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Association between aspirin use and cardiovascular outcomes in ALLHAT participants with and without chronic kidney disease: A post hoc analysis

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Abstract

It is unclear whether aspirin is beneficial for prevention of CVD in patients with CKD. We performed a secondary analysis of the ALLHAT trial to assess the effect of baseline aspirin use on nonfatal myocardial infarction (MI) or fatal coronary heart disease (CHD), all-cause mortality, and stroke. Baseline characteristics of aspirin users and nonusers were used to generate propensity-matched cohorts. Using conditional Cox proportional hazard regression models, we examined the effect of aspirin on the outcomes in the cohort at large and across 3 levels of kidney function (eGFR ≥90, 60–89, and <60). 11 250 ALLHAT participants reported using aspirin at baseline. The propensity-matched dataset included 6894 nonusers matched with replacement to achieve a balanced analysis population (n = 22 500). Risk of fatal CHD or nonfatal MI (HR = 0.94, 95% CI 0.86–1.02) and stroke (HR = 1.01, 95% CI 0.89–1.15) was not significantly different between groups. Aspirin users were at significantly lower risk of all-cause mortality compared to nonusers (HR = 0.82, 95% CI 0.76–0.88). Aspirin use was not associated with incidence of fatal CAD or nonfatal MI in patients with CVD (HR = 0.93, CI 0.84–1.04) or without CVD at baseline (HR = 1.04, CI 0.82–1.32). Results were consistent across strata of GFR (interaction p value NS). In hypertensive patients at high cardiovascular risk, aspirin use is not associated with risk of nonfatal MI, fatal CHD, or stroke; however, aspirin use is associated with lower risk of all-cause mortality. These results are consistent across baseline eGFR.

1 | INTRODUCTION

Chronic kidney disease (CKD) is defined by the presence of kidney damage or decreased kidney function for three or more months. Kidney damage may be established by pathologic abnormalities detected by imaging and kidney biopsy or inferred from abnormal urine sediment or the presence of proteinuria. CKD is highly prevalent in the United States, affecting approximately 15.2% of the population.[1] Those with CKD have high risk of cardiovascular disease (CVD), as well as CVD-related and all-cause mortality.[2,3] Older patients with mild-to-moderate CKD have a greater risk of cardiovascular mortality than of progression to end-stage renal disease, making increased incidence of cardiovascular disease the primary mortality risk burden in this group.[4,5]

Aspirin is effective in the secondary prevention of CVD for those at high risk of occlusive vascular events[6] and plays a role in primary prevention of CVD as well for specific populations.[7] For patients with CKD, however, it remains unclear whether aspirin is useful in either the primary or secondary prevention of CVD. In large part, this results from lack of quality data concerning the safety and efficacy of aspirin in patients with CKD. Moreover, the available literature reveals inconsistent conclusions regarding the benefit and safety of aspirin for CVD prevention in those with CKD.[8–12] Ambiguity as to the cardioprotective effect of aspirin use in the CKD population may be a reflection of an alternative, complex pathophysiology of underlying ischemic heart and vascular disease in CKD patients, despite a high prevalence of traditional cardiovascular risk factors. Additionally, there is an increased burden of non-atherosclerotic cardiac disease from sudden cardiac death, arrhythmia, and cardiomyopathy in those with CKD compared to the general population.[13,14] Therefore, the value of aspirin in primary and secondary prevention of CVD in patients with CKD is an important unresolved question in this field.

We conducted a post hoc analysis of data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT was a double-blind randomized clinical trial that randomized 42 418 participants with hypertension plus one additional risk factor for CVD to receive antihypertensive therapy using either chlorthalidone, amlodipine, lisinopril, or doxazosin with the primary outcome of combined fatal coronary artery disease (CAD) and nonfatal MI. In the present study, we aimed to study the association between aspirin use and risk of CVD in ALLHAT participants with and without established CVD stratified by baseline renal function. In addition, we examined the association between aspirin use and adverse events in the form of gastrointestinal (GI) bleeding or development of end-stage renal disease.

2 | MATERIAL AND METHODS

2.1 | Study population

The design and main results of the ALLHAT have been described previously.[15,16] Briefly, a total of 42 418 participants age 55 and older with hypertension and one additional risk factor for CVD were enrolled to determine whether treatment of hypertension with either lisinopril (n = 9054), amlodipine (n = 9048), or doxazosin (n = 9061) lowered the incidence of coronary artery disease (CAD) or other CVD events versus treatment with chlorthalidone (n = 15 255). Study participants were selected from 623 centers in North America, with mean follow-up of 4.9 years. Major inclusion criteria for the main ALLHAT trial were age of 55 years or older, stage 1 or 2 hypertension with at least one additional risk factor for coronary heart disease events such as previous myocardial infarction or stroke, history of other atherosclerotic cardiovascular diseases, left ventricular hypertrophy, type 2 diabetes, current cigarette smoking, and high-density lipoprotein (HDL) level <35 mmol/L. Key exclusion criteria included serum creatinine >2.0 mg/dl, symptomatic myocardial infarction or stroke within the past 6 months, history of hospitalized or treated symptomatic heart failure, or known ejection fraction less than 35%. The doxazosin study arm was terminated early due to high rates of heart failure.

