ORIGINAL RESEARCH

Association of Low-Density Lipoprotein Cholesterol Levels During Statin Treatment With Cardiovascular and Renal Outcomes in Patients With Moderate Chronic Kidney Disease

Chieh-Li Yen, MD; Pei-Chun Fan (iD), MD; Cheng-Chia Lee (iD), MD; Jia-Jin Chen, MD; George Kuo, MD; Yi-Ran Tu, MD; Pao-Hsien Chu (iD), MD; Hsiang-Hao Hsu (iD), MD, PhD; Ya-Chung Tian, MD, PhD; Chih-Hsiang Chang (iD), MD

BACKGROUND: The benefit of low-density lipoprotein cholesterol (LDL-C) levels in chronic kidney disease populations remains unclear. This study evaluated the cardiovascular and renal outcomes in patients with stage 3 chronic kidney disease with different LDL-C levels during statin treatment.

METHODS AND RESULTS: There were 8500 patients newly diagnosed as having stage 3 chronic kidney disease under statin treatment who were identified from the Chang Gung Research Database and divided into 3 groups according to their first LDL-C level after the index date: <70 mg/dL, 70 to 100 mg/dL, and >100 mg/dL. Inverse probability of treatment weighting was performed to balance baseline characteristics. Compared with the LDL-C ≥100 mg/dL group, the 70≤LDL-C<100 mg/dL group exhibited significantly lower risks of major adverse cardiac and cerebrovascular events (6.8% versus 8.8%; subdistribution hazard ratio [SHR], 0.76 [95% CI, 0.64–0.91]), intracerebral hemorrhage (0.23% versus 0.51%; SHR, 0.44 [95% CI, 0.25–0.77]), and new-onset end-stage renal disease requiring chronic dialysis (7.6% versus 9.1%; SHR, 0.82 [95% CI, 0.73–0.91]). By contrast, the LDL-C <70 mg/dL group exhibited a marginally lower risk of major adverse cardiac and cerebrovascular events (7.3% versus 8.8%; SHR, 0.82 [95% CI, 0.65–1.02]) and a significantly lower risk of new-onset end-stage renal disease requiring chronic dialysis (7.1% versus 9.1%; SHR, 0.76 [95% CI, 0.67–0.85]).

CONCLUSIONS: Among patients with stage 3 chronic kidney disease, statin users with 70≤LDL-C<100 mg/dL and with LDL-C <70 mg/dL had similar beneficial effect in the reduction of risks of major adverse cardiac and cerebrovascular events and new-onset end-stage renal disease compared with those with LDL-C >100 mg/dL. Moreover, the 70≤LDL-C<100 mg/dL group seemed to have a lowest risk of intracerebral hemorrhage, although the incidence was low.

Key Words: cardiovascular disease ■ chronic kidney disease ■ low-density lipoprotein cholesterol ■ statin ■ stroke

Accumulating evidence from animal,[1] epidemiological,[2] genetic,[3] and clinical studies[4,5] unanimously indicates that a high low-density lipoprotein cholesterol (LDL-C) level, because of its effect on atherosclerotic plaque progression[6] and endothelial inflammation,[7] is the leading cause of atherosclerotic cardiovascular disease and consequent cardiovascular deaths. Statin, a 3-hydroxy-3-methylglutaryl-coenzyme A inhibitor, can effectively

CLINICAL PERSPECTIVE

What Is New?

- This is the first study to compare the study outcomes across different low-density lipoprotein cholesterol (LDL-C) levels in statin users, which is more consistent with the target-driven strategy adopted in most current treatment guidelines.
- This is the first large-scale study that enrolled a total of 8500 patients, designed to evaluate the benefit of low LDL-C levels, specifically in patients with stage 3 chronic kidney disease.

What Are the Clinical Implications?

- No direct evidence is available from randomized control trials to support the current target LDL-C levels in patients with different chronic kidney disease stages.
- This large-scale observational study reveals that among patients with stage 3 chronic kidney disease, the LDL-C levels in the range of 70 to 100 mg/dL or <70 mg/dL might have similar benefits in cardiovascular and renal outcomes compared with LDL-C >100 mg/dL.
- For patients aged younger than 65 years or with apparent proteinuria, controlling LDL-C levels <70 mg/dL might provide slightly more benefit in reducing cardiovascular events.

Nonstandard Abbreviations and Acronyms

CGRD	Chang Gung Research Data Set
GBM-IPTW	generalized boosted modeling-inverse probability of treatment weighting
MACCE	major adverse cardiac and cerebrovascular event

reduce plasma LDL-C levels and has therefore been extensively used as a lipid-lowering agent.[8] Numerous randomized control trials (RCTs),[4,9] large-scale cohort studies,[10] and meta-analyses[11] have indicated that reduction of LDL-C levels with statins is a crucial preventive strategy for cardiovascular events, especially for high-risk populations, such as those with a history of atherosclerotic cardiovascular disease and diabetes with target organ damage.[12] Because of the strong association of LDL-C level reduction with a lower risk of cardiovascular events, major medical societies in the United States and Europe have increasingly emphasized the importance of LDL-C control and have lowered their recommended treatment goal of LDL-C levels. For example, the task force of the European Society of Cardiology and European Atherosclerosis Society, in the 2019 European

Society of Cardiology/European Atherosclerosis Society guideline, has lowered the target LDL-C from <70 mg/dL to <55 mg/dL for high-risk populations and from <100 mg/dL to <70 mg/dL for high-risk populations.[13]

In regard to lipid management, patients with chronic kidney disease (CKD) require special consideration when compared with other high-risk groups. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in people with CKD,[14] with a continual increase in the risk of CVD from the early stages of CKD along with a decline in renal function.[15] However, the association between LDL-C level and cardiovascular outcomes in the CKD population seems to be less apparent, and the role of statin treatment in this population is unclear compared with that in other high-risk populations. Most notably, in contrast to the more predominant benefit of LDL-C reduction in high–cardiovascular risk populations, the 4D (Deutsche Diabetes Dialysis Study) and AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) trials have unequivocally proven that statin treatment plays no role in reducing cardiovascular events among patients with end-stage renal disease (ESRD).[16,17] Moreover, subgroup analyses in the SHARP (Study of Heart and Renal Protection) study and recent meta-analyses have revealed a trend of reduced benefit of statins as CKD progressed from stage 3 to stage 5.[18,19] This trend of a weak association between cardiovascular risks and LDL-C levels or statin treatment during advanced CKD stages is believed to be multifactorial. The factors include changes in cholesterol metabolism, such as low LDL-C production but longer plasma residence time and lower LDL-C levels but a higher ratio of oxidized and small-dense LDL, which is more atherosclerotic,[20] and the increase in the risk of nonatherosclerotic cardiovascular disease, such as calcium/phosphate imbalance–induced arterial calcification, hyperkalemia-induced arrythmia, and uremic bleeding tendency–induced hemorrhagic stroke during CKD progression.[21] However, in the current lipid management guidelines of major medical societies, CKD stages are regarded as crucial factors for grouping, and lower target LDL-C levels are set with advancing CKD stages,[22,23] mainly based on the higher cardiovascular risks from early CKD to advanced CKD in observational studies,[21] rather than on the direct evidence between lower LDL-C level and cardiovascular outcomes from clinical trials of CKD populations. The SHARP study, the only RCT that focused on lipid management in the CKD population, was not designed to evaluate the association between LDL-C levels and outcomes and was underpowered to detect the effect of statin across different stages of CKD separately.[24]

Our research team will perform a series of large real-world studies to assess the association between LDL-C levels under statin treatment and cardiovascular

and renal outcomes in patients with CKD from stage 3 to stage 5. It is worth mentioning that, in the research series, only patients who received statin treatment would be enrolled to compare outcomes across different LDL-C levels. Because cholesterol is also regarded as a marker of nutritional status, a low cholesterol level in patients without statin treatment may imply the possibility of malnutrition and would bias the results.[25,26] According to Taiwan's National Health Insurance reimbursement regulations, patients can be treated with statins only if they have LDL-C ≥130 mg/dL or total cholesterol ≥200 mg/dL before the treatment initiation. To only enroll patients under statin treatment in this study may help reduce the interference of nutritional status.

In the current study, by using the Chang Gung Research Data Set (CGRD), a large comprehensive medical database, we evaluated the outcomes of statin treatment across patients with stage 3 CKD with an LDL-C level of <70 mg/dL, 70 to 100 mg/dL, and >100 mg/dL, which refer to the frequently used cutoff points in the current lipid management guidelines.

METHODS

Data Source

The CGRD is a deidentified data set based on medical information from the Chang Gung Memorial Hospital system, which is currently the largest hospital network in Taiwan. The medical system, comprising 4 tertiary medical centers and 3 teaching hospitals across different regions, accounts for approximately 10% of Taiwan's medical services.[27] The database contains comprehensive electronic medical records from these hospitals, including outpatient visits, medication prescriptions, procedure interventions, inpatient orders, laboratory data, and examination reports. Disease diagnosis in the CGRD is based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) before 2016, and the *Tenth Revision* (*ICD-10-CM*) of the classification thereafter. The data set was encrypted for research purposes, and any patient-identifying information in the CGRD is scrambled before the data set is released for research. Therefore, informed consent was waived by the institutional review board of Chang Gung Medical Foundation (approval number: 201900840B0). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

As illustrated in Figure 1, we identified patients aged >20 years with a diagnosis of stage 3 CKD from the CGRD for the period between 2001 and 2018. In this study, a diagnosis of stage 3 CKD was defined as a patient having 2 consecutive documentations of estimated glomerular filtration rate between 30 and 60
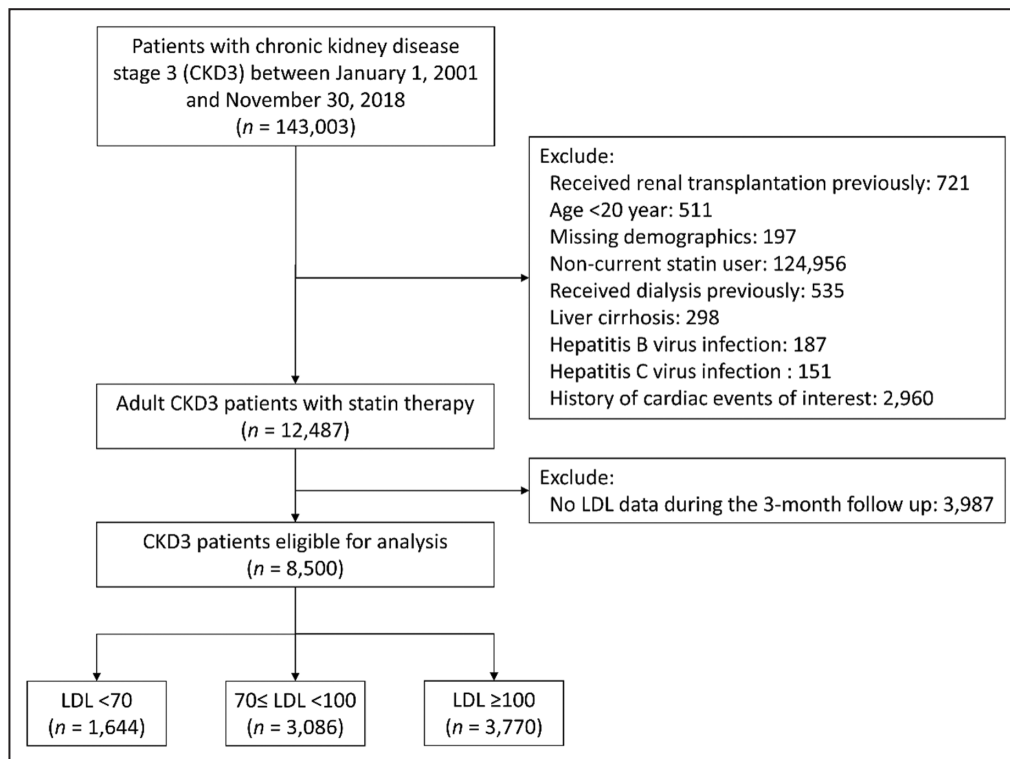

