Statin Use and the Risk of Kidney Disease with Long Term Follow-up (8.4-years Study)

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ABSTRACT

Few studies have examined long-term effects of statin therapy on kidney diseases. The objective of this study was to determine the association of statin use with incidence of acute and chronic kidney diseases after prolonged follow-up. In this retrospective cohort study, we analyzed data from the San Antonio area military health care system from October 2003 through March 2012. Statin-users were propensity score matched to non-users utilizing 82 baseline characteristics including demographics, comorbidities, medications, and health care utilization. Study outcomes were acute kidney injury (AKI), chronic kidney disease (CKD), and nephritis/nephrosis/renal sclerosis. Of the 43,438 individuals included, we propensity score-matched 6,342 statin-users with 6,342 non-users. Statin-users had higher odds of AKI (odds ratio [OR] 1.30, 95% confidence interval [95% CI] 1.14-1.48), CKD (OR 1.36, 95% CI 1.22-1.52), and nephritis/nephrosis/renal sclerosis (OR 1.35, 95% CI 1.05-1.73). In a subset of patients without co-morbidities, the association of statin use with CKD remained significant (OR 1.53, 95% CI 1.27-1.85). In a secondary analysis, adjusting for diseases/conditions that developed during follow-up weakened this association. In conclusion, statin use is associated with increased incidence of acute and chronic kidney disease. These findings are cautionary and suggest that long-term effects of statins in real-life patients may differ from shorter-term effects in selected clinical trial populations.

Key words: statins, acute kidney injury, chronic kidney disease, nephritis, nephrosis.

INTRODUCTION

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines have broadened the scope of statin therapy due to their proven beneficial cardiovascular effects.¹ With broader application, previously under-recognized adverse events are likely to become apparent. Two large population-based studies demonstrated an association between kidney dysfunction and statin use.^{2,3} However, several randomized control trials (RCT) have not confirmed this association.^{4,5} A position paper from an international lipid expert panel supports the use of statins in patients with kidney diseases; however, it acknowledges that statins may be associated with increased risk of acute renal failure and proteinuria.⁶ Whereas RCTs are the gold standard to establish efficacy of medication, they may underestimate adverse events.^{7,8} The objective of this study was to examine the association of statin use with the risk of kidney disease after prolonged follow-up in a military health care system in which patients have similar health care access and standards.

METHODS

This retrospective cohort study was approved by the Institutional Review Boards at the Brooke Army Medical Center and VA North Texas Health Care System. We analyzed data from Tricare Prime or Plus enrollees in the San Antonio area. The database and study population have been described elsewhere.^{9,10} Briefly, data were extracted from October 1, 2003 to March 1, 2012 and encompassed outpatient and inpatient medical records, medical benefit claim data, laboratory data performed within military facilities, and pharmacy data regardless of dispensing pharmacy location or affiliation.^{11,12}

The study was divided into a baseline period (October 1, 2003 to September 30, 2005), used to describe baseline characteristics, and a follow-up period (October 1, 2005 to March 1, 2012), used to ascertain outcomes. Study participants were 30-85 years old, had ≥ 1 outpatient visit during the baseline period, had ≥ 1 visit during the follow-up period, and received ≥ 1 prescription medication during the baseline period. All patients were enrolled in the system during both the study baseline and follow-up periods with no missing data.

Exclusion criteria were: 1) patients with trauma or burns (based on International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes);¹⁰ 2) patients who began statin therapy after September 30, 2005 (end of the baseline period) to allow for the creation of statin-user and non-user groups with equal periods of follow-up; and 3) patients who received statins for < 90 days.

