

Change in lipid profile and risk of new-onset atrial fibrillation in patients with chronic heart failure

A 3-year follow-up observational study in a large Chinese hospital

Chen Liu, MD^{a,b}, Jin Geng, MD^c, Xiao Ye, MD^d, Xiaochen Yuan, PhD^b, Aihua Li, MD^b, Zhengang Zhang, PhD^b, Biao Xu, MD, PhD^{a,*}, Yingwei Wang, PhD^{e,*}

Abstract

In chronic heart failure (CHF), new-onset atrial fibrillation (AF) is associated with increased morbidity and mortality. We aimed to evaluate the influence of dyslipidemia on the incidence of new-onset AF in patients with CHF.

In this single-center observational study, 308 patients with CHF and no history of AF were followed-up for 3 years. Of the 291 patients who attended the 1-year follow-up, 78 had developed AF (AF group; 10 deaths), while 213 had not (sinus rhythm [SR] group). Changes in lipid profile (Δ TC for total cholesterol and Δ LDLc for low-density lipoprotein cholesterol) were analyzed.

The groups differed significantly regarding the decrease in lipid levels from baseline to the 1-year follow-up (AF vs SR: for Δ LDLc, 23.35 vs 7.80 mg/dL, $P = .02$; for Δ TC, 23.95 vs -2.76 mg/dL, $P = .001$). At the 3-year follow-up, new-onset AF was noted in 21 of the 188 living patients in the SR group. Cox proportional hazards analysis revealed Δ LDLc and Δ TC as independent risk factors for new-onset AF (hazard ratio, 1.018 and 1.013, respectively, per standard deviation increment), with higher incidence of new-onset AF for Δ TC > 9.65 mg/dL ($P = .02$) and for Δ LDLc > 9.73 mg/dL ($P = .005$).

In CHF, pronounced decrease in LDLc and TC is associated with new-onset AF.

Abbreviations: 95%CI = 95% confidence interval, ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, CHF = chronic heart failure, FT3 = serum free triiodothyronine, FT4 = serum free thyroxine, HbA1c = glycated hemoglobin, HDLc = high-density lipoprotein cholesterol, HR = hazard ratio, LAD = left atrial dimension, LDLc = low-density lipoprotein cholesterol, LVEDD = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, NYHA class = New York Heart Association class, SR = sinus rhythm, TC = total cholesterol, TG = triglycerides, TSH = thyroid stimulating hormone.

Keywords: atrial fibrillation, chronic heart failure, dyslipidemia

1. Introduction

Atrial fibrillation (AF) is a common complication in patients with chronic heart failure (CHF). Patients with AF and CHF have poorer prognosis, higher socioeconomic burden, and higher

mortality.^[1-4] The order in which CHF and AF develop may also influence prognosis.^[5,6] Growing evidence indicates that, in CHF, mortality is higher among patients with new-onset AF than among those with preexisting AF.^[4,7,8] Therefore, it is important to identify the risk factors for new-onset AF in patients with CHF.

Many factors have been reported to affect the development of AF, including age, hypertension, coronary artery disease, obesity, and diabetes.^[9-12] A recent epidemiological investigation reported that higher levels of low-density lipoprotein cholesterol (LDLc) and total cholesterol (TC) were associated with a lower incidence of AF.^[13-15] However, some studies yielded paradoxical results in that the risk of developing AF was associated with the levels of high-density lipoprotein cholesterol (HDLc) and triglycerides (TG) but not LDLc or TC.^[16] Moreover, it is unknown whether lipid profile disorders affect the risk of new-onset AF in CHF patients. Accordingly, the purpose of the present study was to explore the correlation between lipid profile disorders and the risk of new-onset AF in CHF patients.

2. Methods

2.1. Patients and study design

This observational study included patients diagnosed with CHF and admitted to Yangzhou First People's Hospital in 2013. The inclusion criteria were as follows: available data regarding lipid levels and electrocardiography findings on admission; New York Heart Association (NYHA) class III or IV; and age, 18–80 years. The exclusion criteria were as follows: history of AF or atrial flutter, including paroxysmal, persistent, or permanent AF;

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CL and JG contributed equally to this study and should be regarded as co-first authors.