Figure 1. Patient inclusion–exclusion flowchart.
CKD3 indicates stage 3 chronic kidney disease; and LDL, low-density lipoprotein.

mL/min per 1.73 m², with an interval of >3 months, and the second estimated glomerular filtration rate date was defined as the index date. The patients with the following conditions were excluded: (1) missing demographics (ie, sex and age), (2) no receipt of any type of statin within 3 months preceding the index date, (3) unavailability of LDL-C data within 3 months after the index date, (4) receipt of kidney transplantations or any type of dialysis before the index date, (5) liver dysfunction including hepatitis virus infection and liver cirrhosis, and (6) a history of major adverse cardiac and cerebrovascular events (MACCEs), including acute myocardial infarction, ischemic stroke, and cardiovascular death, before the index date. The eligible patients with stage 3 CKD undergoing statin treatment were divided into 3 groups: LDL-C <70 mg/dL, 70≤LDL-C<100 mg/dL, and LDL-C ≥100 mg/dL, according to their first available LDL-C data within 3 months after the index date (Figure 1), which refer to the frequently used cutoff points in the current lipid management guidelines.

Covariates

Covariates in this study were demographics (age, sex, and body mass index), use of medical resources (outpatient visits and number of hospitalizations in the year before the index date), primary disease for CKD, comorbidities, medications at baseline, and laboratory data at baseline. Body mass index was determined using the most recently available data in the year preceding the index date. Primary disease for CKD included polycystic kidney disease, hypertension nephropathy, diabetes nephropathy, glomerulonephritis (ie, immunoglobulin A [IgA] nephropathy, lupus nephritis, minimal change disease, focal segmental glomerulosclerosis), obstructive nephropathy, interstitial nephritis, and others. Comorbidities included hypertension, diabetes, atrial fibrillation dementia, and heart failure. Primary disease for CKD and comorbidities were identified if reported at >2 outpatient visits or 1 inpatient stay in the year before the index date. Baseline laboratory data, including hemoglobin, glycohemoglobin, proteinuria, serum creatinine, estimated glomerular filtration rate, blood urine nitrogen, uric acid, and alanine aminotransferase, were identified using the most recent data within 3 months preceding the index date. However, to avoid lipid profile detection before the initiation of statin treatment, the latest data during the first 3-month follow-up was used to identify the lipid profile, including LDL, high-density lipoprotein, and total cholesterol. Finally, the use of antihypertensive agents, antidiabetic drugs, and other medications was identified according to the prescriptions received in the 3 months before the index date. The high-potency statins were defined as atorvastatin >40 mg/d or rosuvastatin >20 mg/d.

Outcomes Measures

The primary outcome of this study was the occurrence of MACCEs, defined as a composite of acute myocardial infarction, ischemic stroke, and cardiovascular death. The secondary outcomes were all-cause mortality, cardiovascular death, acute myocardial infarction, ischemic stroke, intracerebral hemorrhage, new-onset ESRD requiring dialysis, hepatitis-related hospitalization, and rhabdomyolysis-related hospitalization. These outcomes were identified from the medical records of the CGRD. All-cause mortality and cardiovascular death were identified as a documented mortality in the CGRD. New-onset ESRD requiring dialysis was defined by receipt of dialysis along with a catastrophic illness certificate for exemption from medical expenditure. The other outcomes were defined according to the first 5 discharge diagnoses following hospitalization. At least 1 record of creatine kinase >1000 IU/L during hospitalization was required for ascertaining the diagnosis of rhabdomyolysis-related hospitalization. Although it is difficult to ensure the direct causal relationship between the use of statins and hepatitis-related hospitalization, we excluded all types of infectious hepatitis, such as hepatitis B and hepatitis C, and only analyzed noninfectious hepatitis-related hospitalization in this study. The follow-up period was from the index date to the first occurrence of any study outcome independently until 3 years after the index date, or until the end date of the study period (November 31, 2018).

Statistical Analysis

To achieve comparability among the 3 study groups (namely LDL<70, 70≤LDL<100, and LDL ≥100 mg/dL), we conducted a generalized boosted modeling-inverse probability of treatment weighting (GBM-IPTW) based on propensity scores to balance the distribution of baseline characteristics among groups, except for lipid profile, potency of the statin, and the use of ezetimibe. In the GBM estimation, the depth of interaction was set as 3 layers, the optimal iteration was set as 10 000 trees, and the stopping rule was defined according to the maximum of the absolute standardized biases across all the covariates.[28] The propensity scores were obtained from all of the baseline characteristics (listed in Table 1) against the study groups, except for lipid profile, potency of the statin, and the use of ezetimibe. The follow-up year was not included in the calculation of propensity scores, but the index year was included. Notably, because substantial data on the baseline characteristics were missing, the GBM-IPTW was conducted using the imputed data with a single expectation, algorithm maximization. All variables (with or without missing values) were used for imputation. The balance among the study groups before and after GBM-IPTW was assessed using the

Table 1. Baseline Characteristics of the Original Cohort Before GBM-IPTW

Variables	No. of missing	Total, n=8500	LDL-C <70, n=1644	70≤LDL-C<100, n=3086	LDL-C ≥100, n=3770	MASD
Age, y	0	65.1±11.7	66.1±11.7	66.0±11.2	64.0±12.1	0.19
Age ≥65 y	0	4520 (53.2)	910 (55.4)	1743 (56.5)	1867 (49.5)	0.14
Men	0	4678 (55.0)	983 (59.8)	1720 (55.7)	1975 (52.4)	0.15
Body mass index, kg/m²	2188	26.4±4.9	26.5±4.8	26.4±4.9	26.3±4.9	0.04
Primary renal disease	0					
Interstitial nephritis, obstructive nephropathy, and unknown origin		540 (6.4)	81 (4.9)	205 (6.6)	254 (6.7)	0.08
Polycystic kidney		25 (0.3)	6 (0.4)	6 (0.2)	13 (0.3)	0.04
Hypertension nephropathy		2049 (24.1)	363 (22.1)	735 (23.8)	951 (25.2)	0.07
Diabetes nephropathy		4674 (55.0)	996 (60.6)	1691 (54.8)	1987 (52.7)	0.16
Glomerulonephritis		1212 (14.3)	198 (12.0)	449 (14.6)	565 (15.0)	0.09
Comorbidities						
Hypertension	0	6721 (79.1)	1330 (80.9)	2457 (79.6)	2934 (77.8)	0.08
Diabetes	0	5382 (63.3)	1143 (69.5)	1947 (63.1)	2292 (60.8)	0.18
Atrial fibrillation	0	339 (4.0)	87 (5.3)	124 (4.0)	128 (3.4)	0.10
Dementia	0	255 (3.0)	64 (3.9)	101 (3.3)	90 (2.4)	0.09
Heart failure	0	261 (3.1)	73 (4.4)	88 (2.9)	100 (2.7)	0.10
No. of outpatient visits in the previous year	0	9.3±7.6	8.7±7.3	9.2±7.5	9.6±7.7	0.12
No. of admissions in the previous year	0	0.20±0.63	0.24±0.70	0.18±0.58	0.21±0.64	0.08
Medication at baseline						
ACEi/ARB	0	5982 (70.4)	1188 (72.3)	2209 (71.6)	2585 (68.6)	0.08
β-Blocker	0	2500 (29.4)	503 (30.6)	940 (30.5)	1057 (28.0)	0.06
Calcium-channel blocker	0	3612 (42.5)	659 (40.1)	1341 (43.5)	1612 (42.8)	0.07
Mineralocorticoid receptor antagonist	0	428 (5.0)	101 (6.1)	148 (4.8)	179 (4.7)	0.06
Loop diuretic	0	1342 (15.8)	229 (13.9)	445 (14.4)	668 (17.7)	0.10
Nitrates	0	1392 (16.4)	303 (18.4)	508 (16.5)	581 (15.4)	0.08
Vasodilator	0	126 (1.5)	31 (1.9)	51 (1.7)	44 (1.2)	0.06
Thiazide	0	947 (11.1)	162 (9.9)	337 (10.9)	448 (11.9)	0.06
Antiplatelet agent	0	3571 (42.0)	791 (48.1)	1366 (44.3)	1414 (37.5)	0.22
NSAID	0	1238 (14.6)	243 (14.8)	415 (13.4)	580 (15.4)	0.06
Steroid	0	424 (5.0)	69 (4.2)	149 (4.8)	206 (5.5)	0.06
Proton pump inhibitor	0	676 (8.0)	142 (8.6)	241 (7.8)	293 (7.8)	0.03
Insulin	0	794 (9.3)	159 (9.7)	258 (8.4)	377 (10.0)	0.06
Thiazolidinediones	0	738 (8.7)	135 (8.2)	291 (9.4)	312 (8.3)	0.04
Sulfonylurea	0	3664 (43.1)	780 (47.4)	1351 (43.8)	1533 (40.7)	0.14
DPP-4 inhibitor	0	1354 (15.9)	398 (24.2)	536 (17.4)	420 (11.1)	0.36
Metformin	0	3815 (44.9)	864 (52.6)	1437 (46.6)	1514 (40.2)	0.25
α-Glucosidase inhibitor	0	723 (8.5)	174 (10.6)	253 (8.2)	296 (7.9)	0.10
Pentoxyfillin	0	418 (4.9)	86 (5.2)	155 (5.0)	177 (4.7)	0.03
Fibrate	0	352 (4.1)	55 (3.3)	114 (3.7)	183 (4.9)	0.08
Ezetimibe	0	754 (8.9)	219 (13.3)	252 (8.2)	283 (7.5)	0.19

