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Statins for primary prevention of cardiovascular disease and the risk of acute kidney injury

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Abstract

Purpose: To investigate the risk of acute kidney injury (AKI) in subjects initiating statin therapy for primary prevention of cardiovascular disease (CVD).

Methods: A nationwide cohort study using French hospital discharge and claims databases was performed, studying subjects from the general population aged 40 to 75 years in 2009, with no history of CVD and no lipid-lowering drugs during the preceding 3-year period, followed for up to 7 years. Exposure to statins (type, dose, and time since first use) and to other drugs for CVD risk was assessed. The primary outcome was hospital admission for AKI.

Results: The cohort included 8 236 279 subjects, 818 432 of whom initiated a statin for primary prevention. During 598 487 785 person-months exposed to statins, 700 events were observed, corresponding to an incidence of AKI of 4.59 per 10 000 person-years (7.01 in men, 3.01 in women). AKI mainly occurred in the context of organ failure, sepsis, and genitourinary disease. A 19% increased rate of AKI (hazard ratio = 1.19, 95%CI: 1.08-1.31) was observed in men exposed to statins, whereas no increase in the overall risk of AKI was observed in women. However, exposure to high-potency statins was associated with a 72% to 116% increased risk in both genders and a dose-effect relationship observed for rosuvastatin and atorvastatin. No temporal pattern of occurrence nor interaction with drugs for CVD risk was observed.

Conclusions: Although the overall risk of AKI appears moderately increased, more attention should be paid to renal function in subjects taking statins for primary prevention both in clinical practice and from a research viewpoint.

KEYWORDS

acute kidney injury, primary prevention, statins

1 | INTRODUCTION

Statins have become a cornerstone treatment in the primary and secondary prevention of atherosclerotic cardiovascular disease (CVD).[1,2] Statins are generally well tolerated, with only rare serious, life-threatening adverse events (AE).[3] Most well-documented AEs associated with statins are related to muscle toxicity, including rhabdomyolysis.[4,5] Kidney diseases, notably acute kidney injury (AKI), have been reported to be associated with statins, independently of rhabdomyolysis. In early clinical trials involving high doses (>40 mg daily), rosuvastatin was suspected to cause proteinuria, hematuria, and AKI.[6,7] Several observational and real life studies have also demonstrated that other statins can be associated with some degree of kidney disease, usually in a dose-dependent manner.[8-10] However, in all but one of these studies, which considered the context of statin prescription (primary or secondary prevention),[10] their results may have been confounded by bias relative to statin indication and other factors related to the patients' pathological background, such as CVD, which increase the risk of AKI. Because the primary prevention population is of particular interest, given the relevance of safety issues in this population and because it can be used to study the relationships between statins and AEs with only limited confounding from multiple morbidities and comedications, we investigated the risk of AKI associated with statins in this context. We therefore conducted a large nationwide cohort study in France on subjects starting statins for primary prevention using the French population-based hospital discharge and claims databases, which cover all of the country's 66 million inhabitants. Particular attention was paid to the type of statin, dose, time since first use, interaction with other drugs for CVD risk, and the pathological context in which AKI occurs.

2 | MATERIAL AND METHODS

2.1 | Study design and data source

We carried out a nationwide cohort study in France using the comprehensive French national health insurance claims database (*Système National d'Information Inter-Régimes de l'Assurance Maladie*) linked to the French hospital discharge database (*Programme de Médicalisation des Systèmes d'Information*). The claims database contains comprehensive data on all reimbursements of dispensed drugs, ambulatory care procedures, as well as care related to a severe or costly long-term disease (LTD), classified according to the International Classification of Diseases, 10th Revision (ICD-10).[11] This database also contains vital status, age, gender, place of residence, deprivation index of the municipality of residence,[12] and Complementary Universal Health Insurance (CMUc) status, which provides free health cover for low-income residents. The French hospital discharge database contains information about each patient admitted to a public or private hospital in France. This database contains discharge diagnoses (recorded by ICD-10 code), medical procedures performed, and length of stay. Claims data from the general health insurance scheme of mainland France,

available since 2006, were used in this study, which was approved by the French data protection agency (*Commission Nationale Informatique et Libertés*). All databases used in this study only contain anonymous patient records.

