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Evaluation of the Paradoxical Association Between Lipid Levels and Incident Atrial Fibrillation According to Statin Usage: A Nationwide Cohort Study

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ABSTRACT

Objective: Higher levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are associated with a lower risk of atrial fibrillation (AF). Statin use might exert confounding effects on the paradoxical associations; however, the relationships that distinguish statin users from non-users have not been thoroughly evaluated.
Methods: From the Korean National Health Insurance Database, we included 9,778,014 adults who underwent a health examination in 2009. The levels of TC and LDL-C at the health examination were categorized into quartile values of the total study population. We grouped the study population into statin users and non-users and investigated the associations between TC, LDL-C, and the risk of incident AF.
Results: Of the total population, 867,336 (8.9%) were taking statins. During a mean follow-up of 8.2 years, inverse associations of TC – AF and LDL-C – AF were observed; higher levels of TC and LDL-C were associated with the lower risk of AF in the total population. Overall, statin users showed higher AF incidence rate than non-users, but the inverse associations of TC – AF and LDL-C – AF were consistently observed irrespective of statin usage; adjusted hazard ratio with 95% confidence interval was 0.81 (0.79–0.84) for statin users and 0.81 (0.80–0.83) for non-users in the highest TC quartile, and 0.84 (0.82–0.87) for statin users and 0.85 (0.84–0.86) for non-users in the highest LDL-C quartile (all $p<0.001$).
Conclusion: The paradoxical relationship between lipid levels (TC and LDL-C) and the risk of AF remains consistent in both statin users and non-users.

Keywords: Atrial fibrillation; Cholesterol; Association; Lipid

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Conflict of Interest

Eue-Keun Choi: Research grants or speaking fees from Abbott, Bayer, BMS/Pfizer, Biosense Webster, Chong Kun Dang, Daewoong Pharmaceutical Co., Daiichi-Sankyo, DeepQure, Dreamtech Co., Ltd., Jeil Pharmaceutical Co. Ltd, Medtronic, Samjinpharm, Seers Technology, and Skylabs. Gregory Y. H. Lip: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally.

Author Contributions

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INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with an increased risk of stroke, heart failure, myocardial infarction, and death.[1-3] The prevalence of AF and related health care costs and clinical burden is rapidly rising[4]; thus, recent guidelines have highlighted the need for appropriate evaluation and characterization of AF,[5] followed attention to cardiovascular risk factors as part of holistic and integrated care management of AF.[6,7]

Several risk factors—such as age, hypertension, diabetes mellitus, and obesity—are associated with incident AF, and are also related to the development of cardiovascular disease (CVD).[8] However, there is a one exception with an apparent inverse association, whereby high blood lipid levels are a well-known risk factor for atherosclerotic CVD,[9] yet is associated with a lower risk of incident AF, a phenomenon known as the cholesterol paradox.[8,10-12] Of note, a low level of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) is linked to the high risk of AF, while relationships with high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels have been inconsistent.[11-14]

The HMG Co-A inhibitors ('statins') are potent LDL-C lowering agents and is commonly used in patients with hyperlipidemia.[15,16] The use of statins has been suggested to be associated with a lower risk of AF attributed to its pleiotropic roles in anti-inflammation, antioxidant properties, and atrial remodeling prevention.[17,18] However, large trials and meta-analyses have produced contradictory results regarding the association between statin therapy and the development of AF.[11,19,20] Although there have been concerns that statin use might introduce bias in the association between lipid level and AF risk by its cholesterol-lowering effect and other favorable biological mechanisms, several studies have indicated that the cholesterol paradox is valid independently of statin use.[13,21]

Nevertheless, the possible confounding effects of statin use in the AF-cholesterol paradox have not been thoroughly evaluated in a large population, especially in Asia, where the overall prevalence of AF is relatively lower than in Western countries and the burden of comorbidity is higher due to the aged population.[22] Also, the AF-cholesterol paradox was primarily validated in ethnic groups other than Asians.[6,23] Therefore, the aim of this study was to investigate whether statin use alters the inverse relationship, particularly for TC and LDL-C, by demonstrating the associations individually in statin users and non-users from a large Asian nationwide-population cohort.

