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Effect of Aspirin on CKD Progression in Older Adults: Secondary Analysis From the ASPREE Randomized Clinical Trial

To the Editor:

Aspirin is a commonly prescribed and "over-the-counter" therapy in older persons. While its use in the secondary prevention of cardiovascular disease (CVD) events is well established,[1] aspirin is not recommended for primary CVD prevention in adults aged 60 years or older.[2] Low-dose aspirin increases the risk of bleeding in older persons,[3] but whether it has any effect on kidney function is not clear.[4,5]

We sought to investigate the effect of low-dose aspirin on kidney function in healthy older persons enrolled in the Aspirin in Reducing Events in the Elderly (ASPREE) trial (Clinicaltrials.gov identifier, NCT01038583).[6] ASPREE was a large double-blind, randomized, placebo-controlled trial designed to assess whether daily treatment with 100 mg of enteric-coated aspirin could extend the duration of life free of dementia and persistent physical disability.

The aim of the present study was to compare the trajectory of kidney measures, namely estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio (UACR), in participants randomized to aspirin treatment or placebo from the trial's commencement until its cessation.

In brief, 19,114 healthy community-dwelling individuals aged ≥70 years (aged ≥65 years for African American and Hispanic participants in the United States) were recruited in Australia and in the United States. Recruitment took place from March 2010 through December 2014, with annual assessments conducted from randomization until the intervention period ended in June 2017 (median follow-up, 4.7 years). Participants were randomly assigned to receive a 100 mg tablet of enteric-coated aspirin or matching placebo daily in double-blind fashion. For this analysis, 7 participants with stage G5 chronic kidney disease[7] were omitted, as were 1,349 participants missing baseline kidney measures. Full details, including the ASPREE trial protocol and main results, are reported in detail elsewhere and in Item S1.[6,8,9]

Table 1. Baseline Characteristics of the Participants Randomized to Aspirin Versus Placebo

	Placebo (n = 8,938)	Aspirin (n = 8,820)
Age at randomization, y	75.1 ± 4.5	75.2 ± 4.6
Female sex	5,035 (56.3%)	4,987 (56.5%)
Ethnicity		
White/Australia	7,600 (85.0%)	7,514 (85.2%)
White/United States	531 (5.9%)	525 (6.0%)
Black	435 (4.9%)	438 (5.0%)
Hispanic	236 (2.6%)	227 (2.6%)
Other/unknown	136 (1.5%)	116 (1.3%)
Location: Australia (vs United States)	7,770 (86.9%)	7,653 (86.8%)
Smoking history		
Never smoked	4,923 (55.1%)	4,869 (55.2%)
Former smoker	3,655 (40.9%)	3,619 (41.0%)
Current smoker	360 (4.0%)	332 (3.8%)
Alcohol intake		
Current	6,840 (76.5%)	6,758 (76.6%)
Never	1,563 (17.5%)	1,528 (17.3%)
Former	535 (6.0%)	534 (6.1%)
Diabetes mellitus	950 (10.6)	964 (10.9%)
Hypertension		
No	2,278 (25.5%)	2,286 (25.9%)
Yes; on medication, normal BP	2,208 (24.7%)	2,170 (24.6%)
Yes; on medication, high BP	2,466 (27.6%)	2,488 (28.2%)
Yes; not on medication, high BP	1,986 (22.2%)	1,876 (21.3%)
Systolic BP, mm Hg	139 ± 17	139 ± 16
Diastolic BP, mm Hg	77 ± 10	77 ± 10
Frailty		
Not frail	5,246 (58.7%)	5189 (58.8%)
Pre-frail	3,509 (39.3%)	3425 (38.8%)
Frail	183 (2.0%)	206 (2.3%)
BMI category[a]		
Underweight: <20 kg/m^2	162 (1.8%)	171 (1.9%)
Normal: 20-<25 kg/m^2	2,143 (24.1%)	2,164 (24.6%)
Overweight: 25-<30 kg/m^2	3,970 (44.6%)	3,864 (44.0%)
Obese: ≥30 kg/m^2	2,619 (29.4%)	2,587 (29.4%)
BMI, kg/m^2[a]	28.1 ± 4.7	28.1 ± 4.8
eGFR, mL/min/1.73 m^2	73.0 ± 13.9	72.9 ± 14.0
UACR, mg/mmol	0.8 [0.5-1.5]	0.8 [0.5-1.5]
Baseline eGFR < 60 mL/min/1.73 m^2	1,615 (18.1%)	1,637 (18.6%)
Baseline albuminuria	1,035 (11.6%)	1,010 (11.5%)

Continuous variables given as mean ± SD or median [interquartile range]. eGFR calculated with Chronic Kidney Disease Epidemiology Collaboration equation. Abbreviations: BMI, body mass index; BP, blood pressure.
[a]Baseline BMI missing in n = 78.

Exposure was randomization to aspirin or placebo. Outcome measures were change in kidney function, assessed as annual eGFR decline and, separately, annual increase in UACR. No participant was documented as commencing dialysis or receiving a kidney transplant during the intervention period, and participants reaching sustained eGFR <15 mL/min/1.73 m^2 during the trial period were not removed from the analysis.