2.2 | Study population

To study a presumably healthy population that may initiate statin therapy for primary prevention of CVD, in accordance with recent American College of Cardiology/American Heart Association guidelines,[1] we assembled a cohort of all subjects aged 40 to 75 years in 2009, presenting the following characteristics: no known CVD (cardiovascular, neurovascular or peripheral artery disease), no LTD (including hypertension, diabetes, most kidney conditions), not more than 8 days of hospitalization over a 1-year period, no prescription of lipid-lowering drugs, and no hospitalization for AKI between 1 January 2006 and 1 January 2009 (Figure 1, Supplementary Table 1).

2.3 | Drug exposure

New statin users were identified during the 7-year study period (1 January 2009-31 December 2015) (Supplementary Table 1). Statin exposure was considered as a time-varying variable and was measured on a daily time-scale (days covered by the dispensed medications). A 30-day gap without coverage was used to define exposure discontinuation: subjects were considered to be exposed during this 30-day gap and nonexposed thereafter until the end of follow-up or censorship, or until treatment was resumed. Subjects who had never taken statins were considered to be nonexposed until the end of follow-up or censorship. High-potency statin therapy was defined as at least 10-mg rosuvastatin, at least 20-mg atorvastatin, or at least 40-mg simvastatin.[13] Changes in dose and type of statin were defined by any difference between N and N + 1 dispensings considered on a daily time-scale.

2.4 | Outcomes

The primary endpoint was hospital admission for AKI. All discharge diagnoses (ICD-10 code: N17 "Acute kidney failure") were used to define the endpoint, and the event was considered to occur on the first day of admission to hospital. However, in a sensitivity analysis, the effect of using a narrower definition of AKI was explored, considering only severe cases requiring hemodialysis or hemofiltration (Supplementary Table 1).

2.5 | Follow-up

Patients were followed for up to 7 years from 1 January 2009 until predefined outcome, CVD, LTD, hospitalization for more than 8 days over a 1-year period, death from any cause, or 31 December 2015, whichever came first. In the presence of CVD, the subject would no longer correspond to the context of primary prevention and the presence of serious disease (LTD or hospitalization ≥8 days, eg, for cancer)
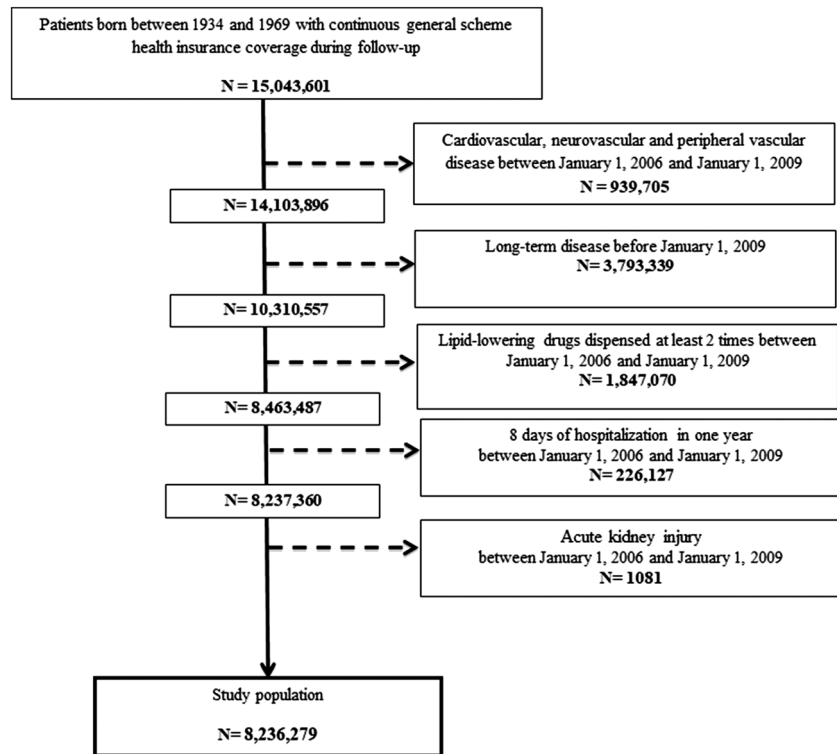
FIGURE 1 Study population flow chart

would probably require review of the need for or the priority of primary prevention of CVD.

