Kidney Medicine

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

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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 m^2. Median follow-up was 11.5 (IQR, 7.4-13) 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.

Visual Abstract included

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Chronic kidney disease (CKD) is a risk enhancing factor for cardiovascular disease (CVD) and is the leading cause of death in this population.[1,2] 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.[1,3] 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.[4,5]

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.[6] 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.[7] 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 m^2 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.[8-10] 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.[11,12]

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.[13–15] Briefly, the CRIC study enrolled 3,939 adults from the initial enrollment period with eGFR 20-70 mL/min per 1.73 m^2 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.[16] 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.

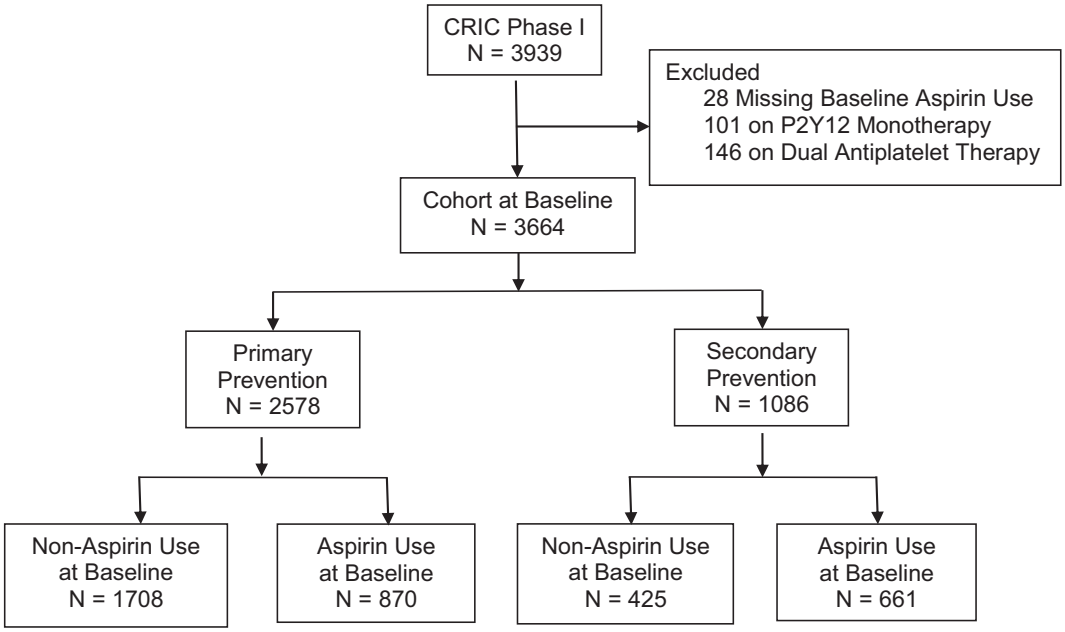

Figure 1. Flowchart of patients. Abbreviation: CRIC, Chronic Renal Insufficiency Cohort.

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. Peripheral 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 published *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 χ^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, β-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 m^2, protein-to-creatinine ratio <0.15 or ≥0.15, and body mass index <30 or ≥30 kg/m^2).

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/m^2	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	1066 (41.3%)	585 (34.3%)	481 (55.3%)	< 0.001
Smoking status				
Current smoker	307 (11.9%)	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 m^2	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 (7.3-392.8)	46.1 (7.9-450.1)	30 (6.4-312.9)	< 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. (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 m^2; 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, 0.77-1.63; 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