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^a Department of Cardiology, Drum Tower Hospital, Nanjing Medical University, Nanjing, ^b Department of Cardiology, Yangzhou First People's Hospital, Yangzhou, ^c Department of Cardiology, Huai'an First People's Hospital, Nanjing Medical University, Huai'an, ^d Department of Endocrinology, Zhejiang Provincial People's Hospital, Hangzhou, ^e School of Basic Medical Sciences, Nanjing Medical University, Nanjing, PR China.

* Correspondence: Biao Xu, Department of Cardiology, Drum Tower Hospital, Nanjing Medical University, No. 321 Zhongshan Road, Gulou District, 210008 Nanjing City, Jiangsu Province, PR China (e-mail: biaoxu001@qq.com), Yingwei Wang, School of Basic Medical Sciences, Nanjing Medical University, No. 101 Longmian Avenue, Jiangning District, 211166 Nanjing City, Jiangsu Province, PR China (e-mail: wangyingwei018@qq.com).

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valvular heart disease; permanent pacemaker; expected lifetime below 3 years; atheroma, severe infection, or another condition requiring heart transplant; thyroid dysfunction; and pregnancy or lactation. All patients provided informed consent for undergoing the necessary procedures and investigations, and the study was approved by the institutional ethics committee of Yangzhou First People's Hospital (number of the approval: 2016003).

2.2. Baseline assessments

At each visit, the medical history (including use of medications) was reviewed and physical examination was performed. Serum lipid levels were evaluated as follows. TC and TG levels were assessed using automated enzymatic assays. HDLc levels were measured using the chemical precipitation method. LDLc levels were calculated using the Friedewald formula^[17] in patients with serum TG levels ≤ 400 mg/dL, and obtained by direct measurement using the immunoseparation method in patients with serum TG levels > 400 mg/dL. Other serum parameters including creatinine, uric acid, thyrotropin, free thyroxine, free triiodothyronine, and glycated hemoglobin levels were also measured. Echocardiography was used to determine left atrial dimension (LAD), left ventricular end-diastolic dimension, and left ventricular ejection fraction.

2.3. Follow-up assessments

The patients were followed up for 3 years on an outpatient basis. The present analysis used data from the 1-year and 3-year follow-up visits. Lipid levels, including TC, LDLc, HDLc, and TG levels were measured at the end of the 1-year follow-up visit. The patients were stratified into 2 groups based on whether new-onset AF was noted at the 1-year follow-up (AF group vs sinus rhythm [SR] group). For the purpose of the present study, only patients without new-onset AF at the 1-year follow-up (i.e., from the SR group) were included in the analysis of data from the 3-year follow-up visit. Patients included in the 3-year follow-up analysis were further stratified into subgroups according to the change in lipid levels (Δ lipid) from baseline to the 1-year follow-up (high vs low Δ lipid subgroups). The primary outcome of this study was the incidence of AF at the 3-year follow-up (i.e., in patients who did not develop AF within the first year of follow-up). AF was defined based on the findings of 12-lead electrocardiography and 24-hour Holter monitoring findings. AF cases were confirmed by consensus among 2 trained cardiologists.

2.4. Data analysis

As the study used data from the 1-year and 3-year follow-up visits, data regarding patients lost to follow-up were excluded. Only data regarding living patients were used in the analysis of SR subgroups. All data were reviewed by 2 experts with statistical background to reduce bias. All data were summarized and recorded as mean \pm standard deviation for normally distributed, continuous variables, and as median and interquartile range for non-normally distributed continuous variables. Between-group differences in baseline and follow-up characteristics were evaluated using the unpaired *t*-test for continuous variables and the chi-square test for categorical variables. Within-group differences reflecting changes from baseline to the 1-year follow-up were evaluated using the paired *t*-test for continuous variables and the paired chi-square test (McNemar test) for categorical variables. Cox proportional hazards models were used to analyze the relationship of lipid profiles with the incidence of new-onset

AF in CHF patients. The analysis was repeated after adjusting the models for the following variables: age, sex, statin use, amiodarone use, NYHA functional class, CHF duration, and LAD. All statistical analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL). Two-sided *P*-values $< .05$ were considered to indicate statistical significance.