(Continued)

Table 1.   **Continued**

Variables	No. of missing	Total, n=8500	LDL-C <70, n=1644	70≤LDL-C<100, n=3086	LDL-C ≥100, n=3770	MASD
High potency statin	0	601 (7.1)	124 (7.5)	223 (7.2)	254 (6.7)	0.03
Laboratory data at baseline						
Creatinine, mg/dL	0	1.7±1.2	1.7±1.4	1.6±1.1	1.7±1.2	0.06
eGFR, mL/min per 1.73m^2	0	44.7±13.6	45.1±13.5	45.4±13.4	44.0±13.7	0.10
Blood urine nitrogen, mg/dL	4700	30.4±19.4	30.7±21.0	29.8±19.8	30.8±18.3	0.06
Proteinuria group, mg/dL	4162					0.20
Negative, 0–4		1651 (38.1)	333 (37.6)	642 (42.3)	676 (34.9)	
Trace, 5–29		476 (11.0)	110 (12.4)	162 (10.7)	204 (10.5)	
≥1+, ≥30		2211 (51.0)	442 (49.9)	712 (47.0)	1057 (54.6)	
Triglyceride, mg/dL	587	138 [97, 204]	145 [95, 226]	130 [93, 188]	142 [102, 201]	0.14
HbA1C, %	2225	7.6±1.8	7.5±1.7	7.6±1.7	7.8±1.9	0.15
Hemoglobin, g/dL	4398	12.1±2.2	12.0±2.2	12.2±2.2	12.2±2.2	0.07
Uric acid, mg/dL	3416	7.3±1.9	7.3±1.9	7.3±1.9	7.4±1.9	0.08
ALT, U/L	2040	20 [15, 29]	20 [15, 28]	20 [15, 29]	20 [15, 30]	0.09
Lipids profile during the 3-mo follow-up						
LDL-C, mg/dL	0	103.1±46.9	56.7±10.2	84.4±8.5	138.6±48.8	2.78
HDL-C, mg/dL	736	46.0±13.9	44.2±14.5	46.1±13.4	46.6±14.0	0.17
Total cholesterol, mg/dL	574	179.9±49.7	134.3±28.7	161.0±23.9	214.2±48.5	2.07

Data are presented as frequency (percentage), mean±SD, or median [25th, 75th percentile]. ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ALT, alanine aminotransferase; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GBM-IPTW, generalized boosted modeling-inverse probability of treatment weighting; HbA1C, glycohemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and MASD, maximum absolute standardized difference.

maximum absolute standardized difference, and a maximum absolute standardized difference of <0.2 indicated a favorable balance among the groups.[28]

The outcomes were compared among the groups using the GBM-IPTW adjusted cohort. The risk of fatal outcomes (all-cause mortality, cardiovascular death, and MACCEs) among the groups was compared using a Cox proportional hazards model. The incidence of other time-to-event outcomes among the groups was compared using the Fine-Gray subdistribution hazard model, which considered death during follow-up a competing risk. Two sensitivity analyses were conducted to assess the robustness of the results. First, we included only patients with normal LDL (<130 mg/dL), because including the patients without achieving the target for the general population in the >100 mg/dL group would exaggerate the benefit in the 2 other groups. Second, the multivariable covariates adjustment was conducted to consider the confounding effect instead of doing a GBM-IPTW. Finally, a subgroup analysis of MACCEs and new-onset ESRD requiring dialysis by prespecified baseline characteristics (namely age, sex, hypertension, diabetes, and baseline proteinuria level) was conducted.

To explore the possibility of nonlinearity between the LDL level and the risk of MACCEs, we conducted a Cox model in which LDL was treated as a restricted cubic spline. All of the covariates used to calculate propensity scores were adjusted in this alternative Cox model. Four knots were used, located at the 5th, 35th, 65th, and 95th percentiles. A 2-sided P value of <0.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), including the phreg procedure for conducting the survival analysis and the TWANG macro for estimating GBM-IPTW.

RESULTS

Patient Characteristics

As illustrated in Figure 1, data of 8500 adult patients diagnosed as having stage 3 CKD between 2001 and 2018 and with available LDL-C data after statin treatment were extracted from the CGRD. Of these patients, 1644 were allocated to the LDL-C <70 mg/dL group, 3086 to the 70≤LDL-C<100 mg/dL group, and the remaining 3770 to the LDL-C ≥100 mg/dL group. The demographics, comorbidities, medication, and baseline laboratory data across the study groups are presented in Table 1. The mean LDL-C level for the

LDL-C <70 mg/dL, 70≤LDL-C<100 mg/dL, and LDL-C ≥100 mg/dL groups was 56.7, 84.4, and 138.6 mg/dL, respectively, and the median triglycerides level was 145, 130, 142 mg/dL, respectively. Compared with the other 2 groups, the following characteristics of the LDL-C <70 mg/dL group were identified before applying IPTW: it comprised older patients; it had a male predominance; the prevalence of diabetes and diabetes nephropathy was higher; the rate of prescriptions for antiplatelet agents, sulfonylureas, dipeptidyl peptidase 4 inhibitors, high-potency statins, ezetimibe, and metformin was higher; and the glycohemoglobin level was lower. By contrast, the LDL-C ≥100 mg/dL group had younger patients, male predominance, lower prevalence of diabetes and peripheral artery disease, were prescribed fewer antiplatelet agents and oral hypoglycemic agents, and had a higher glycohemoglobin level. Finally, for imbalanced covariates, the data of the 70≤LDL-C<100 mg/dL group were mostly positioned between the other 2 groups, except for proteinuria, for which this group had the lowest proportion.

After IPTW application, all of the maximum absolute standardized difference values were <0.2, which indicated that the clinical characteristics of the 3 groups were well balanced (Table 2).

Three-Year Follow-Up Outcomes

Table 3 presents the study outcomes after a 3-year follow-up. After IPTW application, compared with the LDL-C ≥100 mg/dL group, the 70≤LDL-C<100 mg/dL group exhibited significantly lower risks of MACCEs (6.8% versus 8.8%; hazard ratio [HR], 0.76 [95% CI, 0.64–0.91]), ischemic stroke (2.7% versus 4.8%; subdistribution HR [SHR], 0.56 [95% CI, 0.47–0.66]), intracerebral hemorrhage (0.23% versus 0.51%; SHR, 0.44 [95% CI, 0.25–0.77]), and new-onset ESRD requiring chronic dialysis (7.6% versus 9.1%; SHR, 0.82 [95% CI, 0.73–0.91]). By contrast, compared with the LDL-C ≥100 mg/dL group, the LDL-C <70 mg/dL group exhibited a marginally lower risk of MACCEs (7.3% versus 8.8%; HR, 0.82 [95% CI, 0.65–1.02]), a significantly lower risk of ischemic stroke (2.9% versus 4.8%; SHR, 0.60 [95% CI, 0.51–0.72]), and a significantly lower risk of new-onset ESRD requiring chronic dialysis (7.1% versus 9.1%; SHR, 0.76 [95% CI, 0.67–0.85]). The risk of all-cause mortality, cardiovascular death, acute myocardial infarction, hepatitis-related hospitalization, and rhabdomyolysis-related hospitalization did not significantly differ across the 3 study groups. Figure 2 presents the cumulative event rates of MACCEs, ischemic stroke, new-onset ESRD requiring chronic dialysis, and noninfectious hepatitis–related hospitalization.

For sensitivity analysis, we performed a Cox proportional hazard model using multivariable covariates adjustment instead of doing a GBM-IPTW,

and the results did not change (Table S1). Moreover, even if we excluded patients with the highest LDL-C level (LDL-C >130 mg/dL) and reperformed GBM-IPTW, the main results of MACCEs, ischemic stroke, and hemorrhagic stroke would still be consistent (Table S2).

In addition, to further confirm the association between LDL-C level and the risk of MACCEs, we performed the Cox model that treated LDL level as a restricted cubic spline (Figure 3), and it illustrated that the relationship between LDL level and the risk of MACCEs was generally linear (P for nonlinearity >0.05). The result showed that the higher LDL level was associated with a higher risk of MACCEs at a proportional scale. Using 70 mg/dL as the reference level, the result demonstrated that an LDL level >106 mg/dL was associated with a significantly greater risk of MACCEs.

Subgroup Analysis

To further analyze whether the different clinical conditions or potency of statin modified the association between LDL-C level and primary outcomes, we performed subgroup analyses for MACCEs and new-onset ESRD requiring chronic dialysis. In regard to MACCEs, the benefit of low LDL-C levels seemed to be more pronounced in patients younger than 65 years or in those with proteinuria. No apparent differences were noted in other subgroups (Table 4). In regard to new-onset ESRD, the protective effect of low LDL-C levels seemed to be more evident in patients younger than 65 years, with comorbid diabetes or hypertension and in those with proteinuria. In other subgroups, the differences were nonsignificant (Table 5).

DISCUSSION

In the highest cardiovascular risk populations, LDL-C reduction through statin treatment is considered a crucial preventive strategy for CVD. Current large-scale studies on PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors have found that in high-risk patients with lipid levels well controlled through statin treatment, further reduction of LDL-C by PCSK9 inhibitors can provide additional protective effects.[29] This finding encouraged the major medical societies to set a lower LDL-C treatment target for high-risk patients in their current treatment guideline. By contrast, in CKD and ESRD populations, the association between LDL-C reduction through statin treatment and subsequent risk of CVD seems to be less obvious.[17,24] Because relevant evidence was lacking, this study evaluated the association between LDL-C level and subsequent outcomes among patients with stage 3 CKD.