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	61.3 (8.3)	59.7 (8.8)	62.4 (7.8)	<.001
Female	428 (39.4%)	172 (40.5%)	256 (38.7%)	0.57
Non-Hispanic White	408 (37.6%)	130 (30.6%)	278 (42.1%)	<.001
Non-Hispanic Black	531 (48.9%)	223 (52.5%)	308 (46.6%)	.
Hispanic	108 (9.9%)	57 (13.4%)	51 (7.7%)	.
Other race	39 (3.6%)	15 (3.5%)	24 (3.6%)	.
BMI, kg/m^2	32.9 (7.9)	33.3 (8.4)	32.7 (7.5)	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	1,086 (100.0%)	425 (100%)	661 (100%)	.
CHF	331 (30.5%)	140 (32.9%)	191 (28.9%)	0.16
MI	691 (63.6%)	222 (52.2%)	469 (71%)	<.001
PVD	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 m^2	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
HDL, mg/dL	45 (13.9)	45.6 (14.7)	44.6 (13.3)	0.24
LDL, mg/dL	95.9 (35.7)	102.5 (38.7)	91.7 (33.1)	<.001
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.

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

Aspirin Users						
	Primary Prevention			Secondary Prevention		
Outcome	Number of Events, Average Follow-up Time in Years (Event Rate in 100 Person-Years)	Hazard Ratio (95% CI)	*P*	Number of Events, Average Follow-up Time in Years (Event Rate in 100 Person-Years)	Hazard Ratio (95% CI)	*P*
Death	451, 11.63 (2.1)	0.84 (0.7-1.01)	0.06	621, 9.31 (4.7)	0.88 (0.77-1.02)	0.08
CVD death	110, 11.63 (0.5)	1.12 (0.77-1.63)	0.56	216, 9.31 (1.6)	0.95 (0.74-1.21)	0.67
CVD composite	268, 10.52 (1.4)	0.97 (0.77-1.23)	0.79	368, 7.81 (3.1)	1.08 (0.89-1.31)	0.46
Stroke	80, 10.93 (0.4)	0.72 (0.47-1.1)	0.13	96, 8.41 (0.8)	1.08 (0.76-1.53)	0.66
MI	159, 10.78 (0.8)	1.07 (0.79-1.45)	0.65	206, 8.16 (1.7)	1.22 (0.94-1.58)	0.13
PAD	62, 10.94 (0.3)	1.3 (0.8-2.11)	0.29	106, 8.18 (0.9)	1.06 (0.75-1.5)	0.73
Kidney failure	516, 11.24 (2.6)	0.95 (0.79-1.13)	0.53	603, 7.18 (5.2)	0.99 (0.85-1.15)	0.91
Major bleeding	138, 10.60 (0.7)	0.84 (0.61-1.15)	0.27	190, 7.91 (1.6)	0.76 (0.58-1)	0.05

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; 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, 0.77-1.14; 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

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

Aspirin Users				
	Primary Prevention		Secondary Prevention	
Outcome	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 (0.7-1.48)	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, diastolic, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, statins, β-blockers, 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: CVD, cardiovascular disease; 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.

