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Subgroup analysis of the ASPirin in Reducing Events in the Elderly randomized clinical trial suggests aspirin did not improve outcomes in older adults with chronic kidney disease

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AUTHOR CONTRIBUTIONS

RWo, JBW, RLW, JJM, HG, PR, RWa, AMM, and KRP conceived the research questions and designed the study. RLW, JJM, MRN, CMR, RCS, MEE, JEL, AMT, WPA, PG, EMW, SEM, JDW, GAD, GCC, and AMM were involved in acquisition and interpretation of data. RWo and KRP analyzed the data. RWo, JBW, and KRP prepared the initial draft of the manuscript. All authors contributed to revising the paper, and all authors approved the final version of the manuscript.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Additional Description of ASPREE Trial Methods. Protection of human research participants, recruitment, detailed exclusion criteria, laboratory measures, and supplementary references.

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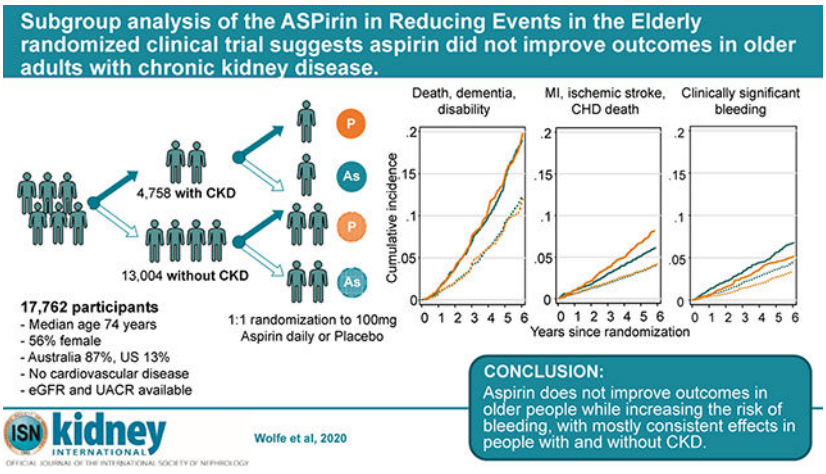
Abstract

The role of aspirin for primary prevention in older adults with chronic kidney disease (CKD) is unclear. Therefore, post hoc analysis of the randomized controlled trial ASPirin in Reducing Events in the Elderly (ASPREE) was undertaken comparing 100 mg of enteric-coated aspirin daily against matching placebo. Participants were community dwelling adults aged 70 years and older in Australia, 65 years and older in the United States, all free of a history of dementia or cardiovascular disease and of any disease expected to lead to death within five years. CKD was defined as present at baseline if either eGFR under 60mL/min/1.73m^2 or urine albumin to creatinine ratio 3 mg/mmol or more. In 4758 participants with and 13004 without CKD, the rates of a composite endpoint (dementia, persistent physical disability or death), major adverse cardiovascular events and clinically significant bleeding in the CKD participants were almost double those without CKD. Aspirin's effects as estimated by hazard ratios were generally similar between CKD and non-CKD groups for dementia, persistent physical disability or death, major adverse cardiovascular events and clinically significant bleeding. Thus, in our analysis aspirin did not improve outcomes in older people while increasing the risk of bleeding, with mostly consistent effects in participants with and without CKD.

Graphical Abstract



Keywords

aspirin; bleeding; cardiovascular events; chronic kidney disease; elderly; randomized clinical trial

Chronic kidney disease (CKD) is common in older people. Its prevalence increases with age, [1] and more than one-half of adults aged ≥70 years will develop CKD.[2] CKD is important because it is a powerful and potentially modifiable risk factor for cardiovascular disease (CVD),[3,4] with more than one-half of the deaths occurring in people with CKD attributable to CVD.[5] In the elderly, CKD is associated with increased risk of all-cause mortality and end-stage kidney disease compared with younger individuals.[6]

Thrombosis and thromboembolism are important in the pathobiology of major cardiovascular events. Although the role of aspirin is well established for secondary prevention of CVD,[7] its efficacy in primary prevention in lower-risk populations is less clear. A systematic review of 13 clinical trials encompassing more than 164,000 CVD-free participants across a broad range of age groups reported that aspirin was associated with a lower risk of cardiovascular events and increased risk of major bleeding.[8] In addition, a recent clinical trial provides key insight into the effects of aspirin in older individuals. The ASPirin in Reducing Events in the Elderly (ASPREE) trial was a large (n = 19,114) double-blind, randomized, placebo-controlled trial conducted in community-dwelling people predominately aged >70 years without a history of atherothrombotic cardiovascular disease.[9–11] The trial assessed whether daily treatment with 100 mg of enteric-coated aspirin decreased the risk of the composite endpoint of dementia, persistent physical disability, or death or, conversely, extended the duration of life free of dementia and disability ("disability-free survival"), noting that dementia is a highly undesirable disease outcome for older people who are otherwise generally healthy. CVD events and clinically significant bleeding were prespecified secondary endpoints in ASPREE. Key findings included that treatment with aspirin had no beneficial effect on disability-free survival or on rates of CVD events, but it increased the risk of clinically significant bleeding and of cancer-related death. As a result, guidelines no longer recommend aspirin for primary prevention of atherosclerotic CVD in adults aged >70 years.[12]

Despite the known high CVD risk in individuals with CKD, the efficacy of aspirin for primary prevention in individuals with CKD has not been explicitly studied in randomized trials and is a research priority.[13–17] The ongoing Aspirin To Target Arterial events in Chronic Kidney disease (ATTACK) trial[18] has a composite of major adverse cardiovascular events (MACE) as a primary endpoint, but this study is not due to report until 2025. Older age and CKD represent 2 important CVD risk factors, and their co-occurrence identifies a population subgroup that may provide a stronger rationale for aspirin use. However, any putative benefits of aspirin could be offset by an increased risk of bleeding in elderly individuals with CKD, given that CKD heightens the risk of bleeding due to effects on platelet aggregation.[19] Older people with CKD form an important subgroup in both the ASPREE and ATTACK trials, and although the primary endpoints of the 2 trials differ, both disability-free survival and MACE are important outcomes to study in older people with CKD.