After randomization, ALLHAT participants were seen after 1 month, then every 3 months for the first year of trial participation, and then every 4 months thereafter for routine data collection and drug dosage titration. Goal blood pressure for all arms of ALLHAT was less than 140/90, using the lowest possible dose of the first-line drug. For those patients unable to attain goal blood pressure using the maximum tolerable dosage of the first-line drug, open-label second- and third-line antihypertensive drugs were added.[16] In the present study, the 31 346 participants randomized

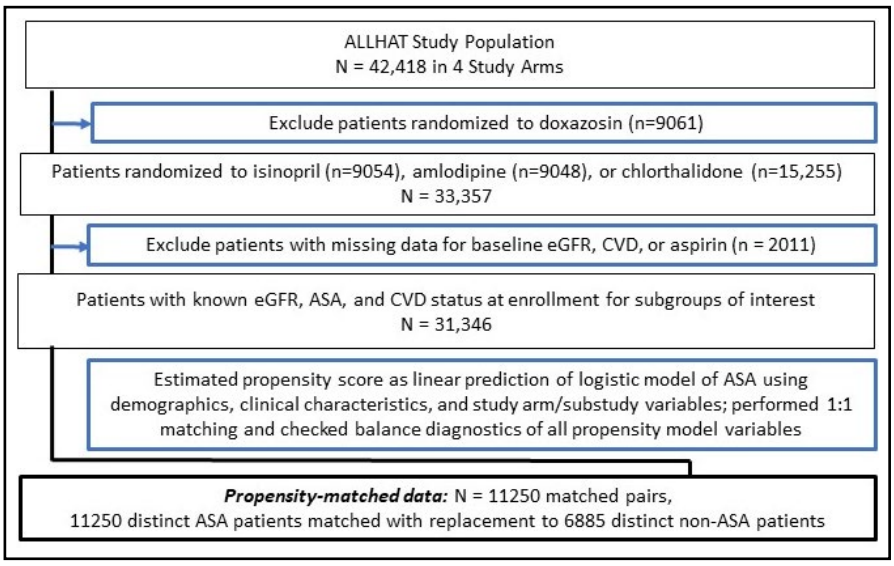

FIGURE 1 CONSORT flow diagram of ALLHAT study population with application of exclusion criteria and propensity matching [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 ALLHAT population by baseline eGFR, pre-existing CVD, and aspirin (n = 31 346 patients with non-missing baseline eGFR, pre-existing CVD, and ASA use)

	All analysis patients	No aspirin at baseline	Aspirin at baseline	
	n = 31 346	*n* = 19 804	*n* = 11 542	*p*-value
eGFR (ml/min/1.73 m^2)	78 ± 20	78 ± 20	77 ± 19	<.0001
Age, y	67 ± 8	66 ± 8	67 ± 7	<.0001
Systolic BP, mm Hg	146 ± 16	147 ± 16	146 ± 16	<.0001
Diastolic BP, mm Hg	84 ± 10	85 ± 10	83 ± 10	<.0001
Ethnicity				
White, non-hispanic	15 116 (48)	7853 (40)	7263 (63)	<.0001
Black, non-hispanic	9625 (31)	7132 (36)	2493 (22)	
Hispanic	5976 (19)	4377 (22)	1599 (14)	
Others	1539 (5)	1105 (6)	434 (4)	
Sex				
Female	14 562 (46)	10 423 (53)	4139 (36)	<.0001
Male	16 784 (54)	9381 (47)	7403 (64)	
Receiving antihypertensive treatment	27 194 (87)	16 863 (85)	10 331 (90)	<.0001
Eligibility risk factors (all presented as *N* (%) of patients)				
Cigarette smoker	19 653 (63)	11 742 (59)	7911 (69)	<.0001
Composite CVD				
Prior MI or stroke	7362 (23)	3233 (16)	4129 (36)	<.0001
History of coronary revascularization	4132 (13)	982 (5)	3150 (27)	<.0001
Hx of major ST depression or T-wave inversion	3208 (10)	2108 (11)	1100 (10)	.0021
Other ASCVD*	7451 (24)	3988 (20)	3463 (30)	<.0001
Type 2 diabetes	11 267 (36)	7408 (37)	3859 (33)	<.0001
HDL-C < 35 mg/dl	3679 (12)	2147 (11)	1532 (13)	<.0001
LVH by electrocardiogram	5070 (16)	3470 (18)	1600 (14)	<.0001
LVH by echocardiogram	1430 (5)	975 (5)	455 (4)	.0001
Body mass index (kg/m^2)	30 ± 6	30 ± 6	29 ± 5	<.0001
Current medication use				
Aspirin	11 542 (37)	0 (0)	11 542 (100)	–
Estrogen supplementation (women only)	2639 (8)	1750 (9)	889 (8)	.0005
ALLHAT study arm assignment				
Chlorthalidone	8498 (27)	5351 (27)	3147 (27)	.6032
Amlodipine	14 360 (46)	9115 (46)	5245 (45)	
Lisinopril	8488 (27)	5338 (27)	3150 (27)	
Lipid-lowering substudy	7842 (25)	5358 (27)	2484 (22)	<.0001