2.6 | Statistical analysis

Cox proportional hazards models were used to estimate the hazard ratios of AKI for statins. Time-varying definitions for drug exposures were employed, allowing patients to fluctuate between exposure statuses (nonexposed, exposed at dose X_1 of statin Y_1, at dose X_2 of statin Y_2, etc.) and to simultaneously contribute time to multiple exposure categories. As recommended,[14] a discrete time dataset was formed, in which follow-up time was segmented into 84 one-month intervals. The type and dose of specific statin regimens were studied only for the first sequence of statin prescribed (ie, before the first treatment was stopped or changed). Hazard ratios and 95% confidence intervals (CI) were adjusted for all measured factors found to be associated with both statin prescription and AKI: age, CMUc, and the deprivation index of the patient's municipality of residence among baseline covariates, and antihypertensive, antidiabetic, and nonsteroidal anti-inflammatory drugs, aminoglycosides, imaging procedures with administration of iodinated contrast media among time-dependent exposures (Supplementary Table 1). Due to large differences in exposures and incidence of AKI, all analyses were conducted separately by gender.

3 | RESULTS

The cohort included 8 236 279 subjects, 3 230 868 men and 5 005 411 women, followed for an average of 72.7 months, among whom

325 815 men and 492 617 women initiated a statin for CVD primary prevention. Atorvastatin and rosuvastatin were the most commonly prescribed statins, followed by simvastatin and pravastatin (Table 1). No major difference in terms of the main sociodemographic characteristics, exposure to statins, and main drugs for CVD risk (antidiabetics and antihypertensives) was observed according to gender.

Seven hundred events were observed in subjects exposed to statins, producing an empirically larger incidence of AKI (4.59 events per 10 000 person-years, 95% CI: 4.26-4.94 per 10 000 person-years) than in the overall cohort (14 952 events, 3.00 events per 10 000 person-years, 95% CI: 2.95-3.05 per 10 000 person-years) (Table 2). The incidence of AKI was much higher in men than in women either exposed to statins (422 cases, 7.01 per 10 000 person-years, 95% CI: 6.37-7.71 per 10 000 person-years in men, vs 278 cases, 3.01 per 10 000 person-years, 95% CI: 2.68-3.39 per 10 000 person-years in women) or not exposed to statins (4.69 per 10 000 person years, 95% CI: 4.59-4.79 per 10 000 person-years in men vs 1.87 per 10 000 person-years, 95% CI: 1.83-1.92 per 10 000 person-years in women).

Baseline characteristics and short-term outcome of cases of AKI are presented in Table 2 (primary definition) and Supplementary Table 2 (cases treated by hemodialysis only). Cases treated by hemodialysis (N = 3112, 21%) were similar in terms of sociodemographic characteristics and statin exposure, but obviously presented more severe outcome, with a hospital mortality rate more than twofold higher than that observed in the overall cohort (55% vs 25%). There were 144 fatal cases among the 700 AKI events occurring on statin therapy (mean age: 61 years, case fatality rate: 21%), mostly concerning men (90/144). Twenty-seven deaths occurred on high-potency statin therapy (out of the 119 AKI events occurring on high-

TABLE 1 Cohort characteristics and exposures according to gender. Values are expressed as numbers (percentages) unless stated otherwise

