Aspirin for Primary and Secondary Prevention of Mortality, Cardiovascular Disease, and Kidney Failure in the Chronic Renal Insufficiency Cohort (CRIC) Study

Jonathan J. Taliercio, Georges Nakhoul, Ali Mehdi, Wei Yang, Daohang Sha, Jesse D. Schold, Scott Kasner, Matthew Weir, Mohamed Hassanein, Sankar D. Navaneethan, Geetha Krishnan, Radhika Kanthety, Alan S. Go, Rajat Deo, Claudia M. Lora, Bernard G. Jaar, Teresa K. Chen, Jing Chen, Jiang He, and Mahboob Rahman; on behalf of the CRIC study Investigators

Rationale and Objective: Chronic kidney disease is a risk enhancing factor for cardiovascular disease (CVD) and mortality, and the role of aspirin use is unclear in this population. We investigated the risk and benefits of aspirin use in primary and secondary prevention of CVD in the Chronic Renal Insufficiency Cohort Study.

Study Design: Prospective observational cohort.

Setting & Participants: 3,664 Chronic Renal Insufficiency Cohort participants.

Exposure: Aspirin use in patients with and without preexisting CVD.

Outcomes: Mortality, composite and individual CVD events (myocardial infarction, stroke, and peripheral arterial disease), kidney failure (dialysis and transplant), and major bleeding.

Analytical Approach: Intention-to-treat analysis and multivariable Cox proportional hazards model to examine associations of time varying aspirin use.

Results: The primary prevention group was composed of 2,578 (70.3%) individuals. Mean age was 57 ± 11 years, 46% women, 42% Black, and 47% had diabetes. The mean estimated glomerular filtration rate was 45 mL/min/1.73 m². Median follow-up was 11.5 (IQR, 7-13) years. Aspirin was not associated with all-cause mortality in those without preexisting cardiovascular disease (CVD) (HR, 0.84; 95% CI, 0.7-1.01; P = 0.06) or those with CVD (HR, 0.88; 95% CI, 0.77-1.02; P = 0.08). Aspirin was not associated with a reduction of the CVD composite in primary prevention (HR, 0.97; 95% CI, 0.77-1.23; P = 0.79) and in secondary prevention because the original study design was not meant to study the effects of aspirin.

Limitations: This is not a randomized controlled trial, and therefore, causality cannot be determined.

Conclusions: Aspirin use in chronic kidney disease patients was not associated with reduction in primary or secondary CVD events, progression to kidney failure, or major bleeding.

Chronic kidney disease (CKD) is a risk enhancing factor for cardiovascular disease (CVD) and is the leading cause of death in this population. In the general population, low-dose aspirin (75-100 mg/d) is effective in secondary prevention of CVD. As a result, major guidelines recommend low-dose aspirin in patients with CKD for secondary prevention of CVD and avoidance of aspirin for primary prevention and those at increased risk of bleeding. However, data to support its use in the CKD population is lacking because of the exclusion or underrepresentation of patients with CKD in clinical trials.

The use of aspirin in primary prevention in the non-CKD population has been tempered after the publication of the Aspirin in Reducing Events in the Elderly (ASPREE) Trial. Based on these results, 2 major professional societies have amended their recommendations. The 2021 US Preventive Services Task Force recommended low-dose aspirin use for the primary prevention of CVD in adults aged 50-59 years who have a 10% or greater 10-year CVD risk, not at increased risk for bleeding and have a life expectancy of at least 10 years. The CKD population is not addressed in the US Preventive Services Task Force guidelines. The 2019 American College of Cardiology/American Heart Association guidelines suggest that low-dose aspirin should not be used for primary prevention in patients aged greater than or equal to 70 years or in individuals who have an increased bleeding risk. The guideline identifies CKD, estimated glomerular filtration rate (eGFR) 15-59 mL/min/1.73 m² with or without albuminuria, as a higher risk. The Atherosclerotic Cardiovascular Disease risk calculator excludes CKD staging or eGFR as an imputable variable, and Framingham Risk Score and Pooled Cohort equations have, at best, moderate performance in patients with CKD, which makes risk stratification especially challenging. Therefore, clinicians may not be able to accurately risk stratify patients with CKD. In addition to the potential lack of benefit of aspirin in primary prevention of CVD in patients with CKD, there may be harm from an increased risk of bleeding and progression of CKD.

The aim of this study is to assess the risk and benefits of aspirin therapy in primary and secondary prevention of mortality, CVD events, progression to kidney failure, and major bleeding in the Chronic Renal Insufficiency Cohort (CRIC) Study.
PLAIN-LANGUAGE SUMMARY
Traditionally, aspirin has been recommended for the prevention of primary and secondary cardiovascular disease and death in the general population and in high-risk groups such as patients with chronic kidney disease (CKD). Recent emerging data suggests a lack of benefit in the primary prevention of cardiovascular disease (CVD) and an increased bleeding risk in the general population. To date, many studies exclude patients with CKD, who are at higher CVD risk. This study evaluates the risks and benefit of aspirin in CVD risk reduction in people with moderate to severe CKD enrolled in the Chronic Renal Insufficiency Cohort Study. We found that aspirin use in patients with CKD was not associated with reduction in primary or secondary CVD, progression to kidney failure, or major bleeding.

METHODS
Study Population
We used the CRIC study dataset from 2003-2018 to study the effects of aspirin use in CKD patients. Of the 3,939 CRIC phase 1 participants, 28 with missing data, 146 on dual antiplatelet therapy (aspirin and P2Y12), and 101 on P2Y12 monotherapy and were excluded from analysis (Fig 1). Because of the small sample size of the latter 2 groups, we did not perform further analysis of these subgroups. The prospective, observational CRIC study design and participant characteristics have been previously published. Briefly, the CRIC study enrolled 3,939 adults from the initial enrollment period with eGFR 20-70 mL/min per 1.73 m² from 7 clinical centers throughout the United States. Major criteria excluded people with transplant, polycystic kidney disease, glomerulonephritis on active immunosuppression, New York Heart Association class III-IV heart failure, and cirrhosis. The institutional review board (#5969) approved the study protocol and all participants signed written consent.

Event Ascertainment
The major aims of the CRIC study were to examine the determinants of CKD progression, CVD, and mortality. All CRIC participants had annual in-person visits followed by a phone follow-up every 6 months. During the annual in-person visit, participants had blood samples taken and underwent reviews of medication, medical history, and hospitalizations. Clinical event history was obtained during the in-person visit and 6-month phone call. CRIC investigators retrieved and collected all relevant medical records, which included the International Classification of Diseases, Ninth/Tenth Revision (ICD-9/10) hospital discharge codes. Codes from medical records were used to identify major bleeding events. Acceptable ICD 9/10 codes for major bleeding in CKD patients have been previously published and used for our analysis. The CRIC Adjudication Committee reviewed all deidentified medical records to determine cardiovascular, cerebrovascular, and kidney clinical endpoints. Time and cause of death were ascertained through the National Death Index. Kidney failure status and timing were confirmed using the US Renal Data System.