MATERIALS AND METHODS

1. Study population

We used the National Health Information Database (NHID, https://nhiss.nhis.or.kr/) to define a nationwide population-based cohort that included all data from the National Health Insurance Service, which covers the entire population of the Republic of Korea (hereafter, Korea). All insured adults are encouraged to have complimentary biannual general health screenings. The NHID contains routine health examination results, including anthropometric measurements, laboratory results, detailed lifestyle questionnaires about smoking, alcohol habit, and exercise—sociodemographic data, income-based insurance contributions, prescription records, inpatient and outpatient utilization, and the date of

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death. Each individual's diagnosis records are included in the database as International Classification of Diseases, Tenth Revision, and Clinical Modification (ICD-10-CM) diagnostic codes.[24-26] The Institutional Review Board at the Seoul National University Hospital (E-2003-169-1112) authorized this study.

We selected 10,585,843 adults who underwent health examinations in 2009. Individuals with prevalent AF or who were diagnosed with AF within the first year of follow-up were excluded, as were those with missing health examination data. Finally, we included 9,778,014 adults in the study (**Fig. 1**).

2. Categorization of lipid levels and statin usage

Among lipid levels, TC and LDL-C were evaluated of which have been reported to have a relatively consistent relationship with the risk of AF.[11,27] The levels of TC and LDL-C were categorized in quartiles and deciles of the total study population. First, the associations of TC – AF and LDL-C – AF were assessed throughout the entire study population. Second, the study population was divided into statin users and non-users based on the status of statin prescriptions at the baseline health examination. The TC – AF and LDL-C – AF relationships were reevaluated in each group.

3. Covariates, follow-up, and clinical outcomes

During the follow-up period, the incidence of AF was assessed. The diagnostic codes (ICD-10-CM) and inpatient and outpatient utilization records were used to determine clinical outcomes. **Supplementary Table 1** provides detailed operational definitions of comorbidities and AF.[26] The follow-up period was defined as the time from the date of the baseline health examination to the first occurrence of AF, death, or the end of the study period (31 December 2018), whichever came first.

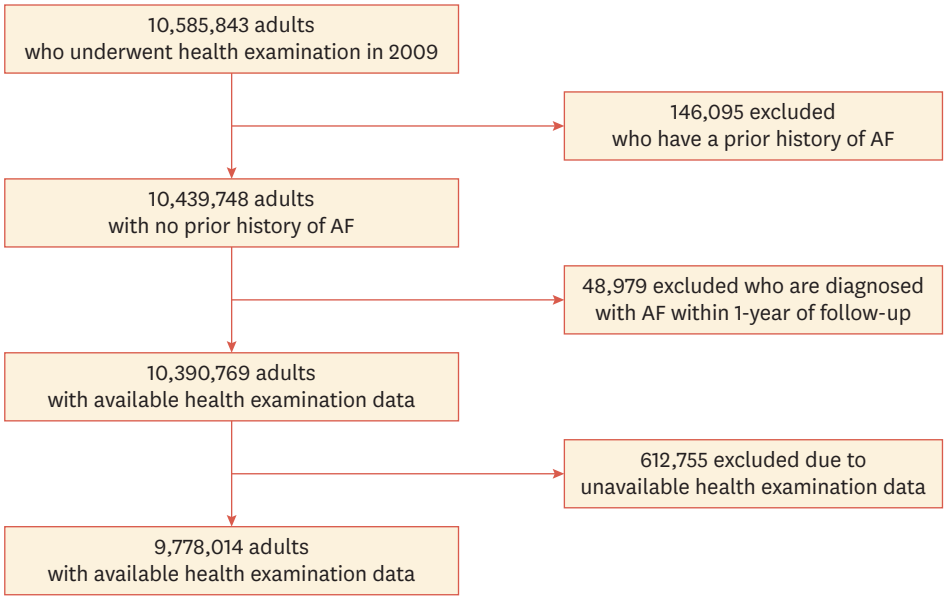

Fig. 1. Study enrollment flow.
AF, atrial fibrillation.

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4. Statistical analysis

Continuous variables are expressed in terms of mean ± standard deviation or median (interquartile range), while categorical variables are expressed in terms of numbers (%). The χ^2 test and one-way analysis of variance were used to assess the differences in baseline characteristics of each age group. The crude incidence rates (IRs) of AF were calculated by dividing the number of AF development cases by the entire follow-up time. Using Cox proportional hazards regression models, we evaluated the association between lipid levels and the risk of AF. The risk of AF was estimated by hazard ratios (HRs) with 95% confidence intervals (CIs) based on the range of lipid levels. Model 1 was unadjusted, and Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, lifestyle behaviors (smoking status, alcohol intake, and regular exercise), comorbidities (hypertension, diabetes mellitus, dyslipidemia, heart failure, myocardial infarction, peripheral artery disease, and chronic kidney disease), and low-income status.