Note: Other ASCVD includes 50% or more coronary occlusion by angiography or Doppler ultrasound, transient ischemic attack, intermittent claudication, or ankle brachial index < 0.9.

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; ASCVD, atherosclerotic vascular disease; LVH, left ventricular hypertrophy.

* p-value < .05 is considered significant.

to amlodipine, chlorthalidone, or lisinopril for whom baseline creatinine values, aspirin exposure, and CVD status were available, and were stratified based on eGFR, as determined by the Modified Diet in Renal Disease (MDRD) study equation (Figure 1).[17] The main exposure variable was self-reported aspirin use at baseline. Using estimated propensity scores from a logistic model, 11 250 distinct aspirin uses were matched with replacement to 6885 distinct nonaspirin users.

Pre-existing cardiovascular disease was defined as prior MI or stroke, history of coronary revascularization, history of major ST depression or T-wave inversion on electrocardiogram, or other noncardiac atherosclerotic vascular diseases.

CKD was defined as an eGFR < 60 ml/min/m^2. Proteinuria data were not available in ALLHAT participants.

2.2 | Study end points

The primary end point was a composite of fatal CAD and nonfatal myocardial infarction (MI). Secondary end points included 1) all-cause mortality; 2) fatal and nonfatal stroke; 3) combined CHD, defined as a composite of the primary outcome plus coronary revascularization and angina requiring hospitalization; and 4) combined CVD, defined as combined CHD, stroke, any angina, heart failure, and peripheral artery disease (PAD). Also examined were potential adverse outcomes associated with aspirin use, defined as hospitalization for GI bleeding and progression to ESRD. Study end points were assessed at follow-up visits and were adjudicated based on clinic investigator reports, hospital discharge summaries, and death certificates. Occurrences of GI bleeding were obtained from Center of Medicare and Medicaid Services and Department of Veterans Affairs databases.[15,16] ESRD, reported from clinical study sites, is defined as death due to kidney disease, kidney transplantation, or initiation of renal replacement therapy.[18]

2.3 | Statistical methods

We summarized the patient demographics and clinical characteristics of the full population (3 arms) and the subset with non-missing baseline values for ASA, pre-existing CVD, and eGFR, and then subgroups with and without ASA at baseline (Table 1). Continuous variables (age, systolic/diastolic BP, eGFR, and BMI) were presented as mean with sample standard deviations;