CRIC Phase I
N = 3939

Excluded
28 Missing Baseline Aspirin Use
101 on P2Y12 Monotherapy
146 on Dual Antiplatelet Therapy

Cohort at Baseline
N = 3664

Primary Prevention
N = 2578

Secondary Prevention
N = 1086

Non-Aspirin Use at Baseline
N = 1708

Aspirin Use at Baseline
N = 870

Non-Aspirin Use at Baseline
N = 425

Aspirin Use at Baseline
N = 661

Figure 1. Flowchart of patients. Abbreviation: CRIC, Chronic Renal Insufficiency Cohort.
**Primary Exposure and Outcome**

The primary exposure was self-reported aspirin use, which may change annually. Adjudicated clinical outcomes were ascertained at 6-month intervals and broadly grouped into composite and individual endpoints. The composite of CVD events included definite, probable, and possible acute myocardial infarction (MI), definite and probable stroke, and peripheral arterial disease. Peripherally arterial disease included amputation or revascularization. Stroke included hemorrhage (intraparenchymal, subarachnoid) and cerebral infarction. Patients who did not have a self-reported CVD event prior to CRIC enrollment were allocated to the primary prevention group. Kidney failure included either dialysis or kidney transplant. Cardiovascular death included death from atherosclerotic coronary heart disease, cerebrovascular, other atherosclerotic disease, and other cardiovascular disease. To explore a risk benefit analysis of aspirin use and risk of major bleed, we used previously accepted ICD-9/10 codes broadly grouped into upper and lower gastrointestinal bleeding, intracerebral bleed, subarachnoid bleed, and nontraumatic intracranial bleed.16

**Covariates**

Participants provided information on their medical history, current medication list, and hospitalizations during their baseline, subsequent in-person, and telephone visits. Demographics such as age, sex, and race/ethnicity, diabetes status, smoking status, and prior CVD disease was obtained at baseline and each study visit. During the baseline and annual office visit, anthropometric measurements, blood pressure, body mass index, and blood work was obtained. Serum creatinine was measured using standard assays, and eGFR was calculated using the CRIC equation.17 No serum creatinine measurements outside of the CRIC study were used. Additional assays performed at baseline included measurements of hemoglobin, hemoglobin A1C, 24-hour protein, serum albumin, low-density lipoprotein, high-density lipoprotein, phosphate, calcium, parathyroid hormone, and fibroblastic growth factor-23 levels and urine protein-to-creatinine ratio. Transthoracic echocardiogram was performed 1 year after enrollment, and when able, included data such as ejection fraction, left ventricular mass and index.

**Statistical Analysis**

The CRIC was analyzed using SAS. We compared the baseline characteristics of all participants who were self-reported as nonaspirin and aspirin users (Table S1). We also stratified participants into 2 groups at CRIC enrollment based on the absence of CVD (primary prevention) and the presence of CVD (secondary prevention) by aspirin use (Tables 1 and 2). The characteristics of the population were described using mean (standard deviation) or median (interquartile range [IQR]) for continuous variables and frequency and percentage for categorical variables. The comparisons were made between the aspirin and nonaspirin use groups using t test, Wilcoxon rank sum test, and \( \chi^2 \) test, as appropriate.

Because aspirin use may change over time, we analyzed the data by emulating the design and intention-to-treat analysis of the randomized trial.18 At each annual clinic visit, a study participant’s aspirin use is considered a separate assignment, and we aim to examine its association with outcomes during the entire subsequent follow-ups. Each participant contributed multiple records depending on the number of annual clinic visits. The maximum possible number of records from an individual was equal to the number of years of follow-up. Item S1 provides more detail on how the analytical dataset for the analysis was constructed. Cox proportional hazards model was used to evaluate the association of aspirin use at each annual visit and subsequent outcomes that included both composite and individual CVD outcomes, kidney failure, all-cause death, CVD mortality, and major bleeding, adjusting for covariates measured at the same clinic visit of aspirin assignment. Confounders were chosen a priori based on their association with CVD and mortality.19,20 The models were adjusted for sex, race/ethnicity, and time-updated covariates that included age, diabetic status, tobacco use, antihypertension drug use, systolic and diastolic blood pressure, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use, statin use, \( \beta \)-blocker use; fibroblastic growth factor-23, phosphorus, hemoglobin, low-density lipoprotein, high-density lipoprotein, and hemoglobin A1C levels; eGFR; and the symptom of easy bruising or bleeding. Urine protein-to-creatinine ratio was used to perform time-updated adjustments because albumin-to-creatinine ratios were only collected at the baseline visit. Because each individual may contribute multiple records depending on the number of annual clinic visits, the sandwich estimator was used for estimating the variance. We only considered the first incident event during the follow-up. In a sensitivity analysis, we examined the association of aspirin use with outcome ascertained starting at 1 year after the exposure, to reduce potential confounding.21,22 In both primary prevention and secondary prevention groups, subgroup analyses were completed in the following categories (age less than 65 or greater than or equal to 65 years old, sex, race, diabetic status, eGFR <30, 30-44, 45-59 or ≥60 mL/min/1.73 m², protein-to-creatinine ratio <0.15 or ≥0.15, and body mass index <30 or ≥30 kg/m²).

**RESULTS**

**Baseline Characteristics**

A total of 3,664 patients were identified and included in this analysis. Forty-two percent (n = 1,531) of the CRIC were taking aspirin at study entry, and approximately half reported aspirin use at each study visit (Fig S1). Seventy percent (n = 2,578) of the patients did not have preexisting CVD (primary prevention) (Table S1). At baseline, the primary prevention group compared with secondary prevention group were younger, female, had less diabetes and hypertension, and higher eGFR (Tables 1 and 2).
Table 1. Baseline Characteristics by Aspirin use in Primary Prevention Cohort