5. Sensitivity and subgroup analyses

Sensitivity analysis was performed by excluding statin-nonusers who initiated statin within the first year of follow-up (n=9,762,374) and censoring statin-nonusers when they initiated statin during follow-up. The robustness of the associations of TC – AF and LDL-C – AF stratified by statin usage was evaluated. We conducted subgroup analyses of the association between lipid levels and the incidence of AF by sex and age (<40, 40–64, and ≥65 years) to look for potential effect modification. Data collection and statistical analysis were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) from July 2021 to September 2021.

RESULTS

Detailed features of 9,778,014 subjects based on their statin use are shown in **Table 1**. Of the total population, 867,336 (8.9%) were on statin use. The mean age of the total study population was 47.0±14.0 years, and statin users were older than non-users, with a mean age of 58.4±10.6 years. The proportion of males was 54.6% of the overall population and 44.1% of the statin users. Comorbidities—hypertension, diabetes mellitus, heart failure, myocardial infarction, peripheral artery disease, and chronic kidney disease—were all more prevalent in those with statin use; 98.5% have underlying dyslipidemia in the statin group. Statin users showed a higher level of both TC and LDL-C level compared to non-users: mean TC level, 194.1±39.5 mg/dL and 208.4±55.6 mg/dL (p<0.001), and mean LDL-C level, 121.3±226.3 mg/dL and 123.0±102.2 mg/dL (p<0.001) for statin non-users and users, respectively. The baseline characteristics of the study population stratified by the development of AF are summarized in **Supplementary Table 2**. Those who developed incident AF had similar TC levels but lower LDL-C levels and were more on statin use than those who did not have incident AF during follow-up; the mean TC level was 195.4±41.3 mg/dL and 195.4±44.7 mg/dL (p=0.884), mean LDL-C level was 121.5±219.6 mg/dL and 116.3±104.9 mg/dL (p<0.001), and statin usage was 8.7% and 18.5% (p<0.001) in patients without and with incident AF, respectively.

1. Association between lipid levels and the risk of AF

The risk of AF according to the quartile level of TC and LDL-C is presented in **Table 2**. TC quartile (Q) levels of the overall population were <170, 170–192, 193–217, and ≥218 mg/dL for Q1, Q2, Q3, and Q4, respectively. For LDL-C, each Q level was <91, 91–111, 112–134, and ≥135 mg/dL from Q1 to Q4. During a mean follow-up of 8.2±1.0 years, the associations of TC – AF and LCL-C – AF were inverse correlations; the higher levels of TC and LDL-C were associated

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Table 1. Baseline characteristics of the study population according to statin usage

	Total	Statin use		
		No	Yes	*p*-value
No. of subjects	9,778,014	8,910,678 (91.13)	867,336 (8.87)	
Age (yr)	47.03±13.98	45.92±13.77	58.43±10.60	<0.001
<40	3,070,171 (31.40)	3,036,040 (34.07)	34,131 (3.94)	<0.001
40–64	5,464,246 (55.88)	4,888,982 (54.87)	575,264 (66.33)	
≥65	1,243,597 (12.72)	985,656 (11.06)	257,941 (29.74)	
Sex (male)	5,335,994 (54.57)	4,953,650 (55.59)	382,344 (44.08)	<0.001
Body mass index (kg/m^2)	23.69±3.45	23.56±3.45	25.03±3.12	<0.001
Smoking				<0.001
Non	5,821,487 (59.54)	5,237,506 (58.78)	583,981 (67.33)	
Ex	1,396,206 (14.28)	1,256,293 (14.10)	139,913 (16.13)	
Current	2,560,321 (26.18)	2,416,879 (27.12)	143,442 (16.54)	
Alcohol consumption				<0.001
Non	5,035,921 (51.50)	4,458,238 (50.03)	577,683 (66.60)	
Mild	3,962,298 (40.52)	3,724,694 (41.80)	237,604 (27.39)	
Heavy	779,795 (7.97)	727,746 (8.17)	52,049 (6.00)	
Regular exercise	1,751,411 (17.91)	1,561,232 (17.52)	190,179 (21.93)	<0.001
Comorbidities				
Diabetes mellitus	844,641 (8.64)	600,329 (6.74)	244,312 (28.17)	<0.001
Hypertension	2,492,044 (25.49)	1,953,491 (21.92)	538,553 (62.09)	<0.001
Dyslipidemia	1,753,772 (17.94)	899,806 (10.10)	853,966 (98.46)	<0.001
Peripheral artery disease	603,923 (6.18)	431,349 (4.84)	172,574 (19.90)	<0.001
Myocardial infarction	6,438 (0.07)	2,145 (0.02)	4,293 (0.49)	<0.001
Heart failure	4,693 (0.05)	2,703 (0.03)	1,990 (0.23)	<0.001
Chronic kidney disease	664,038 (6.79)	552,387 (6.20)	111,651 (12.87)	<0.001
Laboratory values				
Systolic BP (mmHg)	122.42±15.06	121.89±14.90	127.82±15.60	<0.001
Diastolic BP (mmHg)	76.31±10.06	76.09±10.03	78.53±10.14	<0.001
Fasting glucose (mg/dL)	97.25±23.82	96.11±22.17	108.91±34.66	<0.001
TC (mg/dL)	195.35±41.36	194.08±39.47	208.35±55.63	<0.001
HDL-C (mg/dL)	56.48±32.7	56.52±32.48	56.03±34.93	<0.001
LDL-C (mg/dL)	121.41±218.14	121.25±226.27	123.02±102.16	<0.001
Triglyceride (mg/dL)	112.66 (112.62–112.70)	110.19 (110.15–110.23)	141.50 (141.34–141.67)	<0.001