Statin-users filled statin prescriptions for a cumulative period of ≥ 90 days from October 1, 2004, to September 30, 2005. Non-users did not receive a statin throughout the entire study period. High and low-moderate intensity statin use was defined according to the 2013 ACC/AHA cholesterol guidelines with modification to include simvastatin 80 mg in the high-intensity group, which was widely used during the study period.¹

Outcomes were defined using pre-specified diagnosis groups of kidney diseases, using ICD-9-CM codes, as identified by the Agency for Healthcare Research and Quality Clinical Classifications Software (AHRQ-CCS).¹³ Our prespecified outcomes were: 1) acute and unspecified kidney injury (AKI): AHRQ-CCS category 157; 2) chronic kidney disease (CKD): AHRQ-CCS category 158; and 3) nephritis/nephrosis/renal sclerosis: AHRQ-CCS category 156 (Appendix A). The AHRQ-CCS has been previously validated,^{14,15} and has been widely used in

health care research.^{9,10,16,17} The use of ICD-9 codes to ascertain outcomes of CKD has been widely utilized in calculating Charlson comorbidity index using Deyo's method.¹⁸

We identified the following 2 main cohorts: a) Overall Cohort: This cohort included all patients who met the study criteria. From this cohort, we created a "propensity score (PS)-matched overall cohort" using 82 baseline characteristics (Appendix B) including demographics, comorbidities, Charlson comorbidity index,¹⁸ presence of renal diseases at baseline, health care utilization, and use of 20 classes of medications;¹⁹ and b) Healthy Cohort: This cohort included patients who used statins for primary prevention, and were without severe comorbidities, as described in a previous study;¹⁰ hence, we excluded patients with: 1) any Charlson comorbidity index element (including diabetes and CKD); 2) any cardiovascular diseases; and 3) conditions that might limit life expectancy or physical activity (Appendix C). We subsequently created a "PS-matched healthy cohort" of statins-users and non-users.

Our primary analysis examined outcomes in the two PS cohorts (PS-matched overall cohort and PS-matched healthy cohort). We also performed the following secondary analyses: 1) risk of outcomes in a "No-Charlson Comorbidity Subgroup" of the overall cohort: Patients with a Charlson comorbidity index > 0 at baseline were excluded; 2) risk of outcomes in a "Renal Disease Incident Subgroup" of the Overall Cohort: Patients with renal diseases at baseline were excluded; 3) risk of outcomes in the "High-Intensity Statin-users Subgroup" of the Overall Cohort: we restricted statin-users to those who used a high-intensity statin therapy at any point during the study period and examined the risk of outcomes in comparison to non-users; 4) risk of outcomes in a "Four-year Statin-users Subgroup" of the Overall Cohort: In this analysis, we restricted statin-users to those who used statins for ≥ 4 years and examined the risk of outcomes in comparison to non-users; and 5) risk of outcomes in the healthy cohort; 6) risk of outcomes in

each of PS-matched overall cohort and PS-matched healthy cohort adjusting for other diseases/conditions that may have developed during the follow-up period such as incident diabetes mellitus,¹⁰ hypertension requiring antihypertensive medications, and the number of coronary or arterial revascularization procedures during follow-up period; and 7) time-to-event analysis of outcomes in PS-matched overall cohort using Cox proportional hazard analysis.

We also performed the following sensitivity analyses: 1) dose-response in the overall cohort: we compared the risks of outcomes between high intensity statin-users and low-moderate intensity statin-users from the overall cohort and 2) dose-response in the healthy cohort: we compared the risks of outcomes between high intensity statin-users and low-moderate intensity statin-users from the healthy cohort.

Baseline characteristics of the groups were compared using chi-square analysis for categorical variables and unpaired 2-tailed Student's t test for continuous variables. A logistic regression model was used to create the PS and perform nearest number matching to achieve 1:1 matching and balance between groups at $p > 0.05$ (Fig 1), as described previously.^{9,10} For the PS-matched analyses, we calculated the odds ratios using conditional logistic regression, since the cohorts were matched with no statistically significant imbalances. We calculated the number needed to be exposed for 1 additional person to be harmed according to a published formula.²⁰ For secondary and sensitivity analyses, we used separate logistic regression models for each outcome, in which the outcome was the dependent variable, statin use (or high-intensity statin use) was the independent variable, and adjusted for propensity score. Risk of outcome was represented as odds ratio (OR) and 95% confidence interval (95%CI). A two-tailed P value of ≤ 0.05 was considered to be statistically significant. Statistical analyses were performed using Stata version 12 (College Station, TX) and SPSS version 19 (Armonk, NY).