| Characteristics                          | Overall N = 2,578 | Nonaspirin N = 1,708 | Aspirin N = 870 | P  |
|------------------------------------------|-------------------|-----------------------|-----------------|----|
| Age, y                                    | 55.7 (11.7)       | 53.7 (12.2)           | 59.8 (9.5)      | < 0.01 |
| Female                                    | 1,242 (48.2%)     | 848 (49.6%)           | 394 (45.3%)     | 0.04 |
| Non-Hispanic White                       | 1,116 (43.3%)     | 713 (41.7%)           | 403 (46.3%)     | 0.01 |
| Non-Hispanic Black                       | 1,000 (38.8%)     | 659 (38.6%)           | 341 (39.2%)     | .    |
| Hispanic                                  | 353 (13.7%)       | 264 (15.5%)           | 89 (10.2%)      | .    |
| Other race                                | 109 (4.2%)        | 72 (4.2%)             | 37 (4.3%)       | .    |
| BMI, kg/m²                                | 31.7 (7.8)        | 31.5 (8.0)            | 32.2 (7.4)      | 0.02 |
| Comorbid conditions                       |                   |                       |                 |     |
| Hypertension                              | 2,139 (83.0%)     | 1,354 (79.3%)         | 785 (90.2%)     | < 0.001 |
| Diabetes                                  | 1,066 (41.3%)     | 585 (34.3%)           | 481 (55.3%)     | < 0.001 |
| Smoking status                            |                   |                       |                 |     |
| Current smoker                            | 307 (1.9%)        | 219 (12.8%)           | 88 (10.1%)      | 0.01 |
| Past smoker                               | 958 (37.2%)       | 596 (34.9%)           | 362 (41.6%)     | .    |
| Never smoker                              | 1,313 (50.9%)     | 893 (52.3%)           | 420 (48.3%)     | .    |
| Medications                               |                   |                       |                 |     |
| ACE inhibitor or ARB taker                | 1,665 (64.6%)     | 1,061 (62.1%)         | 604 (69.4%)     | < 0.001 |
| Statin taker                              | 1,172 (45.5%)     | 663 (38.8%)           | 509 (58.5%)     | < 0.001 |
| β-blocker taker                           | 982 (38.1%)       | 568 (33.3%)           | 414 (47.6%)     | < 0.001 |
| Measurements                              |                   |                       |                 |     |
| Systolic BP, mmHg                         | 126.9 (21.1)      | 125.9 (20.9)          | 128.9 (21.3)    | < 0.001 |
| Diastolic BP, mmHg                        | 72.7 (12.5)       | 73.8 (12.5)           | 70.7 (12.1)     | < 0.001 |
| Hemoglobin A1C, %                         | 6.45 (1.48)       | 6.32 (1.48)           | 6.68 (1.44)     | < 0.001 |
| eGFR, CRIC Equation, mL/min/1.73 m²       | 47.3 (17.6)       | 47.9 (18.3)           | 46 (16.1)       | 0.01 |
| Serum creatinine, mg/dL                   | 1.69 (0.59)       | 1.69 (0.60)           | 1.70 (0.57)     | 0.71 |
| 24-h urine protein, g/d (IQR)             | 0.2 (0.07-0.81)   | 0.2 (0.07-0.90)       | 0.1 (0.06-0.66) | < 0.001 |
| UACR, μg/mg (IQR)                         | 39.1 (73-392.8)   | 46.1 (79-450.1)       | 30 (64-312.9)   | < 0.01 |
| UPCR, mg/mg (IQR)                         | 0.1 (0.05-0.67)   | 0.1 (0.06-0.75)       | 0.1 (0.05-0.55) | 0.001 |
| Calcium, mg/dL                            | 9.2 (0.5)         | 9.2 (0.5)             | 9.2 (0.5)       | 0.44 |
| Serum phosphate, mg/dL                    | 3.7 (0.7)         | 3.7 (0.7)             | 3.7 (0.7)       | 0.50 |
| Serum albumin, g/dL                       | 4 (0.5)           | 4 (0.5)               | 4 (0.4)         | 0.37 |
| PTH, pg/mL (IQR)                          | 50 (33-83.0)      | 52 (33-84.1)          | 47 (32-80)      | 0.10 |
| Hemoglobin, g/dL                          | 12.7 (1.8)        | 12.8 (1.8)            | 12.6 (1.7)      | 0.06 |
| HDL, mg/dL                                | 48.8 (16.2)       | 49.2 (16.9)           | 48.1 (14.7)     | 0.09 |
| LDL, mg/dL                                | 106.8 (35.2)      | 110 (35.8)            | 100.4 (33.1)    | < 0.001 |
| LV mass index, Cornell                    | 49.5 (13)         | 48.7 (12.9)           | 51 (13.0)       | < 0.001 |
| Ejection fraction                         | 55.4 (7.1)        | 55.3 (6.9)            | 55.7 (7.3)      | 0.19 |

Note: Data are expressed as n (%) or mean (SD), unless otherwise indicated.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CRIC, Chronic Renal Insufficiency Cohort; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; LV, left ventricular; PTH, parathyroid hormone; SD, standard deviation; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

The primary prevention patients treated with aspirin were more likely to be older, men, patients taking statins, patients with hypertension, and patients with diabetes. Patients taking aspirin had a slightly lower eGFR (46 vs 48 mL/min/1.73 m²; P = 0.01), and proteinuria (0.1 vs 0.2 g/d; P < 0.001), with a higher usage of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Similarly, the secondary prevention group on aspirin also had more traditional CVD risk factors (Table 2).

**All-Cause and Cardiovascular Mortality**

In survival analysis using multivariable Cox models, aspirin was not associated with mortality in primary prevention (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.7-1.01; P = 0.06) and secondary prevention (HR, 0.88; 95% CI, 0.77 to 1.02; P = 0.08) (Table 3). Sensitivity analysis results using 1-year delayed aspirin exposure were similar (Table 4). In addition, aspirin was not associated with CVD mortality in primary prevention (HR, 1.12; 95% CI, 0.77 to 1.02; P = 0.56) or in secondary prevention (HR, 0.95; 95% CI, 0.74-1.21; P = 0.67) in both models (Tables 3 and 4).

**Cardiovascular Events (MI, Stroke, Peripheral Arterial Disease)**

In the multivariable analyses, aspirin use was not associated with CVD composite in the primary prevention cohort.
(HR, 0.97; 95% CI, 0.77-1.23; P = 0.79) and secondary prevention groups (HR, 1.08; 95% CI, 0.89-1.31; P = 0.46) (Tables 3 and 4). There was no benefit of aspirin in primary prevention of individual endpoints in stroke (HR, 0.72; 95% CI, 0.47-1.1; P = 0.13), MI (HR, 1.07; 95% CI, 0.79-1.45; P = 0.65), or peripheral arterial disease (HR, 1.3; 95% CI, 0.8-2.11; P = 0.29). Individual CVD endpoints findings were similar in patients who were taking aspirin for secondary prevention. There was no benefit or risk found in subgroup analysis for primary and secondary prevention groups presented in the forest plot (Figs 2 and 3).

