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CLINICAL RESEARCH
Clinical trials

Aspirin, cardiovascular events, and major bleeding in older adults: extended follow-up of the ASPREE trial

Rory Wolfe [1,*], Jonathan C. Broder[1], Zhen Zhou [1], Anne M. Murray [2,3], Joanne Ryan [1], Andrew T. Chan [4,5], Mark R. Nelson[1,6], Robyn L. Woods[1], Michael E. Ernst[7,8], Suzanne G. Orchard[1], Brenda Kirpach[2], Christopher M. Reid[1,9], Raj C. Shah[10], Nigel Stocks[11], Karen L. Margolis[12], Johannes T. Neumann[1,13,14], Michelle Wilson[1], Sharyn Fitzgerald[1], Suzanne E. Mahady[1], Erica M. Wood[1], Shara Ket[1], Charles B. Eaton[15], Peter Hand[16,17], Mobin Malik[18], Walter P. Abhayaratna[19], Prasanna Venkataraman[1,20], Peter Chan[1], Geoffrey C. Cloud[16,17], Geoffrey A. Donnan[21], Jeff D. Williamson[22], and Andrew M. Tonkin[1]

[1]School of Public Health and Preventive Medicine, Monash University, 553 St Kilda Road, Melbourne 3004, VIC, Australia; [2]Berman Centre for Outcomes and Clinical Research, Hennepin Healthcare Research Institute, Minneapolis, MN, USA; [3]Division of Geriatrics, Department of Medicine, Hennepin HealthCare, University of Minnesota, Minneapolis, MN, USA; [4]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital, Boston, MA, USA; [5]Division of Gastroenterology, Massachusetts General Hospital, Boston, MA, USA; [6]Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia; [7]Department of Pharmacy Practice and Science, College of Pharmacy, The University of Iowa, Iowa, IA, USA; [8]Department of Family Medicine, Carver College of Medicine, The University of Iowa, Iowa, IA, USA; [9]School of Population Health, Curtin University, Perth, WA, Australia; [10]Department of Family & Preventive Medicine and the Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA; [11]Discipline of General Practice, University of Adelaide, Adelaide, SA, Australia; [12]HealthPartners Institute, Minneapolis, MN, USA; [13]Department of Cardiology, University Heart & Vascular Center, Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [14]German Center for Cardiovascular Research (DZHK), Partner Site, Hamburg/Kiel/Lübeck, Hamburg, Germany; [15]Center for Primary Care and Prevention, Brown University, Providence, RI, USA; [16]Stroke Unit, Department of Neurology, The Alfred Hospital, Melbourne, VIC, Australia; [17]Department of Neuroscience, School of Translational Medicine, Monash University, Melbourne, VIC, Australia; [18]California Heart & Vascular Clinic, San Diego, CA, USA; [19]College of Health and Medicine, The Australian National University, Canberra, Australia; [20]Department of Cardiology, St Vincent's Hospital, Melbourne, Australia; [21]Melbourne Brain Centre, Royal Melbourne Hospital, University of Melbourne, Parkville, VIC, Australia; and [22]Sticht Center on Aging and Alzheimer's Prevention, Section on Gerontology and Geriatric Medicine, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA

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Abstract

Background and Aims Guidelines recommend against routine initiation of low-dose aspirin in older adults for primary prevention of atherosclerotic cardiovascular disease events. This study aimed to estimate long-term and post-trial effects of aspirin on major adverse cardiovascular events (MACE) and major haemorrhage using extended follow-up of participants from the ASPREE trial.

Methods In-trial (2010–17) and post-trial (2017–22) data were analysed. At enrolment, participants were aged ≥70 years (≥65 years for US minorities) without prior cardiovascular events, dementia, or independence-limiting physical disability. Randomization was to daily low-dose aspirin or matching placebo for the 4.7 years of the trial.

Results Of the 19 114 participants randomized (9525 aspirin, 9589 placebo), 15 668 without in-trial MACE consented to post-trial follow-up. No long-term benefit of randomization to aspirin was observed for MACE for the entire in-trial and post-trial period [hazard ratio (HR) 1.04, 95% confidence interval (CI) .94, 1.15]. However, during the post-trial period (median

* Corresponding author. Tel: +61 042 292 2606, Email: rory.wolfe@monash.edu

4.3 years), there was a higher rate of MACE (HR 1.17, 95% CI 1.01, 1.36) in those randomized to aspirin compared with placebo. Over the entire period, a higher rate of major haemorrhage was observed in the randomized aspirin group compared with placebo (HR 1.24, 95% CI 1.10, 1.39).

Conclusions The present study provides novel evidence concerning long-term MACE and haemorrhage following aspirin use in initially healthy older adults. The finding of no long-term MACE benefit needs to be considered in clinical decision-making if aspirin is being considered for use in this context.

Structured Graphical Abstract

Key Question

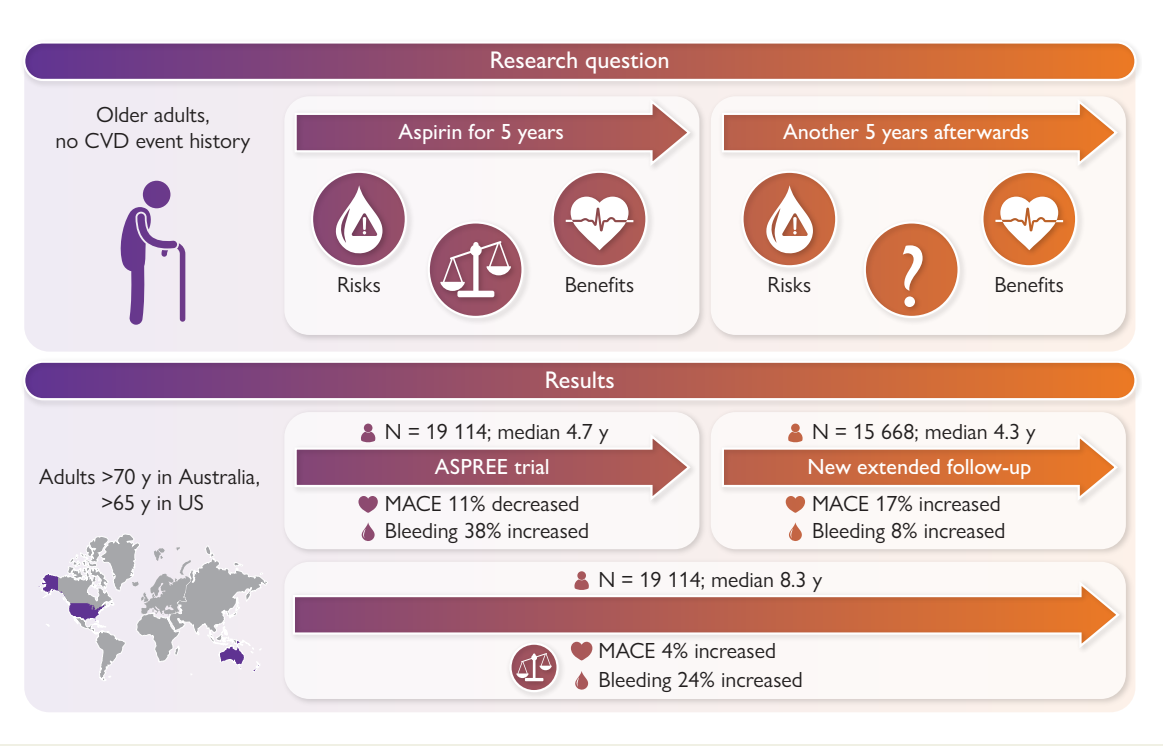
Aspirin is not routinely recommended for primary prevention of cardiovascular disease events in older adults. It might be considered in high-risk subgroups. The long-term effect on cardiovascular events of taking aspirin for several years in this setting is uncertain.

