Impact of Low-density Lipoprotein Cholesterol Levels on Outcomes in Nonvalvular Atrial Fibrillation: Results from the China Atrial Fibrillation Registry Study

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Background: Low-density lipoprotein cholesterol (LDL-C) reduction improves cardiovascular outcomes. This study investigates the relationship between lipid levels and outcomes in patients with nonvalvular atrial fibrillation by LDL-C quartiles.

Material/Methods: Patients with atrial fibrillation were enrolled from 31 typical hospitals in China. Of 19,515 patients, 6,775 with nonvalvular atrial fibrillation (NVAF) were followed for 5 years or until an event occurred.

Results: Hyperlipidemia was not an independent risk factor for stroke/thromboembolism and cardiovascular mortality among patients with NVAF (hazard ratio 0.82, 95% CI 0.7-0.96, \( P = 0.82 \)). When patients were divided into quartiles according to LDL-C levels at the time of enrollment (Q1, <1.95; Q2, 1.95-2.51; Q3, 2.52-3.09; and Q4, >3.09 mmol/L), as LDL-C increased, events tapered off according to Kaplan-Meier curves for patients who were without oral anticoagulants and off statins (non-OAC; log-rank=8.3494, \( P = 0.0393 \)) and for those with oral anticoagulants (OAC; log-rank=6.7668, \( P = 0.0797 \)). This relationship was stronger for patients who were without OAC treatment and off statins than for those with OAC treatment. The relationship was not significant in patients with or without OAC and on statins (log-rank=2.5080, \( P = 0.4738 \)). This relationship also existed in patients with CHA\(_2\)DS\(_2\)-VASc scores <2 (log-rank=5.893, \( P = 0.1167 \)). For those with CHA2DS2-VASc scores \( \geq 2 \) (log-rank=6.6163, \( P = 0.0852 \)), the relationship was stronger.

Conclusions: In patients with NVAF using standard or no lipid-lowering medication, low plasma LDL-C levels were related to an increased risk of stroke/thromboembolism and cardiovascular mortality.

Keywords: Atrial Fibrillation • Cardiology • Membrane Lipids • Stroke

Abbreviations: LDL-C – low density lipoprotein cholesterol; CHD – chronic coronary heart disease; AF – atrial fibrillation; OAC – oral anticoagulants; TIA – transient ischemic attack; NVAF – nonvalvular atrial fibrillation

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Atrial fibrillation (AF) is a clinically common arrhythmia, and the mortality and associated incidence of stroke and heart failure in patients with AF are significantly higher than in the general population [1,2]. Compared with stroke from other causes, stroke associated with AF tends to be more severe and has higher mortality and morbidity [3,4]. The number of AF-related ischemic strokes at age >80 years has tripled over the last 25 years, despite the introduction of anticoagulants, and is projected to triple again by 2050, along with the number of systemic emboli. Improving AF-related stroke and systemic embolism outcomes in older people with AF should be a major public health priority [5]. Higher CHADS2 scores, based on a history of congestive heart failure (1 point), hypertension (1 point), stroke or transient ischemic attack (TIA) or thromboembolism (2 points), diabetes mellitus (1 point), and age ≥75 years (1 point), are associated with increased risk for stroke or systemic embolism, bleeding, and death in patients with AF receiving oral anticoagulants (OAC) [6]. Statins exert antiarrhythmic effects by improving endothelial nitric oxide availability and reducing inflammation, oxidative stress, and neurohormonal activation, in addition to lowering blood lipid levels [7,8], so their role in the treatment of AF is of interest [9,10]. A meta-analysis has shown that statin therapy provides high levels of protection for all-cause mortality and nonhemorrhagic strokes [11]. Lipid-lowering therapy (LLT) has been associated with lower all-cause mortality, cardiovascular mortality, and ischemic stroke in patients with AF [12]. Another study showed that statin treatment is associated with improved survival and reduced risk for future cardiovascular events in patients with AF-related stroke [13], but blood lipid levels were not monitored. Based on the 2013 American College of Cardiology and American Heart Association cholesterol management guidelines, statins were recommended for 67.4% (7720/11 461) of participants with AF in the Chinese Atrial Fibrillation Registry (CAFR), but only 43.4% (3352/7720) of patients with appropriate indications were taking statins [14]. First, doctors in tertiary hospitals are busier and looking after more patients; therefore, they have limited time to consider the importance of statin therapy. Second, doctors in tertiary hospitals focus more on anticoagulation therapy and even more invasive and expensive interventions, such as ablation therapy, while statin therapy is of interest [9,10]. A meta-analysis has shown that statin therapy provides high levels of protection for all-cause mortality and nonhemorrhagic strokes [11]. Lipid-lowering therapy (LLT) has been associated with lower all-cause mortality, cardiovascular mortality, and ischemic stroke in patients with AF [12]. Another study showed that statin treatment is associated with improved survival and reduced risk for future cardiovascular events in patients with AF-related stroke [13], but blood lipid levels were not monitored. Based on the 2013 American College of Cardiology and American Heart Association cholesterol management guidelines, statins were recommended for 67.4% (7720/11 461) of participants with AF in the Chinese Atrial Fibrillation Registry (CAFR), but only 43.4% (3352/7720) of patients with appropriate indications were taking statins [14]. First, doctors in tertiary hospitals are busier and looking after more patients; therefore, they have limited time to consider the importance of statin therapy. Second, doctors in tertiary hospitals focus more on anticoagulation therapy and even more invasive and expensive interventions, such as ablation therapy, while statin therapy is ignored. However, the aim of our study is to determine whether patients with AF need intensive LLT.