Table 2. Baseline Characteristics by Aspirin Use in Secondary Prevention Cohort

| Characteristics, n (%) or Mean (SD) | Overall N = 1,086 | Nonaspirin N = 425 | Aspirin N = 661 | P |
|------------------------------------|------------------|------------------|----------------|---|
| **Age, y**                          |                  |                  |                |    |
| Male                               | 61.3 (8.3)       | 59.7 (8.8)       | 62.4 (7.8)     | <.001 |
| Non-Hispanic White                 | 428 (39.4%)      | 172 (40.5%)      | 256 (38.7%)    | 0.57 |
| Hispanic                           | 408 (37.6%)      | 130 (30.6%)      | 278 (42.1%)    | <.001 |
| Non-Hispanic Black                 | 531 (48.9%)      | 223 (52.5%)      | 308 (46.6%)    | .   |
| Other race                         | 108 (9.9%)       | 57 (13.4%)       | 51 (7.7%)      | .   |
| BMI, kg/m²                         | 32.9 (7.9)       | 33.3 (8.4)       | 32.7 (7.8)     | 0.21 |
| **Comorbid conditions**            |                  |                  |                |    |
| Hypertension                       | 997 (91.8%)      | 392 (92.2%)      | 605 (91.5%)    | 0.68 |
| Diabetes                           | 662 (61.0%)      | 235 (55.3%)      | 427 (64.6%)    | 0.01 |
| **Cardiovascular events**          |                  |                  |                |    |
| CHF                                | 691 (63.6%)      | 222 (52.2%)      | 469 (71%)      | <.001 |
| MI                                 | 211 (19.4%)      | 76 (17.9%)       | 135 (20.4%)    | 0.31 |
| Stroke                             | 302 (27.8%)      | 140 (32.9%)      | 162 (24.5%)    | 0.01 |
| **Smoking status**                 |                  |                  |                |    |
| Current smoker                     | 164 (15.1%)      | 79 (18.6%)       | 85 (12.9%)     | 0.02 |
| Past smoker                        | 553 (50.9%)      | 199 (46.8%)      | 354 (53.6%)    | .   |
| Never smoker                       | 369 (34.0%)      | 147 (34.6%)      | 222 (33.6%)    | .   |
| **Medications**                    |                  |                  |                |    |
| ACE inhibitor or ARB taker         | 838 (77.2%)      | 322 (75.8%)      | 516 (78.1%)    | 0.38 |
| Statin taker                       | 781 (71.9%)      | 251 (59.1%)      | 530 (80.2%)    | <.001 |
| β-blocker taker                    | 768 (70.7%)      | 281 (66.1%)      | 487 (73.7%)    | 0.01 |
| **Measurements**                   |                  |                  |                |    |
| Systolic BP (mmHg)                 | 131.4 (23.9)     | 131.5 (24.3)     | 131.3 (23.7)   | 0.89 |
| Diastolic BP (mmHg)                | 69.3 (13.2)      | 71 (13.4)        | 68.2 (13)      | <.001 |
| Hemoglobin A1C                     | 7.03 (1.66)      | 6.89 (1.69)      | 7.12 (1.64)    | 0.03 |
| eGFR, CRIC Equation, mL/min/1.73 m²| 40.1 (14.1)      | 39.8 (14.7)      | 40.3 (13.7)    | 0.57 |
| Serum creatinine, mg/dL            | 1.85 (0.55)      | 1.87 (0.55)      | 1.84 (0.56)    | 0.25 |
| 24-h urine protein (g/d) (IQR)     | 0.2 (0.08-1.17)  | 0.3 (0.09-1.21)  | 0.2 (0.08-1.12)| 0.31 |
| UACR, μg/mg (IQR)                  | 85 (12.9-652.4)  | 78.5 (13.5-693)  | 86.3 (12.2-649.5)| 0.59 |
| UPCR, mg/mg (IQR)                  | 0.2 (0.07-1.07)  | 0.2 (0.07-1.09)  | 0.2 (0.07-1.04)| 0.26 |
| Calcium, mg/dL                     | 9.2 (0.5)        | 9.1 (0.5)        | 9.2 (0.5)      | 0.01 |
| Serum phosphate, mg/dL             | 3.8 (0.7)        | 3.8 (0.8)        | 3.8 (0.7)      | 0.34 |
| Serum albumin, g/dL                | 3.9 (0.5)        | 3.9 (0.5)        | 3.9 (0.5)      | 0.02 |
| PTH, pg/mL (IQR)                   | 62.1 (39.6-106.4)| 65.2 (41.7-112)  | 61.2 (38.5-105.9)| 0.14 |
| Hemoglobin, g/dL                   | 12.4 (1.8)       | 12.4 (1.7)       | 12.4 (1.8)     | 0.8  |
| LDL, mg/dL                         | 45 (13.9)        | 45.6 (14.7)      | 44.6 (13.3)    | 0.24 |
| LV mass index                      | 57.4 (14.9)      | 58.9 (15.1)      | 56.5 (14.7)    | 0.03 |
| Ejection fraction                  | 51.4 (10.8)      | 51.3 (11.2)      | 51.6 (10.6)    | 0.71 |

Note: Data are expressed as n (%) or mean (SD), unless otherwise indicated.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CHF, congestive heart failure; CRIC, Chronic Renal Insufficiency Cohort; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; LV, left ventricular; MI, myocardial infarction; PTH, parathyroid hormone; PVD, peripheral vascular disease; SD, standard deviation; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.
Aspirin Users

Table 3. Survival Analysis on Primary and Secondary Prevention Patients Taking Aspirin

| Outcome                  | Primary Prevention | Secondary Prevention |
|--------------------------|--------------------|----------------------|
|                          | Number of Events,  |                       |
|                          | Average Follow-up  |                       |
|                          | Time in Years      |                       |
|                          | (Event Rate in 100 | (Event Rate in 100   |
|                          | Person-Years)      | Person-Years)         |
| Death                    | 451, 11.63 (2.1)   | 621, 9.31 (4.7)       |
| CVD death                | 110, 11.63 (0.5)   | 216, 9.31 (1.6)       |
| CVD composite            | 268, 10.52 (1.4)   | 368, 7.81 (3.1)       |
| Stroke                   | 80, 10.93 (0.4)    | 96, 8.41 (0.8)        |
| MI                       | 159, 10.78 (0.8)   | 206, 8.16 (1.7)       |
| PAD                      | 62, 10.94 (0.3)    | 106, 8.18 (0.9)       |
| Kidney failure           | 516, 11.24 (2.6)   | 603, 7.18 (5.2)       |
| Major bleeding           | 138, 10.60 (0.7)   | 190, 7.91 (1.6)       |

Note: All models are adjusted for age, sex, race, diabetes status, antihypertension medication, any pre-CVD history, smoking status, systolic and diastolic blood pressure; angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, statins, β-blocker, phosphate, complete blood count hemoglobin, log-transformed fibroblast growth factor, previous bruising or bleeding, eGFR CRIC equation, log-transformed urinary protein-to-creatinine ratio from 24-h urine test, HDL, LDL.

CVD composite includes definite, probable, and possible acute myocardial infarction, definite and probable stroke, and PAD. CVD death includes death from atherosclerotic coronary heart disease, cerebrovascular, other atherosclerotic disease, and other cardiovascular disease. Stroke includes hemorrhage (intraparenchymal, subarachnoid) and cerebral infarction. PAD includes amputation or revascularization. Bleeding includes ICD-9/10 codes of upper and lower gastrointestinal bleeding, intracerebral bleed, subarachnoid bleed, and nontraumatic intracranial bleed.