Given that the ASPREE trial included a large number of older individuals with CKD, we undertook a post hoc exploratory analysis to examine the potential benefits and harms of aspirin in this population and to compare and contrast the effects in participants with CKD and those without CKD. Specifically, we hypothesized that the benefits and harms of aspirin would be similar in the 2 groups of elderly participants.

RESULTS

Study participants

Of the 19,114 participants randomized to receive aspirin or placebo in the ASPREE trial, 7 (0.04%) were excluded from the present analysis because of stage 5 CKD or self-reported history of dialysis or kidney transplant, and 1345 (7.0%) were excluded because of missing estimated glomerular filtration rate (eGFR) or urine albumin:creatinine ratio (UACR) data at baseline, leaving 17,762 participants for analysis (Figure 1). The characteristics of participants with and without missing eGFR or UACR data were similar, as shown in Supplementary Table S1. Characteristics of the 4758 participants with CKD and the 13,004 participants without CKD have been compared previously.[20] Characteristics of the participants with CKD were well balanced between the group randomized to aspirin and the group randomized to placebo (Table 1). The mean age was 76.1 ± 5.2 years for the aspirin group and 76.1 ± 5.1 years for the placebo group, and the proportion of females in the 2 groups was 56.5% and 57.0%, respectively. Distributions of participants across eGFR and albuminuria categories were also similar in the 2 treatment groups.

Rates of endpoints in the aspirin and placebo groups by CKD status

Endpoint rates were compared between aspirin and placebo groups, as shown in Table 2 and Figures 2 and 3. The rates of the composite endpoint of dementia, persistent physical disability, or death (Figure 2a), MACE (Figure 2b), and clinically significant bleeding (Figure 2c) were almost double in the participants with CKD compared with those without CKD.

The hazard ratios for aspirin compared with placebo (Table 2) were generally similar in the subset of participants with CKD compared with those without CKD for the composite of dementia, persistent physical disability, or death (CKD: hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.83–1.12; no CKD: HR, 1.05; 95% CI, 0.93–1.18), MACE (CKD: HR, 0.77; 95% CI, 0.61–0.99; no CKD: HR, 0.98; 95% CI, 0.80–1.19), and clinically significant bleeding (CKD: HR, 1.28; 95% CI, 0.98–1.68; no CKD: HR, 1.38; 95% CI, 1.12–1.70). Tests of interaction for these endpoints provided no evidence of differing effects of aspirin between the CKD and no-CKD groups. Among other endpoints, there was evidence of a beneficial effect of aspirin on ischemic stroke for participants with CKD but not for participants without CKD (CKD: HR, 0.63; 95% CI, 0.44–0.91; no CKD: HR, 1.10; 95% CI, 0.82–1.47; P for interaction = 0.02). A numerically similar relationship was also seen for cardiovascular mortality (CKD: HR, 0.63; 95% CI, 0.39–0.99; no CKD: HR, 1.10; 95% CI, 0.75–1.61), although the interaction was not statistically significant (P = 0.07).

Regarding hemorrhagic events, hemorrhagic stroke occurred in 24 participants with CKD, including 15 in the aspirin group and 9 in the placebo group (HR, 1.69; 95% CI, 0.74–3.86), and in 48 participants without CKD, 25 in the aspirin group and 23 in the placebo group (HR, 1.10; 95% CI, 0.62–1.94; *P* for interaction = 0.40).

The proportional hazards assumption was satisfied in all of these analyses.

Comparisons stratified by level of UACR and eGFR

Baseline characteristics of all 17,762 participants in the aspirin and placebo groups are summarized by UACR in Supplementary Table S2 and by eGFR in Supplementary Table S3. The comparisons of endpoint rates for the composite endpoint of dementia, persistent physical disability, or death; MACE; and clinically significant bleeding between the aspirin and placebo groups, stratified by UACR and eGFR levels, are shown in Table 3. Although there were no major differences for the composite endpoint or for clinically significant bleeding, MACE rates were lower in participants randomized to aspirin than for participants randomized to placebo with UACR ≥3 mg/mmol (HR, 0.58; 95% CI, 0.41–0.83), but not for those with UACR <3 mg/mmol (HR, 0.99; 95% CI, 0.84–1.17; *P* for interaction = 0.01). In contrast, when stratifying participants by eGFR, the comparison of MACE rates between the aspirin and placebo groups did not vary (*P* for interaction = 0.90). Results for other endpoints are shown in Table 4. In the case of ischemic stroke, there was evidence that aspirin had an effect in participants with UACR ≥3.0 mg/mmol (HR, 0.45; 95% CI, 0.26–0.77) but not in participants with UACR <3 mg/mmol (HR, 1.04; 95% CI, 0.81–1.35; *P* for interaction = 0.01). There were no differences among the other endpoints tested.

A subgroup analysis of the 4758 participants with CKD was undertaken to examine the effects of aspirin on the composite outcome of dementia, persistent physical disability, or death; MACE; or clinically significant bleeding and whether there was any interaction with demographic factors, comorbidity (diabetes, hypertension), or medication use (previous aspirin use, nonsteroidal anti-inflammatory drug use, and use of angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers). Interactions were observed for the composite endpoint in CKD participants, suggesting different effects of aspirin in the USA compared with Australia (*P* for interaction = 0.001; Supplementary Figure S1), by ethnicity/race (*P* for interaction = 0.03), and by previous regular aspirin use (*P* for interaction = 0.005). Importantly, among those with CKD, 41% of USA participants compared with 7% of Australian participants had been using aspirin at baseline, hence the interactions by previous aspirin use, country, and ethnicity/race may arise from a common source. No clear differences in the HRs for aspirin on MACE were seen across clinically important subgroups in the CKD population (Supplementary Figure S2). Similarly, the comparisons of aspirin and placebo groups for risk of clinically significant bleeding did not vary markedly across CKD subgroups (Supplementary Figure S3).