Key Finding

In the ASPREE trial older patients were randomized to daily low-dose aspirin or placebo. During the post-trial period (median 4.3 years) there was a higher rate of major cardiovascular events in those randomized to aspirin compared to placebo. Over the entire period, a higher rate of major haemorrhage was observed in the randomized aspirin group compared to placebo.

Take Home Message

Increased cardiovascular event risk post-trial in those initially randomized to aspirin has several possible theoretical explanations. Clinical decision making for personalised prescribing of aspirin for primary prevention should consider established bleeding risks and the possible absence of long-term cardiovascular benefit.



Effects of aspirin on cardiovascular events and major haemorrhage in ASPREE extended follow-up. CVD, cardiovascular disease; MACE, major adverse cardiovascular events; ASPREE, ASPirin in Reducing Events in the Elderly.

Keywords Aspirin • Major adverse cardiovascular events • Coronary artery disease • Stroke • Haemorrhage • Clinical trial • Observational follow-up

Introduction

Prior to 2018, there was insufficient evidence to reliably inform whether daily, low-dose aspirin offered a potential benefit in older persons without atherosclerotic cardiovascular disease (CVD) events. The ASPirin in Reducing Events in the Elderly (ASPREE) randomized clinical trial (RCT) found that aspirin did not extend disability-free

survival or significantly reduce CVD events over a median of 4.7 years, but increased the risk of major haemorrhage and cancer death.[1–3] This evidence contributed to new recommendations in clinical guidelines against routine aspirin initiation in older adults for primary prevention of atherosclerotic CVD events.[4–6] Notwithstanding this, after the guidelines were updated, an estimated 23%–46% of older adults in the US population still regularly take low-dose aspirin for primary prevention.[7–9]

We have previously reported the immediate effects of aspirin within the ASPREE trial, both as a randomized comparison with placebo[1–3] (and according to actual use and non-use of aspirin[10]) including a hazard ratio (HR) of .95 [95% confidence interval (CI) .83, 1.08] for CVD events, a secondary endpoint. We also reported effects on major adverse cardiovascular events (MACE), which included the conditions related to ischaemia and thrombosis that are most likely to be affected favourably by low-dose aspirin.[2] Concerning MACE, a HR of .89 (95% CI .77, 1.03) for effects of aspirin vs placebo was seen in-trial. This, while not statistically significant, was of a magnitude consistent with significant results in meta-analyses. Specifically, meta-analyses of placebo-controlled trials of low-dose aspirin for primary prevention both before and after ASPREE and two contemporary trials [A Study of Cardiovascular Events iN Diabetes (ASCEND) and Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) in patients at moderate risk of CVD] showed significant reductions in vascular event rates in those assigned aspirin.[11–15] These meta-analyses also found that any reduction in vascular events was accompanied by significantly elevated risk of major haemorrhage and no significant benefit on either vascular or all-cause death.[11,14,15] Thus, consideration of aspirin for use in the primary prevention of MACE must weigh up relatively small cardiovascular benefits against established bleeding risks. This balance is of particular importance in older adults for whom the risks of both CVD events and bleeding are substantially elevated and in whom the ASPREE study found an elevated risk of all-cause death with aspirin.[1,11]

Theoretically, both immediate effects (impact of a pharmacologic intervention while it is being taken, estimable from data collected during a RCT's intervention phase) and legacy effects (impact of the intervention after it has ceased, estimable from data collected during a post-trial observational period) could contribute to the overall long-term effects of a pharmacologic intervention. The long-term effect is estimable from the entirety of in-trial and post-trial periods.[16] A legacy effect of aspirin could present as either a consequence of drug cessation, due to short-term rebound from unmasking extant CVD risk, or possibly as a delayed effect of the accumulation of several years of exposure to aspirin use, noting that some evidence has suggested delayed effects of aspirin may exist for colorectal cancer but have not been described for CVD events.[17–20]

This paper presents estimates of the long-term and post-trial effects of aspirin on MACE and major haemorrhage in the setting of primary prevention for older individuals, using data from the ASPREE trial and its extended observational follow-up.

Methods

The ASPREE was a large-scale placebo-controlled randomized trial (NCT01038583) of daily low-dose (100 mg) enteric-coated aspirin conducted in 19 114 adults aged over 70 years residing in Australia and the USA (≥ 65 years for US minorities) who had no prior cardiovascular events, dementia, or independence-limiting physical disability at trial enrolment.[21] The median enrolment age of the cohort was 74 years [interquartile range (IQR) 72–78]. Recruitment was undertaken between 2010 and 2014, and participants were followed for a median of 4.7 years (IQR 3.6–5.7) during the in-trial period. The ASPREE protocol included the annual distribution of study drug supply bottles to participants with receipt and pill counting, of the prior year's unused medication.

The trial ended 6 months early on 12 June 2017 due to conditional power calculations showing it was unlikely that a beneficial effect on the primary endpoint of disability-free survival would be shown.[3] At this time, a notification letter was sent to all participants advising them to cease taking study medication immediately and return unused pills to their study coordinator. The letter also advised that any participant taking open-label aspirin on the recommendation of their treating doctors should continue to do so.

From 13 June 2017, participants provided consent to ASPREE-eXTension (ASPREE-XT), an extended observational period.[22] For a further 15 months, participants remained blinded to their study medication assignment and unaware of the trial's principal findings. An unblinding letter including a summary of the trial's findings was sent to all participants on 14 September 2018 when the results were published.[1–3]

During both the ASPREE (in-trial) and ASPREE-XT (post-trial) periods, a wide range of clinical data were collected from participants via scheduled annual in-person visits and 6-monthly telephone calls. For those who were unable to be seen directly or contacted, a telephone call visit or review of the participant's medical records was conducted by research staff. The present analysis uses data from randomization until the fourth ASPREE-XT annual visit, conducted in 2021–22.

Outcomes

The primary outcomes of interest for this analysis were (i) incident MACE [a composite of the first occurrence of non-fatal myocardial infarction (MI), fatal and non-fatal ischaemic stroke, and coronary heart disease death] and (ii) major haemorrhage (haemorrhagic stroke, symptomatic intracranial bleeding, or clinically significant extracranial bleeding). All-cause death was also analysed.

Event definitions were as previously described.[2] Non-fatal MI was based on widely adopted definitions in cardiology guidelines.[23] Non-fatal stroke was defined as rapidly developing clinical signs of focal or global disturbance of cerebral function lasting >24 h (unless interrupted by surgery or death), with no apparent cause other than ischaemic or haemorrhagic cerebrovascular disease.[24] Clinically significant bleeding was defined as bleeding that led to transfusion, hospitalization, prolongation of hospitalization, surgery, or death.[25]

The occurrence of these clinical events occurring after 12 June 2017 was ascertained and adjudicated with the same rigour as during ASPREE. Documentation for each event including clinical notes, hospitalization records, pathology results, and imaging studies (computed tomographic scans or magnetic resonance images) was compiled. Using these documents, all major clinical events were adjudicated by expert committees who were masked to treatment randomization and post-trial status with respect to aspirin use.[1–3]

Study drug adherence

Study drug adherence during the trial may have moderated the effect of randomized aspirin on post-trial MACE and bleeding. Adherence was assessed using study pill count (from participants' annual return of bottles) and classification as adherent also required an absence of open-label aspirin use. Adherence was defined dichotomously, with two definitions using different thresholds to enable sensitivity analyses: (i) the average annual proportion of study pills used ≥15% (and no open-label aspirin use in-trial, i.e. no report of aspirin in concomitant medication lists) and (ii) average annual proportion of study pills used ≥85% (and no open-label aspirin use in-trial). Further details are shown in Supplementary data online, *Table S1*. Study pill adherence during the trial was bimodally distributed, with most participants assessed as either ≥85% or <15% adherent.