RESULTS

A total of 43,438 patients met inclusion and exclusion criteria (13,626 statin-users and 29,812 non-users; Figure 1). Statin-users were older, had more comorbidities, and utilized more health care; a full description of this cohort was previously described.^{9,10} The mean duration of follow-up was 6.19 ± 0.64 years (median follow-up = 6.42 years; interquartile range = 6.21, 6.48 years). Simvastatin was most commonly prescribed (73.5%), followed by atorvastatin (17.4%), pravastatin (7%), and rosuvastatin (1.7%). Mean cumulative duration of statin use was 4.65 ± 1.82 years. Approximately 38% (n=5,214) of statin-users were prescribed high-intensity statins.

We matched 6,342 pairs of statin-users and non-users in the PS-matched overall cohort and 3,351 pairs in the PS-matched healthy cohort with no significant differences in characteristics between the treatment arms (table 1 and 2). In the PS-matched overall cohort, statin-users had statistically significant higher OR for AKI, CKD, and nephritis/nephrosis/renal sclerosis. In the PS-matched healthy cohort, statin-users were more likely to have CKD as compared to healthy non-users, but not AKI and nephritis/nephrosis/renal sclerosis (table 3).

For secondary analyses, statin-users were overall more likely to have all outcomes. However, this association was weakened and occasionally disappeared upon adjustment for incident diseases/conditions that occurred during the follow-up period (although they were balanced at baseline). Time-to-event analysis yielded similar results (figure 2). In sensitivity analyses, high-intensity statin-users in the overall cohort had a higher incidence of outcomes compared to low-moderate intensity statin-users (table 4).

DISCUSSION

This study demonstrated a significant association between statin use and risk of kidney disease in a cohort of patients who were followed for up to 6.5 years. In the PS-matched overall cohort, statin-users were 30% more likely to develop AKI and 36% more likely to develop CKD. Several secondary analyses showed generally consistent associations of statin use and kidney diseases and sensitivity analyses showed that use of high-intensity statins in comparison to lower-intensity statins was associated with higher odds ratios of outcomes.

In a separate study from this same cohort, statin-users had a higher risk of incident diabetes and diabetic complications during follow-up,¹⁰ which might be expected to increase the risk of incident kidney diseases. Additionally, statin-users may be more likely to undergo revascularization procedures during follow-up, which can increase the risk of kidney diseases. Adjusting for these variables in secondary analyses weakened the association of statin therapy with CKD and AKI and completely abolished the association with nephritis/nephrosis/renal sclerosis.

Some studies noted a similar association between statin use and kidney diseases (table 5).^{2,3,21} Cerivastatin was associated with higher risk of renal failure,²² and rosuvastatin 80 mg daily was found to be associated with persistent proteinuria and hematuria (1.3% at 40 mg dosage and approximately 6% at 80 mg).²³ On the other hand, other studies did not show such an association and even suggested that statins may exhibit nephro-protective effects (table 5).^{4,5,24-30}

How does one reconcile these differences? There are important methodological considerations to be taken into account.⁸ Observational data can be very valuable in delineating medication adverse events, specifically those that are slower to develop beyond the relatively short study time period of most clinical trials.⁸ Observational studies are more likely to represent the diversity of the general population. However, observational studies can be influenced by

unrecognized confounders and their inability to determine causation. Sample size in RCTs is based on efficacy outcomes and not usually powered to detect adverse effects. RCTs commonly exclude patients with preexisting significant comorbid conditions or those with polypharmacy. Non-adherence and withdrawal from trials may result in underreporting adverse events.⁷ RCTs have relatively short duration of follow-up and may be prematurely terminated once efficacy outcomes are reached. It is common to find serious adverse effects in post-marketing surveillance studies as a result of wider application to unselected population.