	Men (n = 3 230 868)	Women (n = 5 005 411)
Total person-months of follow-up	228 739 344	369 748 441
Mean age at baseline (SD), year	52.2 (9.3)	52.0 (9.2)
CMUc[a] patient	123 723 (4)	250 159 (5)
Quintiles of deprivation index		
First quintile (least deprived)	691 061 (21)	1 073 801 (21)
Second quintile	679 458 (21)	1 053 824 (21)
Third quintile	628 627 (19)	979 720 (20)
Fourth quintile	634 945 (20)	982 243 (20)
Fifth quintile (most deprived)	596 777 (18)	915 823 (18)
Exposure to statins during the follow-up period		
Exposure to statins	325 815 (10)	492 617 (10)
Exposure to high-potency statins[b,c]	58 769 (18)	71 853 (15)
Person-months exposed to statins	7 227 419	11 082 906
Person-months exposed to high-potency statins[c]	878 970	1 013 273
Exposure to antidiabetic drugs during follow-up (cumulative incidence)	134 284 (4)	189 084 (4)
Exposure to antihypertensive drugs during follow-up (cumulative incidence)	1 058 166 (33)	1 781 532 (36)
First sequence of statins:		
type and initial dose of specific statin given		
Atorvastatin[b]	89 705 (28)	126 554 (26)
Dose 10 mg[d]	66 455 (74)	99 009 (78)
Dose 20 mg [d]	14 994 (17)	18 861 (15)
Dose ≥40 mg [d]	8256 (9)	8684 (7)
Fluvastatin[b]	5202 (2)	9291 (2)
Pravastatin[b]	57 292 (18)	90 137 (18)
Dose 10 mg [d]	10 611 (19)	19 948 (22)
Dose 20 mg [d]	37 515 (65)	60 805 (67)
Dose 40 mg [d]	9166 (16)	9384 (10)
Rosuvastatin[b]	111 381 (34)	165 938 (34)
Dose 5 mg [d]	95 131 (85)	146 670 (88)
Dose 10 mg [d]	14 705 (13)	17 360 (10)
Dose 20 mg [d]	1545 (1)	1908 (1)
Simvastatin[b]	61 904 (19)	100 567 (20)
Dose 10 mg [d]	13 625 (22)	26 091 (26)
Dose 20 mg [d]	45 213 (73)	70 815 (70)
Dose 40 mg [d]	3066 (5)	3661 (4)
Simvastatin/Ezetimibe combination[b]	5526 (2)	7178 (1)
Combination or coprescription of lipid-lowering drugs at initiation[b]	5263 (2)	7181 (1)

[a]CMUc complementary universal health insurance which provides free health cover for low-income residents.

[b]Percentages among those exposed to statins.

[c]High-potency statin treatment was defined as at least 10-mg rosuvastatin, at least 20-mg atorvastatin, and at least 40-mg simvastatin; all other statin treatments were defined as low-potency.

[d]Percentages among those exposed to the specific statin.

dose statin therapy, resulting in a case fatality rate of 23%). AKI mainly occurred in the context of organ failure (41%), sepsis (34%), and genitourinary system disease (36%) (Supplementary Table 3). No major differences in the distribution of comorbidities and associated conditions were observed between cases occurring with or without statin therapy; in particular, rhabdomyolysis was reported equally

TABLE 2 Baseline characteristics of cases (acute kidney injury) and immediate outcome according to gender. Values are expressed as numbers (percentages) unless stated otherwise

	Men	Women
Number of cases	9075	5877
Incidence per 10 000 person-years (95% CI)	4.76 (4.66-4.86)	1.91 (1.86-1.96)
Mean age at baseline (SD), year	57.9 (10.0)	58.8 (10.3)
CMUc[a] patient	690 (8)	574 (10)
Discharge status		
Death	2233 (25)	1434 (24)
Home	4898 (54)	3054 (52)
Other (institution for inpatient care, rehabilitation, nursing facility …)	1944 (21)	1388 (24)
Median time to death (Q1-Q3), day	6 (2-18)	5 (2-17)
Exposed to statins at the time of the event		
Exposed to statins	422	278
Incidence per 10 000 person-years (95% CI)	7.01 (6.37-7.71)	3.01 (2.68-3.39)
Death as discharge status	90 (21)	54 (19)
Mean age at baseline (SD) when death as discharge status	59.9 (7.9)	61.8 (8.4)
Exposed to high-potency statin[b]	69 (16)	50 (18)
Death as discharge status	18 (26)	9 (18)
Type and dose of specific statin given (only cases exposed to statins during first sequence)		
Exposed to atorvastatin	70	41
Exposed to fluvastatin	1	5
Exposed to pravastatin	25	26
Exposed to rosuvastatin	95	42
Exposed to simvastatin	38	20
Exposed to simvastatin/ezetimibe combination	3	1
Duration of treatment at the time of the event (all cases exposed to statins)		
1-30 days[c]	65 (15)	37 (13)
31-60[c]	55 (13)	28 (10)
61-90[c]	28 (7)	18 (6)
> 90[c]	274 (65)	195 (70)

Abbreviation: CI, confidence interval.