Aspirin exposure

To assess the as-treated effects of actual aspirin use over the entire period of in-trial and post-trial, aspirin exposure per year was defined using a combination of study aspirin pill count data and self-reported open-label aspirin use. Aspirin exposure per year was defined dichotomously for each year. Two definitions based on different thresholds to identify regular use each year were used. To provide a definition with high sensitivity, exposure was first defined as any of ≥15% adherence to aspirin (during the trial for those randomized to aspirin), participant reporting aspirin use on two or more days per week in questionnaires (only collected post-trial), or study records of aspirin in concomitant medications (both in-trial and post-trial). This threshold was similar to that used in a previous observational follow-up of an aspirin trial.[19] To provide a definition with higher specificity, the second exposure definition was either ≥85% adherence to in-trial study aspirin pills, participant reporting aspirin use on six or more days per week in post-trial questionnaires, or study recording of aspirin in concomitant medications. See Supplementary data online, *Table S1* for further details.

Statistical analyses

Participant characteristics at the end of the trial were presented by initial randomized treatment groups for those who consented to ASPREE-XT and also repeated for those who additionally were not censored for MACE during the trial. For categorical variables, counts and percentages were presented, while for numeric variables, means and standard deviations were reported if approximately symmetrically distributed and medians and IQRs otherwise. Aspirin exposure was visualized by country and randomized arm for the pre-trial, in-trial, and post-trial periods, both censored at the time of MACE and without that censoring. Two-sided 5% significance levels were used for statistical significance throughout, without adjustment for the multiple outcomes being tested, and all analyses were conducted using R (version 4.4.1) and Stata (version 18). See Supplementary data online, *Methods* for more details on statistical analyses. A pre-specified statistical analysis plan was followed.[26]

Long-term effects

In the first group of analyses, effects over the long-term were estimated using an intention-to-treat (ITT) approach. For each outcome, time to first event was analysed in a Cox proportional hazards model to compare randomized treatment arms, with a participant's time at risk censored at their fourth ASPREE-XT annual visit or loss to follow-up, whichever occurred first. For outcomes other than all-cause death, cause-specific hazards were estimated with death from causes other than those included in the model outcome treated as a censoring event. Cumulative incidence curves with competing risk of death were obtained using the Aalen–Johansen estimator. Rates per 1000 person-years for each year in study were also visualized. Proportional hazards assumptions were checked by visual inspection of Schoenfeld residuals against time. An interaction test was performed by adding a product term in the Cox model to assess the heterogeneity of treatment effects across different subgroups. Adjusted analyses considered characteristics at randomization [age, sex, body mass index (BMI), smoking status, cancer history, hypertension, diabetes, dyslipidaemia, estimated glomerular filtration rate (eGFR), and Modified Mini-Mental State (3MS) score] added to the Cox proportional hazards model.

Due to the cessation of study drug at the end of the trial, it was possible that the ITT treatment effect would not be constant across the entire in-trial and post-trial follow-up. To account for potential non-proportional hazards, we calculated restricted mean time lost with competing risk of death and a generalized (combined) test of treatment effect comparing restricted mean survival time difference at 10 equally spaced intervals.[27–29]

Post-trial effects

The second group of analyses was used to estimate the post-trial effects of a multi-year daily aspirin strategy for primary prevention in older people. An ITT analysis was conducted by resetting the follow-up time zero to the first day of post-trial observation, 13 June 2017. For each endpoint separately, participants who were free of the particular endpoint as of 13 June 2017 and had consented to ASPREE-XT were included in the post-trial analyses. Consequently, the number of individuals at risk on 13 June 2017 varied by endpoint. Subgroup and adjusted analysis were also conducted following the same approach used for estimation of long-term effects.

To address potential selection bias, inverse probability weighting (IPW) for consent to ASPREE-XT was calculated using baseline (randomization) characteristics and occurrence of in-trial events, and, as a separate sensitivity analysis, also with measurements of characteristics at the end of the randomized trial. In the sensitivity analysis using characteristics at trial end, ~75% of participants had missing data in at least one characteristic, prompting the use of multiple imputation with chained equations and 75 imputed datasets.[30] The distributions of the imputations were inspected, and convergence was checked by visual inspection of the mixing plots.[31] Weight calculations and Cox models were completed within each imputed dataset, and estimates were combined using Rubin's rules.[32]

As-treated long-term effects

Finally, we undertook as-treated analyses to evaluate the long-term (in-trial and post-trial) effects of aspirin use on MACE and major haemorrhage.

To estimate the as-treated effect of actual aspirin use, analysis was conducted using inverse probability of censoring weighting (IPCW) for treatment switching. We censored at the first time point at which treatment switching occurred. For those randomized to aspirin, a treatment switch was defined when the participant stopped using study pills and did not commence open-label aspirin within the same year. For those randomized to placebo, a treatment switch was defined when the participant began use of open-label aspirin. The switch times were determined using the two aspirin exposure thresholds of 15% and 85%. The exact timing of each switch was unknown, and switches were assumed to have occurred at the annual visit where the aspirin use data were collected. Follow-up was discretized into 30-day intervals and pooled logistic regression used for both the weight-generating and outcome models.

Results

Of the 19 114 participants randomized (9525 to aspirin, 9589 to placebo), baseline characteristics were well balanced between the randomized groups, as previously reported.[3] In participants previously randomized to aspirin, who were not censored for MACE, actual use of aspirin (based on the 15% aspirin exposure threshold) gradually declined during the trial, and there was a sharp decrease when the trial ended, due to the cessation of study medication (*Figure 1*). Conversely, in those previously randomized to placebo who were not censored for MACE, aspirin use gradually increased during the trial and rose further when the trial ended (*Figure 1*).

In the post-trial period, aspirin exposure was similar between those initially randomized to aspirin and placebo and was higher in US participants compared with participants in Australia. This was consistent with pre-trial aspirin use being higher in US participants. Aspirin use post-trial among all randomized participants mirrored the trends over time seen in those who were not censored for MACE, though with slightly higher rates overall (see Supplementary data online, *Figure S1*).

Characteristics at the end of the trial for participants who consented to ASPREE-XT were similar between the randomized aspirin and placebo groups, apart from slightly lower haemoglobin and fasting blood glucose levels in those initially randomized to aspirin compared with placebo (*Table 1*). See Supplementary data online, *Table S2* for additional characteristics. The proportion of participants who had major haemorrhage during the trial was higher, and the proportion that had an in-trial MACE was lower, in those randomized to aspirin. Characteristics at

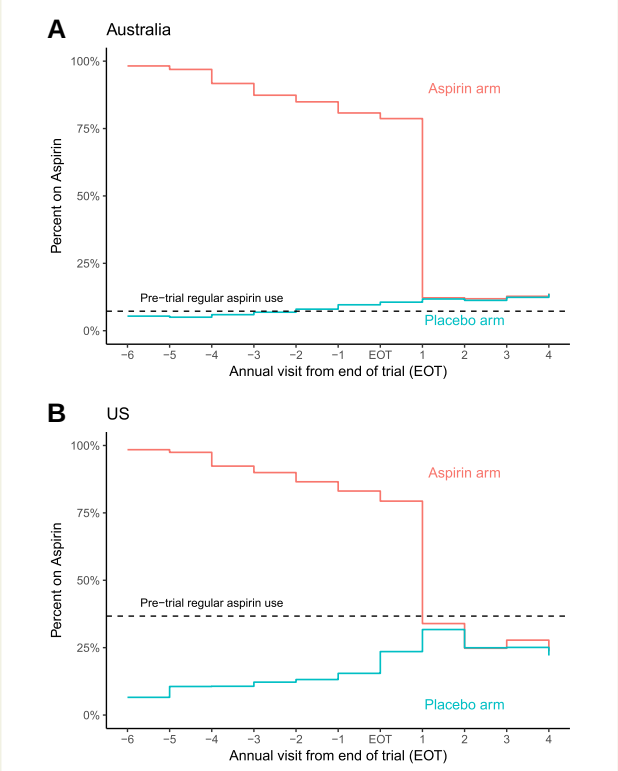


Figure 1 Aspirin exposure pre-, in-, and post-trial by country and randomised arm in ASPREE. The annual visits are presented relative to the end of the trial with participants censored at the time of a major adverse cardiovascular event. Aspirin exposure was defined as 15% or more adherence to study aspirin pills (for those randomized to aspirin only), or reporting aspirin use on two or more days per week in questionnaires, or recording aspirin in concomitant medications list