The purpose of the present study was to investigate the relationship between lipid profiles and outcomes in nonvalvular AF (NVAF) to determine the potential relationship between lipid reduction and prognosis. Namely, we aimed to determine if LDL-C levels influenced outcomes in patients with NVAF depending on the use of lipid-lowering medication.

**Material and Methods**

The CAFR was reviewed and the study was approved by the Ethics Committee of Beijing Anzhen Hospital (no. D11110700300000). Written informed consent was obtained from each patient. This work was supported by the National Key Research and Development Program of China (grant no. 2018YFC1312501, 2016YFC0900901).

**Chinese Atrial Fibrillation Registry**

The CAFR is a prospective, multicenter, hospital-based, ongoing registry study of patients diagnosed with AF in Beijing, China. The majority of tertiary and nontertiary hospitals providing a clinical service for AF management in Beijing participated in this registry study. Data collected between August 2011 and August 2016 from 31 hospitals were used for analysis. Trained personnel, including doctors from tertiary and nontertiary hospitals, enrolled unselected eligible outpatients and inpatients with AF from their daily practices. Abstracted data were submitted to the CAFR website. Eligible patients were those aged ≥18 years, with no paroxysmal AF, valvular AF, mitral stenosis, or catheter ablation documented via either electrocardiogram (ECG) or Holter in the previous ≥6 months. AF was diagnosed by a local investigator via a baseline 12-lead ECG or Holter recording. Those patients with transient and reversible AF, with other diseases with a life expectancy ≤6 months, aged <18 years, or with valvular AF, mitral stenosis, or catheter ablation were excluded from this analysis.

Fasting blood lipids, including total cholesterol (TC), triglycerides (TG), LDL-C, and high-density lipoprotein cholesterol (HDL-C), were measured in each patient at the time of enrolment (baseline) by an automatic biochemistry analyzer, regardless of whether they took lipid-lowering drugs before, as was appropriate at each institution. Hyperlipidemia was defined as TC ≥5.2 mmol/L, TG ≥1.7 mmol/L, LDL-C ≥3.64 mmol/L, and/or a history of hyperlipidemia. All patients were categorized into 4 groups according to the LDL-C level quartile at admission: group 1, <1.95 mmol/L; group 2, 1.95-2.51 mmol/L; group 3, 2.52-3.09 mmol/L; and group 4, >3.09 mmol/L.