Linear mixed models were used, which included the group (randomized aspirin vs placebo, ie, intention to treat), annual visit number (0 [baseline], 1, 2, 3, 4, 5, and 6 years; referred to as "time"), a participant-specific intercept (baseline eGFR or UACR), and a participant-specific slope describing change in eGFR or UACR over time (per annual visit). A treatment-by-time interaction was included to examine whether the trajectory of eGFR or UACR for an average participant differed between the treatment groups. As the UACR distribution was skewed, it was $\log_2$-transformed in all models. To account for dropout owing to death, a sensitivity analysis was performed using a shared random effect joint model for longitudinal eGFR or UACR and the overall survival outcome.[10] The survival component was modeled using a Cox proportional hazards model, adjusted for baseline age,

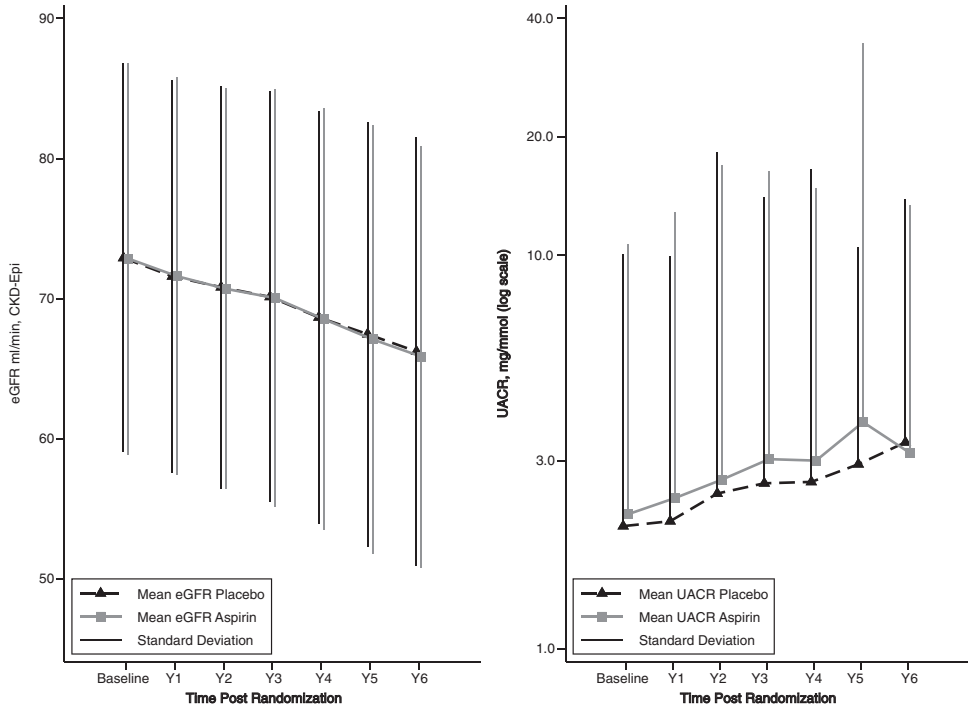

Figure 1. Mean eGFR and UACR by treatment allocation and study visit. Error bars represent 1 SD either side of the mean (eGFR) and above the mean (UACR). UACR y-axis has log scale.

sex, aspirin, diabetes, and time-dependent value of eGFR or UACR.

The primary analysis comprised 17,758 participants (Fig S1). Baseline characteristics were well matched across treatment arms (Table 1). The mean age of the cohort was 75.1 ± 4.5 (SD) years and 56.4% were female. The median number of eGFR and UACR values per patient were 5 (range, 1-7) and 4 (range, 1-7), respectively. Among participants included in the primary analysis, 983 deaths occurred (523 in the aspirin group, 460 in the placebo group).

Summary measures over time for eGFR and UACR, by treatment assignment, are shown in Fig 1. Results of the mixed models are in Table S1. Mean annual eGFR decline was not different in participants randomized to aspirin (−0.97 [95% CI, −1.02 to −0.92] mL/min/1.73 m^2) compared with those randomized to placebo (−0.99 [95% CI, −1.04 to −0.94] mL/min/1.73 m^2; P for interaction = 0.6). Likewise, annual increase in UACR was similar in participants randomized to aspirin (mean $\log_2$(UACR), 0.055 [95% CI, 0.050-0.059]) compared with placebo (0.051 [95% CI, 0.046-0.056]; P for interaction = 0.3). Results of the joint longitudinal and survival models for both outcomes are in Table S2. Results were all consistent with the results of the main analysis models, with no evidence of an effect of aspirin treatment on either eGFR decline or UACR increase over time, allowing for loss to follow-up owing to mortality.

In summary, we found no evidence of an effect of aspirin on kidney measure trajectories, as assessed separately by eGFR and UACR, in healthy community-dwelling older persons, over an average of nearly 5 years of follow-up. The results of our study, the largest-available trial of older individuals receiving aspirin compared with placebo, suggests that fears over decline in kidney function associated with low-dose aspirin among older individuals may not be justified.

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Supplementary Material

Supplementary File (PDF)

Figure S1; Item S1; Tables S1-S2.

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Dialysis Prevalence in Zimbabwe: A Cross-sectional Descriptive Study

To the Editor:

The contribution of chronic kidney disease (CKD) to the global burden of disease is growing, accounting for an estimated 1.2 million deaths worldwide in 2017.[1,2] In the low- and lower-middle-income countries of sub-Saharan Africa, such as Zimbabwe, the burden of CKD is poorly understood, with little data on even the most severe form, kidney failure. This poverty of data was highlighted by the recent Assessment of Global Kidney Health Atlas being unable to report a prevalence of treated kidney failure across most of Africa, including Zimbabwe.[3]

The Dialysis in Zimbabwe (DIAZ) project was designed to collect and report on prevalence, incidence, characteristics, and outcomes of treated kidney failure patients. All dialysis patients in Zimbabwe were approached for participation in February 2018, with participants providing written informed consent. The study had an observational cohort design and used World Bank population estimates for the year 2018 as the denominator in describing prevalence (Item S1). Ethics approval was granted by the Medical Research Council of Zimbabwe (approval number MRCZ/A/2202).

The 16 participating dialysis units are located across Zimbabwe's major cities (Fig 1, Table S1), with the majority in the capital, Harare. Peritoneal dialysis (PD)