the end of the trial were also generally similar between the aspirin and placebo groups when restricted to participants who had not had a MACE during the trial (see Supplementary data online, *Table S3*). Among these 15 668 participants, the median age at the end of the trial was 79 years (IQR 76–82). Among participants who remained free of MACE during the trial, the post-trial 5-year predicted MACE risk was similar between those randomized to aspirin and those randomized to placebo (see Supplementary data online, *Table S3*). Including those with in-trial MACE (assigned a 100% predicted risk), among all ASPREE-XT participants, the mean predicted 5-year MACE risk was slightly higher in the placebo group than in the aspirin group because of the slightly higher proportion of participants in the placebo group with in-trial MACE (*Table 1*).

Major adverse cardiovascular events

Participants were followed for a median of 4.3 years (IQR 4.0–4.6) for MACE and major haemorrhage in the post-trial period.

Long-term effects of aspirin were estimated to be close to null (HRs close to 1) for MACE for the entire period including the in-trial and post-trial follow-up (median follow-up of 8.3 years, IQR 7.0–9.5) (*Table 2*). Adjusting for baseline covariates did not change these results (see Supplementary data online, *Table S4*). Subgroup analysis also showed no evidence of heterogeneity of treatment effects for MACE (*Figure 2*). Consistently, differences in restricted mean time lost between the randomized aspirin and placebo groups were generally estimated to be close to zero days (see Supplementary data online, *Table S5*).

However, the effect of aspirin on MACE changed over the full period of follow-up. This was evidenced by the proportional hazards assumption not being satisfied, as shown in *Table 2* and *Figure 3*. Specifically, during the post-trial period, there were higher rates of MACE (HR 1.18, 95% CI 1.02, 1.37) and also myocardial infarction (HR 1.25, 95% CI 1.01, 1.54) in those randomized to aspirin compared with those randomized to placebo, whereas during the trial, these rates were lower in the aspirin group compared with placebo (*Table 2*). The increased risk of MACE post-trial in those randomized to aspirin was not limited to the first year of post-trial follow-up (see Supplementary data online, *Figure S2*).

Inverse probability weighting calculated from characteristics at randomization resulted in all absolute standardized differences of ≤.1 between those who did and did not consent to follow-up in ASPREE-XT (see Supplementary data online, *Table S6*). Inverse probability weighting with end-of-trial characteristics substantially improved balance compared with the unweighted sample, though some characteristics had an absolute standardized difference between .1 and .2 (see Supplementary data online, *Table S7*). Estimated HRs for effects of aspirin in the post-trial period were similar with both baseline and end-of-trial IPW (see Supplementary data online, *Table S8*, e.g. MACE IPW HR 1.17, 95% CI 1.01, 1.36) compared with the unweighted analyses presented in *Table 2* (e.g. MACE unweighted HR 1.18, 95% CI 1.02, 1.37). Additional adjustment for characteristics with absolute standardized differences between .1 and .2 produced very similar results (MACE IPW HR 1.16, 95% CI 1.00, 1.35). No heterogeneity of aspirin effects in the post-trial period was apparent for MACE using characteristics either at randomization (see Supplementary data online, *Figure S3*) or the end (see Supplementary data online, *Figure S4*) of the trial. This included the observation that ITT effects in the post-trial period were similar regardless of in-trial study drug adherence (see Supplementary data online, *Figure S4*).

Major haemorrhagic events

Over the entire period of the in-trial and post-trial follow-up, higher rates of major haemorrhage were observed in those randomized to aspirin compared with placebo (HR 1.24, 95% CI 1.10, 1.39), and likewise upper gastrointestinal bleeding (HR 1.43, 95% CI 1.13, 1.81), and bleeding at another site (HR 1.25, 95% CI 1.01, 1.54) (*Table 3*). Adjusted HRs were consistent with the main results (see Supplementary data online, *Table S4*), and there was generally no evidence of effect heterogeneity in subgroups (see Supplementary data online, *Figure S5*). Time lost to bleeding was greater in the aspirin group than the placebo group for major haemorrhage (difference in restricted mean time lost = 32 days, $P < .01$) and upper gastrointestinal bleeding (difference = 13 days, $P < .01$) (see Supplementary data online, *Table S5*).

During the post-trial period alone, there was no significant difference in rates of major haemorrhage between the randomized aspirin and placebo groups (*Table 3* and *Figure 4*) with a HR for overall major haemorrhage of 1.08 (95% CI .91, 1.29), although the difference between the ITT aspirin effects during the post-trial and in-trial time periods was not significant ($P = .06$). However, there was a significant difference in as-randomized comparisons during the post-trial and in-trial periods for intracranial bleeding ($P = .03$) and upper gastrointestinal bleeding ($P = .03$).

Estimates with IPW of post-trial effects on bleeding (see Supplementary data online, *Table S8*, e.g. major haemorrhage IPW HR 1.08, 95% CI .91, 1.28) were similar to the unweighted analyses presented in *Table 3*

Table 1 Demographic characteristics and cardiovascular risk factors at the end of the ASPREE randomized clinical trial: by randomization group for participants who provided consent for extended observational follow-up in ASPREE-XT

Characteristics[a]	Aspirin (*N* = 8098)	Placebo (*N* = 8259)	Total (*N* = 16357)	*P* value
Age (yrs)	79.6 (4.6)	79.6 (4.5)	79.6 (4.5)	.33
Country				.59
AUS resident	7359 (90.9%)	7525 (91.1%)	14884 (91.0%)	
US resident	739 (9.1%)	734 (8.9%)	1473 (9.0%)	
Male	3513 (43.4%)	3594 (43.5%)	7107 (43.4%)	.86
Ethnicity				.33
Australian white	7232 (89.3%)	7352 (89.0%)	14584 (89.2%)	
US white	365 (4.5%)	383 (4.6%)	748 (4.6%)	
African American	245 (3.0%)	239 (2.9%)	484 (3.0%)	
Hispanic	162 (2.0%)	159 (1.9%)	321 (2.0%)	
Other[b]	94 (1.2%)	126 (1.5%)	220 (1.3%)	
Years of education				.69
<12	3706 (45.8%)	3805 (46.1%)	7511 (45.9%)	
12–15	2308 (28.5%)	2305 (27.9%)	4613 (28.2%)	
16+	2083 (25.7%)	2149 (26.0%)	4232 (25.9%)	
Living home alone	2619 (34.7%)	2685 (34.7%)	5304 (34.7%)	.96
Current smoker	186 (2.5%)	185 (2.4%)	371 (2.4%)	.78
Current alcohol use	5296 (70.2%)	5386 (69.7%)	10682 (69.9%)	.53
BMI (kg/m^2) (*N* = 14 629)	27.6 (4.7)	27.7 (4.7)	27.6 (4.7)	.77
Waist circumference (cm) (*N* = 14 540)	97 (13)	97 (13)	97 (13)	.31
Heart rate (b.p.m.)	70 (11)	70 (11)	70 (11)	.56
SBP (mm/Hg) (*N* = 14 720)	136 (17)	136 (17)	136 (17)	.58
DBP (mm/Hg) (*N* = 14 720)	74 (10)	74 (10)	74 (10)	.24
LDL cholesterol (mg/dL) (*N* = 12 265)	109.9 (34.8)	111.0 (34.9)	110.5 (34.8)	.10
Total cholesterol (mg/dL) (*N* = 12 492)	195.5 (39.6)	196.3 (39.7)	195.9 (39.6)	.31
Haemoglobin (g/dL) (*N* = 13 555)	13.9 (1.4)	14.0 (1.4)	13.9 (1.4)	< .01
Fasting blood glucose (mg/dL) (*N* = 12264)	99.4 (19.7)	100.4 (21.3)	99.9 (20.5)	< .01
eGFR[b] (mL/min/1.73 m^2) (*N* = 13 295)	68.9 (14.6)	68.7 (14.6)	68.8 (14.6)	.59
Hypertension (*N* = 14 720)	5575 (76.6%)	5642 (75.8%)	11 217 (76.2%)	.23
Dyslipidaemia (*N* = 12 263)	4102 (67.5%)	4205 (68.0%)	8307 (67.7%)	.54
Diabetes history	1198 (14.8%)	1294 (15.7%)	2492 (15.2%)	.12
Chronic kidney disease (*N* = 10 483)	1870 (36.0%)	1884 (35.7%)	3754 (35.8%)	.74
Grip strength, dominant hand (kg) (*N* = 10 489)	25.3 (9.4)	25.3 (9.3)	25.3 (9.4)	.85
Gait time to walk 3 m (s) (*N* = 10 472)	3.4 (1.0)	3.3 (1.0)	3.4 (1.0)	.44
Fried frailty (*N* = 10 198)				.37
Not frail	2341 (46.5%)	2409 (46.7%)	4750 (46.6%)	
Pre-frail	2338 (46.4%)	2421 (46.9%)	4759 (46.7%)	
Frail	358 (7.1%)	331 (6.4%)	689 (6.8%)	
3MS (*N* = 10 456)[c]	95 (92, 98)	95 (92, 98)	95 (92, 98)	.89