Data are presented as mean ± standard deivation, median (interquartile range), or number (percentages). Percentages may not total 100 because of rounding.
BP, blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 2. The risk of AF according to the level of TC and LDL-C in quartile

Characteristics	No. of participants	AF	IR (1,000 PY)	HR (95% CI)		
				Model 1	Model 2	Model 3
TC (mg/dL)						
Q1 (<170)	2,443,079	43,331	2.18	1.000 (Ref.)	1.000 (Ref.)	1.000 (Ref.)
Q2 (170–192)	2,457,570	40,180	2.00	0.916 (0.904–0.929)	0.878 (0.867–0.890)	0.899 (0.887–0.911)
Q3 (193–217)	2,425,094	41,104	2.07	0.949 (0.936–0.962)	0.841 (0.830–0.853)	0.862 (0.850–0.874)
Q4 (≥218)	2,452,271	43,560	2.17	0.995 (0.982–1.008)	0.804 (0.793–0.815)	0.797 (0.786–0.809)
				p<0.001	*p*<0.001	*p*<0.001
LDL-C (mg/dL)						
Q1 (<91)	2,470,047	43,919	2.19	1.000 (Ref.)	1.000 (Ref.)	1.000 (Ref.)
Q2 (91–111)	2,448,132	39,406	1.97	0.899 (0.887–0.912)	0.881 (0.869–0.893)	0.922 (0.909–0.935)
Q3 (112–134)	2,432,623	41,113	2.07	0.943 (0.931–0.956)	0.841 (0.830–0.853)	0.888 (0.876–0.900)
Q4 (≥135)	2,427,212	43,737	2.20	1.005 (0.992–1.019)	0.799 (0.788–0.810)	0.832 (0.820–0.843)
				p<0.001	*p*<0.001	*p*<0.001

Model 1 was unadjusted. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, lifestyle behaviors (smoking status, alcohol intake, and regular exercise), comorbidities (hypertension, diabetes mellitus, dyslipidemia, heart failure, myocardial infarction, peripheral artery disease, and chronic kidney disease), and low-income status.
AF, atrial fibrillation; IR, incidence rate; PY, person-years; HR, hazard ratio; CI, confidence interval; Q, quartile; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol.