Our study has several strengths as well as limitations (table 5). The use of ICD-9-CM codes may lack sensitivity and may not provide accurate information on disease severity. The lack of laboratory data, such as creatinine clearance, is a major limitation of this study. Since laboratory results were available only if tests were performed within military facilities, they were not available for a majority of our population. However, these limitations are more likely to be non-differential and would affect both treatment arms equally. The use of pharmacy data to account for medication use assumes patient compliance. Importantly, 88% of statin-users in this study filled their prescription for ≥ 2 years. Although we accounted for several baseline characteristics and created propensity score-matched groups, the presence of residual confounders cannot be excluded.

The findings of this study, though cautionary, suggest that short-term RCTs may not fully describe long-term adverse effects of statins. On the one hand, statins lower cardiovascular morbidity and mortality; on the other hand, statins increase the risk of incident diabetes and possibly kidney diseases; both of which paradoxically increase long-term morbidity and mortality. Statins' primary prevention RCTs were occasionally prematurely terminated once efficacy in reducing major acute cardiovascular events was achieved, and rarely had total

mortality as a primary outcome. Therefore, further studies, specifically primary prevention studies, are urgently needed in which the long-term effects of statins on total mortality and total comorbidity indices (not only cardiovascular morbidity) are set as the primary outcomes.

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Figure 1. Study flow diagram.

Figure 2. Hazards of kidney disease outcomes in propensity score-matched overall cohort (6,342 non-users and 6,342 statin-users).

Legend: Legend: Upper panel depicts hazard ratios of outcome events using Cox proportional hazard analysis without further adjustment since treatment groups were balanced at baseline; lower panel depicts hazard ratios of outcome events using Cox proportional hazard analysis with adjustment to presence of hypertension requiring treatment during follow-up period and number of coronary or peripheral arterial revascularization procedures during follow-up period.

HR = hazard ratio, 95%CI = 95% confidence interval. Horizontal axis is days from beginning of follow-up period to outcome event.

Table 1. Selected baseline characteristics of propensity score-matched statin-users and non-users from the overall cohort

Variable	Statin-user		<i>P</i> value
	No (n = 6,342)	Yes (n = 6,342)	
Age (years)	56.0 ± 12.0	55.7 ± 12.4	0.1
Women	2,856 (45.0%)	2,924 (46.1%)	0.2
Alcohol-related disorders	83 (1.3%)	78 (1.2%)	0.7
Substance-related disorders	24 (0.4%)	22 (0.3%)	0.8
Smoker*	534 (8.4%)	509 (8.0%)	0.4
Overweight/obese**	993 (15.7%)	960 (15.1%)	0.4
Diabetes mellitus	743 (11.7%)	789 (12.4%)	0.2
Diabetes mellitus with complications	220 (3.5%)	247 (3.9%)	0.2
Heart valve disorder	402 (6.3%)	403 (6.4%)	0.97
Hypertension	3,766 (59.4%)	3,707 (58.5%)	0.3
Hypertension with complications and secondary hypertension†	176 (2.8%)	181 (2.9%)	0.8
Hypertension with complications	171 (2.7%)	175 (2.8)	0.9
Secondary hypertension	8 (0.1%)	11 (0.2%)	
Acute myocardial infarction	20 (0.3%)	25 (0.4%)	0.5
Coronary atherosclerosis and other heart disease	277 (4.4%)	314 (5.0%)	0.1
Dysrhythmia	874 (13.8%)	887 (14.0%)	0.8
Cerebrovascular disease	128 (2.0%)	125 (2.0%)	0.9
Peripheral and visceral atherosclerosis	153 (2.4%)	169 (2.7%)	0.4
Aortic, peripheral, and visceral artery aneurysms	39 (0.6%)	54 (0.9%)	0.1
Aortic and peripheral arterial embolism or thrombosis	12 (0.2%)	14 (0.2%)	0.9
Chronic obstructive pulmonary disease and bronchiectasis†	734 (11.6%)	742 (11.7%)	0.8
Chronic obstructive pulmonary disease	721 (11.4%)	740 (11.7%)	0.6
Bronchiectasis	19 (0.3%)	4 (0.1%)	0.003
Asthma	375 (5.9%)	366 (5.8%)	0.7
Nephritis, nephrosis, renal sclerosis, and chronic kidney disease	88 (1.4%)	93 (1.5%)	0.8
Acute and unspecified renal failure	65 (1.0%)	78 (1.2%)	0.3
Rheumatoid arthritis and related disease; systemic lupus erythematosus and connective tissue disorders	172 (2.7%)	156 (2.5%)	0.4
Number of inpatient admissions during baseline period	0.25 ± 0.75	0.26 ± 0.77	0.8
Number of outpatient medical encounters during baseline period	31.67 ± 36.76	31.81 ± 40.63	0.8
Number of encounters for immunization during baseline period	0.48 ± 1.60	0.49 ± 3.71	0.8
Charlson comorbidity total score‡	0.64 ± 1.23	0.66 ± 1.25	0.3
Medications at baseline			
Beta-blocker	1,099 (17.3%)	1,123 (17.7%)	0.6
Diuretic	1,740 (27.4%)	1,718 (27.1%)	0.7