Continued

Table 1 *Continued*

Characteristics[a]	Aspirin (*N* = 8098)	Placebo (*N* = 8259)	Total (*N* = 16357)	*P* value
CESD-10 overall score[c]	3 (1, 6)	3 (1, 6)	3 (1, 6)	.35
MACE risk prediction (% risk in 5 years) (*N* = 11 586)[c]	4.6 (3.0, 7.0)	4.6 (3.0, 7.2)	4.6 (3.0, 7.1)	.03
MACE risk prediction quartile (*N* = 11 586)				.14
0–25th percentile	1479 (25.8%)	1482 (25.3%)	2961 (25.6%)	
25–50th percentile	1469 (25.6%)	1486 (25.4%)	2955 (25.5%)	
50–75th percentile	1502 (26.2%)	1470 (25.1%)	2972 (25.7%)	
75–100th percentile	1284 (22.4%)	1414 (24.2%)	2698 (23.3%)	
Study drug adherence (15%)	6509 (80.4%)	6620 (80.2%)	13129 (80.3%)	.72
Study drug adherence (85%)	4374 (54.0%)	4577 (55.4%)	8951 (54.7%)	.07
Major adverse cardiovascular event during trial	211 (2.6%)	260 (3.1%)	471 (2.9%)	.04
Major haemorrhage during trial	237 (2.9%)	172 (2.1%)	409 (2.5%)	< .01

3MS, Modified Mini-Mental State examination; BMI, body mass index; CESD-10, Center for Epidemiologic Studies Depression Scale 10 Item; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]Characteristics were ascertained at the last annual visit within 15 months before the end of trial (12 June 2017). *N* displayed if missing data are evident in >10% of the cohort. Number (percent) presented for categorical characteristics and mean (SD) presented for continuous measures.
[b]Other ethnicity includes Asian, Aboriginal/Torres Strait Islander, American Indian, Native Hawaiian/Pacific Islander, multiple races/ethnic groups, and those who were not Hispanic but did not state another race/ethnic group; hypertension was defined as antihypertensive medication use or SBP/DBP ≥ 140/90 mm/Hg; diabetes was defined as self-report or fasting blood glucose ≥ 126 mg/dL or on treatment for diabetes at any time before or at the end of the trial; dyslipidaemia was defined as cholesterol lowering medication use, or total cholesterol ≥ 212 mg/dL for AUS and ≥240 mg/dL for US, or ≥160 mg/dL LDL cholesterol; CKD was defined as urine albumin creatinine ratio of ≥3 mg/mmol, or eGFR of <60 mL per minute per 1.73 m^2; Fried frailty was defined as a deficit in grip strength, gait speed, exhaustion, physical activity, and body weight loss; major adverse cardiovascular events (MACE) risk prediction was based on 5-year risk prediction in MACE (for those ≥70 years of age) with those who had MACE during trial defined as 100%.
[c]Medians and 25/75th percentiles presented due to strong non-normality.

Table 2 Effects of aspirin as randomized on first major adverse cardiovascular events and all-cause death in the ASPREE trial and post-trial

Endpoint	In-trial[d]	Post-trial effects[e]				In-trial and post-trial (long-term effects)		
	Hazard ratio (95% CI)	Aspirin *N* (rate)[f]	Placebo *N* (rate)[f]	Hazard ratio (95% CI)	In-trial vs post-trial *P*[g]	Aspirin *N* (rate)[f]	Placebo *N* (rate)[f]	Hazard ratio (95% CI)
Major adverse cardiovascular event[a]	.89 (.77, 1.03)	381 (12.1)	328 (10.3)	1.18 (1.02, 1.37)	<.01	741 (10.0)	721 (9.6)	1.04 (.94, 1.15)
Fatal or non-fatal myocardial infarction	.93 (.76, 1.15)	193 (6.0)	157 (4.8)	1.25 (1.01, 1.54)	.03	376 (5.0)	350 (4.6)	1.09 (.94, 1.26)
Fatal or non-fatal ischaemic stroke[b]	.89 (.71, 1.11)	185 (5.7)	157 (4.8)	1.20 (.97, 1.48)	.07	347 (4.6)	333 (4.4)	1.06 (.91, 1.23)
Vascular death[c]	.82 (.56, 1.20)	124 (3.6)	103 (2.9)	1.23 (.95, 1.60)	.05	191 (2.4)	178 (2.2)	1.09 (.89, 1.34)
All-cause death	1.14 (1.01, 1.29)	822 (23.9)	820 (23.3)	1.02 (.93, 1.13)	.26	1547 (19.3)	1481 (18.2)	1.06 (.99, 1.14)

[a]Major adverse cardiovascular event (MACE) is a composite of coronary heart disease death, non-fatal myocardial infarction, or fatal or non-fatal ischaemic stroke.
[b]Ischaemic stroke includes cases adjudicated as ischaemic stroke, stroke type uncertain, and ischaemic stroke with haemorrhagic transformation.
[c]Vascular death includes all fatal components of MACE, i.e. a composite of coronary heart disease death and fatal ischaemic stroke.
[d]As published in McNeil JJ, *et al.* Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med.* 2018;379(16):1509–1518.
[e]Does not include participants who did not consent to ASPREE-XT (who may have follow-up and endpoints between 13 June 2017 and 31 January 2018).
[f]Number of participants with event (rate per 1000 person-years).
[g]*P* interaction effect between in-trial and post-trial time periods.