Abbreviations: CI, confidence interval; CRIC, Chronic Renal Insufficiency Cohort; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; ICD-9/10, International Classification of Diseases, Ninth/Tenth Revision; LDL, low-density lipoprotein; MI, myocardial infarction; PAD, peripheral arterial disease.

Kidney Failure Events

Aspirin use was not associated with dialysis or kidney transplant in primary prevention patients (HR, 0.95; 95% CI, 0.79-1.13; P = 0.53). The sensitivity analysis with lagged exposure showed similar results (HR, 0.94; 95% CI, 0.79-1.13; P = 0.53). Participants with preexisting CVD had similar findings (Tables 3 and 4).

Major Bleeding

There were no adverse effects of major bleeding in the primary and secondary prevention patients taking aspirin (HR, 0.84; 95% CI, 0.61-1.15; P = 0.27 and HR, 0.76; 95% CI, 0.58-1; P = 0.05 respectively). The sensitivity analysis with lagged exposure demonstrated that patients taking aspirin for secondary prevention actually had a lower risk of major bleeding (HR, 0.74; 95% CI, 0.55-0.99; P = 0.04), which we suspect was because of confounding (Tables 3 and 4).

DISCUSSION

In this large ambulatory diverse population, aspirin use was not associated with a significant reduction in all-cause mortality among primary prevention patients. However, there were no adverse effects of major bleeding in primary or secondary prevention patients taking aspirin. The sensitivity analysis with lagged exposure demonstrated a lower risk of major bleeding in secondary prevention patients taking aspirin, which could be due to confounding factors.

Table 4. Sensitivity Analysis of Events in Primary and Secondary Prevention Patients After One Year of Taking Aspirin

| Outcome                  | Primary Prevention | Secondary Prevention |
|--------------------------|--------------------|----------------------|
|                          | Hazard Ratio (95% CI) | P | Hazard Ratio (95% CI) | P |
| Death                    | 0.86 (0.7-1.04) | 0.12 | 0.89 (0.77-1.03) | 0.12 |
| CVD death                | 1.17 (0.76-1.81) | 0.47 | 0.93 (0.71-1.21) | 0.58 |
| CVD composite            | 0.99 (0.77-1.28) | 0.94 | 1.04 (0.84-1.28) | 0.74 |
| Stroke                   | 0.71 (0.45-1.13) | 0.15 | 1.02 (0.71-1.48) | 0.93 |
| MI                       | 1.09 (0.78-1.52) | 0.61 | 1.16 (0.88-1.53) | 0.3 |
| PAD                      | 1.44 (0.86-2.42) | 0.17 | 1.1 (0.76-1.61) | 0.61 |
| Kidney failure           | 0.94 (0.77-1.14) | 0.53 | 0.98 (0.83-1.16) | 0.83 |
| Major bleeding           | 0.84 (0.59-1.18) | 0.3 | 0.74 (0.55-0.99) | 0.04 |

Note: All models are adjusted for age, gender, race, diabetes status, antihypertension medication, any pre-CVD history, smoking status, systolic and diastolic blood pressure; angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, statins, β-blocker, phosphate, complete blood count hemoglobin, log-transformed fibroblast growth factor, previous bruising or bleeding, eGFR CRIC equation, log-transformed urinary protein-to-creatinine ratio from 24-h urine test, HDL, LDL.

CVD composite includes definite, probable, and possible acute myocardial infarction, definite and probable stroke, and PAD. CVD death includes death from atherosclerotic coronary heart disease, cerebrovascular, other atherosclerotic disease, and other cardiovascular disease. Stroke includes hemorrhage (intraparenchymal, subarachnoid) and cerebral infarction. PAD includes amputation or revascularization. Bleeding includes ICD-9/10 codes of upper and lower gastrointestinal bleeding, intracerebral bleed, subarachnoid bleed, and nontraumatic intracranial bleed.

Abbreviations: CI, confidence interval; CRIC, Chronic Renal Insufficiency Cohort; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; ICD-9/10, International Classification of Diseases, Ninth/Tenth Revision; LDL, low-density lipoprotein; MI, myocardial infarction; PAD, peripheral arterial disease.
mortality, CVD mortality, or prevention of primary or secondary CVD events in patients with CKD. This study also demonstrated that aspirin use was not associated with kidney failure or increased risk of major bleeding in patients with CKD.

CKD is a CVD risk enhancing factor. CKD promotes CVD by a variety of mechanisms, which include but are not limited to inflammation, oxidative stress, and epigenetic alterations promoting vascular damage. Previous randomized controlled trials in this high-risk population have shown CVD risk reduction in statin use and blood pressure control. Prescribing low-dose aspirin (75–100 mg/d) has conflicting results in primary prevention of mortality and CVD. The AASER study is the only completed randomized controlled trial that evaluated 111 participants with eGFR 15–60 mL/min/1.73 m² without previous cardiovascular events and randomized them to 100 mg/d or usual therapy. Aspirin did not reduce the CVD composite endpoint (HR, 0.39; 95% CI, 0.14–1.07; P = 0.07) but reduced the risk of coronary events (log-rank, 5.99; P = 0.01). Aspirin did not increase the risk for bleeding and did not lead to progression of CKD after adjusting for albuminuria.

In a CKD subgroup analysis by Wolf et al using ASPREE data, aspirin effects were similar between users and nonusers in all-cause mortality (HR, 1.08; 95% CI, 0.89–1.32), major adverse cardiovascular events (HR, 0.77; 95% CI, 0.61–0.99), and MI (HR 0.94; 95% CI, 0.66–1.33). Patients with CKD on aspirin experienced a 37% reduction in ischemic stroke (HR, 0.63; 95% CI,
0.44–0.91), and there was no increase in clinically significant bleeding. Our study did not show benefit of aspirin in either group.

In a post hoc analysis of the ALLHAT Trial, investigators reported that baseline aspirin use in primary prevention did not reduce all-cause mortality in the matched, propensity-scored population. Additionally, there was no association with fatal coronary artery disease or nonfatal MI in patients with or without a history of CVD and results were consistent across eGFR categories.

A meta-analysis of 4,468 patients with nondialysis requiring CKD taking aspirin for primary prevention failed to show benefit in reducing cardiovascular events (risk ratio, 0.92; 95% CI, 0.49-1.73; P = 0.79) or mortality (risk ratio, 0.74; 95% CI, 0.55-1.00; P = 0.05), though the risk of major bleeding was elevated in patients taking aspirin (risk ratio, 1.98; 95% CI, 1.11-3.52; P = 0.02). In a post hoc analysis of the FAVORIT Trial, propensity-matched kidney transplant recipients who took aspirin and had no history of CVD did not have a risk reduction in incident CVD, all-cause mortality, or kidney failure. More recent systemic reviews and meta-analysis have been reported with similar results and notably significant heterogeneity in the studied population.