**Definition of End Points**

Patients were followed for 5 years or until an event, whichever occurred first. Main end events included stroke/thromboembolism and cardiovascular mortality. Stroke/thromboembolism included symptomatic ischemic stroke, TIA, and systemic embolism events. Cardiovascular mortality included myocardial infarction, heart failure, sudden death, and other cardiovascular causes.
Statistical Analysis

1. Baseline characteristics analysis: Categorical variables are shown as n (%), whereas continuous variables are shown as means ± standard deviation, SD. Continuous variables were compared using either unpaired t tests or the Mann-Whitney U test, whereas categorical variables were compared using the chi-squared test. Trends among the quartiles were tested by the Cochran-Armitage test for categorical variables or the Jonckheere-Terpstra test for continuous variables, as appropriate. A P value <0.05 was considered statistically significant.

2. Stroke/thromboembolism and cardiovascular mortality-free survival rate were based on quartiles of LDL-C without OAC treatment, with OAC, with CHA\_DS\_VASc score <2, or with CHA\_DS\_VASc score ≥2. The Kaplan-Meier product limit method was used to estimate the probability of each outcome for OAC or non-OAC treatment and for CHA\_DS\_VASc score <2 or CHA\_DS\_VASc score ≥2. The CHA\_DS\_VASc was calculated as follows: history of congestive heart failure (1 point), hypertension (1 point), diabetes mellitus (1 point), stroke or TIA or thromboembolism (2 points), vascular disease (1 point), age 65 to 74 years (1 point), age ≥75 years (2 points), and female sex (1 point). Differences in Kaplan-Meier curves among LDL-C quartiles were evaluated with the log-rank test.

We investigated the influence of CHA\_DS\_VASc scores on stroke/thromboembolism and cardiovascular mortality rate in the OAC or non-OAC treatment groups, and with or without statins, expressed as percentages. Event ratios of CHA\_DS\_VASc score quartiles at the time of enrollment or at the end of the follow-up period were calculated as percentages.

3. Univariate and multivariable Cox regression models were used to analyze risk of stroke/thromboembolism and cardiovascular mortality among patients with AF. A Cox proportional hazards model was used to investigate the influence of each baseline variable on events. The covariates studied in these univariate analyses were age, sex, estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, heart rate >80 bpm, body mass index (BMI) >28 kg/m^2, left atrial (LA) diameter >40 mm, alcohol use, smoking, persistent AF, chronic obstructive pulmonary disease (COPD), hyperthyroidism, moderate-severe mitral regurgitation, heart failure, hypertension, diabetes mellitus, previous stroke/TIA/thromboembolism, hyperlipidemia, vascular disease, previous bleeding, and use of OAC. Factors that were significant in the univariate analyses were included in the multivariate Cox model. For the univariate analysis, the level of significance was set at 10% to reduce the risk of a type II error. In the final multivariate analyses, the level of significance was set at 5%. Associations are presented as hazard ratios (HR) with their corresponding 95% confidence intervals (95% CI). Explanatory variables for multivariate analysis were adopted from well-known risk factors. The results are shown in the appendix. All analyses were conducted using SAS software, version 9.2.

Limitations

The present study has some limitations. First, lipid profiles were unavailable before and after LLT and at the time of events. Second, statin use was defined at enrollment, so patients that started statins during the follow-up period were classified as nonusers. Third, this was a multicenter retrospective study. Further nationwide, multicenter prospective cohort studies enrolling patients with AF should be conducted to clarify our findings. Given the high incidence of AF-related ischemic stroke/systemic embolism and cardiovascular death, further confirmation via a randomized trial is advisable to substantiate a novel indication for the use of statins in clinical practice.

Results

Of 19 515 patients with AF enrolled in the CAFR, 12 740 were excluded: 464 had valvular AF, 6368 underwent catheter ablation, 1994 had a follow-up of less than 6 months, and 3914 had no LDL-C measurement. Therefore, a total of 6775 patients with NVAF were included in the present analysis. Patients were followed for 5 years or until an event, whichever occurred first. Patients will continue to be followed up after the occurrence of 1 of the endpoint events in this study, which was only the median follow-up for the long-term outcomes.