Angiotensin converting enzyme inhibitor/ Angiotensin receptor blocker	2,137 (33.7%)	2,141 (33.8%)	0.96
Calcium channel blocker	987 (15.6%)	1,001 (15.8%)	0.8
Proton pump inhibitor	2,009 (31.7%)	2,030 (32.0%)	0.7
Aspirin	1,835 (28.9%)	1,890 (29.8%)	0.3
Non-steroidal anti-inflammatory drug	3,729 (58.8%)	3,702 (58.4%)	0.6
Selective serotonin reuptake inhibitor	1,059 (16.7%)	1,067 (16.8%)	0.9
Systemic corticosteroid	257 (4.1%)	249 (3.9%)	0.8
Cytochrome p450§	386 (6.1%)	414 (6.5%)	0.3
Non-statin lipid lowering drug	373 (5.9%)	391 (6.2%)	0.5
Antiplatelet agent (other than aspirin)	101 (1.6%)	112 (1.8%)	0.5

Discrete variables represented as n (%) and continuous variables represented as mean $\pm$ standard deviation. Diagnosis groups are defined as per the Agency of Health Research and Quality-Clinical Classification Software, except if otherwise specified.

* Diagnosis was defined as ICD-9-CM codes 3051 and V1582.

** Diagnosis is based on selected ICD-9-CM diagnosis codes from category 56 of the Agency of Health Research and Quality-Clinical Classification Software (other nutritional; endocrine; and metabolic disorders) related to overweight, obesity and hyperalimentation (codes: 2780, 27800, 27801, 27802, 27803, 2781, 2788, and 7831).¹⁰

† Each of the disease category of “Hypertension with complications and secondary hypertension” and “Chronic obstructive pulmonary disease and bronchiectasis” was introduced into our propensity score as a single variable since each of them was designated as a separate disease category by the Agency of Health Research and Quality-Clinical Classification Software. The subdivisions of these disease categories were not included as separate variables in creating the propensity score.

‡ Charlson comorbidity total score was calculated using Dyeo et al method.¹⁸

§Medications that inhibit the Cytochrome p450 system as identified in an FDA warning.¹⁹

Table 2. Selected baseline characteristics of propensity score-matched statin-users and non-users in the healthy cohort*