Contrarily, a post hoc analysis of 3,619 participants with CKD (eGFR 60 ml/min/1.73 m²) in the Hypertension Optimal Treatment (HOT) Study targeting lower diastolic blood pressures in hypertensive primary prevention patients found that patients with an eGFR < 45 mL/min/1.73 m² had a 66% reduction in major cardiovascular events (95% CI, 33%-83%; P = 0.03) and 49% reduction in all-cause mortality (95% CI, 6%-73%; P = 0.04). However, only 2.9% (n = 264) of the studied CKD population had an eGFR < 45 mL/min/1.73 m². Although...
major bleeding was not significant (HR, 2.81; 95% CI, 0.92-8.84), it overshadowed any benefit of aspirin in primary prevention of CVD.\textsuperscript{1,2} There is some data to suggest that aspirin use for primary prevention in patients with CKD may be associated with greater risk of harm. Kim et al\textsuperscript{34} analyzed 1,884 Korean patients with CKD receiving 100 mg of daily aspirin versus nonusers without a history of CVD using a 1:1 propensity score matching. Aspirin users had an increased risk of any CVD event (HR, 2.26; 95% CI, 1.88-2.71; P < 0.001), doubling of serum creatinine (HR, 1.33; 95% CI, 1.16-1.51; P < 0.001), and kidney failure (HR, 1.31; 95% CI, 1.09-1.56; P = 0.01). Limitations of the study included a homogenous single-center population.

Major guidelines recommend the use of aspirin in secondary prevention, despite excluding or under-representing patients with CKD.\textsuperscript{4} Many of these guidelines are supported by trials included in a meta-analysis from the Anti-Thrombotic Trialists Collaboration group which reviewed 16 secondary prevention CVD studies and concluded an absolute reduction in serious vascular events (6.7% vs 8.2% per year; P < 0.0001), stroke (2.08% vs 2.54% per year; P = 0.01), and coronary events (4.3% vs 5.3% per year; P < 0.0001).\textsuperscript{15} Unfortunately, the meta-analysis did not evaluate CKD subgroups. Additionally, the majority of the studies included for secondary prevention were conducted in the 1970s and 1980s before the widespread use of statins, smoking cessation, and lower blood pressure targets. Lifestyle modification and strict goals and therapies may attenuate the effects of aspirin in the CKD population. The benefit of aspirin in the general population for secondary prevention in acute coronary syndrome is robust.\textsuperscript{36} A review from Jacobsen et al\textsuperscript{37} supports the use of aspirin in acute coronary syndromes but suggests a “reappraisal of lifelong aspirin efficacy in chronic coronary syndrome” for secondary prevention.

Patients with CKD experience a myriad of contradictory hemostatic complications ranging from hypo- and hyperactive platelet dysfunction, increased endothelial activation, diminished vascular integrity, and hypercoag-ulability.\textsuperscript{27,38} Aspirin irreversibly binds to cyclooxygenase 1, which inhibits thromboxane production, a key component of platelet activation. CKD patients may be more resistant to aspirin therapy because they have increased platelet expression and reactivity with an attenuated response to antiplatelet therapy compared with the non-CKD population.\textsuperscript{39} CKD patients have competing risks, and first-line recommendations for the general population may not be applicable to this specialized population. There is lack of mortality benefit in implantable cardioverter-defibrillators in CKD 4 and of statin and warfarin use in atrial fibrillation in the kidney failure population.\textsuperscript{40-43} Dual antiplatelet therapy, aspirin with clopidogrel, has been studied in secondary CVD prevention in patients with CKD and showed no additional cardiovascular benefit.\textsuperscript{44} Because of the small sample size, we did not perform a subgroup analysis on patients who were on dual antiplatelet therapy or P2Y12 inhibitor monotherapy and acknowledge that this group is most likely at higher risk for CVD events. The COMPASS\textsuperscript{45} Trial showed a reduction in CVD events and lower bleeding risk in pre-existing chronic vascular disease patients on rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily compared with aspirin 100 mg daily monotherapy. In a subgroup analysis, 23% of patients who had CKD (eGFR < 60 mL/min/1.73 m$^2$) also showed a net clinical benefit. There is conflicting data to suggest whether the CKD population is at increased risk for major and minor bleeding in the presence of aspirin.\textsuperscript{12,16,46,47} Our study showed that there was no increase in major bleeding in patients with CKD using aspirin for primary or secondary prevention.

Low-dose aspirin may theoretically potentiate CKD progression through a variety of mechanisms, including prostaglandin inhibition, renal vasoconstriction, and salt retention, which can manifest as worsening hypertension, and that risk is magnified when aspirin is taken in conjunction with other analogesics.\textsuperscript{48,49} Our study did not show that aspirin leads to dialysis or transplant in either group. Other large trials confirm these findings but excluded women, minorities, or patients with preexisting kidney disease.\textsuperscript{50}

Our study contributes to the medical literature by examining the associations of aspirin use in primary and secondary prevention of mortality and CVD events in a well-studied CKD population. A major strength of our study is that we analyzed the CRIC, a large diverse ambulatory CKD population with the primary aim of studying kidney disease progression and its associations with CVD. We were able to adjust for multiple potential confounders to strengthen our associations. Medication review was completed every 6 months. All cardiovascular and kidney endpoints were adjudicated, death was verified, and all hospitalizations records and ICD-9/10 codes were used to identify CVD, kidney, and bleeding events.

There are several limitations to our study. The studied population was an observational cohort, and therefore, we cannot determine causality because the original study design was not meant to study the effects of aspirin. Despite using Cox modeling with delayed exposure, unmeasured confounders may still exist. We adjusted for various confounders in individuals who were not on aspirin compared with those who were prescribed it, but indication bias still exists, which limits the interpretation of the results. Despite excluding patients with New York Heart Association class III-IV heart failure, some may have been unintentionally included in the secondary prevention group. Aspirin use was self-reported and doses were not ascertained, so inaccuracies of reporting and medication compliance may limit the interpretations of the results. Finally, bleeding was defined as ICD-9/10 codes but were not adjudicated events.

In conclusion, aspirin use was not associated with reduction in primary or secondary prevention of all-cause mortality and CVD events in patients with CKD. Aspirin use
in the CKD population was not associated with kidney failure or major bleeding. Despite these findings, we advocate for the use of aspirin in secondary prevention in individuals at low risk of bleeding. We anxiously await the results of the ATTACK trial to help shed light on aspirin use in CKD patients for primary prevention and hope for more trials to better assess secondary prevention in this highly vulnerable population.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Aspirin use reported at each study visit.

Item S1: Trial emulation.

Table S1: Baseline Characteristics by Aspirin Use in Overall Cohort.