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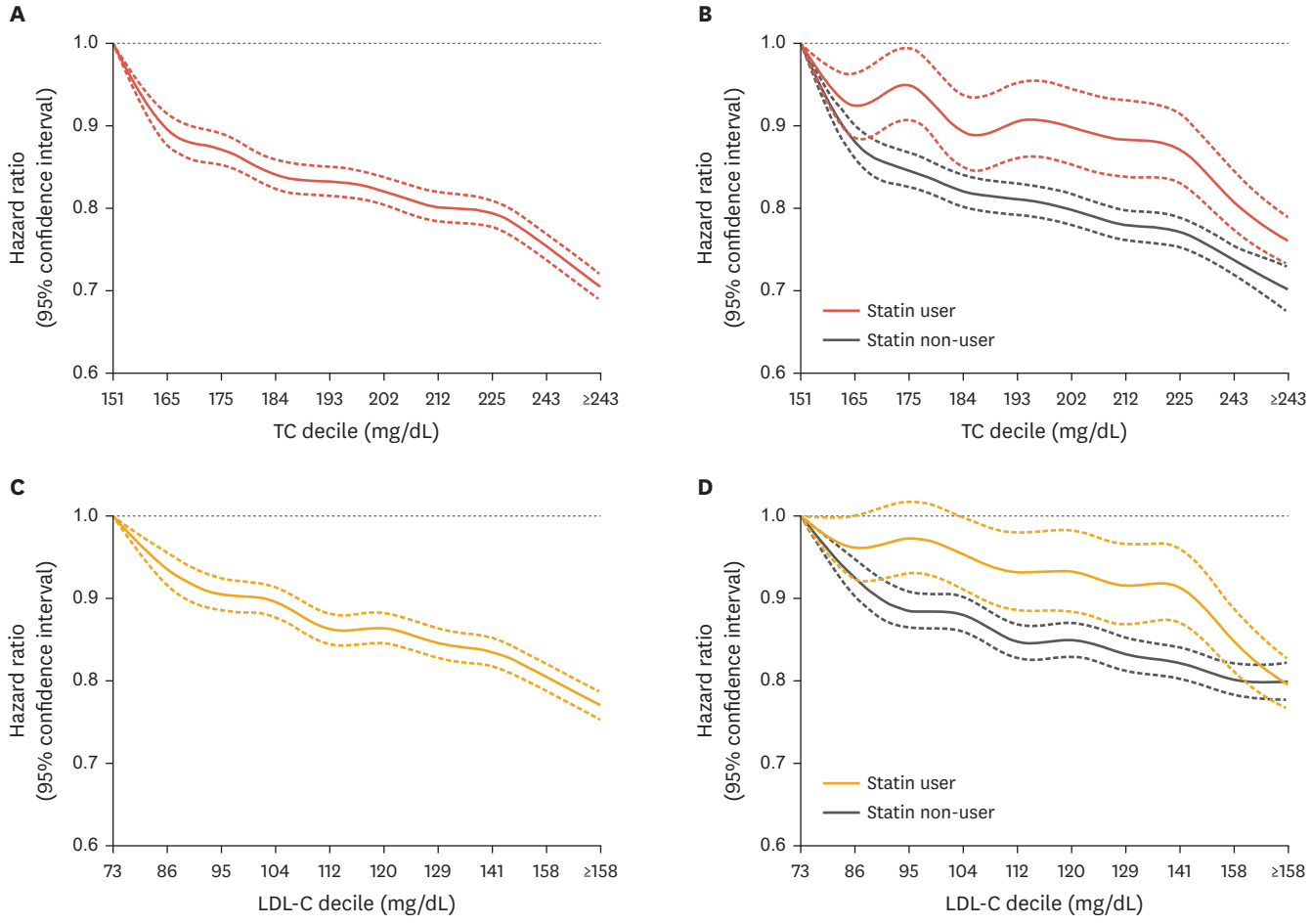

Fig. 2. The risk of atrial fibrillation according to (A) TC level, (B) TC level and statin usage, (C) LDL-C level, and (D) LDL-C level and statin usage.
TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol.

with a lower risk of AF. The HRs and 95% CIs were 0.797 (0.786–0.809) for the highest quartile of TC (Q4, TC ≥218 mg/dL) and 0.832 (0.82–0.843) for the highest quartile of LDL-C (Q4, LDL-C ≥135 mg/dL) when adjusted by Model 3. When divided the levels of TC and LCL-C in decile, more detailed inverse associations between lipid levels and the risk of AF were verified (**Supplementary Table 3**). As shown in **Fig. 2A and C**, increment of lipid levels in both TC and LDL-C was related to the steadily decreased incident AF risk with no deflection points.

2. Statin use and the association between lipid levels and the risk of AF

The associations between lipid levels (TC and LDL-C) and the risk of AF stratified by statin use are described in **Table 3**. The number of IRs of AF increased proportionately to TC and LDL-C levels in non-statin users, whereas the number of IR decreased in statin users. After adjusting with multivariables, both TC and LDL-C levels showed an inverse relationship with AF risk. In addition, while the IRs of AF among statin users were higher than that of non-statin users, the steady inverse connection between lipid levels and AF persisted independent of statin treatment. The association between lipid levels and the risk of AF in statin users is generally consistent with that in non-users demonstrating similar HR in Q4 of TC (0.812, 95% CI, 0.790–0.835) and LDL-C (0.842, 95% CI, 0.819–0.865), but the lower risk of AF according to the increment of TC and LDL-C in Q1–Q3 was slightly attenuated compared to that of non-statin users (p-for-interaction=0.001 for both TC and LDL-C).

