Feasibility of conducting a primary prevention trial of low-dose aspirin for major adverse cardiovascular events in older people in Australia: results from the ASPirin in Reducing Events in the Elderly (ASPREE) pilot study

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ABSTRACT

Aim: To determine the feasibility of performing a large clinical trial of the use of aspirin for the primary prevention of cardiovascular disease in older participants — the ASPirin in Reducing Events in the Elderly (ASPREE) trial.

Design and participants: A randomised double-blind placebo-controlled pilot trial of 100 mg of enteric-coated aspirin tablets daily, in men and women aged 70 years and over who did not have overt cardiovascular disease, and who were followed for 12 months. Participants were identified from the computer databases of general practitioners who were co-investigators in a previous trial.

Setting: The Melbourne metropolitan area between March 2003 and June 2005.

Main outcome measures: The level of response to participation by GPs; the level of response from potential trial participants; the screening-to-randomisation rate to ensure the recruitment target could be achieved; and the retention of participants in the trial after 12 months.

Results: Forty-two GPs (23% of 180 mailed) expressed interest in participating in the pilot trial. Nineteen became co-investigators, of whom six were not required to meet recruitment targets. Letters were sent to 2614 patients, of whom 243 were screened and 209 (86%) were randomly allocated to receive aspirin or placebo. At 12 months,192 (92%) returned for follow-up, and 153 of these (80%) were still taking trial medication. There was a significant reduction in mean haemoglobin level in those taking aspirin.

Conclusions: The recruitment strategy for ASPREE, based on methods developed for the conduct of a previous large-scale trial conducted in general practice, was successfully redeployed in this pilot study, with improved efficiency resulting from computerised database searching, telephone pre-screening, a simpler run-in phase and participant familiarity with the trial drug. We conclude that conducting ASPREE in Australian general practice with 18 000 participants is feasible.

Trial registration: International Standard Randomised Controlled Trial Number Register ISRCTN83772183.

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The recommended use of aspirin for the primary prevention of cardiovascular disease is based on absolute cardiovascular event risk. Age is the greatest determinant of absolute risk, and yet few participants in major primary prevention trials have been elderly. ASPirin in Reducing Events in the Elderly (ASPREE) is a double-blind, randomised, placebo-controlled study of low-dose aspirin for the primary prevention of major adverse and cardiovascular events in older people. The research questions tackle areas of major public health importance.[1] The rationale for the conduct of ASPREE and its protocol have been published elsewhere.[2,3]

To ensure that the proposed trial is relevant to the current community-based management of cardiovascular risk in older people, it will be carried out within general practice in Australia. To address the issues identified above, we have proposed a large-scale trial involving about 18 000 participants aged 70 years and over to determine the risks versus the benefits of low-dose aspirin. Here, we present the results of a feasibility study for the larger trial. The feasibility study was conducted between March 2003 and June 2005 in the Melbourne metropolitan area. The key indicators for feasibility for such a large general-practice-based trial were: (i) the level of response to participation by general practitioners; (ii) the level of response from potential trial participants; (iii) the screening-to-randomisation rate to ensure the recruitment target could be achieved; and (iv) the retention of participants in the trial after 12 months.

METHODS

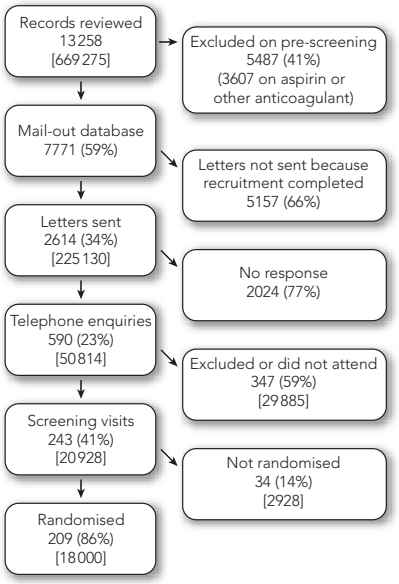
General practitioner recruitment

GP co-investigators were purposefully sampled from those who had participated in the Second Australian National Blood Pressure Study (ANBP2) in Melbourne.[4] GPs were excluded if they did not have Medical Director clinical software (Health Communications Network, Sydney, NSW), as research nurses were trained to prescreen practice databases by participant inclusion and exclusion criteria on this clinical software. GPs vetted these databases to exclude deceased patients and those they considered unsuitable or not their usual patients.