Variable	Statin-user		<i>P</i> value
	No (n =3,351)	Yes (n =3,351)	
Age (years)	53 ± 11	53 ± 11	0.7
Women	1,285 (38.3%)	1,314 (39.2)	0.5
Charlson comorbidity score	0	0	0
Smoker	241 (7.2%)	237 (7.1%)	0.9
Alcohol-related disorders	29 (0.9%)	31 (0.9%)	0.9
Overweight/obese†	493 (14.7%)	455 (13.6%)	0.2
Hypertension	1,704 (50.9%)	1,678 (50.1%)	0.5
Acute kidney injury	5 (0.1%)	5 (0.1%)	1.0
Asthma	102 (3.0%)	96 (2.9%)	0.7
Osteoarthritis, arthropathy, and back disorder	1,534 (45.8%)	1,548 (46.2%)	0.8
Sprains, strains, and trauma-related joint disorders	596 (17.8%)	603 (18.0%)	0.9
Rehabilitation care; fitting of prostheses; and adjustment of devices	506 (15.1%)	544 (16.2%)	0.2
Number of inpatient admissions during baseline period	0.08 ± 0.3	0.08 ± 0.3	0.8
Number of outpatient medical encounters during baseline period	21.1 ± 22.7	21.1 ± 19.1	0.9
Number of encounters for immunization during baseline period	0.40 ± 1.1	0.42 ± 1.14	0.4
Receiving immunization and screening for infectious disease	643 (19.2%)	670 (20.0%)	0.4
Medications at baseline			
Beta-blocker	428 (12.8%)	459 (13.7%)	0.3
Diuretic	728 (21.7%)	742 (22.1%)	0.7
Angiotensin converting enzyme inhibitor/ Angiotensin receptor blocker	886 (26.4%)	899 (26.8%)	0.7
Calcium channel blocker	384 (11.5%)	395 (11.8%)	0.7
Aspirin	777 (23.2%)	826 (24.6%)	0.2
Non-steroidal anti-inflammatory drug	1,911 (57.0%)	1,926 (57.5%)	0.7
Non-statin lipid lowering drug	194 (5.8%)	217 (6.5%)	0.3
Oral hypoglycemic agent	16 (0.5%)	16 (0.5%)	1.0
Cytochrome p450‡	182 (5.4%)	193 (5.8%)	0.6
Selective serotonin reuptake inhibitor	441 (13.2%)	456 (13.6%)	0.6
Systemic steroid	63 (1.9%)	72 (2.1%)	0.5

Discrete variables represented as n (%) and continuous variables represented as mean ± standard deviation

* Full description of characteristics of this cohort was previously published.¹⁰

† Diagnosis is based on selected ICD-9-CM diagnosis codes from category 56 of the Agency of

Health Research and Quality-Clinical Classification Software (other nutritional; endocrine; and metabolic disorders) related to overweight, obesity and hyperalimentation (codes: 2780, 27800, 27801, 27802, 27803, 2781, 2788, and 7831).

‡ Medications that inhibit the Cytochrome p450 system as identified in an FDA warning.¹⁹

users and 3,351 statin-users)

Acute and unspecified renal failure	127 (3.8%)	157 (4.7%)	1.18† 1.07‡	0.93 – 1.50 0.84 – 1.37	0.18 0.57
Chronic kidney disease	193 (5.8%)	287 (8.6%)	1.14† 1.34‡	1.19 – 1.75 1.11 – 1.63	<0.001 0.003
Nephritis; nephrosis; renal sclerosis	18 (0.5%)	25 (0.7%)	1.10† 1.08‡	0.60 – 2.05 0.58 – 2.01	0.75 0.81

NNEH = number needed to be exposed for 1 additional person to be harmed according to a published formula²⁰

* Adjusted odds ratio: adjusting for propensity score

† Adjusted odds ratio: adjusting for presence of diabetes mellitus during follow-up period.

‡ Adjusted odds ratio: adjusting for presence of diabetes mellitus during follow-up period, presence of hypertension and receiving antihypertensive medication during follow-up period, and the number of coronary or arterial revascularization procedures during follow-up period.

Table 4. Sensitivity analyses of risks of kidney disease in high intensity statin-users in comparison to low-moderate intensity statin-users

Variable	Low-moderate intensity statin-users	High intensity statin-users	Odds Ratio	95% Confidence Interval	<i>P</i> value
Dose-response in the overall cohort (8,412 low-moderate-intensity statin-users and 5,214 high-intensity statin-users)					
Acute and unspecified renal failure	1,165 (13.8%)	1,094 (21.0%)	1.24	1.13-1.37	<0.001
Chronic kidney disease	1,803 (21.4%)	1,523 (29.2%)	1.14	1.05-1.25	<0.001
Nephritis; nephrosis; renal sclerosis	464 (5.5%)	558 (10.7%)	1.45	1.27-1.66	<0.001
Dose-response in the healthy cohort (2,827 low-moderate-intensity statin-users and 1,155 high-intensity statin-users)					
Acute and unspecified renal failure	151 (5.3%)	74 (6.4%)	1.12	0.84-1.50	0.4
Chronic kidney disease	267 (9.4%)	146 (12.6%)	1.28	1.03-1.60	0.03
Nephritis; nephrosis; renal sclerosis	17 (0.6%)	17 (1.5%)	2.32	1.18-4.57	0.02