Previous observational studies have revealed that in patients with CKD, the risk of cardiovascular events

Table 2. Baseline Characteristics of the Study Cohort After Imputation and GBM-IPTW

Variables	LDL <70	70≤LD<100	LDL ≥100	MASD
Age, y	65.3±11.2	65.4±11.5	64.8±11.7	0.04
Age ≥65y	53.5	53.8	52.2	0.03
Men	56.1	55.5	54.1	0.04
Body mass index, kg/m^2	26.4±4.0	26.4±4.2	26.4±4.2	0.01
Primary renal disease				
Interstitial nephritis, obstructive nephropathy, and unknown origin	5.5	6.5	6.3	0.04
Polycystic kidney	0.4	0.2	0.3	0.04
Hypertension nephropathy	22.9	23.8	24.5	0.04
Diabetes nephropathy	58.4	54.7	55.1	0.07
Glomerulonephritis	12.8	14.9	13.9	0.06
Comorbidities				
Hypertension	79.8	79.2	78.7	0.03
Diabetes	65.8	62.9	63.0	0.06
Atrial fibrillation	3.8	3.8	3.6	0.01
Dementia	3.1	3.1	2.6	0.03
Heart failure	2.8	2.8	2.6	0.01
No. of outpatient visits in the previous year	8.8±13.9	9.2±11.8	9.3±10.8	0.06
No. of admissions in the previous year	0.19±0.63	0.19±0.58	0.20±0.62	0.03
Medication at baseline				
ACEi/ARB	71.4	71.2	69.5	0.04
β-Blocker	30.3	30.0	28.9	0.03
Calcium-channel blocker	41.1	43.0	41.9	0.04
Mineralocorticoid receptor antagonist	5.2	4.8	4.7	0.02
Loop diuretic	13.0	14.6	16.0	0.08
Nitrates	17.3	16.0	16.1	0.04
Vasodilator	1.5	1.6	1.1	0.04
Thiazide	11.4	11.1	11.1	0.01
Antiplatelet agent	43.9	43.0	40.6	0.07
NSAID	14.6	13.5	14.7	0.03
Steroid	4.0	5.0	5.1	0.05
Proton pump inhibitor	7.2	7.8	7.9	0.03
Insulin	9.2	9.1	9.2	0.00
Thiazolidinediones	8.1	9.0	8.4	0.03
Sulfonylurea	46.0	43.4	42.6	0.07
DPP-4 inhibitor	17.3	16.6	14.9	0.07
Metformin	48.6	45.6	43.9	0.10
α-Glucosidase inhibitor	9.7	8.2	8.3	0.05
Pentoxyfillin	4.7	5.1	4.7	0.02
Fibrate	3.6	3.6	4.3	0.04
Ezetimibe	12.2	7.9	8.2	0.14
High-potency statin	7.2	7.3	6.9	0.02
Laboratory data at baseline				
Creatinine, mg/dL	1.6±1.1	1.7±1.1	1.7±1.1	0.02
eGFR, mL/min per 1.73m^2	45.1±13.0	44.9±13.3	44.7±13.4	0.03
Blood urine nitrogen, mg/dL	26.2±13.5	26.5±14.1	26.7±14.0	0.03

(Continued)

Table 2.   Continued

Variables	LDL <70	70≤LD<100	LDL ≥100	MASD
Proteinuria group, mg/dL				0.06
Negative, 0–4	26.3	25.4	23.7	
Trace, 5–29	10.3	10.1	9.3	
≥1+, ≥30	63.4	64.4	67.0	
Triglyceride, mg/dL	144 [99, 218]	134 [96, 188]	147 [104, 201]	0.10
HbA1C, %	7.6±1.5	7.6±1.5	7.7±1.6	0.04
Hemoglobin, g/dL	12.4±1.6	12.4±1.6	12.4±1.6	0.01
Uric acid, mg/dL	7.3±1.4	7.3±1.5	7.3±1.5	0.02
ALT, U/L	23 [16, 30]	23 [17, 29]	23 [16, 29]	0.05
Lipids profile during the 3-month follow up				
LDL, mg/dL	57.3±9.8	84.5±8.5	136.3±47.6	2.75
HDL, mg/dL	44.5±14.3	46.0±12.8	46.7±13.3	0.16
Total cholesterol, mg/dL	138.4±29.1	161.8±24.0	210.3±45.3	1.93

Data are presented as percentage, mean±SD, or median [25th, 75th percentile]. ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ALT, alanine aminotransferase; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GBM-IPTW, generalized boosted modeling-inverse probability of treatment weighting; HbA1C, glycohemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and MASD, maximum absolute standardized difference.

is higher than the risk of ESRD, and CVD accounts for more than half of all deaths of patients with CKD.[30] Therefore, the association between risks of MACCEs and different LDL-C levels is the most noteworthy study outcome of interest. After IPTW was applied to achieve a favorable balance in terms of every possible confounder across the groups, this study demonstrated that patients with LDL-C <100 mg/dL had a lower risk of MACCEs than those with LDL-C ≥100 mg/dL. In addition, the risks of MACCEs among the LDL-C <70 mg/dL group and 70≤LDL-C<100 mg/dL group were not significantly different. The Cox model treated LDL level as a restricted cubic spine and illustrated similar results; the risk of MACCEs significantly decreased along with lower LDL-C level if LDL-C was ≥106 mg/dL, but the association is not significant in patients with LDL <106 mg/dL. Thus, with a combination of this evidence, statin users with 70≤LDL-C<100 mg/dL and LDL-C <70 mg/dL had a similar beneficial effect in the reduction of MACCEs compared with those with LDL-C >100 mg/dL. Among the MACCEs, the protective effect of lower LDL-C was mainly observed for ischemic stroke, whereas both the LDL-C <70 mg/dL and 70≤LDL-C<100 mg/dL groups exhibited a significantly lower risk of ischemic stroke. The consistent results in most subgroup analyses, including those for statins with different potencies and comorbidities of diabetes and hypertension, implied that the finding could be applied to most patients with stage 3 CKD instead of being limited to some specific subgroups or specific kinds of statins. Only in patients younger than 65 years or with apparent proteinuria, the LDL-C

Table 3.   Time-to-Event Outcomes During the 3-Year Follow-Up in the GBM-IPTW–Adjusted Cohort

Outcome	Event rate, %			HR or SHR (95% CI)	
	LDL-C <70	70≤LDL-C<100	LDL-C ≥100	LDL-C <70 vs LDL-C ≥100	70≤LDL-C<100 vs LDL-C≥100
All-cause mortality	3.2	3.2	3.3	0.97 (0.68–1.38)	0.96 (0.73–1.27)
MACCE*	7.3	6.8	8.8	0.82 (0.65–1.02)	0.76 (0.64–0.91)†
Cardiovascular death	2.4	2.1	2.0	1.16 (0.75–1.79)	1.01 (0.71–1.43)
Acute myocardial infarction	2.8	2.8	2.9	0.93 (0.76–1.13)	0.95 (0.79–1.14)
Ischemic stroke	2.9	2.7	4.8	0.60 (0.51–0.72)†	0.56 (0.47–0.66)†
Intracerebral hemorrhage	0.74	0.23	0.51	1.44 (0.95–2.19)	0.44 (0.25–0.77)†
New-onset ESRD requiring dialysis	7.1	7.6	9.1	0.76 (0.67–0.85)†	0.82 (0.73–0.91)†
Noninfectious hepatitis–related hospitalization	0.69	0.78	0.55	1.24 (0.81–1.88)	1.41 (0.95–2.08)
Rhabdomyolysis related hospitalization	0.27	0.50	0.36	0.93 (0.76–1.13)	0.95 (0.79–1.14)

ESRD indicates end-stage renal disease; GBM-IPTW, generalized boosted modeling-inverse probability of treatment weighting; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACCE, major adverse cardiac and cerebrovascular event; and SHR, subdistribution hazard ratio.

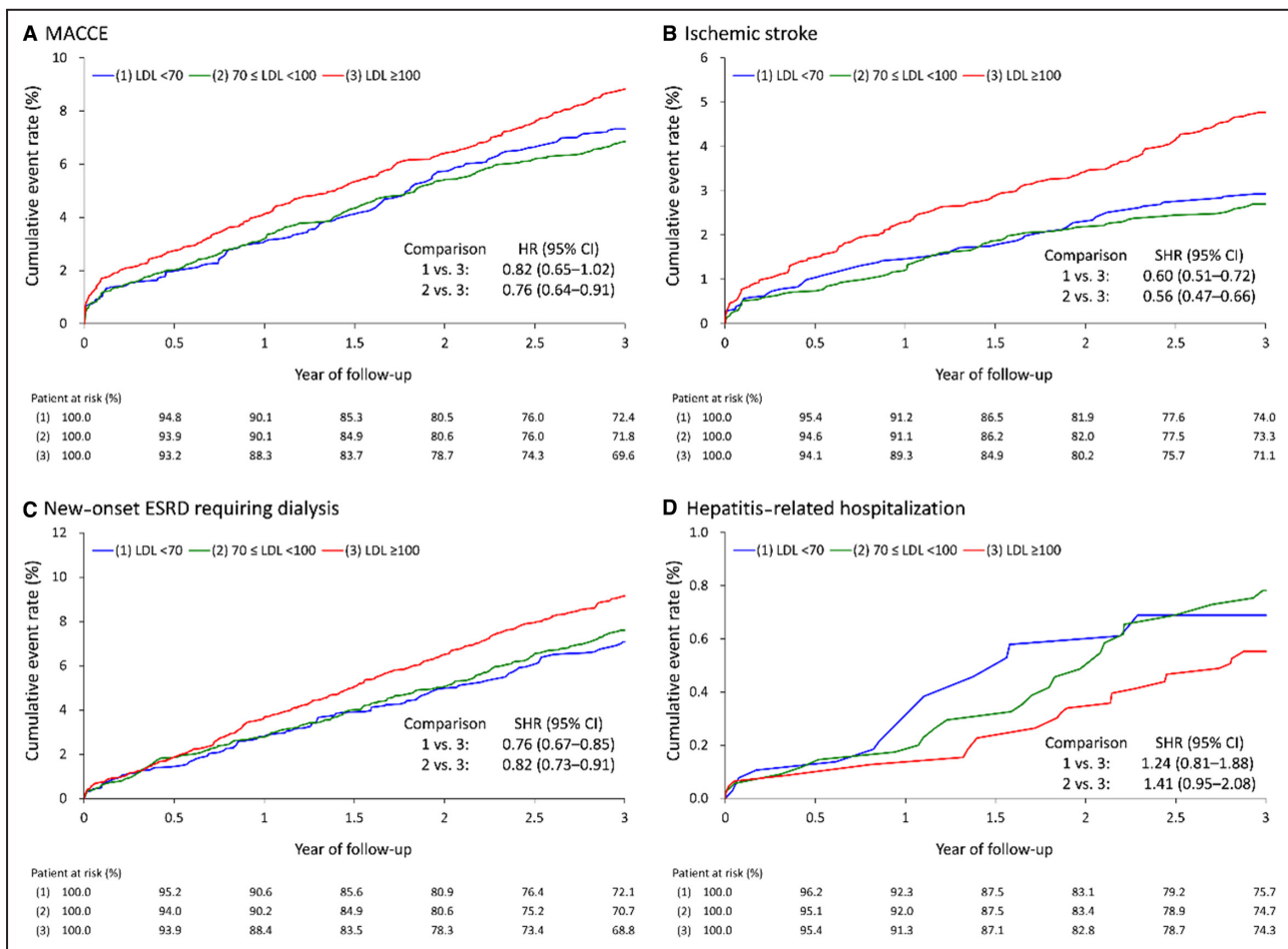*Any of cardiovascular death, acute myocardial infarction, or ischemic stroke.