Baseline Characteristics

With increasing quartiles of LDL-C, the mean age, anteroposterior LA diameter, male sex, eGFR <60 ml/min/1.73 m^2, CHA\_DS\_VASc score ≥2, and percent using statins declined, and the prevalence of persistent AF (PeAF), COPD, moderate-to-severe mitral regurgitation, heart failure, hypertension, diabetes mellitus, previous stroke/TIA/thromboembolism, and vascular disease were lower (Table 1). These differences were statistically significant. The proportion of patients who smoked, had previous bleeding, used antithrombotics (OAC, antiplatelet, or none) was approximately 15.3%, 5.5%, 34.9%, 19.0%, and 46.1%, respectively, and these did not differ across LDL-C quartiles. Patients with heart failure accounted for 27.3% of the total, and 73.0% patients had CHA\_DS\_VASc scores ≥2; the frequency was clearly lower in the highest quartile of LDL-C. Use of OAC treatment was low, but only 34.9% (2365/10 772) with appropriate indications were taking statins. The proportion of patients using lipid-lowering medication was the highest among the lower quartiles of LDL-C (quartile 1, 0.0%; quartile 2, 51.6%; quartile 3, 39.7%; quartile 4, 46.9%).
### Table 1. Baseline patient characteristics and medications.

| Characteristics                      | Overall (N=10,772) | First quartile of LDL-C (N=1682) | Second quartile of LDL-C (N=1702) | Third quartile of LDL-C (N=1672) | Forth quartile of LDL-C (N=1719) | P     |
|--------------------------------------|--------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|-------|
| Age, y                               | 68.5±11.6          | 70.8±11.3                        | 69.5±11.4                        | 67.6±11.4                        | 66.2±11.8                        | <.0001|
| Sex, Male                            | 3904 (57.6)        | 1060 (63.0)                      | 979 (57.5)                       | 979 (56.4)                       | 922 (53.6)                       | <.0001|
| Systolic BP, mmHg                    | 130.±17.9          | 129.2±18.2                       | 130.3±17.9                       | 130.3±17.7                       | 130.5±17.7                       | 0.141 |
| TC, mmol/L                           | 4.3±1.1            | 3.3±0.7                          | 3.9±0.5                          | 4.6±0.6                          | 5.5±0.8                          | <.0001|
| LDL-C, mmol/L                        | 2.6±0.9            | 1.5±0.3                          | 2.2±0.2                          | 2.8±0.2                          | 3.7±0.7                          | <.0001|
| BMI, kg/m²                           | 25.4±3.7           | 25.1±3.6                         | 25.1±3.6                         | 25.5±3.7                         | 25.8±3.7                         | <.0001|
| Heart rate, bpm                      | 81.6±21.6          | 80.8±21.0                        | 81.2±22.2                        | 81.5±21.8                        | 82.0±21.6                        | 0.312 |
| Anteroposterior LA diameter, mm      | 41.5±8.1           | 42.4±8.7                         | 41.8±8.3                         | 41.2±7.8                         | 40.5±7.5                         | <.0001|
| eGFR <60, mL/min/1.73 m²             | 442 (6.8)          | 133 (8.2)                        | 140 (8.5)                        | 85 (5.3)                         | 84 (5.1)                         | <.0001|
| Smoking                              | 1032 (15.3)        | 243 (14.6)                       | 243 (14.3)                       | 266 (16.0)                       | 280 (16.3)                       | 0.263 |
| Drinking                             | 1192 (17.7)        | 260 (15.6)                       | 289 (17.1)                       | 303 (18.2)                       | 340 (19.8)                       | 0.011 |
| AF type                              |                    |                                  |                                  |                                  |                                  |       |
| Newly diagnosed                      | 864 (12.8)         | 199 (11.8)                       | 217 (12.8)                       | 229 (13.7)                       | 201 (11.7)                       | <.0001|