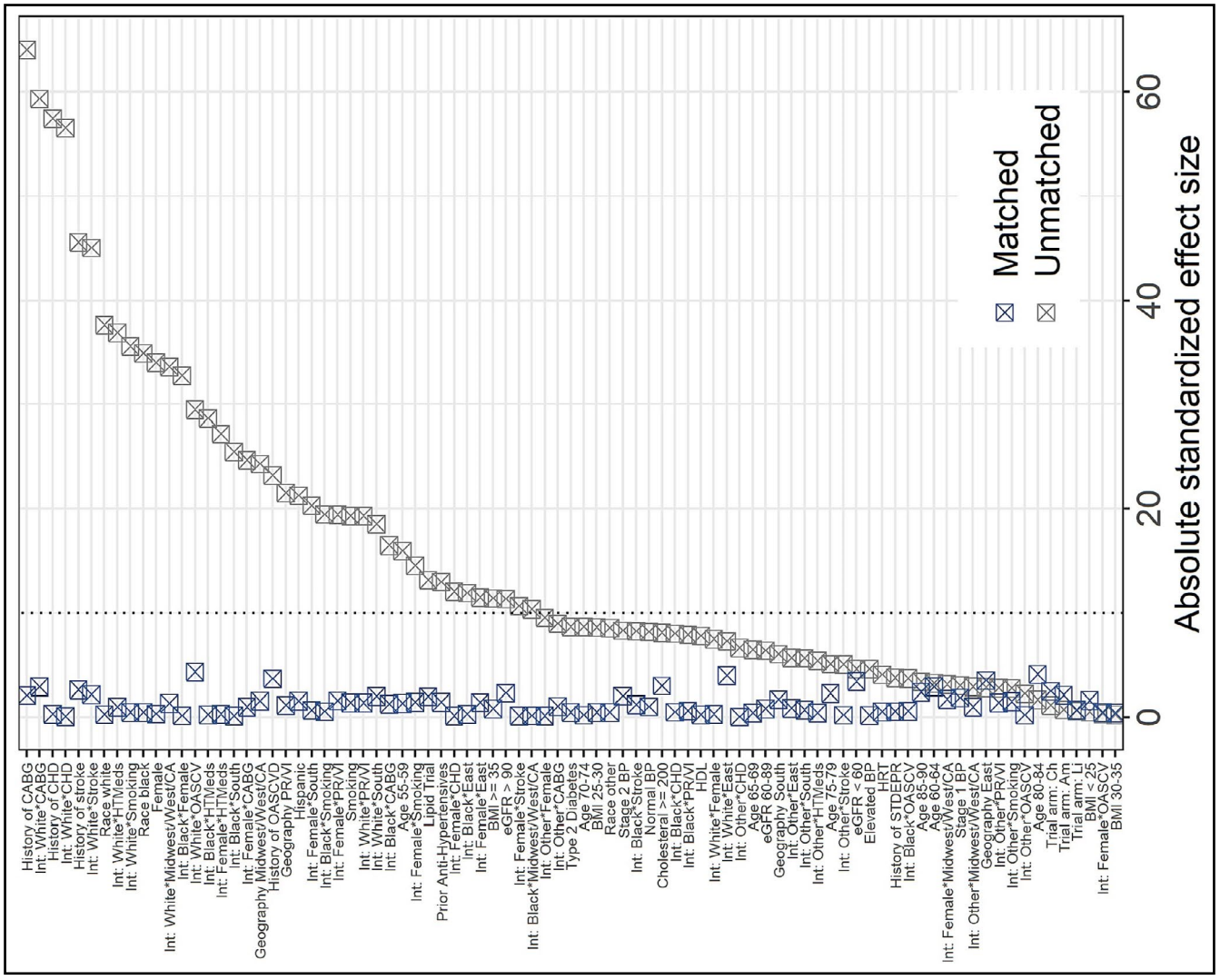

FIGURE 2 Differences between aspirin and nonaspirin populations, before and after propensity score matching [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Association between aspirin use ASA on fatal CAD or nonfatal MI in ALLHAT study participants, overall and stratified by CVD and eGFR at baseline

	Unmatched population				Propensity score-matched population	
	Incidence (events per 100 PY), no baseline ASA use	Incidence (events per 100 PY), baseline ASA use	Unadjusted hazard ratio, cox model (95% CI)	Adjusted hazard ratio, cox model (95% CI)	Hazard ratio, conditional cox model, (95% CI)	*p*-value for interactions, conditional cox model
Total population	1.7 (1.61, 1.78)	2.47 (2.33, 2.6)	1.45 (1.35, 1.57)	1.02 (0.94, 1.11)	0.94 (0.86, 1.02)	N/A
CVD at Baseline	2.15 (2, 2.3)	2.78 (2.61, 2.96)	1.3 (1.18, 1.42)	0.96 (0.86, 1.06)	0.93 (0.84, 1.04)	.53
No CVD at baseline	1.37 (1.28, 1.48)	1.78 (1.59, 2)	1.3 (1.14, 1.49)	1.16 (1.01, 1.33)	1.04 (0.82, 1.32)	
Baseline eGFR ≥ 90 ml/min/1.73 m^2	1.31 (1.17, 1.46)	1.88 (1.64, 2.14)	1.44 (1.21, 1.7)	0.97 (0.79, 1.18)	0.9 (0.57, 1.41)	.65
Baseline eGFR 60–89 ml/min/1.73 m^2	1.6 (1.49, 1.71)	2.5 (2.32, 2.68)	1.56 (1.42, 1.7)	1.09 (0.97, 1.22)	0.91 (0.78, 1.04)	
Baseline eGFR < 60 ml/min/1.73 m^2	2.7 (2.44, 2.98)	3.1 (2.76, 3.47)	1.14 (0.98, 1.3)	0.93 (0.79, 1.1)	0.96 (0.64, 1.4)	

Abbreviations: ASA, aspirin; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

[a]Adjusted population models and propensity models include age, race, ethnicity, sex, geographic region, cardiovascular history (myocardial infarction, stroke, history of coronary artery bypass graft, history of major ST depression or T-wave inversion, and other atherosclerotic vascular diseases), estimated glomerular filtration rate, smoking status, body mass index, blood pressure, diabetes, HDL, prior antihypertensives, cholesterol, hormone replacement, and ALLHAT study arm.