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Table 3. The risk of AF according to the level of TC and LDL-C (in quartile) stratified by statin usage

Characteristics	No. of participants	AF	IR (1,000 PY)	HR (95% CI)		
				Model 1	Model 2	Model 3
TC (mg/dL)						
Statin non-users						
Q1 (<170)	2,217,459	32,613	1.80	1.000 (Ref.)	1.000 (Ref.)	1.000 (Ref.)
Q2 (170–192)	2,317,699	34,625	1.82	1.011 (0.996–1.027)	0.897 (0.883–0.910)	0.894 (0.881–0.908)
Q3 (193–217)	2,292,660	36,290	1.93	1.071 (1.055–1.087)	0.863 (0.850–0.876)	0.856 (0.843–0.869)
Q4 (≥218)	2,082,860	33,551	1.97	1.092 (1.076–1.109)	0.823 (0.810–0.835)	0.812 (0.798–0.826)
p-value				<0.001	<0.001	<0.001
Statin users						
Q1 (<170)	225,620	10,718	6.01	1.000 (Ref.)	1.000 (Ref.)	1.000 (Ref.)
Q2 (170–192)	139,871	5,555	4.95	0.822 (0.796–0.849)	0.919 (0.890–0.950)	0.931 (0.901–0.962)
Q3 (193–217)	132,434	4,814	4.51	0.748 (0.723–0.774)	0.890 (0.861–0.921)	0.913 (0.882–0.944)
Q4 (≥218)	369,411	10,009	3.32	0.548 (0.534–0.563)	0.756 (0.736–0.777)	0.812 (0.790–0.835)
p-value				<0.001	<0.001	<0.001
p-for-interaction				<0.001	<0.001	0.001
LDL-C (mg/dL)						
Statin non-users						
Q1 (<91)	2,204,649	32,215	1.79	1.000 (Ref.)	1.000 (Ref.)	1.000 (Ref.)
Q2 (91–111)	2,303,509	33,637	1.78	0.995 (0.979–1.010)	0.896 (0.882–0.910)	0.915 (0.901–0.929)
Q3 (112–134)	2,303,859	36,505	1.94	1.079 (1.063–1.095)	0.864 (0.851–0.877)	0.885 (0.872–0.898)
Q4 (≥135)	2,098,661	34,722	2.02	1.127 (1.110–1.144)	0.819 (0.807–0.832)	0.849 (0.835–0.863)
p-value				<0.001	<0.001	<0.001
Statin users						
Q1 (<91)	265,398	11,704	5.55	1.000 (Ref.)	1.000 (Ref.)	1.000 (Ref.)
Q2 (91–111)	144,623	5,769	4.97	0.894 (0.866–0.922)	0.949 (0.920–0.979)	0.970 (0.940–1.001)
Q3 (112–134)	128,764	4,608	4.44	0.796 (0.769–0.823)	0.901 (0.871–0.933)	0.934 (0.902–0.966)
Q4 (≥135)	328,551	9,015	3.36	0.601 (0.585–0.618)	0.772 (0.751–0.794)	0.842 (0.819–0.865)
p-value				<0.001	<0.001	<0.001
p-for-interaction				<0.001	<0.001	0.001

Model 1 was unadjusted. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, lifestyle behaviors (smoking status, alcohol intake, and regular exercise), comorbidities (hypertension, diabetes mellitus, dyslipidemia, heart failure, myocardial infarction, peripheral artery disease, and chronic kidney disease), and low-income status.
AF, atrial fibrillation; IR, incidence rate; PY, person-years; HR, hazard ratio; CI, confidence interval; Q, quartile; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol.

More detailed analyses of the associations with the risk of AF evaluated in the decile range of TC and LDL-C are described in **Supplementary Table 4** and **Fig. 2B and D**. Statin users generally showed higher IR and the relative risk of AF than non-statin users. Still, the gradual decrease in AF risk with increasing lipid levels was maintained in both groups with no deviations in trends. While the HRs for AF decreased gradually as TC and LDL-C levels increased up to the 8th decile point of TC (224 mg/dL) and LDL-C (140 mg/dL) in statin users, the inverse correlations became more prominent among those with the highest levels of TC and LDL-C (*p*-for-interaction=0.001 for both TC and LDL-C). **Fig. 2B and D** show the discriminant slopes of the relationships with the AF risk according to the range of lipid levels.

3. Sensitivity and subgroup analyses

The inverse associations of lipid levels (TC and LDL-C) and the risk of AF irrespective of statin usage remained consistent even after excluding statin-nonusers who initiated statin within the first year of follow-up (n=9,762,374) and censoring when they initiated statin during follow-up (**Supplementary Table 5**). Subgroup analyses performed by sex and age are described in **Supplementary Tables 6** and **7**. Female statin users had higher HRs than non-statin users up to a TC level of 217 mg/dL (Q3), indicating an interaction in the association of TC level and the risk of AF according to statin use (*p*-for-interaction=0.006). In the association between LDL-C levels and the risk of AF, both men and women demonstrated

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an interaction based on statin use (*p*-for-interactions were 0.017 and 0.001, respectively, for males and females), with statin non-users usually showing more prominently decreased adjusted HRs of incident AF.