(absolute standardized differences shown in Supplementary data online, *Table S9*). Further, censoring at the occurrence of MACE led to consistent results concerning major haemorrhage (see Supplementary data online, *Table S10*). For post-trial effects, there was no evidence of treatment effect heterogeneity by subgroups defined at trial baseline, except for frailty, and this was only evident with the frailty index and not with the Fried frailty

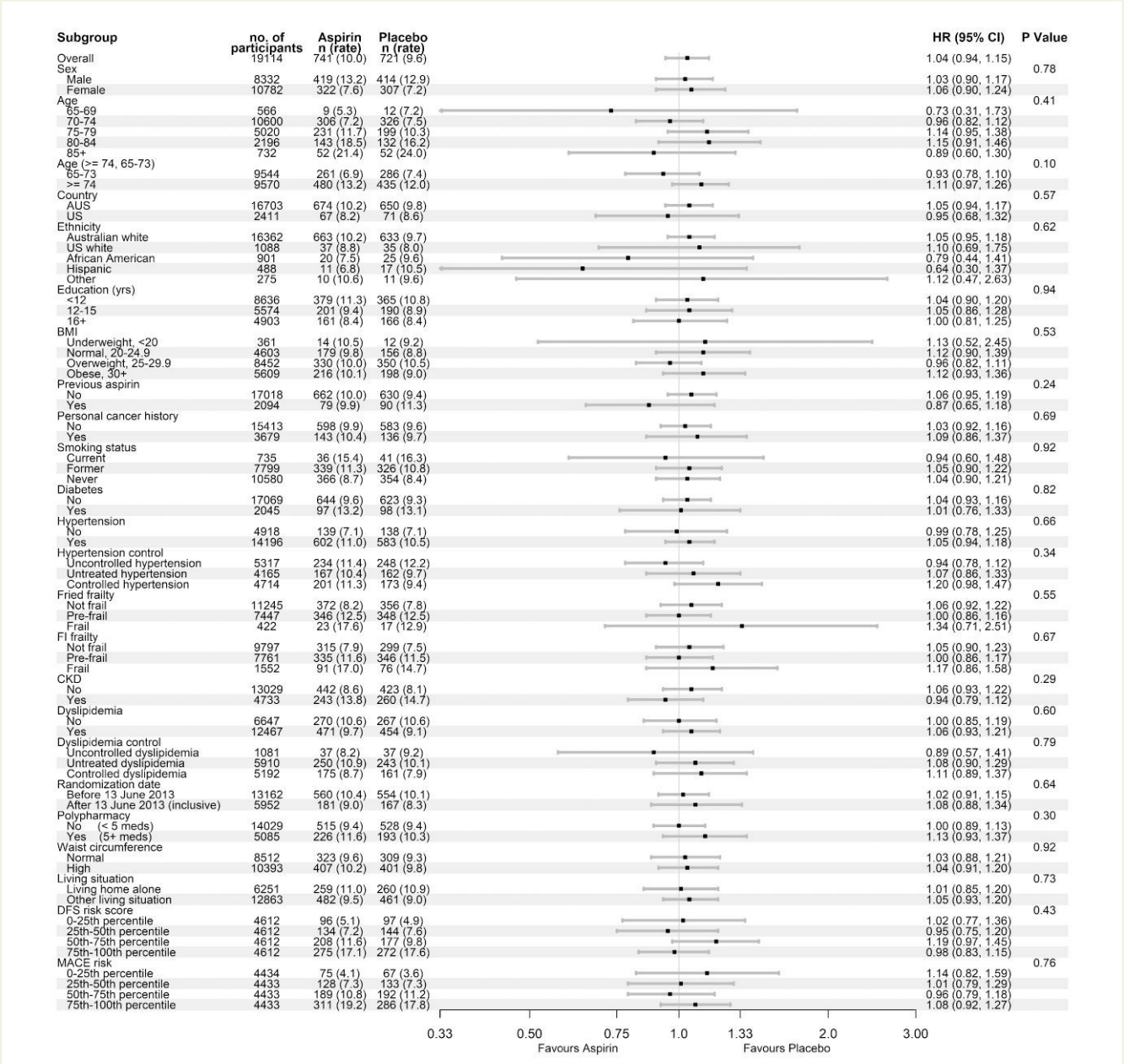


Figure 2 Forest plot of hazard ratios estimating long-term effects of aspirin on major adverse cardiovascular events during the entire period of the in-trial and post-trial. Characteristics were ascertained at trial baseline

definition (see Supplementary data online, *Figure S6*), nor by frailty subgroups at trial end (see Supplementary data online, *Figure S7*). There was borderline statistical significance for an observation of aspirin harm post-trial only in participants who did not adhere to randomized assignment during the trial [*P* interaction adherence (85% definition) = .06, *P* interaction adherence (15% definition) = .09] (see Supplementary data online, *Figure S7*). Of note, those who did not adhere had higher bleeding rates post-trial.

As-treated analyses of aspirin effects

To estimate the effects of aspirin as used across the entirety of the in-trial and post-trial periods, the results for the IPCW for MACE (see Supplementary data online, *Table S11*) showed HRs similar to the ITT analysis presented in *Table 2*. In particular, the estimate of ongoing aspirin use on MACE was HR .97 (95% CI .84, 1.12). The IPCW HRs for major haemorrhagic events (see Supplementary data online, *Table S11*) were greater with ongoing aspirin use compared with the ITT analysis of long-term effects shown in *Table 3*. The IPCW results were generally robust to the aspirin exposure definition used (see Supplementary data online, *Table S11*).

Discussion

Using extended follow-up for a further 4.3 years of participants in the ASPREE trial, we examined long-term effects of aspirin on MACE and major haemorrhage (*Structured Graphical Abstract*). We found an

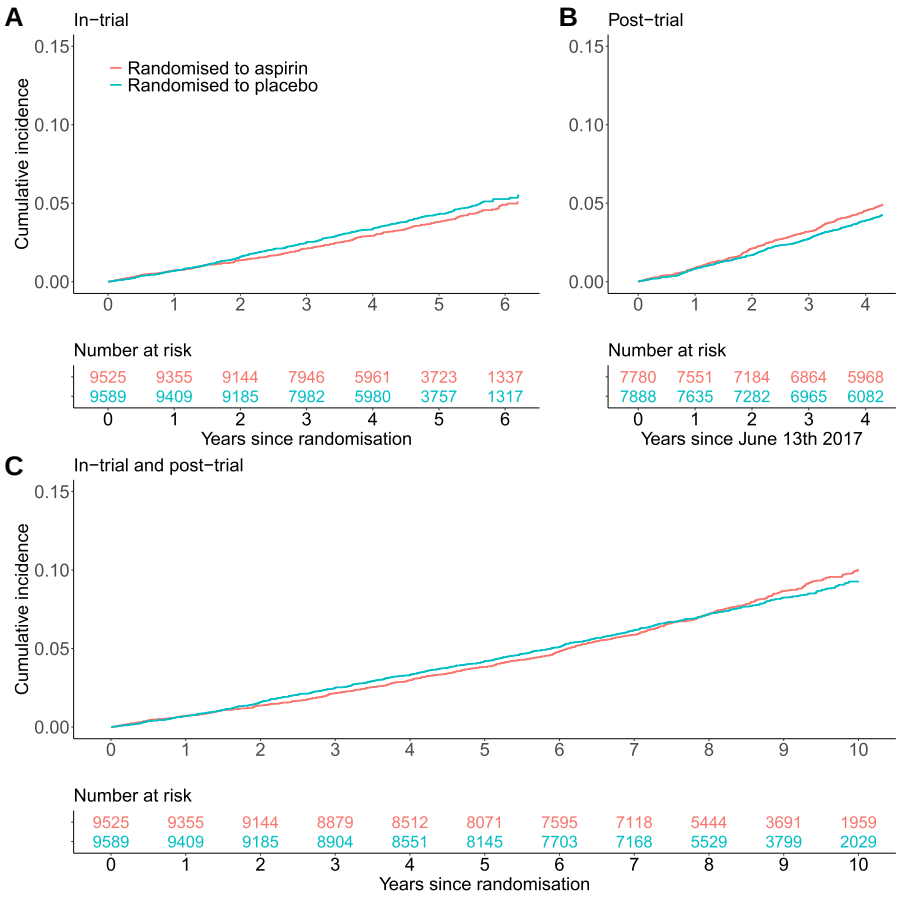


Figure 3 Cumulative incidence of major adverse cardiovascular events. Participants were randomized at various dates during the ASPREE clinical trial (March 2010–December 2014). Consequently, 13 June 2017 does not represent the same time point since randomization for each participant, ranging from 2.5 to 7.3 years

absence of MACE benefit over the total long-term follow-up (median of 8.3 years). However, we also found a notable contrast between the trend towards MACE benefit during the trial (HR .89, 95% CI .77, 1.03) and an elevated risk of MACE post-trial (IPW HR 1.17, 95% CI 1.01, 1.36) in individuals originally randomized to aspirin compared with placebo. The lack of benefit over the long-term was reinforced by as-treated analyses that also found no benefit on MACE with continued ongoing use over the long-term.