DISCUSSION

Persons with CKD are at high risk for CVD,[21,22] and CVD has been linked to incident disability in older adults,[23] providing a basis for the belief that among the older population without disability, individuals with CKD might benefit more from daily aspirin use

compared with CKD-free individuals. However, CKD also heightens aspirin-associated bleeding risks owing to defects in platelet aggregation.[19] Thus, it is uncertain whether the benefits and risks of aspirin are similar for individuals with and without CKD or with increasing severity of CKD. Given the widespread use of aspirin in the community, a study of the effects of aspirin for primary CVD prevention in CKD is imperative. Although the ASPREE trial was not designed specifically to address the impact of aspirin in persons with CKD, it nevertheless provided an opportunity to explore the potential benefits and harms of aspirin in this subset in an older community-dwelling population free of known CVD. However, the results of this analysis must be interpreted carefully, with particular care taken to avoid overinterpretation given the usual caveats and limitations that arise from post hoc exploratory analyses.

Four main findings can be derived from our exploratory analyses. First, event rates for all endpoints examined were substantially higher in participants with CKD compared with those without CKD, reflecting the well-known increased risk of CVD events in the CKD population, and implying that for a given aspirin effect characterized as a relative risk reduction, the absolute reduction in rates would be more substantial in the CKD population.[22] Second, we found no evidence of a differential effect of aspirin by the presence or absence of CKD on the ASPREE composite primary endpoint (ie, disability-free survival), all-cause mortality, or cardiovascular mortality, consistent with the overall findings of the ASPREE trial in older people.[9–11] Third, we found no evidence of differential aspirin effects on MACE rates by CKD status. Fourth, a similarly increased relative risk of clinically significant bleeding with aspirin was observed in participants with CKD and those without CKD.

Our findings indicate that although individuals with CKD have a markedly elevated risk of these outcomes, there is no evidence that aspirin reduced any of these events. We had maintained equipoise about the potential effect on mortality, given that there are theoretical reasons to posit that aspirin would or would not be associated with greater likelihood of disability-free survival. Although a recent meta-analysis also reported no association of aspirin with survival in patients with CKD,[14] the authors noted that had a single individual in the aspirin-treated group not died, a different conclusion would have resulted, suggesting that any conclusions about the effect of aspirin on survival in patients with CKD must be voiced with extreme caution. The present study lends further weight to the possibility that aspirin therapy does not improve survival in CKD patients.

We found no difference in the effect of aspirin on MACE by CKD status. There did appear to be weak evidence of a beneficial effect of aspirin on ischemic stroke, a component of MACE, in participants with CKD that was not present in those without CKD. The explanation for this finding is unclear and it should be viewed with caution. Two meta-analyses of antiplatelet therapy in individuals with CKD[14,24] did find point estimates generally <1 for fatal or nonfatal stroke in clinical trials, indicating reduced risk with antiplatelet agents, but confidence intervals were generally wide.

Unlike previous studies that suggested an increasingly strong benefit of aspirin on CVD events with decreasing eGFR in persons with hypertension,[17] we found no such evidence

when we examined the effects of aspirin by eGFR value. However, when CKD was characterized by the presence of albuminuria, it appeared that aspirin might confer a benefit in reducing the rates of MACE in those with albuminuria, a finding that appears to be consistent with recent data suggesting that albuminuria is a more potent predictor of CVD events than decreasing eGFR.[22] One potential explanation for these findings is that albuminuria is a marker of endothelial dysfunction and thus a more specific marker for cardiovascular risk.

Although the rates of clinically significant bleeding were higher in participants with CKD compared with those without CKD, consistent with CKD as an established risk factor for bleeding,[19] we did not find a differential effect of aspirin on the risk of bleeding in those with CKD or without CKD. This suggests that aspirin and CKD increase bleeding risk independently of each other and that no additive effect of aspirin exists, at least in this population with relatively modest degrees of CKD.

Further insights into the potential benefits and harms of aspirin in the population with CKD may come from a trial that has recently commenced. The ATTACK trial will be the first definitive trial of aspirin for primary CVD prevention in adults with CKD, examining whether the addition of low-dose (75 mg) aspirin to usual care reduces the risk of MACE and if so, to what extent any potential benefit outweighs any harm due to an increased risk of bleeding. Key differences between the ASPREE and ATTACK trials are that the latter will assess outcomes in all adult participants with CKD, not just in older participants. Additional differences are that in ATTACK, unlike in ASPREE, persons with congestive heart failure will be included and deaths from heart failure are included in the MACE definition. Thus, our study does not diminish the rationale for ATTACK, but instead will provide additional evidence when results emerge from that ongoing study.

There are some important limitations of this study to note. First, this analysis is a post hoc secondary analysis of ASPREE, which is not powered to definitively assess the presence of treatment heterogeneity of aspirin in CKD patients. Thus, there remains significant uncertainty in the results presented, and the interpretations that arise cannot be considered definitive. Second, multiple statistical comparisons were performed, and thus the potential for both type I and type II errors needs to be considered. Third, the definition of CKD relied on single measurements of both serum creatinine to determine eGFR and urine creatinine and albumin to assess UACR, whereas the KDIGO guidelines require follow-up measurement 3 months later to confirm a diagnosis of CKD.[25] As a result, misclassification of CKD may occur whereby a number of participants would not have had CKD confirmed in the required follow-up sample and thus should have been in the no CKD group. The misclassification of these participants at lower risk of CKD in the CKD group is likely to have led to point estimates being biased toward a null effect.

Strengths of the study include the large number of participants with CKD and without CKD, the long duration of follow-up, the detailed characterization of participants, and the systematic adjudication of all major outcome events in the trial.