When stratified by age, contradictory correlations between lipid levels (TC and LDL-C) and the risk of AF were obscured in young adults (age <40) with no interaction seen with statin use. Regardless of statin use, middle- and elderly adults had sustained inverse correlations of TC – AF risk and LDL-C – AF risk, while non-statin users had more notably decreased risk with significant interactions (*p*-for-interactions were all 0.05).

DISCUSSION

In this cohort of nearly 9.8 million Korean adults, we confirmed the cholesterol paradox of AF for TC and LDL-C and validated the associations according to statin use. Our major findings are as follows: (1) higher levels of TC and LDL-C are associated with lower AF risk; (2) statin users have a higher IR of AF in all ranges of lipid levels than non-users owing to their higher burden of cardiovascular comorbidities, but the inverse link between lipid levels and AF risk was consistent independent of statin use; and (3) the cholesterol paradox of TC and LDL-C was constant regardless of sex and age whereas the inverse relationship in the young age (age <40) was statistically nonsignificant. We have demonstrated the inverse correlation between TC and LDL-C levels and the risk of AF as in previous studies.[10,11,14] Although there exists some inconsistency, the association has been reported in several different epidemiologic cohorts,[8,28] and now we added further evidence from a large Asian nationwide population cohort.

There have been concerns about the potential confounding role of statin use in the association between lipid levels and the risk of AF since statin is a lipid-lowering agent suggested to have a protective effect in AF development.[17,29] Trying to refine the cholesterol paradox beyond the favorable impact of statin therapy, research from the Multi-Ethnic Study of Atherosclerosis and the Framingham Heart Study evaluated the association excluding lipid-lowering medication users, particularly statins.[21] However, the study found no association between TC and LDL-C levels and AF incidence, inconsistent with our results. Likewise, a recent meta-analysis validated the cholesterol paradox excluding statin users.[11] On the other hand, research from the Atherosclerosis Risk in Communities cohort found no association between statin use and the lipid levels/AF relationship.[13] Given the lack of evidence in the lipid paradox on the risk of AF in a large number of statin users, we have confirmed that the inverse associations between TC, LDL-C, and the risk of AF are not driven by statin therapy, by exploring the relationship in statin users and non-users separately.

When scrutinizing the associations according to lipid level, the inverse associations between TC and the risk of AF was less evident in the levels of TC below the 4th decile (184 mg/dL), and was indeterminate in the range of LDL-C < 4th decile (104 mg/dL). The obscure inverse association in the well-controlled range of lipid level might be interpreted as due to the diluted relationship through the protective effect of statin on AF development. Indeed, in the well-controlled range of TC and LDL-C levels whereby the pharmacological effect of stain is expected to reach the target efficacy, the lower risk of AF according to statin use may offset the higher risk of AF in low lipid levels. On the other hand, the inverse association between lipid levels and the risk of AF became accentuated above high levels (9th decile) of TC (>225 mg/dL) and LDL-C (>141 mg/dL). The overall IR and HR of AF was higher in statin users, possibly attributable to

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the higher prevalence of comorbidities predisposing to AF. Still, the convergence of IR and HR of AF at high levels of lipids, particularly LDL-C, would infer the strength of cholesterol paradox undisturbed by the pleiotropic effect of statin or other unadjusted baseline comorbidities. Not only did we demonstrate a coherent inverse relationship between lipid levels and the risk of AF in statin users, but we also provided discrimination in the degree of lowered AF risk by analyses of AF incidence throughout a wide range of lipid levels.