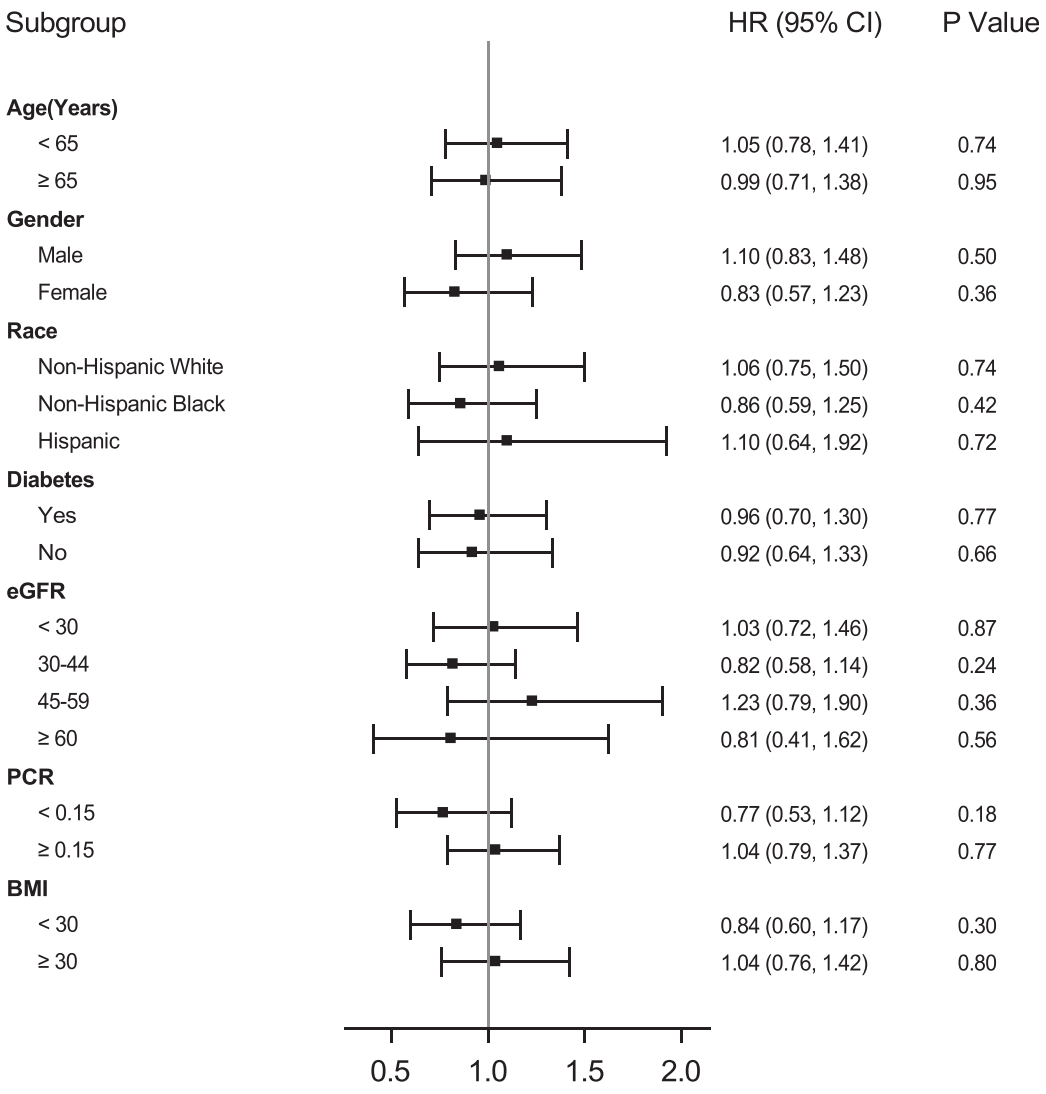

Figure 2. Forest plot: subgroup analysis of aspirin use in primary prevention and CVD composite. Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease, eGFR, estimated glomerular filtration rate; PCR, protein-to-creatinine ratio.

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.[23] Previous randomized controlled trials in this high-risk population have shown CVD risk reduction in statin use and blood pressure control.[24,25] Placebo-controlled studies are lacking and are even less robust in the kidney failure population.[5] Individuals with CKD have been excluded from clinical trials in coronary artery disease.[26,27] The Aspirin to Prevent a First Heart Attack or Stroke in People with Chronic Kidney Disease (ATTACK) is actively attempting to recruit 25,210 participants, but results will not be released until 2025 (ClinicalTrials.gov NCT03796156).

Prescribing low-dose aspirin (75-100 mg/d) has conflicting results in primary prevention of mortality and CVD. The AASER[28] Study is the only completed randomized controlled trial that evaluated 111 participants with eGFR 15-60 mL/min/1.73 m^2 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.[28]

In a CKD subgroup analysis by Wolf et al[29] 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,