FIGURE 3 Association between aspirin use is associated with all-cause mortality. HR: 0.82 (0.76, 0.88) [Color figure can be viewed at wileyonlinelibrary.com]

categorical values were presented as the count and percent of patients with the given characteristic. Means of continuous values were compared across ASA subgroups using independent samples t tests, and differences in distributions of categorical variables were compared using chi-squared tests. Given the nonrandom exposure of patients to aspirin and the likelihood of significant confounding variables, propensity scores were estimated predicting aspirin exposure with the demographic, laboratory, and clinical variables collected in the ALLHAT study including but not limited to trial medication assignment, age, sex, race, smoking status, blood pressure, cholesterol, BMI, diabetes status, history of CVD, and statin use. Nonaspirin participants were matched with replacement to aspirin participants, and the standardized difference between aspirin exposure groups across possible confounders included in the propensity model was calculated for both the unmatched and matched populations to assess covariate balance (Figure 1).

Conditional Cox proportional hazard regression models, in which propensity-matched pairs were considered as strata, were used to determine hazard ratios (HR) with 95% confidence intervals (CI) to compare the risks for the primary and secondary end points for aspirin users versus nonusers overall and separately in each eGFR stratum 1) for participants with pre-existing CVD, to evaluate for secondary prevention benefit, and 2) for participants without pre-existing CVD, to evaluate for primary prevention benefit. Interactions of aspirin use with pre-existing CVD and aspirin use with eGFR stratum were assessed using likelihood ratio tests of nested models. Any value of $p < .05$ (two-tailed) was considered statistically significant. Sensitivity analyses were performed under alternative propensity matching procedures for eGFR subgroups.[19] Cause-specific hazard models were estimated for cardiovascular death and non-cardiovascular death, using cause of death data reported in ALLHAT. All analyses were performed in R version 3.5.1

TABLE 3 Effect of ASA on Secondary End Points in ALLHAT participants, overall and stratified by eGFR

	Overall			eGFR ≥ 90 ml/min/1.73 m^2	eGFR 60–89 ml/min/1.73 m^2	eGFR < 60 ml/min/1.73 m^2	
	All Patients, unadjusted hazard ratio	All patients, adjusted[a] hazard ratio	Propensity-matched[a] hazard ratio	Propensity-matched hazard ratio	Propensity-matched hazard ratio	Propensity-matched hazard ratio	
	Cox model	Cox model	Conditional cox model	Conditional cox model	Conditional cox model	Conditional cox model	Interaction *p*-value, Propensity-matched Dataset (aspirin use[a] eGFR)
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	
All-cause mortality	1.08 (1.01, 1.14)	0.91 (0.85, 0.97)	0.82 (0.76, 0.88)	0.64 (0.45, 0.92)	0.83 (0.73, 0.94)	0.84 (0.62, 1.15)	.04
CV death	1.22 (1.12, 1.33)	1 (0.91, 1.1)	0.87 (0.78, 0.97)	0.56 (0.32, 1)	0.87 (0.73, 1.05)	0.98 (0.64, 1.49)	.28
Non-CV death	0.95 (0.87, 1.04)	0.81 (0.74, 0.89)	0.73 (0.66, 0.81)	0.65 (0.4, 1.06)	0.73 (0.61, 0.89)	0.65 (0.41, 1.03)	.34
Stroke	1.19 (1.07, 1.32)	1.03 (0.92, 1.16)	1.01 (0.89, 1.15)	0.83 (0.46, 1.51)	1.04 (0.83, 1.29)	1.79 (0.93, 3.44)	.2
Combined CHD	1.72 (1.63, 1.81)	1.14 (1.07, 1.22)	1.05 (0.98, 1.12)	0.84 (0.59, 1.17)	1.08 (0.97, 1.21)	1.02 (0.76, 1.38)	.47
Combined CVD	1.61 (1.55, 1.68)	1.13 (1.08, 1.19)	1.09 (1.03, 1.15)	0.97 (0.74, 1.27)	1.1 (1, 1.21)	1.05 (0.82, 1.33)	.78

Abbreviations: ASA, aspirin; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

[a]Adjusted population models and propensity models include age, race, ethnicity, sex, geographic region, cardiovascular history (myocardial infarction, stroke, history of coronary artery bypass graft, history of major ST depression or T-wave inversion, and other atherosclerotic vascular diseases), estimated glomerular filtration rate, smoking status, body mass index, blood pressure, diabetes, HDL, prior antihypertensives, cholesterol, hormone replacement, and ALLHAT study arm.

3 | RESULTS

Baseline clinical and demographic characteristics of study participants stratified by aspirin use (n = 31 346) are presented in Table 1. There were differences in several baseline characteristics between participants taking aspirin compared to those not taking aspirin. Additional descriptive characteristics stratified by eGFR strata and baseline CVD are presented in Table S1. Within strata of CVD and eGFR, patients with aspirin exposure were more often white, male, and cigarette smokers compared to those without aspirin exposure. Rates of aspirin use were higher in patients with CVD. After propensity matching, absolute standardized differences between the two groups on all propensity matching variables were under 0.1, indicating a balanced distribution of possible confounder variables (Figure 2).