Another interesting observation is that the crude IR increased in accordance with lipid levels in statin non-users. However, an inverse association was confirmed after adjusting for possible confounders (Model 3). Statin users were older and had more comorbidities, all known risk factors of incident AF. Therefore, we assume that adjustment of age, sex, several comorbidities, and lifestyle behaviors might affect the association between lipid levels and the risk of AF more in statin users than non-users due to the inherent higher prevalence of confounding factors. Such a contradictory trend between crude IR and estimates of HR was primarily observed in females and the age under 40 years-old group. Even in such a low-risk group of AF—female and young age[6,30]—the trend of lower risk of AF in higher lipid levels was seen. Of note, several studies have reported that the association between lipid levels and AF remained consistent when stratified by sex.[21,31] In the subgroup analysis of age, the trend of a cholesterol paradox was observed throughout the period, but the inverse association was not statistically significant in young age (<40 years-old). Since age is reported to be inversely associated with TC and LDL-C levels and AF incidence rises substantially with age, increasing age is considered to be a significant modifier when interpreting the connections between lipid levels and AF.[8,32,33] A national study in Poland evaluated the paradox stratifying the population by age. They found the associations were still significant in participants aged 50–64 years, the youngest group.[8] Nonetheless our study would be the first to examine the validity of the cholesterol paradox of AF incorporating the young age population. Though the statistical insignificance in young age adults might be originated from the low number of AF development, we might suspect the inverse relationship between TC or LDL-C levels and AF might be partially accounted for a decline in lipid levels and stronger associations in older adults.[13] Further studies are required to evaluate whether the cholesterol paradox of AF is driven or perturbed by age or other crucial intrinsic effect modifiers.

Several mechanisms have been suggested to explain the paradoxical association between lipid levels and incident AF. Cholesterol may alter cell excitability by modulation of the composition and distribution of the myocardial cell membrane, which is in charge of the occurrence of arrhythmia.[34,35] Also, inflammation may play a role in the association between cholesterol levels and the development of AF. TC, LDL-C, and HDL-C levels were shown to be lower during inflammation, while TG levels increased.[36] Decreased cholesterol levels could be a sign of an underlying proinflammatory processes in the host, contributing to developing AF. Hyperthyroidism, which is linked to an increased risk of AF and lower levels of TC and LDL-C, could be another contributing factor.[37-39] Also, complex pathways involved in both pro-and anti-inflammation and oxidative stress are proposed to mediate an inverse relationship between lipid levels and AF.[40-42] Of these intertwined links between lipid levels and incident AF, we tried to evaluate whether the paradox is partly attributable to statin usage in individuals with higher lipid levels. Although prior studies reported inconsistent results about the association between statins and the occurrence of AF—randomized clinical trials reported no association[43,44] whereas observational studies reported reduced AF risk[45,46]—anti-inflammatory, antioxidant, and preventive atrial structural remodeling roles of statin are suggested to protect against AF beyond the lipid-lowering effect of statin.[18,47,48] Given

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the heterogenous triangular links in a statin-lipid-incident AF relationship, we have now provided a consistent paradoxical association between lipid levels and AF risk not affected by statin use which in turn implies the existence of other concrete underlying mechanisms in explaining the cholesterol paradox in AF. Further studies would be required to conclude the possible role of statin affecting the occurrence of incident AF according to lipid levels.

There are several limitations to our study. First, as we report associations between lipid levels and the risk of AF, no causal relationship can be answered; thus, recommended target lipid level for AF prevention should be cautiously interpreted. Second, a single lipid level measurement may not accurately reflect lipid variability and its impact on the risk of AF. Also, the altered status of statin prescription (i.e., initiation or cessation of statin) or misclassification of statin usage at baseline health examination might introduce a bias in the consistent paradoxical associations between lipid levels and the risk of AF across statin usage. Third, since AF was ascertained using diagnostic codes and hospital utilization records rather than a 12-lead electrocardiogram, incident AF might have been underestimated. Third, the generalizability of our results to other ethnic groups might be limited. Fourth, there might be unadjusted confounding factors such as thyroid function or other inflammatory diseases. Given the lack of evidence supporting the validation of the cholesterol paradox in both statin users and non-users in a sizeable epidemiologic cohort with long-term follow-up, our study still extends and strengthens the interpretation of the association between lipid levels and the risk of AF.

In this nationwide population-based data, the paradoxical relationship between lipid levels (TC and LDL-C) and the risk of incident AF remains consistent in both statin users and non-users. Further research is required to investigate a consolidated underlying mechanism to explain the cholesterol paradox of AF which does not seem to be affected by the pleiotropic effects of statin.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Definitions of covariates

Click here to view

Supplementary Table 2
Baseline characteristics of the study population according to the incident AF

Click here to view

Supplementary Table 3
The risk of AF according to the level of TC and LDL-C in decile

Click here to view

Supplementary Table 4
The risk of AF according to the level of TC and LDL-C (in decile) stratified by statin usage

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Supplementary Table 5

Sensitivity analysis of the inverse associations of lipid levels and the risk of AF stratified by statin usage

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Supplementary Table 6

The risk of AF according to the level of TC and LDL-C (in quartile) stratified by statin usage and sex

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Supplementary Table 7

The risk of AF according to the level of TC and LDL-C (in quartile) stratified by statin usage and age

Click here to view

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