Participant recruitment

Volunteers were recruited by a single mail-out of a letter requesting them to call the clinical trials centre on a toll-free telephone number. During this call, patients were screened further and, if eligible and willing, an appointment was made for a study entry visit at their usual general practice clinic by study staff. At this visit, inclusion and exclusion criteria were checked again by a research nurse, and participants were entered into the 4-week placebo run-in phase. During this phase, an appointment to discuss the trial with their GP was also arranged. Following the 4-week run-in period, eligible participants who were compliant in the run-in phase and who were still willing to enter the main trial were accepted and randomly allocated (by an interactive voice randomisation system, stratified by practice and age band [70–79 years and

1 Flow chart of screening and random allocation of participants for the ASPirin in Reducing Events in the Elderly pilot study



Figures in square parentheses are projected numbers for the main study. ◆

2 Pre-screening for exclusion criteria on general practice computer databases

	No. of patients
Total patient records reviewed	13 258
Patients excluded at pre-screening on exclusion criteria (below)	5 487
Patients excluded at pre-screening because they were taking aspirin or anticoagulants	3 607
Exclusion criterion	**No. of reports**
Abdominal aortic aneurysm	91
Myocardial infarction	264
Angina	632
Angioplasty (coronary)	50
Aspirin or anticoagulants	
Anticoagulant	837
Aspirin	538
Astrix	1298
Cardiprin	229
Cartia	176
Disprin	1
Solprin	738
Coronary artery bypass graft	247
Coronary artery disease	567
Cerebral aneurysm	6
Coronary angiography	18
Dementia	37
Diabetes	1121
Gastric ulcer	107
Heart failure	246
Ischaemic heart disease	42
Peptic ulcer	253
Peripheral artery disease	209
Stroke	231
Transient ischaemic attack	195

3 Baseline characteristics of the 209 study participants

Characteristic	Value
Mean age in years (SD)	76.2 (4.6)
Age	
70–74 years	49.8%
75–80 years	31.6%
⩾ 80 years	18.7%
Sex	
Male	40.7%
Family medical history	
None	52.2%
Heart attack	25.4%
Stroke	13.9%
Dementia	4.8%
Heart attack and stroke	2.9%
Heart attack and stroke and dementia	1.0%
First language English	93.3%
Years lived in Australia	
0–14	2.8
15–29	2.8
30–44	25.0
45–59	50.0
60–74	8.3
⩾ 75	11.1
Education	
< 9 years	31.6
9–11 years	33.5
12 years	9.1
13–15 years	13.4
16 years	6.2
17–21 years	6.2

⩾ 80 years]) to receive placebo or aspirin (100 mg enteric-coated, daily).

Baseline measurements

Baseline measurements included demographic data, family and medical history, concomitant medications, and lifestyle risk factors such as smoking history, alcohol use, and physical activity. Blood pressure, height and weight were recorded. Standardised questionnaires were administered: the Geriatric Depression Scale (GDS), the Medical Outcomes Study 36-item short form survey (MOS SF-36), the Instrumental Activities of Daily Living (IADL) scale, the Modified Mini-Mental State (3MS) examination and the Color Trails Test. A biochemical screen at GPs' routine pathology service providers included measurement of fasting lipid, haemoglobin, glucose, and serum creatinine levels.

12-month follow-up

Determinations at 12 months after randomisation included compliance checking by pill count, blood pressure measurement, reassessment of behavioural traits, neuropsychological and quality-of-life tests, and biochemical markers. Adverse events were determined by patient and investigator report, a search of the medical record held by the practice, and further tracing of data to source documents in specialist and hospital records.

Endpoints

The primary endpoints of the pilot study were fatal and non-fatal stroke and coronary events. Secondary endpoints included dementia and clinically significant bleeding (haemorrhagic stroke or gastrointestinal bleeding requiring transfusion or hospitalisation).