[a]CMUc complementary universal health insurance which provides free health cover for low-income residents.

[b]High-potency statin treatment was defined as at least 10-mg rosuvastatin, at least 20-mg atorvastatin, and at least 40-mg simvastatin; all other statin treatments were defined as low-potency (percentages among those exposed to statins).

[c]Percentages among those exposed to statins.

TABLE 3 Adjusted[a] time-dependent hazard ratios (95% confidence intervals) for acute kidney injury (N = 14 952) by type of statin, dosage, and time since initiation

	Men	Women
Exposure to statins	1.19 (1.08-1.31)	1.08 (0.96-1.22)
Exposure to high-potency statins	1.72 (1.37-2.17)	2.16 (1.64-2.85)
Recent exposure to statins (days 1-180)	1.22 (1.07-1.39)	1.09 (0.93-1.28)
Prolonged exposure to statins (days >180)	1.18 (1.03-1.34)	1.06 (0.90-1.25)
First sequence of statin		
Atorvastatin		
Overall exposure effect	1.53 (1.21-1.93)	1.38 (1.02-1.88)
Dose 10 mg	1.45 (1.10-1.90)	1.12 (0.76-1.63)
Dose 20 mg	1.51 (0.81-2.81)	1.50 (0.67-3.34)
Dose ≥40 mg	2.43 (1.22-4.86)	5.32 (2.66-10.64)
Pravastatin		
Overall exposure effect	0.75 (0.51-1.12)	1.06 (0.72-1.56)
Dose 10 mg	0.94 (0.42-2.08)	0.53 (0.17-1.64)
Dose 20 mg	0.62 (0.36-1.06)	1.28 (0.84-1.97)
Dose 40 mg	1.06 (0.47-2.35)	0.79 (0.20-3.16)
Rosuvastatin		
Overall exposure effect	1.50 (1.22-1.83)	0.92 (0.68-1.25)
Dose 5 mg	1.45 (1.16-1.80)	0.85 (0.61-1.18)
Dose 10 mg	1.60 (0.88-2.88)	1.77 (0.84-3.71)
Dose 20 mg	5.19 (1.67-16.10)	0.00 (0.00-∞)
Simvastatin		
Overall exposure effect	1.19 (0.88-1.62)	0.81 (0.53-1.24)
Dose 10 mg	0.90 (0.43-1.90)	0.44 (0.14-1.35)
Dose 20 mg	1.25 (0.87-1.80)	0.94 (0.57-1.53)
Dose 40 mg	1.54 (0.39-6.16)	1.33 (0.19-9345)

[a]Stratified for age (5-year intervals between 40 and 74 years), adjusted for CMUc and the deprivation index of the patient's municipality of residence as baseline covariates and iodinated contrast media, aminoglycosides, non-steroidal anti-inflammatory drugs, antihypertensive drugs, and antidiabetic drugs as time-dependent covariates.

infrequently in combination with AKI occurring in patients receiving statin therapy (5%) and those not receiving statin therapy (5%).

After stratification for age and adjustment for baseline and time-dependent covariates, a 19% increase in the AKI rate (hazard ratio = 1.19, 95% CI: 1.08-1.31) was observed in men exposed to statins (Table 3), whereas no increase in the overall risk was observed in women (hazard ratio = 1.08, 95% CI: 0.96-1.22). However, exposure to high-potency statins was associated with a 72% to 116% increased risk of AKI in both men and women (hazard ratio = 1.72, 95% CI: 1.37-2.17 in men, and 2.16, 95% CI: 1.64-2.85 in women). No interaction was observed between statin and fibrate exposure (however coprescription of statins with other lipid-lowering drugs was observed in less than 2% of prescriptions). No interaction was observed between statins and antihypertensive drugs or antidiabetic drugs, assessed as

classes (Supplementary Table 4). No marked difference of risk according to duration of treatment was observed, but most cases of AKI occurred more than 90 days after initiation of statin therapy (Tables 2 and 3).