In conclusion, in healthy older adults without established CVD, there was no difference in aspirin's effects on disability-free survival between individuals with CKD and those without CKD. Both groups experienced elevated bleeding risk with aspirin. Aspirin may confer benefit in reducing the risk of ischemic stroke in older people with CKD but not in the absence of CKD; in turn, this may manifest as differential aspirin effects on MACE in individuals with CKD relative to those without CKD. Because ASPREE was not specifically designed to address the question of the benefits and risks of aspirin in individuals with CKD, our findings must be considered hypothesis-generating, and as such, more definitive investigations in dedicated trials are eagerly awaited.

METHODS

Study design and population

Recruitment to the ASPREE trial took place in Australia and the USA between March 2010 and December 2014.[26] The details of the protocol and statistical analysis are described in detail elsewhere,[27] and recruitment details are provided in Section 1 of the Supplementary Material. Participants attended annual visits from randomization until the intervention period ended in June 2017.

In brief, participants were excluded if they had conditions likely to lead to death within 5 years, were demented or poorly functional, had a high bleeding risk, had a prior diagnosis of atherosclerotic CVD, were taking anticoagulants or antiplatelet agents, or were poorly adherent to therapy in the run-in period. Detailed exclusion criteria have been outlined elsewhere[26] and are summarized in Section 1 of the Supplementary Material.

Participants who met eligibility criteria at a screening study visit entered a 4-week placebo run-in phase. Participants who had ≥80% adherence during the run-in were randomly assigned, at a 1:1 ratio, to receive a 100-mg tablet of enteric-coated aspirin or matching placebo daily, according to a block randomization procedure with stratification by trial center (in the USA) or general practice clinic (in Australia) and age (65–79 years or ≥80 years). All participants, investigators, endpoint adjudicators, and study staff responsible for data collection were blinded to aspirin/placebo allocation.

Study measures

Participant demographic variables and health measures were assessed at baseline. Diabetes mellitus was defined by self-report, a fasting blood glucose ≥126 mg/dl, or treatment for diabetes. Hypertension was defined as the mean of 3 systolic blood pressure readings >160 mm/Hg or 3 diastolic blood pressure readings >90 mmHg, or by pharmacologic treatment for high blood pressure. Descriptions of specimen collection and laboratory processes for CKD measures are provided in Section 1 of the Supplementary Material. eGFR was calculated based on serum creatinine level using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[28]

CKD was defined using Kidney Disease: Improving Global Outcomes (KDIGO) criteria: eGFR <60 ml/min per 1.73 m^2 or spot UACR ≥3 mg/mmol with eGFR ≥60 ml/min per 1.73 m^2.[25] Participants with stage G5 CKD were excluded (eGFR <15 ml/min per 1.73 m^2, or

requiring dialysis at baseline, or with a self-reported history of kidney transplant). Participants missing baseline assessment of kidney function (i.e., absence of either eGFR or UACR) were also excluded.

Endpoints.—The first endpoint of interest for this analysis was a composite of dementia, persistent physical disability, or death.[9,10] Dementia diagnoses were adjudicated by experts blinded to treatment assignment and according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.[29] Persistent physical disability was considered present when a participant reported an inability to perform, or severe difficulty performing, at least 1 of the 6 basic activities of daily living on 2 consecutive occasions 6 months apart.[30] Adjudicators examined the progression of the final illness or incident and assigned an underlying cause of death, which was considered the single disease most likely to have initiated the trajectory toward death.[11]

MACE, the second endpoint of interest, was defined as a composite of death due to coronary heart disease, nonfatal myocardial infarction, and fatal and nonfatal ischemic stroke, but not including deaths from heart failure. Fatal coronary heart disease included fatal myocardial infarction, sudden cardiac death, and other deaths in which the underlying cause was considered to be coronary heart disease. The definition of nonfatal myocardial infarction was based on joint guidelines from the European Society of Cardiology and the American College of Cardiology.[31] Nonfatal ischemic stroke was defined according to the World Health Organization[32] as rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting >24 hours (unless interrupted by surgery or death) with no apparent cause other than vascular disease (specifically ischemic). Fatal ischemic stroke was defined as any death due to an underlying cause of vascular obstruction of an intracranial vessel with associated infarction. In both Australia and the USA, source documentation including clinical notes, hospitalization records, and imaging (computed tomography scan or magnetic resonance imaging) reports were requested for events suspected of being ASPREE study endpoints. Cardiovascular events were adjudicated by experts blinded to treatment assignment.

The third endpoint of interest was clinically significant bleeding, defined as hemorrhagic stroke, symptomatic intracranial bleeding, or extracranial clinically significant bleeding (defined as bleeding requiring transfusion, hospitalization or prolongation of hospitalization, or surgery, or causing death).[10,33] Bleeding events were adjudicated by experts blinded to treatment assignment.[33]

Other endpoints of interest for the current analysis were fatal and nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, cardiovascular death, and all-cause mortality.

Statistical analysis

All data are presented as number (percentage), mean ± 1 SD, or median (interquartile range), as appropriate. In the intention-to-treat analyses for the time-to-event endpoint, Cox proportional hazards models were used to compare the aspirin group with the placebo group in participants with and without prevalent CKD at baseline. An interaction between randomized group and CKD status tested whether the aspirin effect could be assumed to be

equal in participants with CKD and those without CKD. Cause-specific hazards were used for comparisons, with deaths from causes other than those included in the endpoint of interest treated as censoring events.[34] Proportional hazards assumptions were tested as a null hypothesis of a zero slope in a regression model of scaled Schoenfeld residuals against time.

Cumulative incidence was used to show event risk. The cumulative incidence was based on competing-risk regression models, stratified according to trial group, which allowed for the competing risk of death from causes other than those included in the endpoint of interest.

The effect of aspirin on endpoints of interest was examined by characterizing CKD according to increasing albuminuria (UACR ≥3 mg/mmol) and decreasing eGFR (≥60, 45–59, or <45 ml/min per 1.73 m^2). Effects of aspirin in participants with CKD were also examined by CKD risk factors of interest, including sex, race/ethnicity, country of residence, diabetes, hypertension, previous use of aspirin at baseline, and use at baseline of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or nonsteroidal anti-inflammatory drugs.