3. Results

A total of 308 CHF patients without AF or history of AF were enrolled in this study (Fig. 1). Of these, 17 patients were lost to follow-up and 35 patients died (10 with AF and 25 with SR) by the 1-year follow-up visit. Among the remaining 256 patients, 68 patients had new-onset AF. Thus, 78 patients (68 living, 10 dead) were included in the AF group and 213 patients (188 living, 25 dead) were included in the SR group. Of the 188 living patients in the SR group who were included in the 3-year follow-up analysis, 21 had new-onset AF.

The mean age of the 291 patients included in the analysis was 71.95 ± 10.01 years, and 41.2% of patients were female (Table 1). Patients in the AF group were older than those in the SR group (74.26 ± 9.39 vs 71.11 ± 10.16 years, $P = .02$). At baseline, the percentage of patients with NYHA class IV was significantly higher in the AF group than in the SR group (73.1% vs 47.9%, $P = .002$). No significant between-group differences were found regarding other baseline parameters including blood lipid levels. However, at the 1-year follow-up, TC and LDLc levels were lower in the AF group than in the SR group (129.62 ± 30.14 vs 152.24 ± 38.99 mg/dL, $P < .01$; 67.53 ± 25.68 vs 85.38 ± 32.38 mg/dL, $P < .01$; respectively) (Table S1, Supplemental Content, <http://links.lww.com/MD/C512>, which provides an overview of the clinical parameters at baseline and at the 1-year follow-up).

To explore the relationship between the occurrence of new-onset AF and the changes in lipid profiles, we examined Δ lipid from baseline to the 1-year follow-up (Table 2). The LDLc and HDLc levels in both groups decreased significantly from baseline to the 1-year follow-up, while the TC levels decreased in the AF group but not in the SR group. Furthermore, Δ TC and Δ LDLc were significantly higher in the AF group than in the SR group (mean Δ TC: 23.95 vs -2.76 mg/dL, $P = .001$; mean Δ LDLc: 23.35 vs 7.8 mg/dL, $P = .02$), while Δ HDLc was comparable between the 2 groups.

To study the value of Δ lipid for predicting new-onset AF in CHF patients, the 188 living patients in the SR group were stratified into subgroups according to dichotomized values of Δ TC, Δ LDLc, and Δ HDLc, and the differences in patient characteristics at the 1-year follow-up were analyzed (Tables S2 to S4, Supplemental Content, <http://links.lww.com/MD/C512>, which provide subgroup comparisons according to Δ TC, Δ LDLc, and Δ HDLc, respectively). The corresponding subgroups (i.e., high vs low Δ lipid) were similar in terms of the prevalence of comorbidities (diabetes, hypertension, and coronary artery disease), use of lipid-lowering therapy, and CHF duration. Between the 1-year and 3-year follow-up visits, 21 of the 188 patients analyzed developed new-onset AF, 6 of whom died. We then used the Kaplan–Meier survival curves to illustrate the 2-year AF-free probability in the subgroups defined based on dichotomized values of Δ TC, Δ LDLc, and Δ HDLc (Fig. 2). High Δ LDLc (> 9.73 mg/dL) and Δ TC (> 9.65 mg/dL) were associated with increased risk of new-onset AF ($P = .005$ and $P = .02$, respectively). High Δ HDLc (> 3.72 mg/dL) tended to be associated with increased occurrence of new-onset AF, but this trend was not significant. Finally, we used Cox proportional hazards