We also found that randomization to aspirin was associated with increased risk of major haemorrhage over the total long-term follow-up. However, during post-trial follow-up, there was no longer a substantially elevated risk of bleeding in those originally randomized to aspirin. A finding of elevated bleeding risk with aspirin is consistent with most primary prevention trials of aspirin, and bleeding is a widely acknowledged side effect of aspirin use that is of particular concern in older adults who have higher comorbidity burden and underlying risk of haemorrhage than younger adults.[33]

Our finding of elevated risk for MACE post-trial in those randomized to aspirin suggests three theoretical possibilities: that any benefit on MACE accrued while on aspirin is lost when aspirin treatment is removed either because of forgone benefit or, possibly, a rebound effect; that a modest protective effect on MACE from aspirin may delay events but not prevent them completely; or that our observations post-trial are distorted by the impact of selection bias for open-label use of aspirin. We acknowledge that other explanations of the MACE findings may exist and that the play of chance cannot be entirely excluded. To an extent, our observations should be viewed as hypothesis-generating. We discuss the evidence from our total period of follow-up in the context of these possibilities.

The first possibility is the potential for forgone benefit or rebound effect in ceasing aspirin. For MACE, the HR of .89 (randomized aspirin vs randomized placebo) in-trial was consistent with results in other studies.[14,15] This potential benefit of taking aspirin could have been lost upon cessation of study drug at the trial end, i.e. a forgone benefit. A rebound effect in the form of a relative short-term prothrombotic tendency following the withdrawal of aspirin has been demonstrated in previous epidemiological studies in populations with known atherosclerotic CVD.[34–36] This phenomenon is thought to arise from the recovery of platelet cyclooxygenase activity and synthesis of thromboxane after aspirin cessation, resulting in increased platelet aggregation.[35] The delayed divergence in MACE risk post-trial, as evidenced by the cumulative incidence curves in our study, suggests that the thrombotic rebound effect may extend beyond the short term. This result is consistent with a large Swedish cohort study, in which individuals who discontinued low-dose aspirin had a higher risk of MACE than those who continued (HR 1.37, 95% CI 1.34, 1.41) over an average 3-year follow-up.[18] This could be explained by the fact

Table 3 Effects of aspirin as randomized on first major haemorrhagic events in the ASPREE trial and during post-trial observational follow-up

Endpoint	In-trial[f]	Post-trial effects[e]				In-trial and post-trial (long-term effects)		
	Hazard ratio (95% CI)	Aspirin N (rate)[g]	Placebo N (rate)[g]	Hazard Ratio (95% CI)	In-trial v post-trial P[h]	Aspirin N (rate)[g]	Placebo N (rate)[g]	Hazard ratio (95% CI)
Major haemorrhage[a]	1.38 (1.18, 1.62)	272 (8.6)	258 (8.0)	1.08 (.91, 1.29)	.06	650 (8.8)	537 (7.1)	1.24 (1.10, 1.39)
Intracranial bleeding[b]	1.50 (1.11, 2.02)	76 (2.3)	91 (2.7)	.85 (.63, 1.16)	.03	189 (2.5)	170 (2.2)	1.13 (.92, 1.39)
Upper gastrointestinal bleeding	1.87 (1.32, 2.66)	70 (2.2)	65 (2.0)	1.10 (.79, 1.54)	.03	163 (2.2)	116 (1.5)	1.43 (1.13, 1.81)
Lower gastrointestinal bleeding	1.36 (.96, 1.54)	52 (1.6)	45 (1.4)	1.18 (.79, 1.76)	.64	125 (1.7)	100 (1.3)	1.27 (.97, 1.65)
Bleeding at another site[c]	1.16 (.87, 1.54)	86 (2.7)	66 (2.0)	1.33 (.96, 1.83)	.70	192 (2.5)	156 (2.0)	1.25 (1.01, 1.54)
Fatal major haemorrhage[d]	1.18 (.68, 2.03)	32 (.9)	33 (.9)	.99 (.61, 1.61)	.76	67 (.8)	62 (.8)	1.10 (.78, 1.55)

[a]Major haemorrhage is a composite of haemorrhagic stroke, intracranial bleeding, or extracranial bleeding that resulted in transfusion, prolonged hospitalization, surgery, or death.
[b]Intracranial bleeding includes haemorrhagic stroke (fatal or non-fatal), subarachnoid haemorrhage stroke (fatal or non-fatal), or extradural, intraventricular, parenchymal haematoma, subarachnoid, subdural, or site not determined intracranial bleed.
[c]Bleeding at another site includes haematuria, bleeding at a surgical site, bleeding after trauma, vaginal bleeding, and epistaxis.
[d]Fatal major haemorrhage includes deaths that were adjudicated to be due to major haemorrhage.
[e]Does not include participants who did not consent to ASPREE-XT (who may have follow-up and endpoints between 13 June 2017 and 31 January 2018).
[f]As per McNeil JJ, *et al*. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med*. 2018;379(16):1509–1518.
[g]Number of participants with event (rate per 1000 person-years).
[h]*P* interaction effect between in-trial and post-trial time periods.

that coronary artery stenosis caused by enlarging plaques does not necessarily cause the acute thrombotic complications that generally provoke MACE, but culminates in events some time and possibly years later.[37] Further, aspirin cessation may lead to a pro-inflammatory state which can contribute to the destabilization of atherosclerotic plaques, making them more prone to rupture, potentially years later.[37] Nevertheless, our own cohort analyses designed to compare aspirin cessation between groups of individuals who cease aspirin vs continue its use did not demonstrate elevated risk of MACE with cessation and concluded that cessation, which came with significantly reduced risk of haemorrhage, appeared safe.[38,39]

It should be noted that in our study, cumulative incidence curves post-trial took 2–3 years to display elevated MACE risk in the randomized aspirin group, which also does not seem to concur with short-term rebound harm. It is also noteworthy that the findings concerning haemorrhage post-trial, when no elevated risk was seen in the randomized aspirin group, are discordant with the observation for MACE. This discrepancy may be attributed to the distinct mechanisms through which aspirin influences these outcomes. Although not supported by our previous analyses, aspirin cessation might lead to the recrudescence of underlying conditions that promote the atherosclerotic CVD process and increase the risk of MACE.[40] In contrast, the increased bleeding risk during the trial period caused by aspirin use might diminish after aspirin cessation due to relatively quick recovery of platelet function, and/or mucoprotective prostaglandins.

The study design and our analyses comparing randomized aspirin with randomized placebo groups in the long term do not enable us to distinguish between any effects of ceasing aspirin and any (legacy) effects of having taken aspirin for several years. Hence, a second explanation for elevated MACE risk post-trial in the randomized aspirin group relates to the potential that aspirin delays events rather than preventing them completely. From the pathophysiological viewpoint, the principal effect of aspirin is on platelets which have a short half-life. Therefore, it is unlikely that it would simply delay MACE. Nonetheless, it is possible that aspirin, by causing intraplaque haemorrhage, might be associated with MACE some time later. An early small-scale randomized trial showed that low-dose aspirin (50 mg daily) provided no benefit in preventing carotid plaque growth and might even accelerate it.[41] If this line of reasoning was true, then individuals at the start of the trial at the highest MACE risk may benefit most from aspirin in delaying events but may also be most prone to experiencing those events in the longer term. However, our subgroup analysis by cardiovascular risk score quartile (defined on either baseline or end-of-trial characteristics) found no evidence of heterogeneity in long-term and post-trial aspirin effects on MACE. The effects in the context of ongoing usage of aspirin were also investigated in our as-treated analysis of ongoing aspirin use over a median of 8.3 years of follow-up. We found no benefit on MACE of aspirin use that was ongoing over the total period, although we acknowledge that this analysis was observational in nature rather than based on randomization.