Table 5. Examples of studies that examined the association of statins and kidney diseases

Study	Study description	Results	Limitations
Studies that found an association between statin use and the risk of kidney diseases			
Hippisley-Cox & Coupland ²	Prospective observational study (2,004,692 subjects) from January 2002 to June 2008; new statin users were compared to non-users in primary care setting.	Risk of AKI was increased in statin-users; HR ranged 1.50 to 2.19 depending on the type of statin used; HR increased with increasing dose. Risk returned to baseline within 1 to 3 years of stopping statins.	Observational nature of the study; used multiple imputation to replace missing values.
Dormuth et al ³	Retrospective observational analysis of Administrative databases and meta-analysis to evaluate incidence of hospitalization due to AKI and use of high potency statins versus low potency statins; 2,067,639 statin users.	High-intensity statin-users had a fixed effect rate ratio 1.34, 95% CI 1.25-1.43 of AKI within 120 days of starting therapy as compared to low dose statin-users.	Retrospective observational nature of the study; captured only most severe events that required admission.
Li et al ²¹	Retrospective cohort study of 104,041 adults $\geq$ 66-year-old between June 2002 and March 2013.	Concomitant use of a statin and clarithromycin was associated with increased risk of admission for AKI (adjusted relative risk: 1.65, 95% CI: 1.31-2.09).	Retrospective observational nature of the study; captured only most severe events that required admission.
Studies with mixed findings			
Nikolic et al ²⁹	Meta-analysis of randomized controlled trials; 20 trials including 6452 CKD subjects randomized to statin vs. placebo.	Results support that statins may decrease urinary protein with the effect persisting for short-term therapy ($\leq$ 12 months); decrease serum creatinine, but only for long-term therapy (3 years); statins modestly preserved GFR, with a significant increase between 1-3 years.	The Cochrane Q test for heterogeneity indicated that the studies of effect on several renal outcomes were heterogeneous; many studies were of shorter duration ($<$ 1 year); risk of selective reporting and publication bias.
Ryzs et al ³⁰	Review article of studies published about statin use in patients with chronic kidney diseases.	Examples of the findings include: "..., statins had no influence on creatinine clearance. In another analysis, beneficial effects of statin were observed in patients with overt proteinuria but not with	The article reviewed and presented findings of other metaanalyses and studies but did not synthesize the evidence into conclusive statistical

microalbuminuria or normoalbuminuria”.

figures.

Studies that found no association or beneficial effects of statin use and kidney diseases