†P<0.05.

Figure 2. **The cumulative event rate of MACCE (A), ischemic stroke (B), new-onset ESRD requiring dialysis, (C) and hepatitis-related hospitalization (D) in patients with stage 3 chronic kidney disease by different LDL-C levels after statin treatment in the GBM-IPTW–adjusted cohort.**

ESRD indicates end-stage renal disease; GBM-IPTW, generalized boosted modeling-inverse probability of treatment weighting; HR, hazard ratio; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MACCE, major adverse cardiac and cerebrovascular event; and SHR, subdistribution hazard ratio.

<70 mg/dL group seemed to have additionally lower risk of MACCEs.

The risks of intracerebral hemorrhage and new-onset ESRD requiring dialysis were the 2 other outcomes of interest in this study. In regard to intracerebral hemorrhage, patients with 70≤LDL-C<100 mg/dL had significantly lower risks than those with LDL-C >100 mg/dL; this benefit was not observed in patients with LDL-C <70 mg/dL. Ever since a small increase in the incidence of hemorrhagic stroke was first reported in the SPARCL (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial,[31] the risk of intracerebral hemorrhage during statin treatment has been debated. Whereas most RCTs did not report significantly higher risks of intracerebral hemorrhage in patients allocated to statin or lower LDL-C level groups,[4,32,33] a few observational studies and meta-analysis have still indicated an association between

low LDL-C levels and the risk of intracerebral hemorrhage or hemorrhagic stroke.[34–36] This study showed that the 70≤LDL-C<100 group had the lowest risk of intracerebral hemorrhage among patients with stage 3 CKD. However, considering that the incidence rate of intracerebral hemorrhage is much lower than other outcomes and the prior relevant evidence is still conflicting, the result about intracerebral hemorrhage in this study is far from making any suggestions, and further large-scale RCTs are warranted to validate our findings. Moreover, on renal outcomes, this study demonstrated that both the 70≤LDL-C<100 and LDL-C <70 groups were associated with a significantly lower risk of new-onset ESRD requiring chronic dialysis compared with the LDL-C ≥100 group. Numerous in vitro or animal studies have demonstrated that statin treatment has a potential role in reducing proteinuria and delaying CKD progression through their antioxidation,[37] podocyte
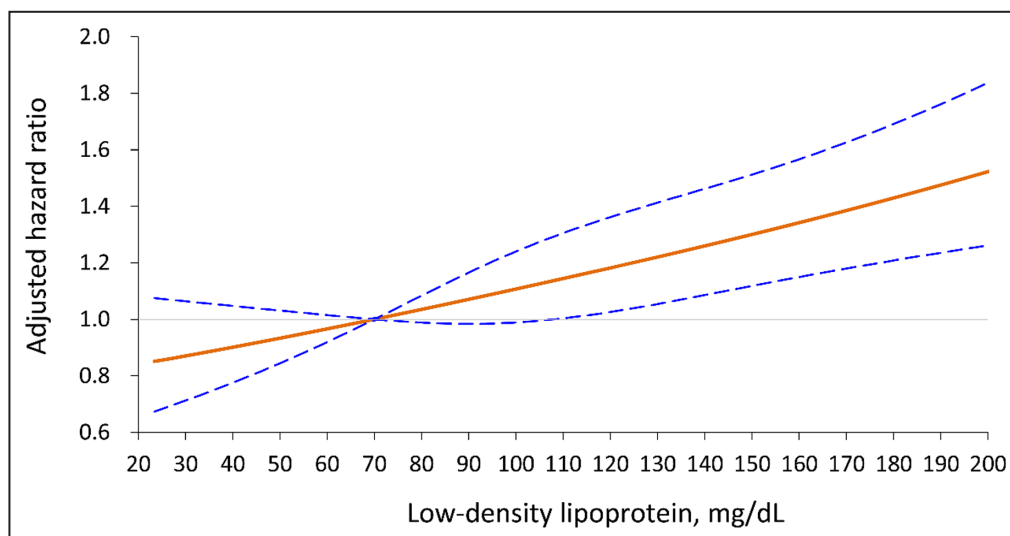
Figure 3. The relationship between LDL level and the risk of MACCEs, in which LDL was treated as a restricted cubic spline.
The LDL-C level of 70 mg/dL was used as the referent. The solid red line is the estimate, and the dashed blue lines are the 95% CIs of the estimate. LDL indicates low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; and MACCEs, major adverse cardiac and cerebrovascular events.

protection,[38] and antiproliferative effect on mesangial cells.[39] However, in in vivo studies, whether statin treatment could delay the initiation of dialysis was inconclusive. We speculated that the inconsistency of renal benefits of statin treatment among previous research might be attributed to the different enrolled populations. For example, the SHARP study, which enrolled patients with stage 3 to 5 CKD in its nondialysis part,

Table 4. Subgroup Analysis of Major Adverse Cardiac and Cerebrovascular Event by Prespecified Baseline Characteristics in the GBM-IPTW–Adjusted Cohort

Subgroup	Event rate, %			HR (95% CI)	
	LDL-C <70	70≤LDL-C<100	LDL-C ≥100	LDL-C <70 vs LDL-C ≥100	70≤LDL-C<100 vs LDL-C ≥100
Age, y					
≤65	3.9	5.0	7.5	0.49 (0.33–0.73)	0.65 (0.48–0.88)
>65	10.3	8.4	10.0	1.05 (0.79–1.38)	0.83 (0.67–1.04)
Sex					
Women	6.6	6.2	7.4	0.88 (0.61–1.27)	0.82 (0.62–1.08)
Men	7.9	7.4	10.0	0.77 (0.58–1.02)	0.73 (0.58–0.92)
Hypertension					
No	7.2	7.8	9.5	0.74 (0.46–1.20)	0.82 (0.56–1.19)
Yes	7.4	6.6	8.7	0.84 (0.65–1.08)	0.75 (0.61–0.92)
Diabetes					
No	5.8	5.5	7.8	0.73 (0.48–1.11)	0.69 (0.50–0.96)
Yes	8.1	7.6	9.4	0.85 (0.65–1.11)	0.80 (0.65–0.99)
Proteinuria					
Negative/trace	7.3	5.3	6.4	1.11 (0.76–1.63)	0.81 (0.57–1.16)
≥1+	7.4	7.7	10.0	0.73 (0.55–0.97)	0.76 (0.62–0.94)
Statin potency					
Low/moderate	7.5	6.9	8.7	0.84 (0.67–1.06)	0.78 (0.65–0.94)
High	5.6	6.0	10.3	0.52 (0.22–1.22)	0.58 (0.30–1.11)

GBM-IPTW indicates generalized boosted modeling-inverse probability of treatment weighting; HR, hazard ratio; and LDL-C, low-density lipoprotein cholesterol.

Table 5. Subgroup Analysis of New-Onset End-Stage Renal Disease Requiring Dialysis by Prespecified Baseline Characteristics in the GBM-IPTW–Adjusted Cohort

Subgroup	Event rate, %			SHR (95% CI)	
	LDL-C <70	70≤LDL-C<100	LDL-C ≥100	LDL-C <70 vs LDL-C ≥100	70≤LDL-C<100 vs LDL-C ≥100
Age, y					
≤65	9.0	10.5	12.4	0.68 (0.59–0.79)	0.83 (0.72–0.95)
>65	5.4	5.1	6.2	0.88 (0.73–1.06)	0.82 (0.68–0.98)
Sex					
Women	6.1	7.7	10.2	0.58 (0.49–0.70)	0.73 (0.63–0.86)
Men	7.8	7.5	8.3	0.93 (0.80–1.09)	0.91 (0.78–1.05)
Hypertension					
No	10.6	8.6	8.5	1.23 (0.97–1.56)	0.99 (0.79–1.26)
Yes	6.2	7.3	9.3	0.65 (0.56–0.74)	0.78 (0.69–0.88)
Diabetes					
No	3.5	4.4	3.8	0.90 (0.67–1.20)	1.14 (0.88–1.48)
Yes	8.9	9.5	12.3	0.71 (0.62–0.80)	0.76 (0.67–0.85)
Proteinuria					
Negative/trace	2.1	1.4	2.0	1.02 (0.69–1.51)	0.72 (0.48–1.09)
≥1+	10.0	11.0	12.7	0.77 (0.68–0.87)	0.86 (0.77–0.96)
Statin potency					
Low/moderate	3.0	2.7	4.7	0.63 (0.52–0.75)	0.57 (0.48–0.68)
High	2.2	2.3	5.8	0.37 (0.18–0.75)	0.40 (0.21–0.76)

GBM-IPTW indicates generalized boosted modeling-inverse probability of treatment weighting; LDL-C, low-density lipoprotein cholesterol; and SHR, subdistribution hazard ratio.

had a much higher probability of new-onset ESRD than this study (around 10% in our study versus 35% in the SHARP study) and indicated that the use of statins could not reduce the risk of new-onset ESRD.[24] Because the progressive glomerulosclerosis and interstitial fibrosis of kidney in late-stage of CKD is irreversible, the renal benefits of this study might imply that only in patients with early-stage of CKD could statin treatment contribute to the reduction of new-onset ESRD. Our next research project focusing on advanced CKD will help verify this speculation. Finally, in line with previous large-scale RCTs that enrolled different populations, which have consistently indicated that statin treatment did not increase the risk of hepatitis or rhabdomyolysis,[17,24] this study further demonstrated that these complications were rare, and a lower LDL-C level was not associated with a significantly higher risk of these complications.

This study has several strengths. It was based on a large comprehensive database and enrolled a total of 8500 patients. Moreover, it was the first study to compare the study outcomes across different LDL-C levels in statin users, which was more consistent with the target-driven strategy adopted in most current treatment guidelines. Furthermore, this was the first large-scale study designed to evaluate the benefit of low LDL-C levels, specifically in patients with stage 3 CKD. However, some limitations should be acknowledged.

First, although IPTW analysis included the most relevant confounders and achieved an ideal balance, because this was an observational study, eliminating all residual bias was impossible and would entail some inherent limitations. Second, the study groups were allocated according to the first available LDL-C data after the index date; however, according to the study design, we could not simply ascertain that enrollees' long-term LDL-C levels were still within the range defined for their original group. Third, multiple testing was not dealt with in this study, and therefore the conclusion should be taken more conservatively. Furthermore, the sample size of the LDL<70 mg/dL group was much lower than the other 2 groups, and therefore the statistical power was limited for comparisons to this group. Finally, because this study used data from a Taiwanese database, the study results may not be applicable to other populations considering the dietary and genetic differences.