Ethical approval

ASPREE was granted ethical approval by the Monash University Standing Committee for Ethics in Research Involving Humans (2002/278) and the Ethics Committee of the Royal Australian College of General Practitioners (NREEC 02/22). ASPREE's trial registry number is ISRCTN83772183.

Data analysis

Differences between groups were analysed by one-way analysis of variance. Data were analysed for change over time using paired *t* tests comparing values within groups at baseline and at 12 months. Haemoglobin levels were analysed by multivariate analysis of covariance (ANCOVA). A two-sided *P* value of < 0.05 was considered significant.

4 Clinical measurements, neuropsychological and quality-of-life test scores* at baseline and 12 months, overall and by treatment group for the 192 participants who returned for 12-month follow-up

	Baseline			12-month follow-up		
Parameter	Overall	Aspirin	Placebo	Overall	Aspirin	Placebo
Height (m)	1.64 (0.09)					
Weight (kg)	71.6 (13.4)	71.8 (12.9)	71.7 (13.9)	71.0 (13.6)	71.3 (13.4)	70.8† (13.8)
Waist circumference (cm)	89.3 (12.1)	89.9 (11.5)	89.2 (12.6)	87.9 (12.1)	87.9† (11.8)	87.9† (12.5)
Systolic blood pressure (mmHg)	142.3 (17.3)	141.3 (18.5)	142.2 (16.0)	145.9 (20.7)	147.5† (23.1)	144.3 (17.8)
Diastolic blood pressure (mmHg)	78.0 (9.4)	77.2 (9.4)	78.3 (9.2)	79.5 (10.9)	80.0† (11.1)	79.0 (10.8)
Total cholesterol (mmol/L)	5.6 (1.0)	5.6 (1.0)	5.6 (0.9)	5.5 (0.9)	5.5 (1.0)	5.4† (0.9)
LDL cholesterol (mmol/L)	3.2 (0.8)	3.3 (0.9)	3.3 (0.8)	3.2 (0.9)	3.2 (0.9)	3.1 (0.9)
HDL cholesterol (mmol/L)	1.7 (0.4)	1.7 (0.4)	1.7 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)
Triglycerides (mmol/L)	1.4 (0.7)	1.4 (0.6)	1.4 (0.7)	1.4 (0.6)	1.4 (0.5)	1.4 (0.6)
Haemoglobin (g/L)	139.7 (12.7)	138.9 (12.6)	140.8 (12.4)	139.0 (14.1)	136.5† (14.4)	141.5 (13.4)
Glucose (mmol/L)	5.1 (0.6)	5.1 (0.8)	5.1 (0.5)	5.0 (0.5)	4.9† (0.6)	5.0 (0.5)
Creatinine (mmol/L)	0.08 (0.02)	0.1 (0.02)	0.1 (0.02)	0.09 (0.02)	0.1 (0.02)	0.1 (0.02)
Median C-reactive protein (IQR) (mg/L)	3.0 (2.9–5.3)	3.0(2.9–5.6)	3.0 (2.9–5.1)	3.0 (3.0–5.0)	3.8 (3.0–5.0)	3.8 (3.0–5.0)
Scores on:						
Geriatric Depression Scale	1.6 (1. 7)	1.7 (1.7)	1.5 (1.6)	2.0 (2.2)	2.1† (2.2)	1.8 (1.9)
Instrumental Activities of Daily Living scale	7.9 (0.4)	7.8 (0.5)	8.0 (0.2)	7.79 (0.60)	7.8 (0.7)	7.8 (0.5)
Short form-36						
Physical component summary	48.7 (8.2)	47.9 (7.7)	49.7 (8.4)	48.3 (8.6)	47.8 (8.2)	48.8 (8.9)
Mental component summary	56.1 (7.0)	55.8 (7.7)	56.3 (6.1)	54.9 (8.4)	54.7 (7.9)	55.1 (9.0)
Color Trails Interference Index (Z-score)[5]	−0.054 (1.20)	−0.057 (1.36)	−0.051 (1.03)	−0.280 (0.99)	−0.269 (1.01)	−0.290 (0.98)
Modified Mini-Mental State examination	93.1 (6.2)	92.7 (6.3)	93.9 (5.4)	93.3 (6.4)	93.0 (6.0)	93.7 (6.8)