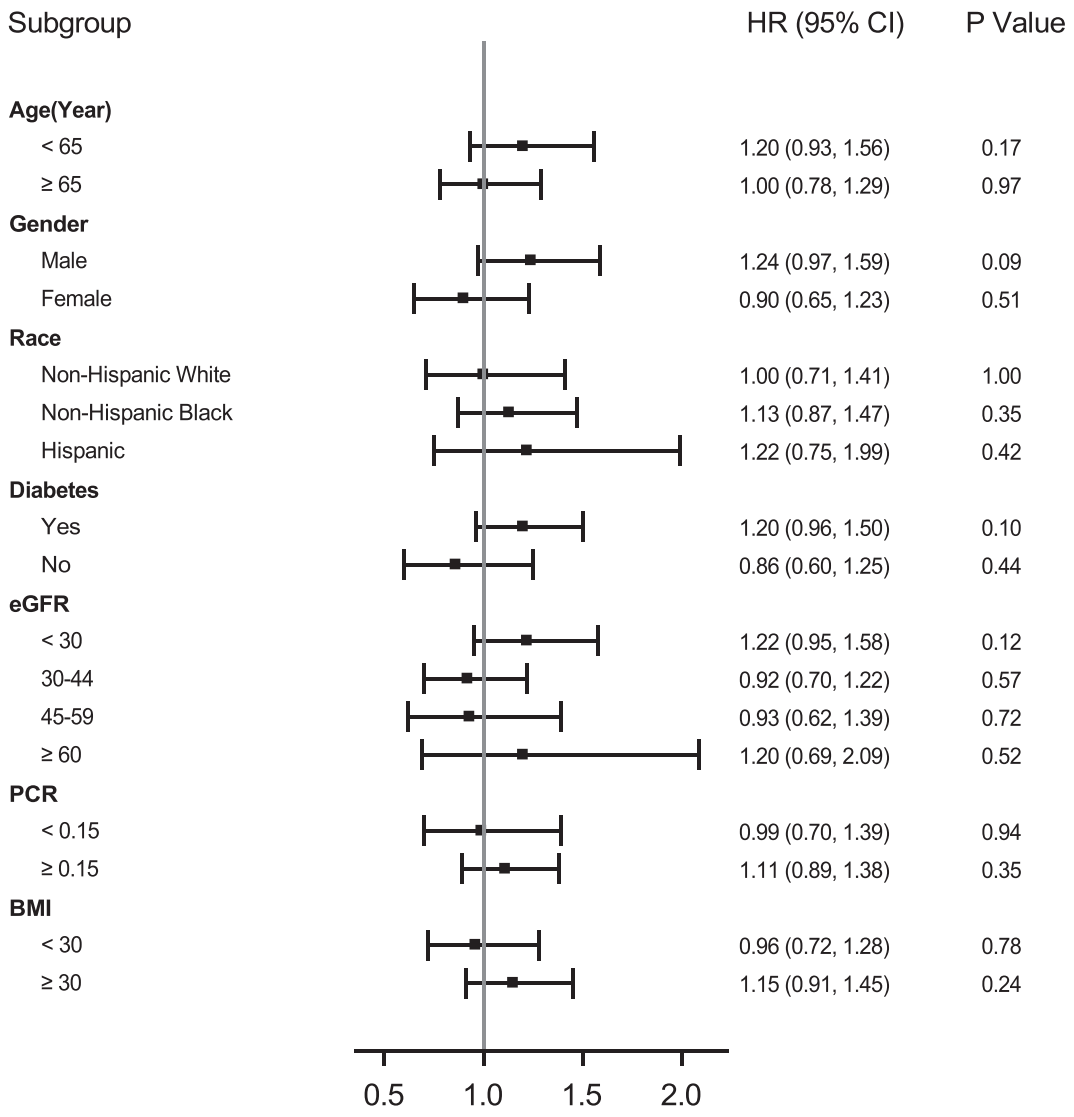

Figure 3. Forest plot: subgroup analysis of aspirin use in secondary prevention and CVD composite. Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease, eGFR, estimated glomerular filtration rate; PCR, protein-to-creatinine ratio.

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[30], 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).[31] In a post hoc analysis of the FAVORIT[32] 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.[33]

Contrarily, a post hoc analysis of 3,619 participants with CKD (eGFR 60 ml/min/1.73 m^2) 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 m^2 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 m^2. 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.[12]

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[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 underrepresenting patients with CKD.[1] 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; $P < 0.0001$).[35] 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.[36] A review from Jacobsen et al[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 hypercoagulability.[27,38] Aspirin irreversibly binds to cyclooygensase 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.[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.[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.[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[45] Trial showed a reduction in CVD events and lower bleeding risk in preexisting 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.[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 analgesics.[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.[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 compliancy 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.