As these analyses were not prespecified subgroup analyses of ASPREE, estimates of aspirin effect are not presented with *P*-values and 95% confidence intervals were not adjusted for multiple comparisons. All analyses were conducted using Stata MP 15 (StataCorp, College Station, TX).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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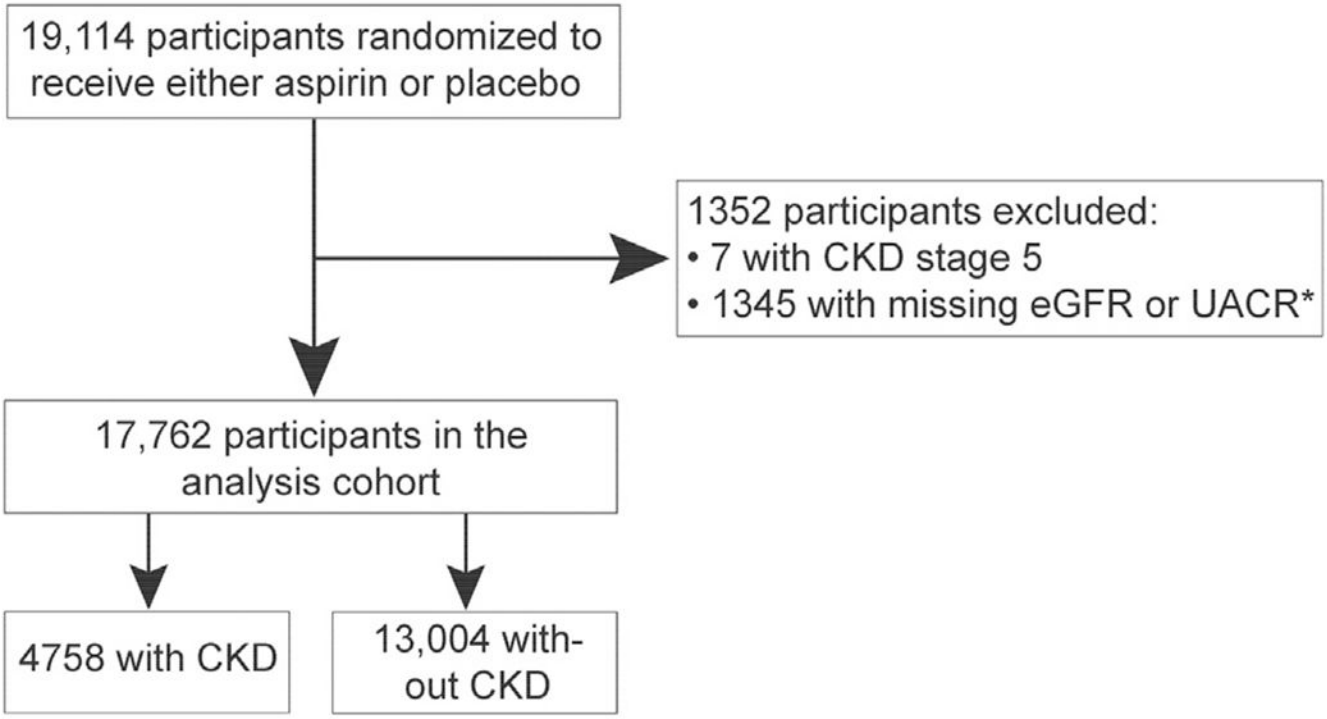

Figure 1. Inclusion of participants in analysis and chronic kidney disease (CKD) status.

*A total of 983 missing urine albumin:creatinine ratio (UACR); an additional 362 missing estimated glomerular filtration rate (eGFR); 104 missing both.