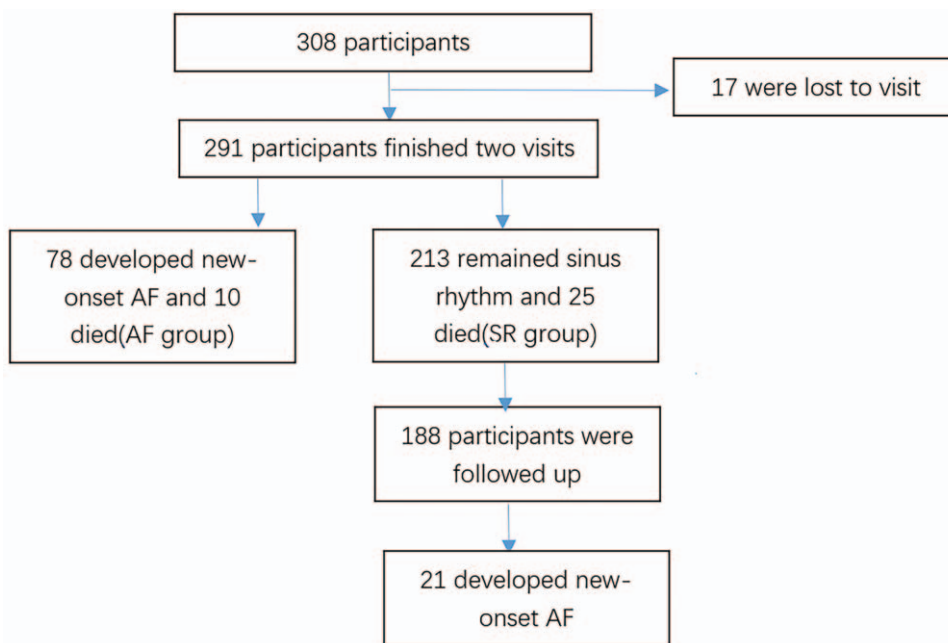


Figure 1. Flow chart of study enrollment and analysis. Patients were followed-up for 3 years and stratified according to whether or not new-onset AF was noted at the 1-year follow-up (AF group vs SR group). AF = atrial fibrillation, SR = sinus rhythm.

Table 1
Baseline characteristics of patients with chronic heart failure.

| Variable | All subjects (n = 291) | SR group (n = 213) | AF group (n = 78) | P-value |
|---------------------------------|------------------------|--------------------|-------------------|---------|
| Age, years | 71.95 ± 10.01 | 71.11 ± 10.16 | 74.26 ± 9.39 | .02 |
| Female sex | 120 (41.2%) | 87 (40.9%) | 33 (42.4%) | .82 |
| NYHA class | | | | .002 |
| III | 132 (45.4%) | 111 (52.1%) | 21 (26.9%) | |
| IV | 159 (54.6%) | 102 (47.9%) | 57 (73.1%) | |
| Heart failure with reduced LVEF | 213 (73.8%) | 152 (71.3%) | 61 (78.2%) | .24 |
| LVEF, % | 43.04 ± 11.12 | 44.45 ± 10.34 | 42.16 ± 12.37 | .11 |
| CHF duration, years | 4.42 ± 3.53 | 4.32 ± 3.23 | 4.48 ± 3.65 | .71 |
| Hypertension | 213 (73.2%) | 153 (71.8%) | 60 (76.9%) | .38 |
| Diabetes mellitus | 75 (25.7%) | 60 (28.2%) | 15 (19.2%) | .12 |
| Ischemic heart disease | 210 (72.2%) | 159 (74.6%) | 51 (65.4%) | .11 |
| Old myocardial infarction | 42 (14.4%) | 33 (15.5%) | 9 (11.4%) | .39 |
| Cerebrovascular disease | 51 (17.5%) | 39 (18.3%) | 12 (15.4%) | .56 |
| Smoking | 57 (19.6%) | 42 (19.7%) | 15 (19.2%) | .90 |
| Alcohol intake | 18 (6.2%) | 12 (5.6%) | 6 (7.7%) | .51 |
| Use of medications | | | | |
| Statins | 21 (7.2%) | 15 (7%) | 6 (7.7%) | .84 |
| Fibrates | 18 (6.2%) | 15 (7%) | 3 (3.8%) | .31 |
| Aspirin | 240 (82.5%) | 174 (81.7%) | 66 (84.6%) | .56 |
| Clopidogrel | 108 (37.1%) | 78 (36.6%) | 30 (38.4%) | .77 |
| ACEI | 252 (86.6%) | 180 (84.5%) | 72 (92.3%) | .08 |
| Furosemide | 225 (77.31%) | 168 (78.9%) | 57 (73.07%) | .29 |
| Spironolactone | 230 (79%) | 168 (78.9%) | 62 (79.4%) | .90 |
| Nitrates | 249 (85.6%) | 186 (87.3%) | 63 (80.8%) | .15 |
| Calcium-channel blockers | 13 (4.4%) | 9 (4.2%) | 4 (5.1%) | .74 |
| Amiodarone | 9 (3.09%) | 6 (3.4%) | 3 (3.8%) | .65 |
| β-blockers | 264 (90.7%) | 192 (90.1%) | 72 (92.3%) | .57 |
| TC, mg/dL | 150.58 ± 41.98 | 149.48 ± 43.41 | 153.57 ± 38.43 | .43 |
| LDLc, mg/dL | 92.57 ± 31.98 | 93.18 ± 32.06 | 90.89 ± 32.33 | .59 |
| HDLc, mg/dL | 45.27 ± 6.49 | 44.48 ± 6.62 | 47.42 ± 6.14 | .20 |
| TG, mg/dL | 52.08 ± 16.97 | 54.12 ± 11.92 | 51.26 ± 10.20 | .06 |
| TSH, mIU/L | 2.74 ± 3.92 | 2.84 ± 4.5 | 2.5 ± 2.19 | .52 |
| FT3, pmol/L | 4.35 ± 0.74 | 4.48 ± 0.64 | 4.30 ± 0.87 | .06 |
| FT4 pmol/L | 13.42 ± 3.59 | 13.75 ± 3.55 | 13.05 ± 3.65 | .14 |
| Serum creatinine, μmol/L | 96.44 ± 47.79 | 92.98 ± 35.54 | 103.88 ± 71.48 | .08 |
| HbA1c, % | 6.96 ± 1.21 | 6.73 ± 1.29 | 7.02 ± 1.12 | .07 |
| LAD, mm | 41.80 ± 5.11 | 42.14 ± 5.28 | 41.14 ± 5.08 | .14 |
| LVEDD, mm | 65.77 ± 9.03 | 65.30 ± 7.84 | 67.14 ± 12.46 | .13 |