3.1 | Unmatched analyses

Without propensity matching, aspirin use was not associated with higher risk of fatal CAD or nonfatal MI in the entire study population (HR = 1.02, CI 0.94–1.11) and in patients with CVD (HR = 0.96, CI 0.86–1.06), but did associate with higher risk in patients without CVD at baseline (HR = 1.16, CI 1.01–1.33) (Table 2). Among the unmatched population, the effect of aspirin use on the risk of fatal CAD or nonfatal MI was modified by eGFR (p = .02, Table S2); aspirin use did not associate with increased risk of fatal CAD or nonfatal MI for patients with eGFR > 90 ml/min/1.73 m^2 (HR = 0.97, CI 0.79–1.18), eGFR 60–89 ml/min/1.73 m^2 (HR = 1.09, CI 0.97–1.22), or in patients with eGFR < 60 ml/min/1.73 m^2 (HR = 0.93, CI 0.79–1.1; Table 2).

3.2 | Propensity-matched analyses

In the propensity score-matched population, aspirin use was not associated with incidence of fatal CAD or nonfatal MI in the total study population (HR = 0.94, CI: 0.86–1.02) or in patients with CVD (HR = 0.93, CI: 0.84–1.04) or without CVD at baseline (HR = 1.04, CI: 0.82–1.32); p = .53 for the interactions. These results were consistent across strata of eGFR (interaction p value .65).

Aspirin use was associated with lower risk of all-cause mortality (HR = 0.82, CI: 0.76–0.88, p < .01) (Figure 3, Table 3). This effect is similarly observed in sensitivity analyses in which separate propensity models were estimated within each eGFR subgroup and/or propensity matches were restricted to the same eGFR subgroup (data not presented). There was a significant interaction between aspirin use and baseline eGFR (interaction p value 0.04). Risk of mortality was significantly lower for aspirin users compared to nonusers in participants with eGFR > 90 ml/min/m^2 (HR = 0.64, CI: 0.45–0.92) and eGFR 60–89 ml/min/m^2 (HR = 0.83, CI: 0.73–0.94), but not in participants with eGFR < 60 ml/min/m^2, (HR = 0.84, CI: 0.62–1.15).

Aspirin use associated with lower risk of both cardiovascular death (HR 0.87, CI: 0.78–0.97, p = .01) and non-cardiovascular death (0.73, CI: 0.66–0.81, p < .01). There was no interaction between aspirin and strata of eGFR for cardiovascular and non-cardiovascular death (interaction p value .28 and .34, respectively). There was no statistically significant association between aspirin use and risk of stroke (HR = 1.01, CI: 0.89–1.15, p = .2) or combined CHD (HR = 1.05, CI: 0.98, 1.12, p = .47, Table 3, Table S3).

The risk of combined CVD was higher in aspirin users compared to nonusers (HR = 1.09, CI 1.03–1.15, p < .01). There was no significant interaction with aspirin across strata of eGFR (interaction p value 0.78, Table S3).

Adverse effects of aspirin use were also examined (Table 4). There was no statistically significant association between aspirin use and GI bleed (HR = 0.96, CI 0.84–1.09) or development of ESRD (HR = 1.04, CI 0.79–1.37); this was consistent across strata of baseline eGFR (Table S4).

4 | DISCUSSION

In this post hoc study of propensity-matched participants in the ALLHAT trial, aspirin use was not associated with risk of fatal CHD or no fatal MI, stroke, or combined CHD. This was consistent across strata of eGFR and for participants with and without heart disease

TABLE 4 Association between aspirin use and adverse outcome overall and stratified by eGFR

			Overall	
	Number of events (% of patients)	Number of events (% of patients)	All patients, unadjusted hazard ratio	All patients, Adjusted[a] hazard ratio
	No ASA	ASA	Cox model (95% CI)	Cox model (95% CI)
GI bleeding	978 (7%)	694 (8%)	1.07 (0.97, 1.18)	0.95 (0.85, 1.05)
Progression to ESRD	265 (1%)	141 (1%)	0.9 (0.73, 1.1)	0.89 (0.7, 1.11)

Abbreviations: ASA, aspirin; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GI, gastrointestinal.

[a]Adjusted population models and propensity models include age, race, ethnicity, sex, geographic region, cardiovascular history (myocardial infarction, stroke, history of coronary artery bypass graft, history of major ST depression or T-wave inversion, and other atherosclerotic vascular diseases), estimated glomerular filtration rate, smoking status, body mass index, blood pressure, diabetes, HDL, prior antihypertensives, cholesterol, hormone replacement, and ALLHAT study arm.

at baseline. Aspirin use was associated with lower risk of mortality, particularly in participants with preserved kidney function. Aspirin use was also associated with higher risk of combined cardiovascular disease; this was consistent across strata of eGFR.