LDL = low-density lipoprotein. HDL = high-density lipoprotein. IQR = interquartile range. Short form-36 = Medical Outcomes Study 36-item short form survey.
* All values are mean (SD) unless otherwise specified. † Indicates a statistically significant difference between baseline and 12 months within group ($P < 0.05$). ◆

RESULTS

GP recruitment

Recruitment letters were mailed to 180 GPs, 65 of whom replied (34 yes, 23 no and eight requesting more information); 21 letters were returned to sender (14 had left the address, four had retired, two were deceased, and no reason was specified for one). Nineteen GPs were enrolled as co-investigators, of whom six were not required to meet the participant enrolment target of 200.

Participant recruitment and characteristics

The identification and enrolment of participants is illustrated in Box 1. The initial step of using additional search criteria in computerised medical records enabled the exclusion of ineligible patients (Box 2). For example, 27% of the general practice population screened were identified as taking aspirin or another anticoagulant. Baseline characteristics of the final 209 participants are shown in Box 3. In general, this was an active, healthy group of men and women aged 70 years and over.

12-month follow-up

The 12-month follow-up was attended by 192 (92%) of the 209 participants, despite this being the first contact since randomisation. Most participants (153; 80%) were still taking trial medication; 63 (33%) reported stopping trial medication for a period of more than 2 weeks in the previous 12 months.

Box 4 shows clinical measurements, neuropsychological testing, and quality-of-life measurements at baseline and at the 12-month follow-up visit, both overall and for participants randomly allocated to receive aspirin or placebo. After 12 months of treatment, there were significant increases in systolic and diastolic blood pressures and GDS scores, and significant reductions in haemoglobin and blood glucose levels, and in waist circumference in the aspirin group. There were no differences between aspirin and placebo groups in changes from baseline in the levels of cognitive function or independent activities. Haemoglobin and glucose levels were significantly lower ($P < 0.05$) and blood pressures higher ($P < 0.05$) in the aspirin-treated participants compared with the placebo-treated group. Health behaviour measures at baseline and at 12 months are shown in Box 5.

Event rates

There were no primary endpoints in the 192 participants during the 12 months. There were 19 secondary endpoints consisting of three cases of Alzheimer disease, four cancers and 12 hospitalisations unrelated to the study drug. There was no major bleeding.

DISCUSSION

ASPREE is a planned major clinical trial based in Australian general practice. Its aim is to examine the net effects (risks and benefits) of low-dose aspirin therapy in apparently healthy older people free of established vascular disease and dementia, both of which impose a major and increasing health burden. ASPREE will also be able

5 Health-related behaviour measures at baseline and 12 months for the 192 participants who returned for 12-month follow-up

Health-related behaviour	Baseline	12 months
Physical activity		
Physically active in the past 2 weeks	70.3%	65.1%
Number of times active in the past 2 weeks (mean [SD])	8.5 (6.3)	7.4 (5.3)
Vigorous activity in the past 2 weeks	43.5%	43.7%
Smoking history		
Current	4.3%	4.2%
Former	39.9%	40.0%
Never	55.8%	55.8%
Number of cigarettes each day (mean [SD])	13 (12)	
Age at which participants started smoking (mean [SD])	20 years (6)	
Alcohol use		
Current	83.3%	80.6%
Former	5.7%	8.9%
Never	11.0%	10.5%
How often participants drink alcohol		
Less than once per week	32.6%	40.4%
1–2 days per week	10.7%	8.2%
3–4 days per week	7.5%	5.3%
5–6 days per week	7.5%	15.2%
Every day	41.7%	31.0%
Number of drinks per day		
1–2	81.7%	85.9%
3–4	11.3%	7.6%
5–8	5.9%	5.3%
9–12	1.1%	1.2%

to assess the efficacy of aspirin in preventing other prevalent conditions of older people, such as cognitive decline and cancer.