The results concerning the first sequence of statin therapy showed marked differences between statin types: exposures to rosuvastatin and atorvastatin were clearly associated with an increased risk of AKI, with generally linear dose-effect relationships in both genders for these two molecules.

The results using the narrower definition of severe AKI (requiring hemodialysis or hemofiltration) are presented in Supplementary Table 5. Associations between this event and statin exposure were very similar to those observed using the standard definition of AKI.

4 | DISCUSSION

This large-scale population-based study conducted in a healthy, primary prevention population showed a moderately increased risk of AKI associated with statin exposure, with marked differences according to gender, potency, and type of statins. Men were at slightly greater risk of AKI overall (+19% increased risk vs +8% for women) as were users of high-potency statins (+72% for men and +116% for women), particularly rosuvastatin and atorvastatin users in whom a dose-effect relationship was observed. No clear temporal pattern nor interaction with antihypertensive drugs and antidiabetic drugs was observed, suggesting that AKI may arise from direct dose-related toxicity, independently of a possible microangiopathic or macroangiopathic background. In addition, rhabdomyolysis was rarely reported in association with AKI in this setting, suggesting that this well-known mechanism plays only a very minor role in AKI risk.

Our results significantly contribute to the scant literature concerning the risk of AKI in statin users. Clinical trials on the kidney safety of statins have generally been short-term and most of them addressed low-potency statins in the context of secondary prevention.[15] However, in the Jupiter trial, rosuvastatin, administered at a dose of 20 mg, was associated with a 19% increased risk of AKI.[16] Apart from two studies reporting discordant results on the risk of AKI in patients concurrently taking a statin and a macrolide antibiotic[17,18] (not addressed here), only three large-scale studies independent of the pharmaceutical industry have addressed the risk of AKI in patients treated with statins. The first[8] considered a 30 to 84-year-old primary care population between 2002 and 2008, in which simvastatin represented 70% of prescriptions, with no distinction according to the context of prevention (primary, secondary): the increased risk of AKI, slightly more pronounced in men (+67% vs +54% in women), remained stable over the 5-year follow-up, and a dose-response relationship was evidenced for simvastatin, atorvastatin, and pravastatin, while the AKI risk could not be investigated in patients treated with rosuvastatin due to the small sample size. The second study[9] only considered patients exposed to statins between 1997 and 2008, with no distinction between primary and secondary prevention: a 34% increased risk of AKI was observed with high-potency versus low-potency statins, with no interaction with

macrolide antibiotics, calcium channel blockers, and fibrates. The last study[10] studied the risk of AKI separately in patients receiving statins between 2003 and 2012 in the context of primary prevention: the authors found an overall increased risk of 25%, lower than in the entire cohort including secondary prevention patients (30%), but did not investigate the time pattern or the type and potency of statins.

The mechanisms underlying the potential nephrotoxicity of statins remain uncertain. An increased risk of statin-induced rhabdomyolysis is well known,[19] but this condition has been reported in only 5% of patients with AKI in our study. However, this complication may have been underreported.[5] Early studies had shown that high doses of rosuvastatin may induce direct nephrotoxicity, with an increased incidence of dose-dependent tubular proteinuria.[20,21] This tubular toxicity has been reported in rare case reports,[22] sometimes associated with tubulointerstitial nephritis.[23] Nevertheless, randomized trials have shown that statins may also have renoprotective effects,[24] especially in diabetic patients,[25] even when prescribed at high doses, or when given for prevention of contrast-induced AKI.[26,27] Of note, a meta-analysis showed similar renoprotective effects in high CVD risk patients treated with atorvastatin and rosuvastatin prescribed at commonly used doses.[28] On the other hand, a double-blind, placebo-controlled randomized clinical trial failed to demonstrate any beneficial nephroprotective effect of perioperative high-dose atorvastatin in patients undergoing cardiac surgery, both for statin-naive patients and patients already taking a statin.[29]

In any event, it should be noted that the renal risk of statins, which appears to be quite low in our study, should be compared with the potential benefit of these drugs in terms of global cardiovascular risk. The JUPITER study has shown that the prescription of rosuvastatin was associated with a reduction of the incidence of major cardiovascular events (HR: 0.56), when given to apparently healthy subjects with LDL-cholesterol levels <1.3 g/L and CRP levels higher than 2 mg/L.[30] A particularly marked benefit of primary prevention with statins has been observed in high-risk populations[31] and even in patients with CKD.[32,33] Although CVD and CKD patients are considered to be at high risk for AKI,[34] the risk-benefit ratio of statin therapy is certainly positive in terms of overall morbidity and mortality.