CONCLUSIONS

This large-scale observational study revealed that among patients with stage 3 CKD, statin users with 70≤LDL-C<100 mg/dL and LDL-C <70 mg/dL had similar beneficial responses in the reduction of cardiovascular events and new-onset ESRD compared with

those with LDL-C >100 mg/dL. Moreover, the 70≤LDL-C<100 mg/dL group seemed to have a favorable outcome in intracerebral hemorrhage, though the much lower incidence rate compared with other outcomes and conflicting previous evidence caused uncertainty over this outcome. For patients younger than 65 years or with apparent proteinuria, to control LDL-C levels <70 mg/dL might provide slightly more beneficial. However, only 1 single observational study is far from enough to reach this conclusion. Further validation of our findings by well-designed prospective studies are warranted.

REFERENCES

1. Babaei S, Picard P, Ravandi A, Monge JC, Lee TC, Cernacek P, Stewart DJ. Blockade of endothelin receptors markedly reduces atherosclerosis in LDL receptor deficient mice: role of endothelin in macrophage foam cell formation. Cardiovasc Res. 2000;48:158–167. doi: 10.1016/S0008-6363(00)00169-3
2. Zhang X, Liu J, Wang M, Qi Y, Sun J, Liu J, Wang Y, Hao Y, Li Y, Zhou M, Zhao D. Twenty-year epidemiologic study on LDL-C levels in relation to the risks of atherosclerotic event, hemorrhagic stroke, and cancer death among young and middle-aged population in China. J Clin Lipidol. 2018; 12:1179–1189.e4. doi: 10.1016/j.jacl.2018.06.011.
3. Sun XM, Patel DD, Knight BL, Soutar AK. Comparison of the genetic defect with LDL-receptor activity in cultured cells from patients with a clinical diagnosis of heterozygous familial hypercholesterolemia. The Familial Hypercholesterolaemia Regression Study Group. Arterioscler Thromb Vasc Biol. 1997;17:3092–3101. doi: 10.1161/01.ATV.17.11.3092
4. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195–2207. doi: 10.1056/NEJMoa0807646
5. Sillesen H, Amarenco P, Hennerici MG, Callahan A, Goldstein LB, Zivin J, Messig M, Welch KM; and Stroke Prevention by Aggressive Reduction in Cholesterol Levels Investigators. Atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis: a secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke. 2008;39:3297–3302. doi: 10.1161/STROKEAHA.108.516450
6. Nicholls SJ. Relationship between LDL, HDL, blood pressure and atheroma progression in the coronaries. Curr Opin Lipidol. 2009;20:491–496. doi: 10.1097/MOL.0b013e32832ec396
7. Hermida N, Balligand JL. Low-density lipoprotein-cholesterol-induced endothelial dysfunction and oxidative stress: the role of statins. Antioxid Redox Signal. 2014;20:1216–1237. doi: 10.1089/ars.2013.5537
8. Michos ED, McEvoy JW, Blumenthal RS. Lipid management for the prevention of atherosclerotic cardiovascular disease. N Engl J Med. 2019;381:1557–1567. doi: 10.1056/NEJMra1806939
9. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendiksen FS, Lindahl C, Szarek M, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005;294:2437–2445. doi: 10.1001/jama.294.19.2437
10. Lind L. Effect of new statin treatment on carotid artery intima-media thickness: a real-life observational study over 10 years. Atherosclerosis. 2020;306:6–10. doi: 10.1016/j.atherosclerosis.2020.06.012
11. Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380:581–590. doi: 10.1016/S0140-6736(12)60367-5
12. Virani SS, Smith SC Jr, Stone NJ, Grundy SM. Secondary prevention for atherosclerotic cardiovascular disease: comparing recent US and European guidelines on dyslipidemia. Circulation. 2020;141:1121–1123. doi: 10.1161/CIRCULATIONAHA.119.044282
13. Zeitouni M, Sabouret P, Kerneis M, Silvain J, Collet JP, Bruckert E, Montalescot G. 2019 ESC/EAS guidelines for management of dyslipidaemia: strengths and limitations. Eur Heart J Cardiovasc Pharmacother. 2021;7:324–333.
14. Chronic Kidney Disease Prognosis Consortium, Matsushita K, Van Der Velde M, Astor BC, Woodward M, Levey AS, De Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–2081. doi: 10.1016/S0140-6736(10)60674-5
15. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–1305. doi: 10.1056/NEJMoa041031
16. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, Ritz E, German D, Dialysis Study I. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353:238–248. doi: 10.1056/NEJMoa043545
17. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Gronhagen-Riska C, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360:1395–1407. doi: 10.1056/NEJMoa0810177
18. Massy ZA, de Zeeuw D. LDL cholesterol in CKD--to treat or not to treat? Kidney Int. 2013;84:451–456. doi: 10.1038/ki.2013.181
19. Messow CM, Isles C. Meta-analysis of statins in chronic kidney disease: who benefits? QJM. 2017;110:493–500. doi: 10.1093/qjmed/hcx040
20. Bermudez-Lopez M, Betriu A, Valdivielso JM, Bretones Del Pino T, Arroyo D, Fernandez E. Beyond the traditional lipid parameters in chronic kidney disease. Nefrologia (Engl Ed). 2018;38:109–113. doi: 10.1016/j.nefroe.2017.11.016
21. Sarnak MJ, Amann K, Bangalore S, Cavalcante JL, Charytan DM, Craig JC, Gill JS, Hlatky MA, Jardine AG, Landmesser U, et al. Chronic kidney disease and coronary artery disease: JACC State-of-the-art review. J Am Coll Cardiol. 2019;74:1823–1838. doi: 10.1016/j.jacc.2019.08.1017
22. Authors/Task Force Members, Guidelines ESCCfP and Societies ESCNC. ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Atherosclerosis. 2019;2019(290):140–205. doi: 10.1016/j.atherosclerosis.2019.08.014
23. Adhyaru BB, Jacobson TA. New cholesterol guidelines for the management of atherosclerotic cardiovascular disease risk: a comparison of the 2013 American College of Cardiology/American Heart Association Cholesterol Guidelines with the 2014 National Lipid Association recommendations for patient-centered management of dyslipidemia. Endocrinol Metab Clin North Am. 2016;45:17–37. doi: 10.1016/j.ecl.2015.09.002
24. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic

kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet.* 2011;377:2181–2192. doi: 10.1016/S0140-6736(11)60739-3

25. Tonelli M, Muntner P, Lloyd A, Manns B, Klarenbach S, Pannu N, James M, Hemmelgarn B, Alberta Kidney Disease Network. Association between LDL-C and risk of myocardial infarction in CKD. *J Am Soc Nephrol.* 2013;24:979–986. doi: 10.1681/ASN.2012080870

26. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis.* 1990;15:458–482. doi: 10.1016/S0272-6386(12)70364-5

27. Shao SC, Chan YY, Kao Yang YH, Lin SJ, Hung MJ, Chien RN, Lai CC, Lai EC. The Chang Gung Research Database—a multi-institutional electronic medical records database for real-world epidemiological studies in Taiwan. *Pharmacoepidemiol Drug Saf.* 2019;28:593–600. doi: 10.1002/pds.4713

28. McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. *Stat Med.* 2013;32:3388–3414. doi: 10.1002/sim.5753

29. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med.* 2017;376:1713–1722. doi: 10.1056/NEJMoa1615664

30. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, Wiebe N, Tonelli M, Alberta Kidney Disease Network. Relation between kidney function, proteinuria, and adverse outcomes. *JAMA.* 2010;303:423–429. doi: 10.1001/jama.2010.39

31. Amarenco P, Bogousslavsky J, Callahan A III, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med.* 2006;355:549–559. doi: 10.1056/NEJMoa061894

32. Gaist D, Goldstein LB, Cea Soriano L, Garcia Rodriguez LA. Statins and the risk of intracerebral hemorrhage in patients with previous ischemic stroke or transient ischemic attack. *Stroke.* 2017;48:3245–3251. doi: 10.1161/STROKEAHA.117.019141

33. Amarenco P, Kim JS, Labreuche J, Charles H, Abtan J, Bejot Y, Cabrejo L, Cha JK, Ducrocq G, Giroud M, et al. A comparison of two LDL cholesterol targets after ischemic stroke. *N Engl J Med.* 2020;382:9–19. doi: 10.1056/NEJMoa1910355

34. Ma C, Gurol ME, Huang Z, Lichtenstein AH, Wang X, Wang Y, Neumann S, Wu S, Gao X. Low-density lipoprotein cholesterol and risk of intracerebral hemorrhage: a prospective study. *Neurology.* 2019;93:e445–e457. doi: 10.1212/WNL.0000000000007853

35. Rist PM, Buring JE, Ridker PM, Kase CS, Kurth T, Rexrode KM. Lipid levels and the risk of hemorrhagic stroke among women. *Neurology.* 2019;92:e2286–e2294. doi: 10.1212/WNL.0000000000007454

36. Wang X, Dong Y, Qi X, Huang C, Hou L. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. *Stroke.* 2013;44:1833–1839. doi: 10.1161/STROKEAHA.113.001326

37. Zhang Y, Lu Y, Ji H, Li Y. Anti-inflammatory, anti-oxidative stress and novel therapeutic targets for cholestatic liver injury. *Biosci Trends.* 2019;13:23–31. doi: 10.5582/bst.2018.01247

38. Hartner A, Klanke B, Cordasic N, Amann K, Schmieder RE, Veelken R, Hilgers KF. Statin treatment reduces glomerular inflammation and podocyte damage in rat deoxycorticosterone-acetate-salt hypertension. *J Hypertens.* 2009;27:376–385. doi: 10.1097/HJH.0b013e32831997d6

39. Fried LF. Effects of HMG-CoA reductase inhibitors (statins) on progression of kidney disease. *Kidney Int.* 2008;74:571–576. doi: 10.1038/ki.2008.231

SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

LGE-CMR imaging

Acquisition protocol: Images were obtained with a 3.0 Tesla CMR (Magnetom Prisma Siemens Healthcare, Germany) and a dedicated 32-channel cardiac coil. LGE-CMR scans were acquired 20 min after an intravenous bolus injection of 0.2 mmol/kg gadobutrol (Gadovist, Bayer Hispania) using a free-breathing 3D navigator and ECG-gated inversion-recovery gradient-eco sequence applied in the axial orientation. The voxel size was 1.25x1.25x2.5 mm. Repetition time/echo time was 2.3/1.4 ms; flip angle, 11º; bandwidth, 460 Hz/pixel; inversion time (TI) 280 to 380 ms; and parallel imaging with GRAPPA technique, with reference lines of R=2 and 72. A TI scout sequence was used to nullify the left ventricular myocardial signal and determine optimal TI. Typical scan time for LGE-CMR sequence was 15 minutes (11-18), depending on heart rate and breathing patterns.