Patients were stratified according to whether new-onset AF was noted at the 1-year follow-up (AF vs SR group). Data are given as mean ± standard deviation or number (percentage). ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, CHF = chronic heart failure, FT3 = serum free triiodothyronine, FT4 = serum free thyroxine, HbA1c = glycated hemoglobin, HDLc = high-density lipoprotein cholesterol, LAD = left atrial dimension, LDLc = low-density lipoprotein cholesterol, LVEDD = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, NYHA class = New York Heart Association class, SR = sinus rhythm, TC = total cholesterol, TG = triglycerides, TSH = thyroid stimulating hormone.

Table 2**Change in lipid profile between baseline and the 1-year follow-up.**

| Parameter | SR group | | | AF group | | | P | P* |
|--------------|-----------------|------------|------|-----------------|-------------|------|------|----|
| | Mean difference | 95%CI | P | Mean difference | 95%CI | P | | |
| ΔTC, mg/dL | -2.76 | -12.1-6.57 | .5 | 23.95 | 12.03-35.87 | <.01 | .001 | |
| ΔLDLc, mg/dL | 7.80 | 0.14-15.45 | .04 | 23.35 | 12.68-34.03 | <.01 | .02 | |
| ΔHDLc, mg/dL | 2.36 | 1.09-3.63 | <.01 | 2.66 | 0.68-4.64 | .01 | .80 | |
| ΔTG, mg/dL | -2.59 | -5.84-0.64 | .11 | -1.07 | -5.93-3.79 | .65 | .61 | |

Patients were stratified according to whether new-onset AF was noted at the 1-year follow-up (AF vs SR group). Differences (Δ) were calculated by subtracting the values noted at the 1-year follow-up from those noted at baseline. The statistical significance is calculated for differences between baseline and 1-year follow-up (within-group comparison, *P*) and between the SR group and AF group (between-group comparison, *P*).

AF=atrial fibrillation, HDLc=high-density lipoprotein cholesterol, LDLc=low-density lipoprotein cholesterol, SR=sinus rhythm, TC=total cholesterol, TG=triglycerides.

models to assess the impact of changes in lipid levels on the incidence of new-onset AF over the course of 2 years (between the 1-year and 3-year follow-up visits). The hazard ratio (HR) with 95% confidence interval (95%CI), which reflect the risk of new-onset AF, were 1.022 (1.007-1.037) and 1.016 (1.004-1.028) for each standard deviation increment in Δ LDLc and Δ TC, respectively; when adjusting the models for age, sex, use of medications, CHF duration, NYHA class, and LAD, these values were 1.018 (1.003-1.033) and 1.013 (1.001-1.025), respectively (Table 3).