| Paroxysmal                           | 3086 (45.0)        | 721 (42.9)                       | 727 (43.3)                       | 725 (46.4)                       | 853 (49.7)                       |       |
| Persistent                            | 2839 (41.9)        | 761 (45.3)                       | 747 (43.9)                       | 667 (39.9)                       | 664 (38.6)                       |       |
| Medical history                      |                    |                                  |                                  |                                  |                                  |       |
| COPD                                 | 112 (1.7)          | 39 (2.3)                         | 27 (1.6)                         | 27 (1.6)                         | 19 (1.1)                         | 0.049 |
| Hyperthyroidism                      | 70 (2.2)           | 21 (2.8)                         | 15 (2.0)                         | 18 (2.3)                         | 16 (1.9)                         | 0.617 |
| Moderate-to-severe mitral regurgitation| 431 (7.6)      | 125 (8.9)                        | 118 (8.2)                        | 78 (5.6)                         | 110 (7.7)                        | 0.007 |
| Heart failure                        | 1849 (27.3)        | 593 (35.3)                       | 491 (28.8)                       | 406 (24.3)                       | 359 (20.9)                       | <.0001|
| Hypertension                         | 74889 (27.3)       | 1285 (76.4)                      | 1246 (73.2)                      | 1198 (71.7)                      | 1160 (67.5)                      | <.0001|
| Diabetes mellitus                    | 1991 (29.4)        | 586 (34.8)                       | 505 (29.7)                       | 445 (26.6)                       | 455 (26.5)                       | <.0001|
| Previous stroke/ TIA/TE              | 1423 (21.0)        | 439 (26.1)                       | 377 (22.2)                       | 301 (18.0)                       | 306 (17.8)                       | <.0001|
| Hyperlipidemia                       | 3735 (55.3)        | 753 (45.1)                       | 764 (45.1)                       | 813 (48.7)                       | 1405 (81.8)                      | <.0001|
| Vascular disease                     | 981 (14.5)         | 400 (23.8)                       | 269 (15.8)                       | 180 (10.8)                       | 132 (7.7)                        | <.0001|
| Previous bleeding                    | 374 (5.5)          | 99 (5.9)                         | 104 (6.1)                        | 90 (5.4)                         | 81 (4.7)                         | 0.284 |
| CHA2DS2-VASc score                   | 2.8±1.8            | 3.3±1.8                          | 2.9±1.8                          | 2.6±1.7                          | 2.4±1.7                          | <.0001|
| <2                                   | 1829 (27.0)        | 283 (16.0)                       | 416 (24.4)                       | 508 (30.4)                       | 622 (36.2)                       |       |
| ≥2                                   | 4945 (73.0)        | 1398 (83.2)                      | 1286 (75.6)                      | 1164 (69.6)                      | 1097 (63.8)                      |       |
| Antithrombotic drugs                 | 2365 (34.9)        | 584 (34.7)                       | 564 (33.1)                       | 582 (34.8)                       | 635 (36.9)                       | 0.338 |
| Antiplatelet only                    | 1290 (19.0)        | 333 (19.8)                       | 321 (18.9)                       | 322 (19.3)                       | 314 (18.3)                       |       |
In contrast, the mean systolic blood pressure (BP), TC, BMI, heartrate, prevalence of paroxysmal AF (PAF), hyperlipidemia, and CHA2DS2-VASc score <2 increased with increasing LDL-C levels (TC, BMI, PAF, hyperlipidemia, P<0.001). The mean systolic BP (SBP) and heartrate were not significantly different.