Post-processing: RA and LA segmentation was performed using ADAS 3D software (Barcelona, Spain). Atrial contours of the wall were manually drawn by two expert operators in each axial plane of the LGE-CMR, without invading the interatrial common septum, and a tridimensional model was constructed. ADAS automatically builds a 3D shell. Subsequently, pulmonary veins at the ostium level, mitral valve plane and left appendage were excluded in the LA, and the superior and inferior vena cava at the ostium level, tricuspid valve plane and coronary sinus were excluded in the RA.

Signal intensity was internally (within each patient) normalized to blood pool intensity to provide an absolute signal intensity value that would allow comparisons between patients. The LA blood pool was automatically identified by the software. It was chosen both for LA and RA wall normalization because it was found to be less

variable than the RA blood pool. Image Intensity Ratio (IIR) was calculated as the ratio between the signal intensity of each single pixel and the mean blood pool intensity for each patient. Each IIR value was colour-coded as healthy (IIR<1.20), interstitial fibrosis (1.20≤IIR≤1.32) and dense scar (IIR≥1.32) using previously standardized thresholds for the LA.[11] Dense scar threshold was defined as those fibrotic patches that were predicted conduction block in re-do procedures. Interstitial fibrosis was defined as atrial tissue with IIR lying between the normality-fibrosis boundary (average IIR + 2SDs in a healthy volunteer cohort) and the dense scar threshold.[11] Of note, however, formal histological validation is missing.

Sphericity assessment: Sphericity evaluates the variation between the chamber and the sphere that best fitted its shape. The radius of such sphere is calculated as the mean of distances between all points of the atrium wall and the center of mass (average radius-AR). Finally, the coefficient of variation of the sphere (CVS = AR standard deviation/AR) was obtained to define the atrium sphericity [(1- CVS)*100]. A comprehensive technical description of the method is provided in its original description[13] and its Supplemental Methods (https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fjce.121 16&file=jce12116-sup-0001-S1.doc). The final sphericity number is a unitless value which may potentially be from 0 to 100 (a perfect sphere), but common values in the LA range from 70 to 90.[13] No previous data are available for the RA.

Table S1. Correlation between RA and LA remodeling parameters for total population and by subgroups.

RA / LA correlation	Overall		Healthy volunteers		Paroxysmal AF		Persistent AF	
	R Pearson	P	R Pearson	P	R Pearson	P	R Pearson	P
Volume (mL)	0.695	<0.0001	0.457	0.25	0.426	0.001	0.581	<0.0001
Surface (cm^2)	0.725	<0.0001	0.473	0.2	0.600	<0.0001	0.547	<0.0001
Total fibrosis (%)	0.589	<0.0001	0.837	0.005	0.468	<0.0001	0.679	<0.0001
Interstitial fibrosis (%)	0.463	<0.0001	0.713	0.031	0.460	<0.0001	0.450	0.002
Dense scar (%)	0.638	<0.0001	0.67	0.054	0.406	0.002	0.784	<0.0001
Sphericity	-0.010	0.92	0.12	0.75	-0.050	0.72	-0.222	0.14

*Abbreviations: AF: atrial fibrillation; LA: left atrium; RA: right atrium

Table S2. Prediction models of RA remodeling - total fibrosis (%), area (cm2) and sphericity- between clinical, electrocardiographic, and echocardiographic parameters, using univariate and multivariate linear regression analysis.

	Univariate			Multivariate		
	Beta	**95% CI**	**p**	**Beta**	**95% CI**	**p**
RA FIBROSIS (%)						
Age	0.05	-0.08 to 0.18	0.45			
Female sex	-0.34	-3.36 to 2.67	0.82			
Bundle branch block	**4.13**	**-0.19 to 8.44**	**0.006**			
QRS	-0.04	-0.10 to 0.03	0.293			
PR	-0.03	-0.08 to 0.01	0.12			
BMI	0.19	-0.05 to 0.42	0.12			
Hypertension	-0.05	-2.81 to 2.70	0.97			
Diabetes	**7.71**	**2.92 to 12.5**	**0.002**	**7.70**	**2.81 to 12.5**	**0.002**
Sleep apnea	1.83	-2.53 to 6.18	0.41			
Atrial Flutter	0.35	-4.02 to 4.72	0.87			
AF pattern	0.08	-2.68 to 2.84	0.96			
LVEF	0.04	-0.15 to 0.22	0.71			
LA diameter	0.16	-0.08 to 0.40	0.19			
TR ≥ moderate	3.52	-0.65 to 7.68	0.10			
RA AREA (cm^2)						
Age	0.01	-0.48 to 0.52	0.96			
Female sex	**-12.57**	**-23.7 to -1.4**	**0.028**	**-14.95**	**-24.9 to -4.94**	**0.004**
Bundle branch block	5.10	-11.6 to -21.8	0.545			
QRS (ms)	-0.01	-0.27 to 0.25	0.92			
PR (ms)	**0.13**	**-0.03 to 0.29**	**0.11**	**0.15**	**0.011 to 0.28**	**0.034**
BMI	0.43	-0.46 to 1.32	0.34			
Hypertension	-3.32	-13.83 to 7.19	0.53			
Diabetes	-3.25	-21.6 to 15.1	0.73			
Sleep apnea	8.57	-8.12 to 25.25	0.31			
Atrial flutter	-3.61	-20.4 to 13.2	0.67			
AF pattern	**27.77**	**18.8 to 36.7**	**<0.0001**	**26.3**	**17.4 to 35.2**	**<0.0001**
LVEF	**-0.801**	**-1.49 to 0.11**	**0.02**			
LA diameter	**1.37**	**0.49 to 2.26**	**0.003**			
TR ≥ moderate	**13.17**	**-2.82 to 29.2**	**0.11**	**12.9**	**-1.11 to 26.9**	**0.07**
RA SPHERICITY						
Age	-0.021	-0.07 to 0.03	0.41			

|						
Female sex	0.534	-0.63 to 1.70	0.36			
Bundle branch block	0.163	-1.53 to 1.86	0.85			
QRS (ms)	-0.003	-0.03 to 0.02	0.85			
PR (ms)	<0.001	-0.02 to 0.02	0.96			
BMI	0.026	-0.07 to 0.12	0.57			
Hypertension	-0.50	-1.56 to 0.57	0.36			
Diabetes	-1.30	-3.15 to 0.55	0.17			
Sleep apnea	-0.14	-1.85 to 1.57	0.87			
Atrial Flutter	0.10	-1.61 to 1.81	0.91			
AF pattern	0.85	-0.21 to 1.92	0.11			
LVEF	-0.05	-0.12 to 0.02	0.17			
LA diameter	-0.03	-0.12 to 0.07	0.59			
TR ≥ moderate	**1.55**	**-0.06 to 3.17**	**0.06**	**1.47**	**-0.17 to 3.10**	**0.08**

*Abbreviations: AF: atrial fibrillation; BMI: body mass index; LA: left atrium; LVEF: left ventricular ejection fraction; RA: right atrium; TR: tricuspid regurgitation

**Figure S1. Correlation between RA remodeling parameters.**
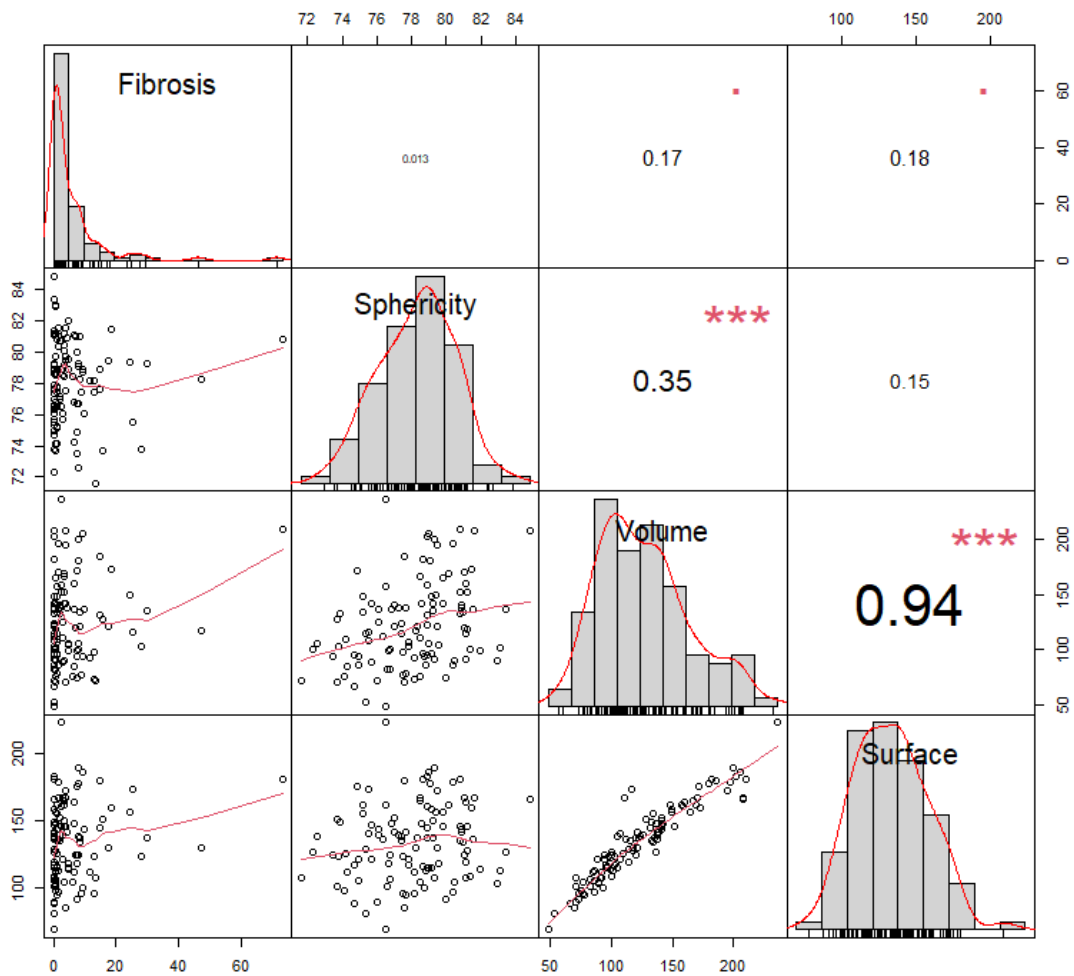
The diagonal cells show the distribution of each fibrosis, sphericity, volume, and surface.

In the lower-left corner, their bivariate scatter plot is shown in the intersection cell. In

the upper-right corner, the magnitude of their correlation (Pearson coefficient) is shown

in number, and the significance in asterisks (***p<0.001; • 0.10<p<0.05; no sign means

p>0.1).