4. Discussion

Lipid disorders, especially those affecting LDLc levels, are strongly associated with an increased risk of cardiovascular disease. Statins are commonly used to lower LDLc levels and thus reduce the risk of coronary heart disease.^[18] However, the exact relationship between lipid profiles and the incidence of arrhythmia remains unclear. AF is a common arrhythmia that usually induces thrombotic complications, leading to increased mortality and economic burden.^[19] Many AF risk factors have been reported, including age, hypertension, diabetes, atrial dilation, and heart failure.^[20] Some clinical studies have examined the relationship between dyslipidemia and AF but reported contradictory conclusions.^[14-16] Specifically, some studies found the risk of new-onset AF to be increased by low HDLc levels, while other studies reported the same for low LDLc levels but not HDLc levels.^[13,16] AF often occurs in patients with CHF partly because these conditions share the same etiology.^[11] Moreover, new-onset AF was found to increase mortality in patients with CHF.^[17,21] Dyslipidemia is typically noted in patients with CHF, and lower baseline TC levels are associated with poor prognosis of heart failure.^[22] However, whether dyslipidemia contributes to new-onset AF in CHF has not been studied.

We designed the present study to investigate the association between dyslipidemia and new-onset AF in patients with CHF. In

our cohort of approximately 300 CHF patients without AF at baseline, 26.8% (78/291) were diagnosed with new-onset AF within the first year, which is higher than the AF incidence in the general population^[16] and thus confirms that patients with CHF have higher risk of AF. In our study, age was higher and baseline heart function was poorer in the AF group than in the SR group, which is likely related to the fact that advanced age and more severe heart dysfunction are usually associated with more complications, and which is consistent with previous observations that the prevalence of AF in the general population increases with age.^[23] Importantly, the 2 groups did not differ regarding baseline characteristics including use of medications, LAD, left ventricular ejection fraction, or blood lipid levels (TC, HDLc, LDLc, and TG). However, at the 1-year follow-up, LDLc and HDLc decreased significantly in both groups, whereas TC decreased only in the AF group; moreover, LDLc and TC were lower in the AF group. These results suggest that, in CHF, the risk of new-onset AF is affected more by dynamic changes in blood lipid levels than by baseline levels. However, it is inappropriate to conclude that dyslipidemia leads to AF since AF itself may account for abnormal lipid metabolism. Hence, to investigate the value of dynamic changes in lipid levels for predicting new-onset AF in patients with CHF, we further examined the occurrence of new-onset AF only in patients with SR at 1 year. Upon adjustment for age, sex, use of medications, CHF duration, NYHA class, and LAD, the decreases in LDLc and TC levels were independent risk factors for new-onset AF, while the decrease in HDLc levels was a less significant factor. Subgroup analysis using the dichotomized values of the change in lipid levels (high vs low Δ lipid) revealed that subgroups with high Δ LDLc and those with high Δ TC had higher incidence of new-onset AF, suggesting that the continuing decreases in LDLc and TC are associated with new-onset AF in CHF. Cholesterol control is one of the most important strategies for prevention and treatment of ischemic

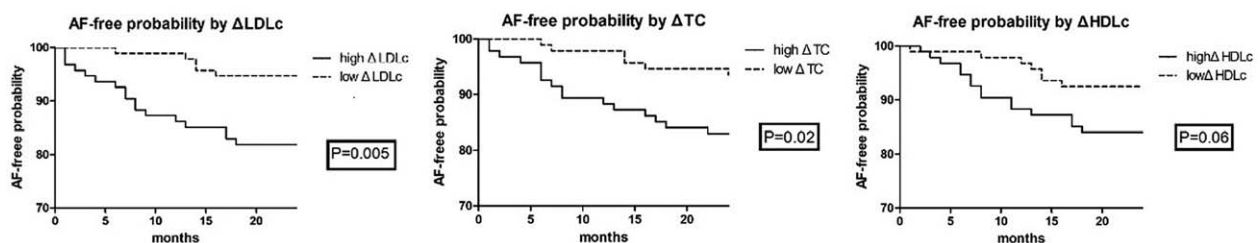


Figure 2. Kaplan-Meier curves describing AF-free probability as a function of lipid profiles. The levels of various indicators were dichotomized (high vs low). Differences (Δ) were calculated by subtracting the values noted at the 1-year follow-up from those noted at baseline. AF=atrial fibrillation, HDLc=high-density lipoprotein cholesterol, LDLc=low-density lipoprotein cholesterol, TC=total cholesterol.