The third explanation for our findings related to MACE is the well-recognized threat of selection bias for post-trial comparisons, requiring particular care in the choice of analytical methods even if analysed by original randomization.[42] In this respect, key strengths of the follow-up of participants from the ASPREE trial were the high consent rate (93%) for the post-trial follow-up period, the continuation for 5 years of annual visits with participants, and the detailed documentation and adjudication of clinical events, strengths that were similar to those of the randomized trial. Our study extension differs from many post-trial follow-up studies that rely on linkage to administrative data which are typically collected for purposes other than research and can suffer from inadequate coverage and accuracy. Our analyses employed IPW to attempt to counter the possibility of selection bias for consent into post-trial follow-up. Ability to avoid confounding due to selection bias requires full balance for factors that influence risks of both MACE

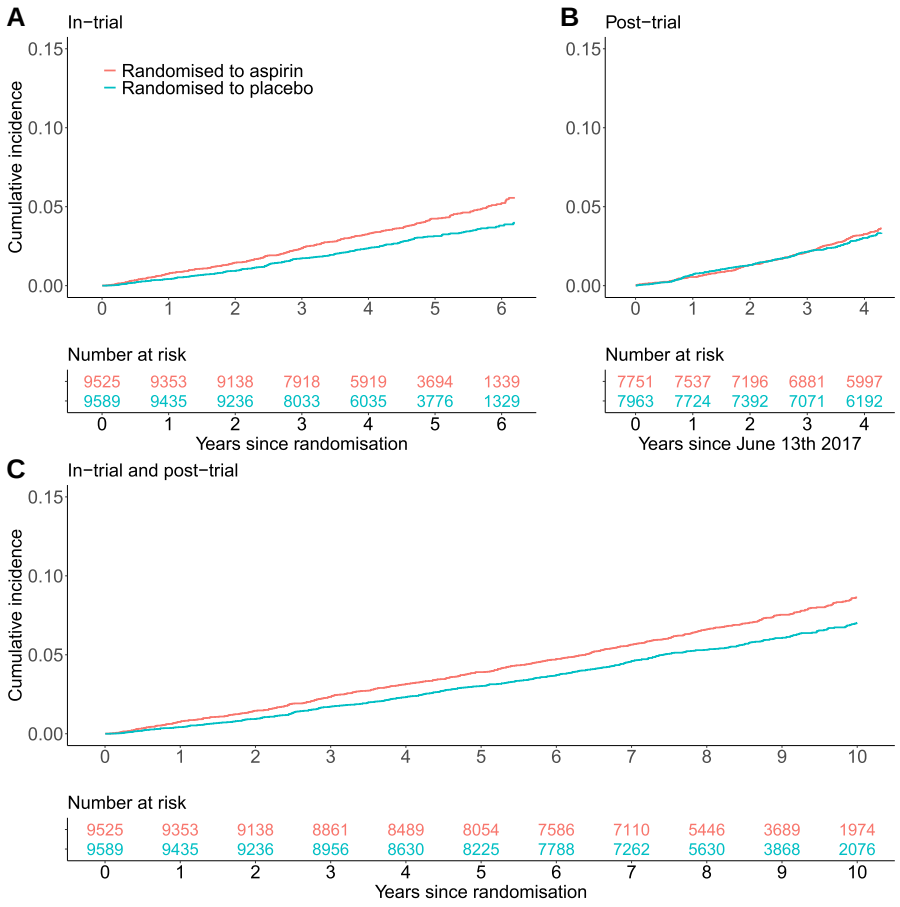


Figure 4 Cumulative incidence of major haemorrhage. Participants were randomized at various dates during the ASPREE clinical trial (March 2010–December 2014). Consequently, 13 June 2017 does not represent the same time point since randomization for each participant, ranging from 2.5 to 7.3 years

and bleeding. Associated with this challenge, these two outcomes share many risk factors such as increasing age, male sex, diabetes, current smoking, increased blood pressure, and high BMI.[11] Our IPW analyses generally achieved balance for important characteristics such as these risk factors. The two exceptions we found were biomarkers that appear to be affected by aspirin. Specifically, differences between the aspirin and placebo groups were seen at the end of the trial in levels of haemoglobin and fasting blood glucose, and we have previously reported different trends in mean levels of these measures between the randomized treatment arms.[43,44]

Another strength of this long-term follow-up of the ASPREE trial was the continued collection of data concerning aspirin use. This enabled us to ascertain that randomized aspirin and placebo groups had similar levels of aspirin use post-trial. It also enabled us to perform as-treated analyses to estimate the effects of ongoing aspirin use. However, this analysis was limited as we could only establish aspirin use to the nearest annual visit and the exact timing of changes in its use (between annual visits) could not be assessed.

Follow-up of participants from other aspirin trials has produced further insights into the drug's other long-term and legacy effects.[19,45–47] In other analyses of ASPREE post-trial follow-up, we are examining evidence for long-term effects in older adults on cancer and on dementia, which may develop over many years and for which ASPREE did not see any shorter-term beneficial effects. It is also possible that individual patient characteristics are important to inform individualized treatment plans, especially consideration of acknowledged markers of CVD risk,[47–49] and possibly biomarkers such as lipoprotein(a) and genotypes associated with higher levels.[50]

In summary, acknowledging the limitation of this being a non-randomized comparison, increased MACE risk post-trial in those initially randomized to aspirin has several possible theoretical explanations. Other research suggests that certain subgroups might benefit from aspirin for primary prevention. However, established bleeding risks and also the possible absence of long-term MACE benefit need to be considered in clinical decision-making.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

A.T. reports receiving research support or honoraria from Merck, Pfizer, and Novartis, as well as from Bayer for materials in the ASPREE trial. C.M.R. reports being funded through a National Health and Medical Research Council Principal Research Fellowship. M.R.N. reports receiving honoraria from Sanofi and Amgen as well as Bayer for materials in ASPREE. Z.Z. reports being funded through a National Heart Foundation Post-Doctoral Fellowship. R.C.S.'s institution, Rush University Medical Center, receives research support for his role as a site principal investigator or site sub-investigator for industry initiated clinical trials and research studies of Alzheimer's disease sponsored by Athira Pharma, Inc., Edgewater NEXT, Eisai, Inc., and Genentech, Inc. A.T.C. reports receiving research support or honoraria from Boehringer Ingelheim, Pfizer Inc., Freenome, an Zoe Ltd for work unrelated to this manuscript. J.T.N. reports having received speaker/consulting honoraria from Abbott Diagnostics, Siemens Healthineers, Roche, and PHC. J.T.N. is listed as co-inventor of an international patent on the use of a computing device to estimate the probability of myocardial infarction (WO2022043229A1) as well as being co-founder and shareholder of the ART-EMIS Hamburg GmbH. Other authors declare that they have no conflict of interests.

Data Availability

Data are available to academic researchers upon request via the ASPREE Principal Investigators. Details for applications are provided through https://aspree.org/aus/for-researchers/ or https://aspree.org/usa/for-researchers/.

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Ethical Approval

The ASPREE and ASPREE-XT studies were approved by local institutional review boards at each participating site, and all participants provided written informed consent for their participation.

Pre-registered Clinical Trial Number

The pre-registered clinical trial numbers are ISRCTN83772183 (International Standard Randomized Controlled Trial Number Register) and NCT01038583 (clinicaltrials.gov).

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