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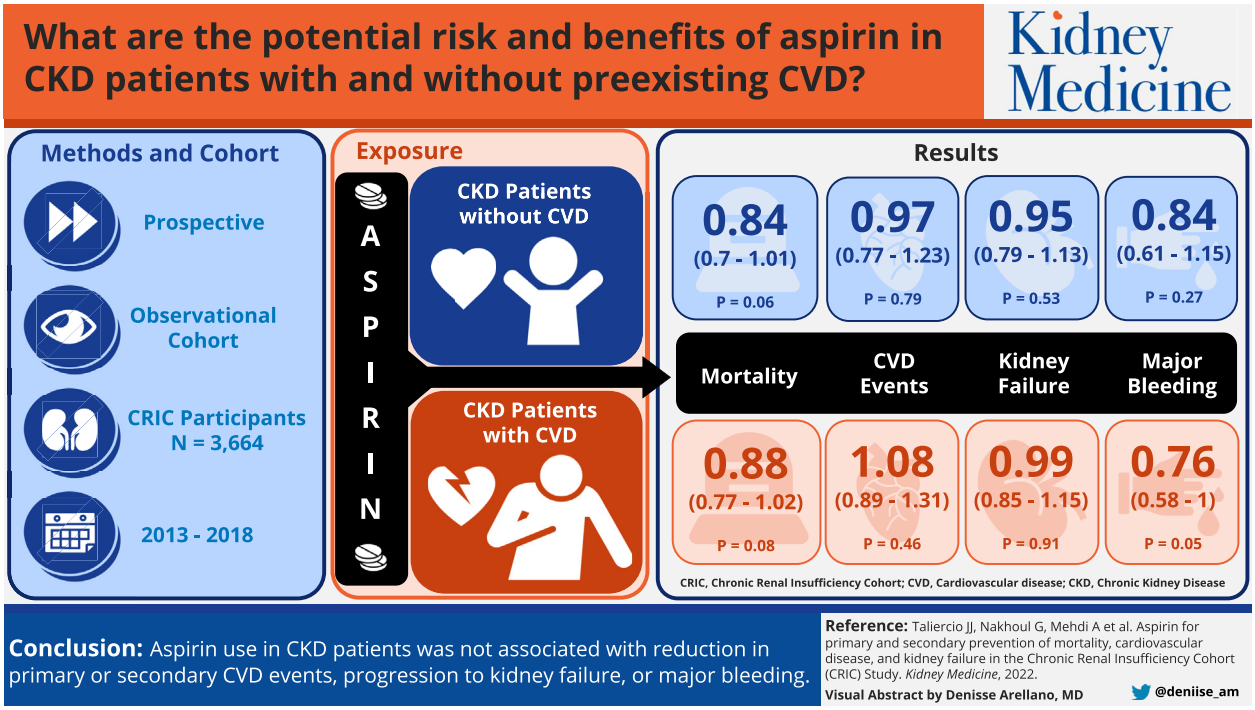
What are the potential risk and benefits of aspirin in CKD patients with and without preexisting CVD?
Kidney Medicine
Methods and Cohort
Prospective
Observational Cohort
CRIC Participants N = 3,664
2013 - 2018
Exposure
ASPIRIN
CKD Patients without CVD
CKD Patients with CVD
Results
0.84 (0.7 - 1.01) P = 0.06
0.97 (0.77 - 1.23) P = 0.79
0.95 (0.79 - 1.13) P = 0.53
0.84 (0.61 - 1.15) P = 0.27
Mortality
CVD Events
Kidney Failure
Major Bleeding
0.88 (0.77 - 1.02) P = 0.08
1.08 (0.89 - 1.31) P = 0.46
0.99 (0.85 - 1.15) P = 0.91
0.76 (0.58 - 1) P = 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 JJ, Nakhoul 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.
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