The primary finding that aspirin use was not protective against fatal CAD and nonfatal myocardial infarction is contrary to the established, long known benefit of aspirin for prevention of cardiovascular disease. Aspirin use as secondary prevention has led to significant reductions in morbidity, mortality, and risk of subsequent vascular events such as myocardial infarction or stroke in survivors of occlusive atherosclerotic cardiovascular events.[20] ALLHAT began in 1994; the study lasted 8 years with mean follow-up time of nearly 5 years. It is possible that during this time period, better preventive strategies in patients with established cardiovascular disease became a common element of clinical practice patterns. Indeed, use of statins to lower serum cholesterol levels became more common. In ALLHAT, nearly 36% of participants in all study groups reported taking lipid-lowering drugs, primarily statins, with some participants taking statins as part of the lipid-lowering arm of the ALLHAT study. Mean cholesterol levels decreased from 216 mg/dl to less than 200 mg/dl in all study groups after 4 years. In our study cohort, participation in the lipid-lowering arm ranged from 16% to 25% across study groups with pre-existing cardiovascular disease. Independent of statin use, participants in ALLHAT were also counseled on lifestyle changes and dietary modification.[15]

In addition to increased statin use and lowered serum cholesterol levels, blood pressure control in all arms of ALLHAT improved considerably over 5 years of follow-up. It is possible that better blood pressure control, dietary counseling, and increased use of statins decreased risk of fatal and nonfatal myocardial infarction and thus minimized the independent effect of aspirin on those same outcomes.

For primary prevention of cardiovascular events, the benefits of aspirin are principally dependent on underlying risk of incident cardiovascular events. In low- and moderate-risk individuals, defined as patients with Framingham risk scores less than 10 percent and 10 to 20 percent, respectively, benefits of aspirin use are limited with respect to all-cause or cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke and are counterbalanced by risk of bleeding. Our findings, consistent with the established literature, show no benefit of aspirin use on the primary outcomes of fatal or nonfatal myocardial infarction ALLHAT population.[21-23]

The association of aspirin and reduced all-cause mortality has been examined previously, with the preponderance of evidence from large meta-analyses suggesting a benefit, particularly in patients with pre-existing cardiovascular disease.[20,24-26] In contrast, studies examining use of aspirin for primary prevention commonly report no reduction in all-cause mortality with one recent study in healthy elderly people associating with an increase in mortality primarily related to increased cancer deaths.[21,27-30]

In this study, aspirin use in the overall population associated with modestly decreased risk of cardiovascular death in the propensity-matched model but with greater risk reduction for non-cardiovascular deaths. It is possible that aspirin administration lowered risk of all-cause mortality by an unidentified effect on common, established risk factors for cardiovascular disease or by reducing mortality burden of an unexamined outcome that was not included in propensity scoring to create matched pairs from the ALLHAT cohort. Examination of other potential causes of death from the ALLHAT study such as gastrointestinal malignancy, for which there is a modest protective effect of aspirin over time,[31] seems unlikely to account for the 18% risk reduction in all studied participants or the 36% risk reduction in participants with preserved renal function, where reductions in cardiovascular death were not seen. It is unclear at this time, from a mechanistic standpoint, how aspirin use could confer significant protective benefit from other common causes of death such as accidents, heart failure, chronic lung disease, sepsis, or dementia that may explain such a marked difference risk of all-cause mortality in our analysis. The underlying characteristics of participants who took aspirin could confer a mortality benefit independent of aspirin use. While our propensity-matched analysis attempted to adjust for confounders, we were limited to the variables collected for the ALLHAT study, which were generally clinical in nature.

The influence of renal function on the impact of aspirin use for prevention of cardiovascular disease is unclear. There was no

	eGFR ≥ 90 ml/min/1.73 m^2	eGFR 60–89 ml/min/1.73 m^2	eGFR < 60 ml/min/1.73 m^2	
Propensity-matched[a] hazard ratio	Propensity-matched hazard ratio	Propensity-matched hazard ratio	Propensity-matched hazard ratio	Interaction *p*-value, propensity-matched dataset (aspirin use[a] eGFR),
Conditional cox model (95% CI)	Conditional cox model (95% CI)	Conditional cox model (95% CI)	Conditional cox model (95% CI)	
0.96 (0.84, 1.09)	0.38 (0.15, 0.96)	0.95 (0.76, 1.19)	0.92 (0.52, 1.62)	.15
1.04 (0.79, 1.37)	1 (0.06, 15.99)	1.56 (0.83, 2.93)	1.91 (0.92, 3.96)	.96

association between aspirin use and prevention of fatal CAD or nonfatal myocardial infarction irrespective of estimated glomerular filtration rate. There was no significant association between aspirin use, eGFR and reduced risk of incident stroke, or combined CHD. However, we detected a significant interaction of eGFR and ASA on all-cause mortality in which the observed effect of aspirin on all-cause mortality diminished with eGFR. There was no association between aspirin use and risk of progression to ESRD, irrespective of baseline renal function.