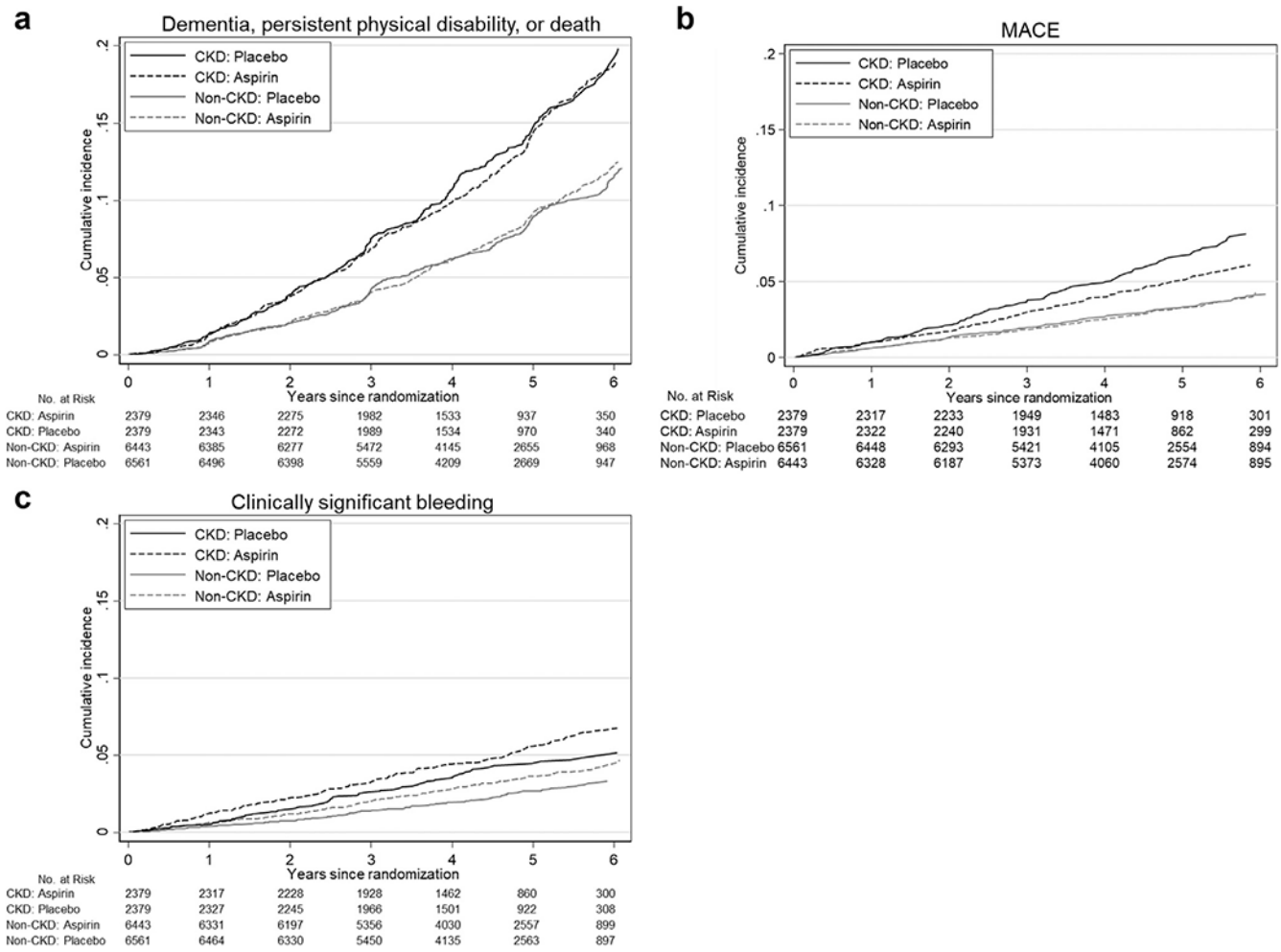

Figure 2.

Cumulative incidence in the aspirin and placebo groups of (a) dementia, persistent physical disability or death; (b) major adverse cardiovascular events (MACE: coronary heart disease death, nonfatal myocardial infarction, or nonfatal ischemic stroke), and (c) clinically significant bleeding. CKD, chronic kidney disease.

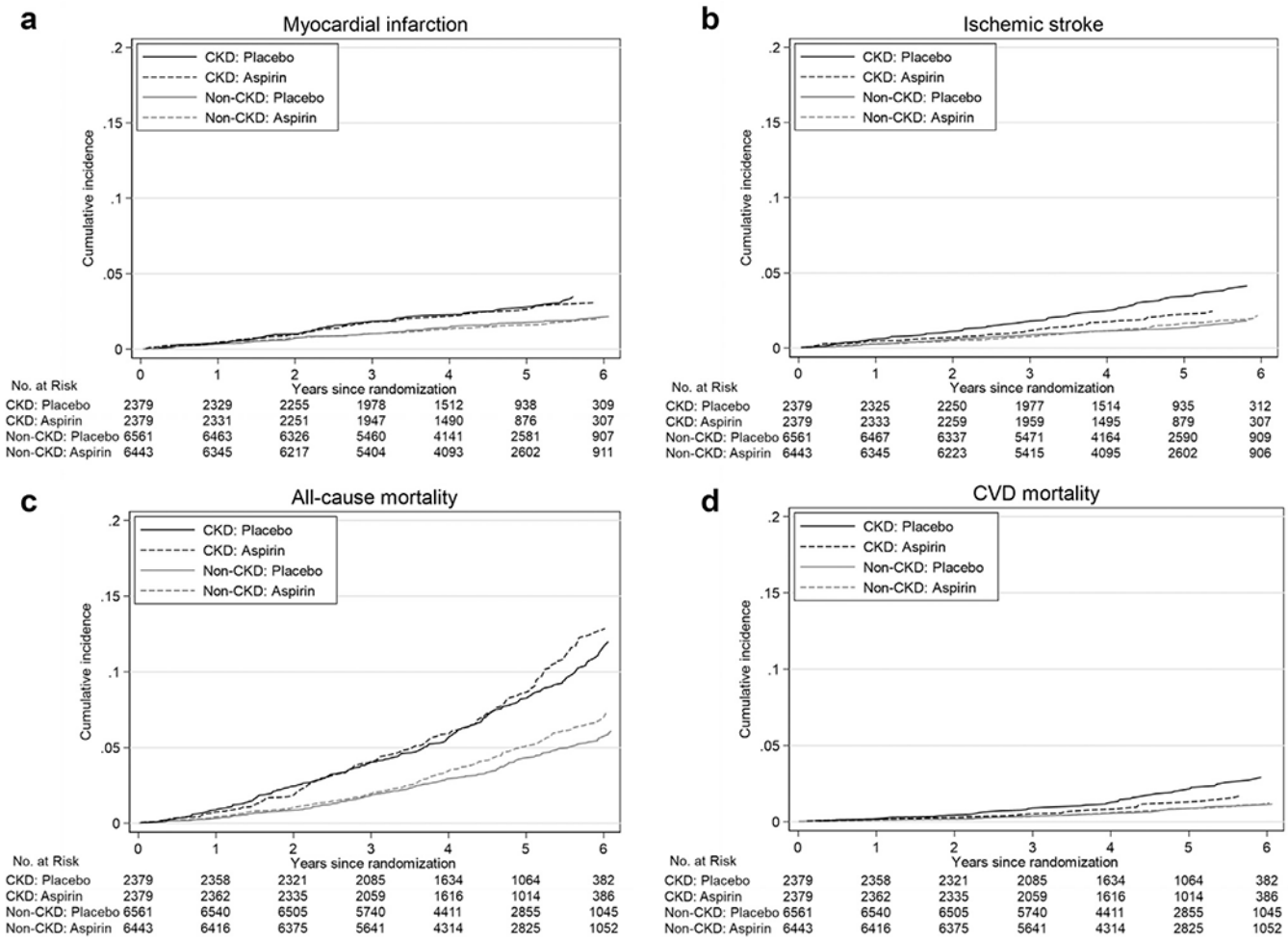

Figure 3.