Figure S2. Bar chart representing percentage of AF patients with fibrosis in RA and LA (total fibrosis and breakdown by type of fibrosis).
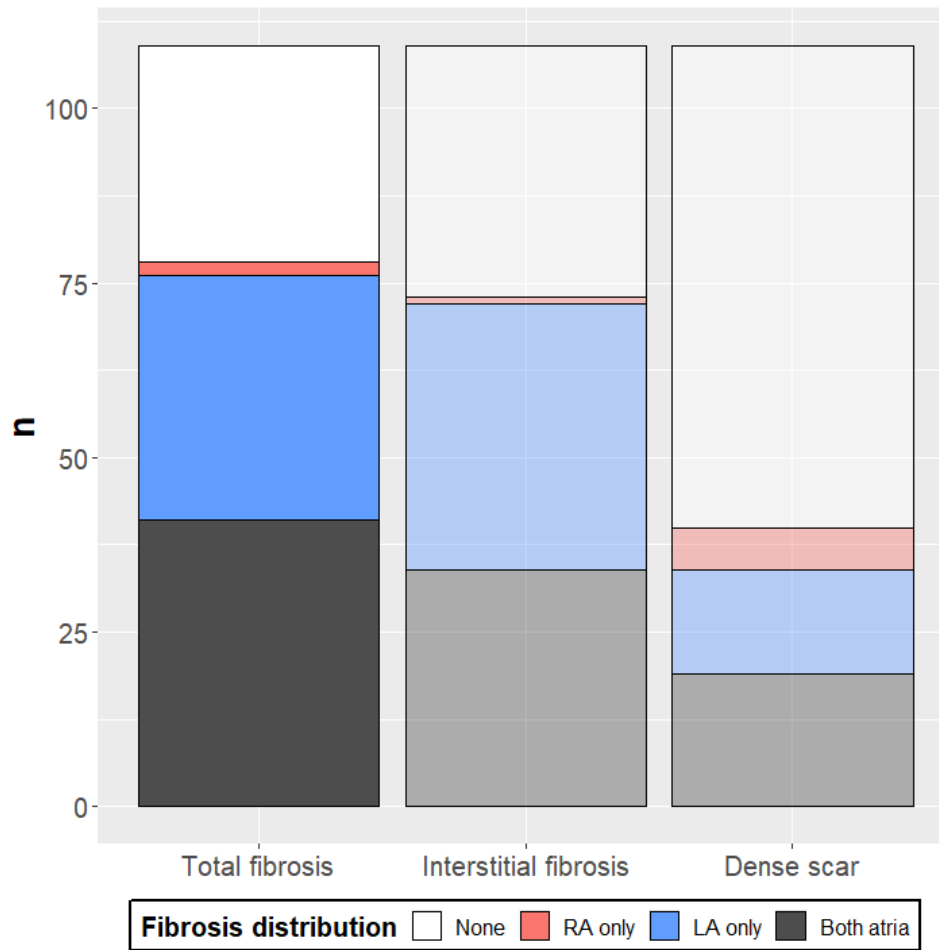

*LA: left atrium; RA: right atrium

Figure S3. Pairwise comparisons of atrial fibrosis burden for each of the RA regions.
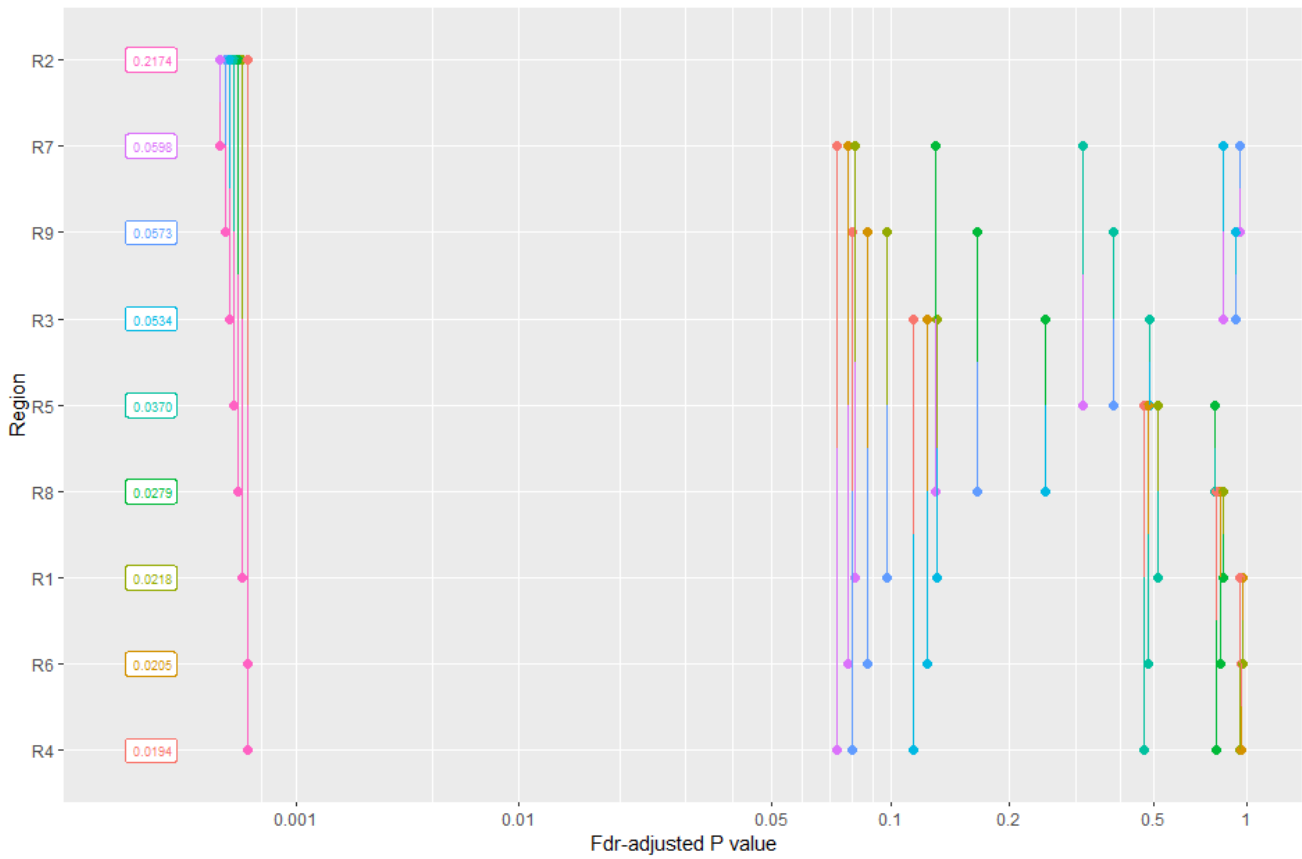
Each region is plotted in the Y-axis (top to low: higher to lower fibrosis burden, labels).

Segments linking two regions are plotted in the X-axis value corresponding to the fdr-adjusted p-value of their pairwise comparison.

Figure S4. Anatomical relationship between right and left atria and ascending and descending aorta.
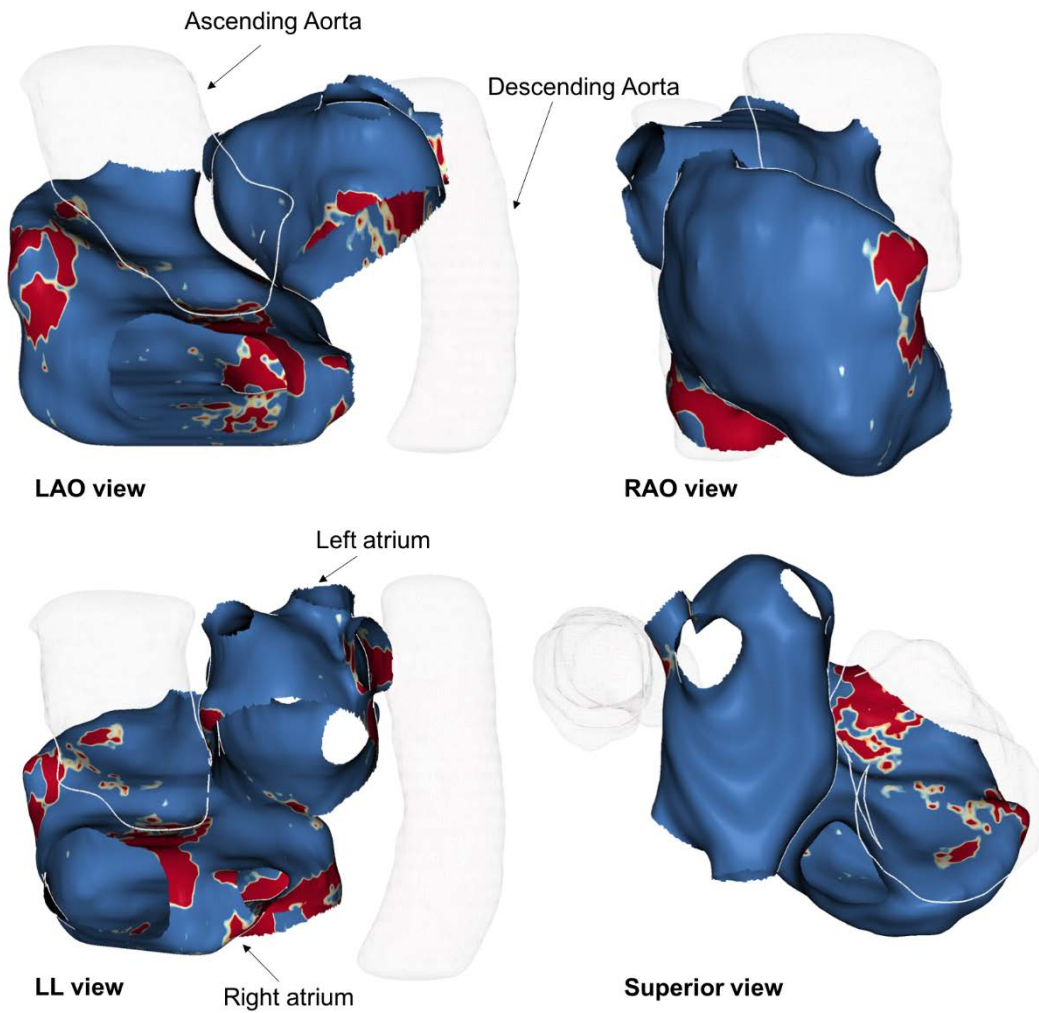
3D shells postprocessed together.

*LAO: left anterior oblique; LL: left lateral; RAO: right anterior oblique