Table 3
Risk of new-onset atrial fibrillation in patients with chronic heart failure.

| Predictor | Model 1 | | Model 2 | |
|-----------|---------------------|---------|---------------------|---------|
| | HR (95%CI) | P-value | HR (95%CI) | P-value |
| ΔTC | 1.016 (1.004–1.028) | .008 | 1.013 (1.001–1.025) | .03 |
| ΔLDLc | 1.022 (1.007–1.037) | .003 | 1.018 (1.003–1.033) | .02 |
| ΔHDLc | 1.05 (0.995–1.108) | .07 | 1.058 (0.992–1.129) | .08 |

Differences (Δ) were calculated by subtracting the values noted at the 1-year follow-up from those noted at baseline. Model 1 was obtained via single-factor regression analysis, while Model 2 was adjusted for sex, age, NYHA class, and left atrial dimension.

95%CI = 95% confidence interval, HR = hazard ratio, HDLc = high-density lipoprotein cholesterol, LDLc = low-density lipoprotein cholesterol, NYHA class = New York Heart Association class, SR = sinus rhythm, TC = total cholesterol.

heart disease. Statins are widely used in atherosclerotic disease. In this study, 72.2% of the enrolled subjects had ischemic heart disease, which did not affect AF incidence as blood lipid levels decreased. Although we did not find a correlation between the use of drugs (including statins) and AF incidence, use of statins in CHF should be cautious.

Our present findings may be explained in terms of the relationship between lipid metabolism and the stability of ion channels in the membrane of cardiac myocytes. Enhanced ectopic rhythmicity, multiple wavelet re-entrant, atrial fibrosis, atrial remodeling, inflammatory response, and oxidative stress are known contributors to AF.^[24–27] Electrical and structural remodeling of atrial cardiomyocytes is regarded as the pathologic foundation of AF.^[28] Abnormal lipid metabolism may detrimentally influence the electrical stability of membrane ion channels in atrial myocytes, since such membranes consist of lipid bilayers.^[29] Patients with end-stage heart failure often show extreme emaciation.^[30] Gastrointestinal congestion and restriction is the main cause of malnutrition in patients with CHF. Malnutrition is usually associated with abnormal lipid metabolism, and decreased serum LDLc levels indicate advanced metabolic imbalance.^[31] Structural abnormalities of the cell membrane, induced by abnormal lipid metabolism, result in abnormal electrical activity across the membrane. Indeed, in vitro studies have shown that cholesterol modulates the distribution and function of some ion channels potentially involved in AF, such as the Kv1.5 potassium channel.^[29] Dyslipidemia was found to be associated with subclinical hyperthyroidism in the elderly.^[32] AF was determined to be an independent predictor of intensive care unit mortality among severely ill patients.^[33] In patients with CHF, decreased blood lipid levels may reflect a higher risk of complications, including AF. Therefore, it may be harmful to reduce serum LDLc levels excessively in patients with heart failure.

Several limitations of this study must be acknowledged. First, this was a single-center study with a limited sample size (approximately 300 patients). Because our data pertains to patients from a single geographical area in China, the findings may not be generalizable to all patients with CHF. We measured the left atrial diameter rather than the atrium volumes by echocardiography. However, atrial volumes may be a more sensitive indicator of atrial remodeling. Finally, we analyzed blood lipid levels at only 2 time points, which may not reflect the characteristics of the entire curve of dynamic change in lipid levels.

Despite the study limitations, we found compelling evidence that decreasing serum levels of LDLc and TC are associated with higher incidence of new-onset AF in patients with CHF, independently of other risk factors, suggesting that aggressive

LDLc and TC lowering may not be appropriate in this patient population, regardless of CHF etiology.

Author contributions

Data curation: Chen Liu, Aihua Li.

Formal analysis: Xiaochen Yuan.

Investigation: Chen Liu, Jin Geng, Xiao Ye, Xiaochen Yuan.

Project administration: Zhengang Zhang, Biao Xu, Yingwei Wang.

Writing – original draft: Chen Liu.

Writing – review & editing: Chen Liu.

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