Cumulative incidence in the aspirin and placebo groups of (a) myocardial infarction, (b) ischemic stroke, (c) all-cause mortality, and (d) cardiovascular mortality. CKD, chronic kidney disease.

Table 1 |

Baseline characteristics of the 4758 ASPREE trial participants with chronic kidney disease, overall and by treatment group

Characteristic	Aspirin (N = 2379)	Placebo (N = 2379)	Overall (N = 4758)
Female sex, n (%)	1345 (57)	1355 (57)	2700 (57)
Age, yr, n (%)			
65–69	59 (2)	62 (3)	121 (3)
70–74	1059 (45)	1025 (43)	2084 (44)
75–79	650 (27)	662 (28)	1312 (28)
80–84	436 (18)	451 (19)	887 (19)
≥85	175 (7)	179 (8)	354 (7)
Country of residence, n (%)			
Australia	2030 (85)	2049 (86)	4079 (86)
USA	349 (15)	330 (14)	679 (14)
Ethnicity/race, n (%)			
White Australian	1991 (84)	2003 (84)	3994 (84)
White USA	177 (7)	144 (6)	321 (7)
African American	115 (5)	135 (6)	250 (5)
Hispanic	65 (3)	58 (2)	123 (3)
Other	31 (1)	39 (2)	70 (1)
Living situation, n (%)			
Home alone	885 (37)	852 (36)	1737 (37)
Home with family, friends, spouse	1480 (62)	1510 (63)	2990 (63)
Residential home	14 (1)	17 (1)	31 (1)
Years of education, n (%)			
<12	1159 (49)	1101 (46)	2260 (47)
12–15	703 (30)	708 (30)	1411 (30)
≥16	517 (22)	570 (24)	1087 (23)
Smoking status, n (%)			
Current	82 (3)	113 (5)	195 (4)
Former	1006 (42)	955 (40)	1961 (41)
Never	1291 (54)	1311 (55)	2602 (55)
Alcohol use, n (%)			
Current	1730 (73)	1731 (73)	3461 (73)
Former	160 (7)	164 (7)	324 (7)
Never	489 (21)	484 (20)	973 (20)
Body mass index, kg/m^2, n (%)			
<20	42 (2)	47 (2)	89 (2)
20–24.9	517 (22)	493 (21)	1010 (21)
25–29.9	999 (42)	1066 (45)	2065 (44)
≥30	811 (34)	762 (32)	1573 (33)

Characteristic	Aspirin (N = 2379)	Placebo (N = 2379)	Overall (N = 4758)
Diabetes mellitus, n (%)	360 (15)	365 (15)	725 (15)
Hypertension, n (%)	1974 (83)	1987 (84)	3961 (83)
Dyslipidemia, n (%)	1594 (67)	1613 (68)	3207 (67)
Personal cancer history, n (%)	496 (21)	522 (22)	1018 (21)
Frailty, n (%)			
Not frail	1216 (51)	1247 (52)	2463 (52)
Prefrail	1078 (45)	1063 (45)	2141 (45)
Frail	85 (4)	69 (3)	154 (3)
Previous regular aspirin use, n (%)	285 (12)	288 (12)	573 (12)
NSAID use at baseline, n (%)	334 (14)	329 (14)	663 (14)
PPI use at baseline, n (%)	630 (26)	637 (27)	1267 (27)
Family history of kidney disease, n (%)	199 (8)	163 (7)	362 (8)
KDIGO eGFR category, ml/min/m^2			
G1, ≥90	76 (3)	71 (3)	147 (3)
G2, 60 to <90	659 (28)	680 (29)	1339 (28)
G3a, 45 to <60	1346 (57)	1344 (56)	2690 (57)
G3b, 30 to <45	274 (12)	265 (11)	539 (11)
G4, 15 to <30	24 (1)	19 (1)	43 (1)
KDIGO albuminuria, mg/mmol, n (%)			
A1, <3	1369 (58)	1343 (56)	2712 (57)
A2, 3–30	933 (39)	970 (41)	1903 (40)
A3, >30	77 (3)	66 (3)	143 (3)
ACE/ARB, n (%)	1243 (52)	1222 (51)	2465 (52)
Aldosterone antagonist, n (%)	22 (1)	21 (1)	43 (1)
Any ACE/ARB/aldosterone antagonist, n (%)	1254 (53)	1236 (52)	2490 (52)

ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Table 2 |

Rates of events in participants with and without CKD, compared by randomized treatment group

	CKD, eGFR <60 ml/min/m^2 or UACR ≥3 mg/mmol (N = 4758)					No CKD, eGFR ≥60 ml/min/m^2 and UACR 3 mg/mmol (N = 13,004)					
	Aspirin		Placebo			Aspirin		Placebo			
Events	*n*[a]	Rate[b]	*n*[a]	Rate[b]	HR (95% CI)	*n*[a]	Rate[b]	*n*[a]	Rate[b]	HR (95% CI)	CKD vs. no CKD, interaction *P* value
Dementia, persistent physical disability, or death	323	30.2	336	31.3	0.97 (0.83–1.12)	546	18.6	529	17.8	1.05 (0.93–1.18)	0.42
MACE	114	11.0	149	14.2	0.77 (0.61–0.99)	196	6.8	203	6.9	0.98 (0.80–1.19)	0.14
Clinically significant bleeding	121	11.7	96	9.1	1.28 (0.98–1.68)	213	7.4	157	5.4	1.38 (1.12–1.70)	0.67
Myocardial infarction[c]	61	5.8	66	6.2	0.94 (0.66–1.33)	99	3.4	107	3.6	0.94 (0.71–1.23)	0.99
Ischemic stroke[c]	46	4.4	74	7.0	0.63 (0.44–0.91)	94	3.2	87	3.0	1.10 (0.82–1.47)	0.02
All-cause mortality	211	19.1	197	17.7	1.08 (0.89–1.32)	314	10.5	266	8.7	1.20 (1.02–1.41)	0.43
Cardiovascular mortality	29	2.6	47	4.2	0.63 (0.39–0.99)	55	1.8	51	1.7	1.10 (0.75–1.61)	0.07

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MACE, major adverse cardiovascular events; UACR, urine albumin:creatinine ratio

[a] *n* = number of events.