ARTICLE INFORMATION

CRIC Study Investigators: Lawrence J. Appel, MD, MPH, Debbie L Cohen, MD, Harold L. Feldman, MD, MSCE, James P. Laish, MD, Robert G. Nelson, MD, PhD, MS, Pandurangana S. Rao, MD, Vallabh O. Shah, PhD, MD, and Mark L. Unruh, MD, MS.

Authors' Full Names and Academic Degrees: Jonathan J. Taliercio, DO, FASN, George N. Nghiem, MD, Med, Ali Mehdi MD, Med, Wei Yang, PhD, Daohang Sha, PhD, Jesse D. Schold, PhD, Scott Kasner, MD, Matthew Weir, MD, Mohamed Hassanain, MD, Sankar D. Navaneethan, MD, Geetha Krishnan, RN, Radhika Kanthety, MD, Alan S. Go, MD, Rajat Deo, MD, Claudia M. Lora, MD, Bernard G. Jaar MD, Teresa K. Chen MD, Jing Chen, MD, Jiang He MD, and Mahboob Rahman, MD on behalf of the CRIC study investigators.

Authors' Affiliations: Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio (JJT, GM, AM); Department of Kidney Medicine, Glickman Urological and Kidney Institute, Cleveland, Ohio (JJT, GM, AM, GK); Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania (WY, DS); Colorado Center for Transplantation Care, Research and Education (CCTCARE), University of Colorado Anschutz, Aurora, Colorado (JDS); Department of Neurology, University of Pennsylvania, Philadelphia, Pennsylvania (SK); Division of Nephrology, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland (MW); Division of Nephrology and Hypertension, University of Mississippi Medical Center Division of Nephrology, Jackson, Mississippi (MH); Section of Nephrology, Department of Medicine, Baylor College of Medicine, Houston, Texas (SDN); University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, Ohio (RK); Division of Nephrology, UCSF School of Medicine, San Francisco, California (ASG); Division of Research, Kaiser Permanente Northern California, Oakland, California (ASG); Section of Cardiac Electrophysiology, Division of Cardiovascular Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania (RD); Division of Nephrology, Department of Medicine, University of Illinois at Chicago, Chicago, Illinois (CML); Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland (BGJ); Nephrology Center of Maryland, Baltimore, Maryland (BGJ); Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, Maryland (BGJ); Division of Nephrology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland (TKC); Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, Maryland (TKC); Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana (JC); Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana (JC, JH); Tulane University Translational Science Institute, New Orleans, Louisiana (JC); Department of Epidemiology, School of Public Health, Medical College of Soochow University, Suzhou, China (JH); and Division of Nephrology and Hypertension, University Hospitals Cleveland Medical Center, Case Western Reserve University, Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, Ohio (MR).

Address for Correspondence: Jonathan J. Taliercio, DO, FASN, Program Director, Nephrology and Hypertension Fellowship, Assistant Professor of Medicine; Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Department of Kidney Medicine, Glickman Urological and Kidney Institute, 9500 Euclid Ave, Q7, Cleveland, OH 44195. Email: talierj@ccf.org

Authors' Contributions: Research idea and study design: JJT, GN, AM, JDS, WY, DS; Data acquisition: WY, DS; Data analysis/intervention: JJT, GN, AM, JDS, WY, DS, SK, MW, MH, SDN, GK, RK, ASG, RD, CML, BJJ, TKC, JCC, JH, MR; Statistical analysis: JDS, WY, DS; Supervision or mentorship: GN, AM, JDS, MR. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: Funding for the CRIC study was obtained under a cooperative agreement from National Institute of Diabetes and Digestive and Kidney Diseases (U01DK060990, U01DK060984, U01DK061022, U01DK061021, U01DK061028, U01DK060980, U01DK060963, U01DK060962 and U24DK060990). In addition, this work was supported in part by: the Perelman School of Medicine at the University of Pennsylvania Clinical and Translational Science Award NIH/NCATS UL1TR000003, Johns Hopkins University UL1 TR000424, University of Maryland GCRC M01 RR-16500, Clinical and Translational Science Collaborative of Cleveland, UL1TR000439 from the National Center for Advancing Translational Sciences (NCATS) component of the National Institutes of Health and NIH roadmap for Medical Research, Michigan Institute for Clinical and Health Research (MICHIR) UL1TR000433, University of Illinois at Chicago CTSA UL1RR029879, Tulane COBRE for Clinical and Translational Research in Cardiometabolic Diseases P20 GM109036, Kaiser Permanente NIH/NCRR UCSF-CTSI UL1 RR-024131, Department of Internal Medicine, University of New Mexico School of Medicine Albuquerque, NM R01DK119199.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received May 16, 2022 as a submission to the expedited consideration track with 3 external peer reviews. Direct editorial input from the Statistical Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form August 07, 2022.

REFERENCES

1. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary prevention of cardiovascular disease: a report of the American college of cardiology/american heart association task force on clinical practice guidelines. J Am Coll Cardiol. 2019;74(10):e177-e232. doi:10.1016/j.jacc.2019.03.010
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-1305. doi:10.1056/nejmoa041031
11. Eknoyan G, Wacksman SJ, Glueck HI, Will JJ. Platelet function