While some studies show the converse,[11,12] multiple reports describing the limited effect of aspirin on CVD risk in CKD patients have been published. Kim et al showed a higher incidence of atherosclerotic CVD in low-dose aspirin users compared to nonusers with CKD in a propensity-matched cohort of participants both with and without pre-existing CVD. All-cause mortality was not significantly different between the two groups. Notably, use of aspirin was associated with increased risk for doubling of serum creatinine and development of ESRD.[10] Another post hoc, observational study of the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial showed no association between aspirin use and incidence of CVD or all-cause mortality in kidney transplant patients.[32] A small randomized controlled trial to examine the role of aspirin in the primary prevention of CVD in patients with CKD 3 and 4 did not show a reduction in fatal or nonfatal cardiovascular events, although aspirin use was associated with reduced renal events.[9]

Several potential mechanisms may account for the blunted beneficial effect of aspirin on mortality in patients with CKD. While traditional risk factors for cardiovascular disease such as hypertension, diabetes, dyslipidemia, and smoking are highly prevalent in patients with CKD, altered bone mineral metabolism, anemia, oxidative stress, abnormal cytokine milieu, and retention of uremic toxins are also common and may contribute to arterial calcification, vascular stiffness, endothelial dysfunction, and left ventricular hypertrophy.[33,34] These non-atherosclerotic conditions are not amenable to antiplatelet therapy, lead to higher rates of heart failure, sudden cardiac death, and arrhythmia, and complicate extrapolation of aspirin benefits.

The main safety concern with chronic aspirin use is bleeding, particularly GI bleeding and intracranial hemorrhage.[35-37] This study did not show any enhanced risk of GI bleeding in all matched pairs across all eGFR strata. We did not have data with regard to any other specific types of bleed. Previous studies addressing aspirin use in CKD patients are variable with regard to bleeding risk with some studies showing an increased risk of minor and major bleeding irrespective of baseline kidney function, while other studies show no increased risk of bleed across all strata of renal function.[9-12]

Our study showed that aspirin use associates with lower all-cause mortality and no increase in GI bleeding in patients with normal renal function or mild chronic kidney disease with hypertension and other risk factors for cardiovascular disease. It seems reasonable to continue to prescribe aspirin to patients with preserved renal function. However, based on results from this study, it is difficult to comment on the differential utility of aspirin use for primary or secondary prevention, as the driver for the reduction in all-cause mortality was not cardiovascular disease.

A major strength of this study is the use of a large, well-characterized cohort from the ALLHAT study which included a substantial proportion of participants with established cardiovascular disease. Additionally, there were large numbers of both aspirin users and nonusers across all included eGFR strata. Because ALLHAT included a substantial percentage of participants with established cardiovascular disease upon study entry, we were able to study the effect of aspirin use as both primary and secondary prevention for cardiovascular events.

However, there are important limitations to this analysis. This is a post hoc analysis of a trial that was neither designed to study the effect of aspirin as primary or secondary prevention for cardiovascular outcomes, nor to assess the benefit of aspirin on cardiovascular outcomes across differing degrees of renal impairment. We focused our analysis on aspirin use at baseline. We acknowledge that changes in both aspirin use and its clinical indications likely occurred throughout the follow-up time of the study but were not uniformly available across patients within the ALLHAT trial or incorporated in this analysis. Additionally, specific doses of aspirin were unavailable; thus, differential risk of adverse vascular occlusive events or bleeding episodes with either low-dose or standard-dose aspirin regimens could not be delineated. Data concerning glycemic control, cholesterol and triglyceride levels, glucose-lowering and cholesterol-lowering medications, or other medications that may have had an impact on overall cardiovascular health were not available. While propensity scoring allowed for the creation-matched pairs of aspirin users and nonusers and may largely eliminate confounding between groups, its use is subject to an inherent inability to control for unmeasured confounders.

In conclusion, this analysis of a propensity-matched cohort of ALLHAT trial participants did not show benefit to aspirin use as either primary or secondary prevention for any of the clinical outcomes examined or harm to aspirin use across strata of eGFR. It did, however, show an association between aspirin use and decreased all-cause mortality. The results of this study reinforce the need for a personalized approach taking into account potential benefits and harms when prescribing aspirin to patients for primary and secondary prevention of cardiovascular disease across the spectrum of chronic kidney disease.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Niraj Desai contributed to original idea for study, manuscript writing, and data collection. Brigid Wilson served as the statistician. Michael Bond contributed to original idea for study, data collection,

and manuscript writing. Alexander Conant reviewed the data and wrote the manuscript. Mahboob Rahman reviewed and edited the manuscript as the senior author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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