There are a number of important findings from this pilot study that suggest that conducting an 18 000-participant general-practice-based study in Australia is feasible. Firstly, computer-based querying of general practice records to identify potential study participants was highly efficient. In our ASPREE feasibility study, instant identification of age-eligible patients and the exclusion of 41% of these by searching for further exclusion criteria (Box 2) significantly reduced recruitment costs. In our previous large-scale general practice initiative (ANBP2), all databases were generated by hand, and age was the only criterion on which letters of invitation were sent.[6] Secondly, the 23% response rate to the letter of invitation is similar to that reported in ANBP2, and reflects a willingness of older people to participate in clinical research. Finally, and most importantly, 86% of those who entered the run-in phase were randomly allocated to receive aspirin or placebo in this ASPREE pilot study. On this basis, and allowing for lower response rates, about 30 000 people aged 70 years and older would need to be entered into the run-in phase to achieve the recruitment target in the main trial (Box 1). Given that 53 242 participants entered into the screening phase of ANBP2 within the 2.5-year recruitment period, the screening target of 30 000 is highly likely to be achievable within a 2-year recruitment phase in the main ASPREE study.

Low-dose aspirin therapy has been shown to reduce the risk of vascular events in those with manifest atherosclerotic disease.[7] In primary prevention, atherosclerotic events can also be reduced.[3,8-13] In addition, there is increasing evidence of the potential, as yet unproven, of low-dose aspirin therapy to reduce the rate of intellectual decline in older people.[14-16] However, part of the benefit of aspirin therapy may be offset by adverse effects, including gastrointestinal and intracranial bleeding. Epidemiological modelling suggests that the routine use of aspirin in people aged 70 years and over who do not have manifest disease has an uncertain balance of risk and benefit, and a trial such as ASPREE is therefore warranted.[17] Because the risks and benefits have not been established in older participants, aspirin is not widely used for primary prevention in Australian general practice. In our screened population, only 27% of patients were currently taking aspirin or another anticoagulant (Box 2). This population estimate needs to be interpreted with caution, as it included patients taking aspirin for both primary and secondary prevention, and aspirin is available over the counter, and hence may not be recorded consistently in GPs' records. The use of aspirin in the community is also likely to increase, given its cardioprotective effects and the recent evidence of cardiotoxicity of other non-selective and selective non-steroidal anti-inflammatory drugs.[18]

The 80% compliance level at 12 months observed in our ASPREE pilot study is consistent with the 81% at 1 year of those randomly assigned to receive aspirin in the United Kingdom general-practice-based Primary Prevention Project (PPP).[13] Experience from PPP and other primary prevention trials suggests that participants stop taking trial medication predominantly in the first year, with relatively low rates of cessation thereafter. The significant reduction in haemoglobin level observed in the active treatment arm of ASPREE was also found in the Prevention with low-dose Aspirin of Cardiovascular disease in the Elderly study.[19] Such an outcome may be trivial in younger, more robust populations, but is likely to be important in older people in whom comorbidity is common. For example, occult blood loss may lead to the development of cardiac failure.[20] Nearly one in five of the cohort of our ASPREE feasibility study were aged 80 or more years. While these numbers will be underpowered for subgroup analysis by age band, it is likely to give trends if the benefits and harms are different in the very old.

The observed significant increase in systolic blood pressure in the aspirin group may be explained as an association between aspirin and hypertension, particularly in women.[21] However, no effect was reported in our own previous pilot study, in any of the six main primary prevention trials or their meta-analyses, or in the Antithrombotic Trialists Group secondary prevention meta-analysis.[8-13,22,23]

Expert groups have also called for the conduct of a trial such as ASPREE.[24,25] In December 2003, the United States Food and Drug Administration (FDA) Cardiovascular and Renal Advisory Committee voted against a labelling indication for aspirin that was based on assessment of absolute risk of coronary heart disease, for which age is the major determinant.[26] The FDA Committee called for a trial to provide the evidence for aspirin use in individuals at moderate cardiovascular risk.

In conclusion, the conduct of ASPREE within Australian general practice is feasible. The study has the potential to enable important conclusions to be drawn about healthy ageing.

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COMPETING INTERESTS

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