Athyros et al ²⁷	A post-hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study; a prospective open label study; 1,600 patients randomized to atorvastatin or usual care.	Statin-users had significantly higher creatinine clearance in comparison to non-users based on measured serum creatinine; benefit seemed more prominent in the elderly.	Primary endpoint was cardiovascular diseases; significant crossover between treatment arms; 12% patients discontinued therapy after 6-8 months.
Bangalore et al ⁴	Metaanalysis of placebo controlled statin trials (24 trials) and high dose versus low dose statin.	Reported no difference in renal adverse events within or after 120 days of randomization.	Significant differences between studies in ascertainment of adverse events and measurement of renal functions; selectivity of clinical trials, short duration or small sample size.
Colhoun et al ²⁴	A post-hoc analysis of the Collaborative Atorvastatin Diabetes Study (CARDS); 2,838 patients with type 2 diabetes were randomized to atorvastatin or placebo, with a median follow-up of 3.9 years.	Atorvastatin treatment was associated with improvement in annual change in eGFR (0.18 mL/min/1.73 m ² /year; 95% CI: 0.04 to 0.32; P = 0.01), but did not influence the incidence of albuminuria or regression to normoalbuminuria.	The study excluded patients with serum creatinine > 1.7 mg/dL; albumin-creatinine examinations were not assessable in 16% of participants; the study was prematurely terminated.
Koren et al ²⁶	A post-hoc analysis of the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) study; a prospective open label study; 2,442 patients randomized to maximized atorvastatin or usual care.	There was no decrease in eGFR in atorvastatin-treated patients during the course of the study.	Primary endpoint was cardiovascular diseases; serum creatinine necessary to calculate eGFR was available in 1,768 patients only; follow-up of atorvastatin patients was restricted to every 6 months; interim data were unavailable for usual-care patients.
Ridker et al ²⁵	A secondary analysis of the Justification for the Use of Statins in Prevention—an Intervention Trial Evaluating Rosuvastatin (JUPITER); 17,802 patients randomized to	The median eGFR at 12 months was marginally improved among those randomly allocated to rosuvastatin as compared with placebo (66.8 vs. 66.6	The study was prematurely terminated with a median follow-up of 1.9 years; out of > 80,000 screened patients, 17,802 participants were selected, and out of those 25% dropped out of

	rosuvastatin or placebo.	ml/min/1.73 m ² , p = 0.02).	the study.
Shepherd et al ²⁸	Sub-analysis of the Treating to New Targets (TNT) Study; 10,001 patients with coronary heart disease randomly assigned to 10 or 80 mg atorvastatin; eGFR was compared at baseline and at the end of follow-up.	eGFR showed an increase of 3.5 ± 0.14 ml/min per 1.73 m ² with 10 mg and 5.2 ± 0.14 ml/min per 1.73 m ² with 80 mg (P < 0.0001 for treatment difference).	Only 9,656 participants had complete renal data; 2,236 patients discontinued the study medication.

Current study

Acharya et al (current study presented in this article)	Retrospective observational study of 43,438 patients followed longitudinally from October 1, 2003 to March 1, 2012, within the same healthcare system with similar access and benefits and no missing data. Examined risks of kidney diseases in PS-matched cohort (6,342 pairs of statin-users and nonusers), and a PS-healthy cohort with no severe comorbidities (3351 pairs of statin-users and nonusers).	Statin-users and non-users were balanced in all baseline characteristics and had complete follow-up throughout the study (8.4 years). Statin use was consistently associated with increased odds ratios of being diagnosed of all outcomes (OR range: 1.3-1.77). However, this association was weakened after adjusting for diseases/interventions that occurred during the follow-up period. High-intensity in comparison with low-moderate-intensity statin-users had higher odds ratios of all outcomes (OR range: 1.12-2.32).	Retrospective nature of the study; use of ICD-9-CM codes in identifying baseline characteristics and outcomes; ICD-9-CM may not adequately describe disease severity; lack of laboratory data of eGFR or serum creatinine.
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AKI = Acute kidney injury; CKD = Chronic kidney disease; eGFR = estimated glomerular filtration rate; HR = Hazard ratio; OR = Odds ratio; PS = Propensity score

All identified individuals (n=59,365)

Excluded: (n=13,116)

- Trauma/burn: (n=2,124)
- Statins after 9/30/2005: (n=13,287)
- Statins <90 days: (n=516)

Individuals who met inclusion & exclusion criteria

(n=43,438: 13,626 statin-users and 29,812 non-users)

Excluded to form the healthy cohort

13,311 patients with CCI > 0.0
3,876 patients with CVS diseases
281 patients with other comorbidities

Statin-users

(n=3,982)

Non-users

(n=21,988)

PS-matching Healthy Cohort

Statin-users

(n=3,351)

Non-users

(n=3,351)

Statin-users

(n=13,626)

Non-users

(n=29,812)

PS-matching Whole Cohort

Statin-users

(n=6,342)

Non-users

(n=6,342)

Figure 2. Hazards of kidney disease outcomes in propensity score-matched overall cohort (6,342 non-users and 6,342 statin-users)