[b] Per 1000 person-years.

[c] Fatal and nonfatal.

Table 3 |

Rates of the composite endpoint of dementia, persistent physical disability, or death; MACE; and clinically significant bleeding, in aspirin and placebo randomized groups and by participant subgroups defined by the presence of albuminuria and eGFR stage

	Aspirin		Placebo			
Endpoints	**n**	**Rate[a]**	**n**	**Rate[a]**	**Aspirin vs. placebo, HR (95% CI)**	**Interaction *P* value**
Dementia, persistent physical disability, or death						
UACR <3 mg/mmol death	715	20.1	691	19.3	1.04 (0.94–1.16)	0.29
UACR ≥3 mg/mmol	154	34.3	174	37.7	0.92 (0.74–1.14)	
eGFR ≥60 ml/min per 1.73 m^2	643	19.7	637	19.2	1.03 (0.92–1.14)	0.67
eGFR 45–59 ml/min per 1.73 m^2	180	29.8	176	29.1	1.02 (0.83–1.26)	
eGFR <45 ml/min per 1.73 m^2	46	34.0	52	40.1	0.85 (0.57–1.26)	
MACE						
UACR <3 mg/mmol	263	7.5	268	7.6	0.99 (0.84–1.17)	0.01
UACR ≥3 mg/mmol	47	10.8	84	18.7	0.58 (0.41–0.83)	
eGFR ≥60 ml/min per 1.73 m^2	224	7.0	251	7.7	0.91 (0.76–1.08)	0.90
eGFR 45–59 ml/min per 1.73 m^2	70	11.9	84	14.2	0.84 (0.61–1.15)	
eGFR <45 ml/min per 1.73 m^2	16	12.2	17	13.3	0.93 (0.47–1.84)	
Clinically significant bleeding						
UACR <3 mg/mmol	268	7.7	197	5.6	1.38 (1.15–1.66)	0.59
UACR ≥3 mg/mmol	66	15.3	56	12.4	1.24 (0.87–1.77)	
eGFR ≥60 ml/min per 1.73 m^2	256	8.0	197	6.0	1.33 (1.10–1.60)	0.65
eGFR 45–59 ml/min per 1.73 m^2	62	10.5	48	8.0	1.30 (0.89–1.89)	
eGFR <45 ml/min per 1.73 m^2	16	12.4	8	6.2	1.98 (0.85–4.63)	

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MACE, major adverse cardiovascular event; UACR, urinary albumin:creatinine ratio.

[a]Per 1000 person-years.

Table 4 |

Rates of myocardial infarction, ischemic stroke, all-cause mortality, and cardiovascular mortality in aspirin and placebo groups by subgroups of 17,762 participants defined by presence of albuminuria and eGFR stage

	Aspirin		Placebo			Interaction
Parameter	**n**	**Rate[a]**	**n**	**Rate[a]**	**Aspirin vs. placebo, HR (95% CI)**	***P* value**
Myocardial infarction						
UACR <3 mg/mmol	135	3.8	140	4.0	0.97 (0.77–1.23)	0.47
UACR ≥3 mg/mmol	25	5.7	33	7.2	0.79 (0.47–1.34)	
eGFR ≥60 ml/min per 1.73 m^2	112	3.5	123	3.8	0.93 (0.72–1.20)	0.75
eGFR 45–59 ml/min per 1.73 m^2	41	6.9	40	6.7	1.03 (0.67–1.59)	
eGFR <45 ml/min per 1.73 m^2	7	5.3	10	7.7	0.69 (0.26–1.82)	
Ischemic stroke						
UACR <3 mg/mmol	121	3.4	117	3.3	1.04 (0.81–1.35)	0.01
UACR ≥3 mg/mmol	19	4.3	44	9.7	0.45 (0.26–0.77)	
eGFR ≥60 ml/min per 1.73 m^2	107	3.3	117	3.6	0.93 (0.72–1.21)	0.50
eGFR 45–59 ml/min per 1.73 m^2	26	4.3	38	6.4	0.69 (0.42–1.13)	
eGFR <45 ml/min per 1.73 m^2	7	5.3	6	4.6	1.13 (0.38–3.38)	
All-cause mortality						
UACR <3 mg/mmol	423	11.6	358	9.7	1.20 (1.04–1.38)	0.32
UACR ≥3 mg/mmol	102	21.9	105	21.7	1.03 (0.78–1.35)	
eGFR ≥60 ml/min per 1.73 m^2	378	11.3	330	9.7	1.17 (1.01–1.36)	0.66
eGFR 45–59 ml/min per 1.73 m^2	110	17.6	105	16.8	1.05 (0.80–1.37)	
eGFR <45 ml/min per 1.73 m^2	37	26.7	28	20.8	1.29 (0.79–2.11)	
Cardiovascular mortality						
UACR <3 mg/mmol	69	1.9	73	2.0	0.96 (0.69–1.33)	0.26
UACR ≥3 mg/mmol	15	3.2	25	5.2	0.63 (0.33–1.20)	
eGFR ≥60 ml/min per 1.73 m^2	64	1.9	62	1.8	1.06 (0.74–1.50)	0.14
eGFR 45–59 ml/min per 1.73 m^2	14	2.2	27	4.3	0.52 (0.27–0.99)	
eGFR <45 ml/min per 1.73 m^2	6	4.3	9	6.7	0.66 (0.24–1.86)	

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MACE, major adverse cardiovascular event; UACR, urinary albumin:creatinine ratio.

[a] Per 1000 person-years.