findings, particularly to frailer older adults, more difficult. Only including people aged ≥70 years also may be seen as a limitation. However, given the projected demographics of ageing over the coming decades, this age group is likely to represent a large proportion of the older population. An underestimation of fall-related hospital presentation endpoints is expected to occur, as participants who present to private hospitals will leave minimal documentation. However, this will occur equally across both groups and is therefore unlikely to introduce any bias in measurements. Strengths of the substudy include blinding of participants and study personnel to treatment and outcome assessment, intention to treat analysis and a very large sample size.

This substudy will determine whether a widely available, simple and inexpensive health intervention—aspirin—reduces the risk of fractures in older Australians. The research outcomes of this substudy have the potential to enhance current fracture prevention practice and policies for older people internationally.

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Box 1

Inclusion and exclusion criteria for the ASPREE principal trial

Inclusion criteria

1. Aged 70 years or above (65 years or above for US participants)
2. Willing and able to provide informed consent

Exclusion criteria

1. A history of a diagnosed cardiovascular disease event defined as myocardial infarction, heart failure, angina pectoris, stroke, transient ischaemic attack, >50% carotid stenosis or previous carotid endarterectomy or stenting, coronary artery angioplasty or stenting, coronary artery bypass grafting or abdominal aortic aneurysm
2. A clinical diagnosis of atrial fibrillation
3. Serious illness likely to cause death within the next 5 years
4. A current or recurrent condition with a high risk of major bleeding
5. Suffering from anaemia
6. An absolute contraindication or allergy to aspirin
7. Current participation in an ongoing clinical trial
8. Current use of aspirin for secondary prevention
9. Current continuous use of other antiplatelet drug or anticoagulant
10. A systolic blood pressure ≥180 mm Hg and/or a diastolic blood pressure ≥105 mm Hg
11. A history of dementia or a Modified Mini-Mental State Examination (3MS) score ≤77
12. Severe difficulty or an inability to perform any one of the 6 Katz activities of daily living
13. Pill-taking compliance <80% during a 4-week placebo run-in phase

Table 1

Measurement schedule for the participants of the ASPREE-Fracture trial

	Recruitment, screening and baseline (0–4 weeks)	Annual 6-monthly phone contact	Annual face-to-face follow-up*					
			Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
ASPREE-Fracture								
Fracture events	✓	✓	✓	✓	✓	✓	✓	✓
Fall events	✓	✓	✓	✓	✓	✓	✓	✓
ASPREE principal trial								
Review inclusion/exclusion criteria; informed consent	✓							
Physical demographics†	✓		✓	✓	✓	✓	✓	✓
Cognitive function‡	✓		✓		✓		✓	
Physical function§	✓			✓		✓	✓	✓
Physical disability¶	✓	✓	✓	✓	✓	✓	✓	✓

*Final annual visit will take place in years 3–7 depending on year of randomisation. Only a small number of participants will have 3 or 7 years of follow-up with an average of 5 years of follow-up across the study. Final visit measurements will be the same as those indicated for year 5.

†Age, sex, height and weight, comorbidities, smoking history, alcohol intake and concomitant medications.

‡Modified Mini-Mental State Examination, Symbol Digit Modalities Test, Hopkins Verbal Learning Test-Revised, Controlled Oral Word Association Test.

§3-metre walk test, grip strength.

¶Katz Activities of Daily Living scale.