### Clinical Outcomes

For Kaplan-Meier curves, in patients without OAC and off statins, the risk of stroke/thromboembolism and cardiovascular mortality gradually decreased with increased LDL according to quartiles of LDL-C at the time of enrollment (Figure 1A).
and there was a significant difference between groups (log-rank=8.3494, P=0.0393) (Figure 1A). This association also existed in the OAC group, although there was no statistical difference (log-rank=6.7668, P=0.0797). The association was stronger between the 2 lower quartiles and 2 upper quartiles of LDL-C (Figure 1B). In patients without OAC and on statins, the relationship was weak (log-rank=2.5080, P=0.4738) (Figure 1A). The association with stroke/thromboembolism and cardiovascular mortality was consistent in CHA₂DS₂-VASc score ≥2 patients (log-rank=6.6163, P=0.0852) (Figure 2B) and was less obvious in patients with CHA₂DS₂-VASc scores <2 (log-rank=5.8983, P=0.1167) (Figure 2A), but there was no significant difference.

In univariate Cox regression models for risk of stroke/thromboembolism and cardiovascular mortality among patients with NVAF, statin use, age, eGFR <60 mL/min/1.73 m², quartile 3 of LDL-C, quartile 4 of LDL-C, SBP >140 mmHg, heart rate > 80 bpm, LA diameter >40 mm, alcohol use, persistent AF, COPD, moderate-severe mitral regurgitation, heart failure, hypertension, diabetes mellitus, previous stroke/TIA/thromboembolism, hyperlipidemia, vascular disease, previous bleeding, and use of OAC (Table 2) were factors that influenced the prognosis of NVAF (P<0.05). Among these, quartile 3 of LDL-C, quartile 4 of LDL-C, alcohol use, hyperlipidemia, and use of OAC were negatively associated with risk of stroke/thromboembolism and cardiovascular mortality among patients with NVAF. However, male sex, quartile 2 of LDL-C, BMI >28 kg/m², smoking, COPD, and hyperthyroidism were not associated factors (P>0.05). In the multivariable Cox regression models, age, eGFR <60 mL/min/1.73 m², heart rate >80 bpm, LA diameter >40 mm, heart failure, previous stroke/TIA/thromboembolism, vascular disease, previous bleeding, and use of OAC were still associated with risk of stroke/thromboembolism and cardiovascular mortality among those with NVAF. (P<0.05).

In univariate Cox regression models (Table 2), statin therapy did not provide protection for stroke/TIA/thromboembolism and cardiovascular mortality with NVAF (HR 1.29, 95% CI 1.1-1.5, P=0.002), and hyperlipidemia was not a risk (HR 0.82, 95% CI 0.7-0.96, P=0.014). In patients in quartile 3 (HR 0.77, 95% CI 0.62-0.95, P=0.015) and quartile 4 of LDL-C (HR 0.66, 95% CI 0.53-0.83, P=0.000), more protection may have been provided than in quartile 2 of LDL-C (HR 0.92, 95% CI 0.75-1.13, P=0.400). However, there was no difference in the multifactorial Cox regression models.

**Discussion**

In the CAFR, patients with NVAF and hyperlipidemia constitute an important, large subgroup. In this analysis, patients taking statins had good compliance, LLT did not show benefit in preventing stroke/thromboembolism and cardiovascular mortality regardless of a history of hyperlipidemia, no hyperlipidemia, taking OAC, not taking OAC, and having a CHA₂DS₂-VASc score <2 or ≥2. More importantly, according to quartiles of LDL-C at the time of enrollment, LDL-C was negatively associated with ischemic stroke/systemic embolism and cardiovascular death in the Kaplan-Meier curves in all groups, with increasing LDL-C, ischemic stroke/systemic embolism, and cardiovascular death gradually declined. Thus, the main finding of this analysis was that lower blood lipids (LDL-C mean 2.6±0.9 mmol/L) before and after statin therapy during the trial were associated with a subsequent increase in risk of ischemic stroke/systemic embolism and cardiovascular death in the without OAC and off statins group.

Previous studies of statin treatment and AF have not shown a consistent association with outcomes. The Japanese Rhythm Management Trial for Atrial Fibrillation (J-RHYTHM) provides...
evidence that statin use does not affect clinical outcomes in patients with paroxysmal AF [15]. The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction (PROVE IT-TIMI 22) analysis showed a progressive reduction in the benefit of intensive LLT with atorvastatin 80 mg over pravastatin 40 mg in statin-naïve patients with acute coronary syndrome as baseline LDL-C declined [16]. Another study showed that in a long-term registry of patients with AF-related stroke, statin treatment was associated with improved survival and reduced risk for future cardiovascular events [17]. An analysis of a National Health Insurance research database showed that statin therapy in elderly patients with hypertension reduced the risk of new-onset AF; statins were more beneficial in patients with a CHADS<sub>2</sub> score ≥2 than in those with a score of 1 [18]. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, a decrease in mortality and adverse cardiovascular events was observed using LLT in patients with AF [19]. In multivariate analysis, LLT use was associated with lower all-cause mortality (HR 0.77, 95% CI, 0.62-0.95, P=0.01), cardiovascular mortality (HR 0.71, 95% CI 0.53-0.95, P=0.02), ischemic stroke (HR 0.56, 95% CI 0.36-0.89, P=0.01), and combined end points (HR 0.81, 95% CI 0.69-0.96, P=0.01) [19]. Yet in our study, statin treatment did not show any benefit. A recent study by Cheng et al partially supports the results of this study.