10. Colantonio LD, Baber U, Banach M, et al. Contrasting

12. Jardine MJ, Ninomiya T, Perkovic V, et al. Aspirin is bene

15. Fischer MJ, Go AS, Lora CM, et al. CKD in Hispanics: baseline

14. Denker M, Boyle S, Anderson AH, et al. Chronic renal insuf

16. Molnar AO, Bota SE, Garg AX, et al. The risk of major hem-

17. Anderson AH, Yang W, Hsu CY, et al. Estimating GFR among

18. Hernán MA, Alonso A, Logan R, et al. Observational studies

3. KDIGO 2012 Clinical Practice Guideline for the evaluation and

4. Konstantinidis I, Nadkarni GN, Yacoub R, et al. Representation

9. Lewis J, Agodoa L, Cheek DA, et al. Comparison of cross-

8. American College of Cardiology. ASCVD risk estimator plus.

5. Maini R, Wong DB, Addison D, Chiang E, Weisbord SD,

6. McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on

7. Guirguis-Blake JM, Evans CV, Perdue LA, Bean SI, Senger CA.

10. Colantonio LD, Baber U, Banach M, et al. Contrasting

11. Eknayan G, Wacksman SJ, Glueck HI, Will JJ. Platelet function

19. Wang K, Zelnick LR, Anderson A, et al. Cardiac biomarkers and

20. Rahman M, Xie D, Feldman HI, et al. Association between

21. Bansal N, Xie D, Sha D, et al. Cardiovascular events after new-

22. Xie D, Yang W, Jepson C, et al. Statistical methods for

23. Carracedo J, Alike M, Vida C, et al. Mechanisms of cardio-

24. Baigent C, Landray MJ, Reith C, et al. The effects of lowering

25. Blood Pressure Lowering Treatment Trialists’ Collaboration,

26. Charytan D, Kuntz RE. The exclusion of patients with chronic

27. Baaten CCFMJ, Schröer JR, Fleuge J, et al. Platelet abnor-

28. Goicoechea M, de Vinueza SG, Quiroga B, et al. Aspirin for

29. Wolfe R, Wetmore JB, Woods RL, et al. Subgroup analysis of the

30. Desai N, Wilson B, Bond M, Conant A, Rahman M. Association

31. Major RW, Oozeer Alan, Dawson S, Riddleston H, Gray LJ,

32. Dad T, Tighiouart H, Joseph A, et al. Aspirin use and incident

Kidney Med
Vol 4 | Iss 11 | November 2022 | 100547

Kidney Medicine

Kidney Int
Suppl

Kidney Med
Vol 4 | Iss 11 | November 2022 | 100547

Kidney Med
Vol 4 | Iss 11 | November 2022 | 100547

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Int
Suppl

Kidney Med
33. Qu B, He Y, Wu L, Lu H, Wu H, Li M. Is there a cardiovascular protective effect of aspirin in chronic kidney disease patients? A systematic review and meta-analysis. *Int Urol Nephrol*. 2020;52:315-324. doi:10.1007/s11255-019-02350-8

34. Kim AJ, Lim HJ, Ro H, et al. Low-dose aspirin for prevention of cardiovascular disease in patients with chronic kidney disease. *PLOS ONE*. 2014;9(8). doi:10.1371/journal.pone.0104179

35. Antithrombotic Trialists’ (ATT) Collaboration; Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373(9678):1849-1860. doi:10.1016/S0140-6736(09)60503-1

36. Institute of Strategic and International Studies. (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet*. 1988;332(8607):349-360. doi:10.1016/S0140-6736(88)92833-4

37. Jacobsen AP, Raber I, McCarthy CP, et al. Lifelong aspirin for all in the secondary prevention of chronic coronary syndrome: still sacrosanct or is reappraisal warranted? *Circulation*. 2020;142(16):1579-1590. doi:10.1161/CIRCULATIONAHA.120.045695

38. Boccardo P, Remuzzi G, Galbusera M. Platelet dysfunction in renal failure. *Semin Thromb Hemost*. 2004;30(5):579-589. doi:10.1055/s-2004-835678

39. Gremmel T, Müller M, Steiner S, et al. Chronic kidney disease is associated with increased platelet activation and poor response to antiplatelet therapy. *Nephrol Dial Transplant*. 2013;28(8):2116-2122. doi:10.1093/ndt/gft103

40. Nakhoul GN, Schold JD, Arrigain S, et al. Implantable cardioverter-defibrillators in patients with CKD: A propensity-matched mortality analysis. *Clin J Am Soc Nephrol*. 2015;10(7):1119-1127. doi:10.2215/CJN.11121114

41. Wanner C, Krane V, März W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005;353(3):238-248. doi:10.1056/nejmoa043545

42. SHARP Collaborative Group. Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. *Am Heart J*. 2010;160(5):785-794. doi:10.1016/j.ahj.2010.08.012

43. Randhawa MS, Vishwanath R, Rai MP, et al. Association between use of warfarin for atrial fibrillation and outcomes among patients with end-stage renal disease: a systematic review and meta-analysis. *JAMA Netw Open*. 2020;3(4):e202175. doi:10.1001/jamanetworkopen.2020.2175

44. Best PJM, Steinhubl SR, Berger PB, et al. The efficacy and safety of short- and long-term dual antiplatelet therapy in patients with mild or moderate chronic kidney disease: results from the Clopidogrel for the Reduction of Events During Observation (CREDO) Trial. *Am Heart J*. 2008;155(4):687-693. doi:10.1016/j.ahj.2007.10.046

45. Steffel J, Eikelboom JW, Anand SS, Shestakovska O, Yusuf S, Fox KAA. The COMPASS trial: net clinical benefit of low-dose Rivaroxaban plus aspirin as compared with aspirin in patients with chronic vascular disease. *Circulation*. 2020;142(1):40-48. doi:10.1161/CIRCULATIONAHA.120.046048

46. Liang CC, Wang SM, Kuo HL, et al. Upper gastrointestinal bleeding in patients with ckd. *Clin J Am Soc Nephrol*. 2014;9(8):1354-1359. doi:10.2215/CJN.09260913

47. Ocak G, Rookmaaker MB, Algra A, et al. Chronic kidney disease and bleeding risk in patients at high cardiovascular risk: a cohort study. *J Thromb Haemost*. 2018;16(1):65-73. doi:10.1111/jth.13904

48. White WB. Cardiovascular effects of the cyclooxygenase inhibitors. *Hypertension*. 2007;49(3):408-418. doi:10.1161/01.HYP.0000258106.74139.25

49. Fored CM, Ejerblad E, Lindblad P, et al. Acetaminophen, aspirin, and chronic renal failure. *N Engl J Med*. 2001;345(25):1801-1808.

50. Rexrode KM, Buring JE, Glynn RJ, Stampfer MJ, Youngman LD, Gaziano JM. Analgesic use and renal function in men. *JAMA*. 2001;286(3):315-321. doi:10.1001/jama.286.3.315
What are the potential risk and benefits of aspirin in CKD patients with and without preexisting CVD?

**Methods and Cohort**
- Prospective Cohort
- Observational Cohort
- CRIC Participants N = 3,664
- 2013 - 2018

**Exposure**
- CKD Patients without CVD
- CKD Patients with CVD

**Results**

|                | Mortality | CVD Events | Kidney Failure | Major Bleeding |
|----------------|-----------|------------|----------------|----------------|
| **ASPIRIN**    | **0.84**  | **0.97**   | **0.95**       | **0.84**       |
|                | (0.7 - 1.01) | (0.77 - 1.23) | (0.79 - 1.13) | (0.61 - 1.15) |
| **P**          | 0.06      | 0.79       | 0.53           | 0.27           |
| **CRIC**       | **0.88**  | **1.08**   | **0.99**       | **0.76**       |
|                | (0.77 - 1.02) | (0.89 - 1.31) | (0.85 - 1.15) | (0.58 - 1)     |
| **P**          | 0.08      | 0.46       | 0.91           | 0.05           |

CRIC, Chronic Renal Insufficiency Cohort; CVD, Cardiovascular disease; CKD, Chronic Kidney Disease

**Conclusion:** Aspirin use in CKD patients was not associated with reduction in primary or secondary CVD events, progression to kidney failure, or major bleeding.

**Reference:** Taliercio J, Nashoul G, Mehdi A et al. Aspirin for primary and secondary prevention of mortality, cardiovascular disease, and kidney failure in the Chronic Renal Insufficiency Cohort CRIC Study, Kidney Medicine, 2022.

Visual Abstract by Denisse Arellano, MD

@denii_ne