This study presents several limitations, mainly due to the use of administrative and claims data. First, there is a potential for misclassification of exposures and outcomes. Poor medication adherence may have interfered with measurement of statin exposure. Outcome misclassification is also a potential limitation, as the validity of the three-character code used for AKI (N17) has not been extensively assessed.[35] However, the mortality rate in our cases, close to that expected,[36,37] does not indicate inconsistent coding, and the consistency of the results obtained using a broad, natural, and unconstrained definition of AKI and those obtained using a narrower definition, only including cases requiring hemodialysis or hemofiltration, is reassuring. Moreover, since exposure and outcome were determined independently, this misclassification is nondifferential and hence produces bias toward the null.

Second, despite careful adjustment for sociodemographic factors associated with both statin prescription (age, CMUc, and deprivation

index) and AKI, and time-dependent exposures, notably antihypertensive, antidiabetic, and other drugs classically associated with AKI, residual unmeasured confounding therefore remains a concern. Exclusion from the cohort, at baseline and during follow-up, of subjects with "LTD" status (with 100% reimbursement for costs associated with these diseases), often proposed in France in the presence of complications of diabetes and hypertension, and adjustment for the condition whenever treatment was dispensed made any serious confounding by hypertension and diabetes and related organ damage, especially kidney damage, unlikely. However, only limited socioeconomic data were available, and no information was available on lifestyle factors such as smoking and physical activity (or mild and asymptomatic chronic diseases such as glucose intolerance or nonalcoholic fatty liver disease). Statin prescription was possibly more frequent in patients presenting risk factors for CVD that could not be evaluated by our study, such as higher body mass index, tobacco use, higher levels of LDL-cholesterol, or family cardiovascular history, and in patients with mild chronic kidney disease (CKD) not registered as LTD. All these conditions have been found associated, albeit weakly, with AKI[38-40] and may confound the relationship between statins and AKI. However, residual confounding due to these unmeasured risk factors is very unlikely to account for the higher risks observed in this study (Supplementary Table 7: E values) and specially to explain the large differences in risk estimates across various types of statins.

Third, we selected a healthy population of subjects, free of any significant disease (at baseline and during follow-up) that might interfere with the decision to prescribe or to regularly take statins for primary prevention. This selection made the cohort more homogeneous and minimized confounding biases but presented a certain disadvantage in terms of external validity. In addition, censorship at the time of intercurrent LTD (or death) and especially censorship at the date of hospitalization for any disease other than AKI may have led to the exclusion of future cases of AKI. All these methodological choices could only lead to underestimation of the strength of the association and could probably explain the apparent protective effect observed in women.

Fourth, although this study was conducted according to an "explicative" approach, in that the study design allowed the construction of homogeneous populations of subjects initiating statins, free of any significant CVD and serious comorbidities, and that adjustment for confounding factors was as complete as possible to obtain the least biased association measures (in contrast with all studies conducted to date) and despite the strength of several associations and dose-response relationships arguing in favor of causal associations, no causal link can be formally proposed in the absence of any clearly defined mechanisms for the development of AKI in these subjects.

Finally, the generalizability of the findings may be limited to similar populations of high-income countries with similar health care system[41] and statin market.

Despite the low incidence and limited excess risk of statin-associated AKI, the increasingly high level of statin use in the general population worldwide makes it important to propose appropriate guidelines concerning the prescription and monitoring of statin treatment in order to limit this type of complication. Guidelines may need to include a statement recommending that renal function should be monitored more closely in all individuals, but especially men, and women taking high-potency statins, for primary prevention. More research is needed to prove a direct kidney toxicity of statins and to understand the mechanisms of renal tubular injury that may explain the results of this study. Future studies will need to determine whether high-dose statins should be discontinued in situations at high risk of AKI, such as surgery, especially in patients with preexisting comorbidities.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.