Table 2. Univariate and multivariate cox regression models for risk of stroke/thromboembolism and cardiovascular mortality among patients with atrial fibrillation.

| Variable                        | Univariate                      |          |          |          |          |          | Multivariate                     |          |          |          |          |
|--------------------------------|---------------------------------|----------|----------|----------|----------|----------|-----------------------------------|----------|----------|----------|----------|
|                                | HR     | 95% CI   | P        | HR     | 95% CI   | P        |
| Statin use                     | 1.29   | (1.1, 1.5) | 0.002   | 0.96   | (0.82,1.14) | 0.668   |
| Age, per y                     | 1.06   | (1.05,1.07) | <0.001  | 1.04   | (1.03,1.05) | <0.001  |
| Sex, Male                      | 0.92   | (0.79,1.08) | 0.317   | 1.10   | (0.93,1.3)  | 0.263   |
| eGFR < 60 mL/min/1.73 m²        | 3.01   | (2.44,3.71) | <0.0001 | 1.71   | (1.37,2.14) | <0.0001 |
| SBP >140 mmHg                  | 1.47   | (1.25,1.72) | <0.0001 |        |          |         |
| Quartile 1 of LDL-C            | Ref    | Ref      | –       | Ref    | Ref      | –       |
| Quartile 2 of LDL-C            | 0.92   | (0.75,1.13) | 0.400   | 1.03   | (0.84,1.27) | 0.778   |
| Quartile 3 of LDL-C            | 0.77   | (0.62,0.95) | 0.015   | 1.08   | (0.87,1.35) | 0.475   |
| Quartile 4 of LDL-C            | 0.66   | (0.53,0.83) | 0.000   | 1.02   | (0.81,1.27) | 0.937   |
| Heart rate >80 bpm             | 1.49   | (1.27,1.73) | <0.0001 | 1.31   | (1.12,1.54) | 0.001   |
| BMI >28 kg/m²                  | 0.84   | (0.67,1.04) | 0.114   | 0.94   | (0.76,1.16) | 0.562   |
| LA diameter >40 mm             | 1.69   | (1.41,2.01) | <0.0001 | 1.21   | (1.14,1.17) | 0.050   |
| Drinking (any)                 | 0.71   | (0.56,0.89) | 0.004   | 1.04   | (0.81,1.33) | 0.761   |
| Smoking (any)                  | 0.95   | (0.76,1.18) | 0.618   |        |          |         |
| Persistent AF                  | 1.27   | (1.09,1.48) | 0.003   | 0.96   | (0.81,1.14) | 0.634   |
| Medical history                |        |          |         |        |          |         |
| COPD                           | 1.67   | (0.92,3.04) | 0.092   | 0.97   | (0.53,1.77) | 0.917   |
| Hyperthyroidism                | 0.91   | (0.29,2.84) | 0.864   |        |          |         |
| Moderate-to-severe mitral regurgitation | 2.04   | (1.59,2.61) | <0.0001 | 1.38   | (1.05,1.81) | 0.021   |
| Heart failure                  | 3.42   | (2.92,4)  | <0.0001 | 2.22   | (1.87,2.64) | <0.0001 |
| Hypertension                   | 1.54   | (1.27,1.88) | <0.0001 | 1.04   | (0.84,1.27) | 0.299   |
| Diabetes mellitus              | 1.44   | (1.23,1.69) | <0.0001 | 1.09   | (0.92,1.28) | 0.331   |
| Previous stroke/TIA/TE         | 2.09   | (1.78,2.46) | <0.0001 | 1.59   | (1.34,1.88) | <0.0001 |
| Hyperlipidemia                 | 0.82   | (0.7,0.96) | 0.014   |        |          |         |
| Vascular disease               | 2.19   | (1.84,2.62) | <0.0001 | 1.43   | (1.18,1.74) | 0.000   |
| Previous bleeding              | 1.91   | (1.46,2.5)  | <0.0001 | 1.55   | (1.18,2.04) | 0.002   |
| Use of OAC                     | 0.62   | (0.52,0.75) | <0.0001 | 0.70   | (0.58,0.85) | 0.000   |
lar mortality gradually decreased with increasing quartiles of LDL-C. This relationship was most obvious in patients without statins and without OAC, and was weaker in those on statins and OAC. In univariate Cox regression models, statin therapy did not provide protection from stroke/TIA/thromboembolism and cardiovascular mortality with NVAF, and LDL-C was a protective factor. However, in the multifactorial Cox regression model, this relationship disappeared due to other factors. Patients with lower baseline LDL-C were older, more likely to be male, had larger anteroposterior LA diameters, higher CHA₂DS₂-VASc scores, higher statin use, and greater comorbidities, such as diabetes and hypertension, which may have contributed more to the risk of future events than did LDL-C.

The number of AF-related ischemic strokes, along with the number of systemic emboli, has increased despite the introduction of anticoagulants [5]. In addition, higher CHADS₂ scores are associated with increased risk for stroke or systemic embolism, bleeding, and death in patients with AF receiving OAC treatment [6]. In our study, the ratio of anticoagulation therapy was not different between quartiles of LDL-C. In patients with a CHADS₂ score ≥2, low levels of LDL are associated with risk of stroke/thromboembolism and cardiovascular mortality among those with AF [6].

Conclusions

In patients with AF, low blood lipid levels were independently associated with a substantially higher risk of ischemic stroke/systemic embolism and cardiovascular death. These data strongly support the need for more research on the treatment of hyperlipidemia to optimally reduce the risk of ischemic stroke/systemic embolism and cardiovascular death in patients with AF.

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Clinical Trial Registration

URL: http://www.chictr.org.cn/showproj.aspx?proj=5831. Unique identifier: ChiCTR-OCH-13003729.

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A recent study found a possibly protective impact of OAC therapy for all-cause mortality in patients with new-onset AF after cardiac surgery; however, it does not appear to impact thromboembolism rates [30]. The risk of stroke/thromboembolism and cardiovascular mortality gradually decreased with increased LDL according to quartiles of LDL-C at the time of enrollment, and there was not a significant difference in the OAC group. The probable cause is that anticoagulation improves all-cause mortality.

We analyzed patients with NVAF with a history of hyperlipidemia or normal blood lipids using statins or no statins at the time of enrollment, and the most significant finding was that patients had an increased risk of ischemic stroke/systemic embolism and cardiovascular death with declining LDL-C levels. Overall, these results underscore the importance of continuous LDL-C measurements to lower the risk of ischemic stroke/systemic embolism and cardiovascular death in patients with NVAF.

Another important observation was that even for patients with AF enrolled in large clinical trials, some research has shown that LLT positively affects outcomes [17-19], while other research showed no effect on prognosis [15]. One issue is that blood lipids are often not measured, and thus blood lipid levels before and after LLT are unknown. An aforementioned study [16] found a progressive reduction in the benefit of intensive LLT as baseline LDL-C declined. This underscores the importance of detecting blood lipid levels both at baseline and after LLT in patients with NVAF.

Our major finding of the present study was that the level of LDL-C may be an important predictor of outcomes in NVAF regardless of the use of statins, OAC, or CHA₂DS₂-VASc scores. In non-OAC, OAC, and CHA₂DS₂-VASc score ≥2 groups, we found that the risk of stroke/thromboembolism and cardiovascular mortality gradually decreased with increasing quartiles of LDL-C. This relationship was most obvious in patients without statins and without OAC, and was weaker in those on statins and OAC. In univariate Cox regression models, statin therapy did not provide protection from stroke/TIA/thromboembolism and cardiovascular mortality with NVAF, and LDL-C was a protective factor. However, in the multifactorial Cox regression model, this relationship disappeared due to other factors. Patients with lower baseline LDL-C were older, more likely to be male, had larger anteroposterior LA diameters, higher CHA₂DS₂-VASc scores, higher statin use, and greater comorbidities, such as diabetes and hypertension, which may have contributed more to the risk of future events than did LDL-C.

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