

Blood Lipid Levels, Lipid-Lowering Medications, and the Incidence of Atrial Fibrillation

The Atherosclerosis Risk in Communities Study

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Background—Several cardiovascular risk factors have been associated with the risk of atrial fibrillation (AF). Limited and inconsistent evidence exists on the association of blood lipid levels and lipid-lowering medication use with AF risk.

Methods and Results—We analyzed 13 969 participants (25% African American, 45% men) free of AF at baseline from the Atherosclerosis Risk in Communities study. Fasting high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol (LDLc), triglycerides, and total cholesterol were measured at baseline (1987–1989) and each of 3 follow-up visits. The incidence of AF was ascertained through 2007. The association of the use of statins and other lipid-lowering medications with AF was estimated in 13 044 Atherosclerosis Risk in Communities participants attending visit 2 (1990–1992), adjusting for covariates from the previous visit. During a median follow-up of 18.7 years, there were 1433 incident AF cases. Multivariable hazard ratios (HRs) and 95% CIs of AF associated with a 1-SD increase in lipid levels were as follows: HDLc, 0.97 (0.91–1.04); LDLc, 0.90 (0.85–0.96); total cholesterol, 0.89 (0.84–0.95); and triglycerides, 1.00 (0.96–1.04). Participants taking lipid-lowering medications had an adjusted HR (95% CI) of AF of 0.96 (0.82–1.13) compared with those not taking medications, whereas those taking statins had an adjusted HR of 0.91 (0.66–1.25) compared with those taking other lipid-lowering medications.

Conclusions—Higher levels of LDLc and total cholesterol were associated with a lower incidence of AF. However, HDLc and triglycerides were not independently associated with AF incidence. No association was found between the use of lipid-lowering medications and incident AF. (*Circ Arrhythm Electrophysiol.* 2012;5:155-162.)

Key Words: lipids ■ epidemiology ■ atrial fibrillation ■ statins

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting >2.3 million US adults, and that number is expected to more than double in the next 5 decades as the population ages.¹ AF is associated with increased risks of heart failure (HF), stroke, and cardiovascular death.² Major predictors for AF include age, white race/European ancestry, obesity, left ventricular hypertrophy, and hypertension, along with certain lifestyle factors.^{3–6} Many of these predictors are also risk factors for coronary heart disease (CHD) or HF, which often precedes the onset of AF.² Blood lipid levels, which are established risk factors for CHD, could also influence the risk of AF. In fact, low high-density lipoprotein cholesterol (HDLc) levels have been associated with a 20% to 40% increased risk of AF, with no association seen between triglyceride levels and the risk of

AF.^{7–9} However, limited and inconsistent data exist on the association of triglycerides, total cholesterol, and low-density lipoprotein cholesterol (LDLc) with incident AF, especially independently of other components of the metabolic syndrome.^{10–14}

Clinical Perspective on p 162

Numerous studies have provided evidence of the effectiveness of statins in the prevention and treatment of cardiovascular diseases, potentially beyond their lipid-lowering effect.¹⁵ Accordingly, statins might be effective in preventing AF.¹⁶ Randomized controlled trials have found that use of statins was significantly associated with a decreased risk of postoperative AF and a decreased recurrence of AF.^{17,18} Decreases in mortality and cardiovascular events have been

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observed in patients receiving statins after an AF diagnosis.¹⁹ However, observational data and clinical trial evidence have produced mixed results regarding the impact of statins on the incidence of AF in otherwise healthy populations. An observational study reported that statin use reduced the risk of developing AF independently of the reduction in serum cholesterol levels.²⁰ However, a large randomized clinical trial, The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed no relationship between randomly assigned pravastatin use and a reduction in incident AF, after a follow-up of 6 years.⁸ These data are consistent with a meta-analysis in which the analysis of randomized controlled trials showed no significant effect of statins on AF incidence but indicated statins significantly reduced the relative risk of AF in observational studies.²¹ To the best of our knowledge, no information exists on the effect of other lipid-lowering medications on the risk of AF.

The present study estimates the association of participants' blood lipid profile over time with the incidence of AF in the Atherosclerosis Risk in Communities (ARIC) cohort, a community-based study of cardiovascular disease in the United States. We also assess whether use of statins or other cholesterol-lowering medications affects the risk of AF, taking advantage of the many incident AF cases and ample follow-up time in the ARIC cohort.

Methods

Study Population

The ARIC study is a prospective cohort study of cardiovascular disease and atherosclerosis risk factors. Participants at baseline (1987–1989) included 15 792 men and women, aged 45 to 64 years, recruited from 4 communities in the United States (Washington County, MD; the suburbs of Minneapolis, MN; Jackson, MS; and Forsyth County, NC). Participants were mostly white in the Washington County and Minneapolis centers, only African American in the Jackson center, and both races in Forsyth County. After the initial assessment, study participants were examined 3 additional times (1990–1992, 1993–1995, and 1996–1998). Response rates for surviving participants at each examination were 93%, 86%, and 80%, respectively. In addition, ARIC participants have received annual follow-up calls since baseline, and survivors have a response rate $\geq 90\%$. The study was approved by institutional review boards at each participating center, and all study participants provided written informed consent.

Ascertainment of AF

AF diagnoses were ascertained by 3 different sources in the ARIC study: ECGs performed at study visits, hospital discharge codes, and death certificates.³ At each ARIC study visit, a 10-second 12-lead ECG was performed using an MAC PC cardiograph (Marquette Electronics Inc; Milwaukee, WI) and transmitted to the ARIC ECG Reading Center for coding, interpretation, and storage. All ECGs automatically coded as AF were visually checked by a trained cardiologist to confirm AF diagnosis.²²

Annual follow-up calls and a review of local hospital discharges identified hospitalizations in ARIC participants through the end of 2007. The *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) code of 427.31 or 427.32, listed as a discharge diagnostic code, identified AF cases. AF events associated with cardiac surgery were excluded in this study. Validity was sufficient because $\approx 90\%$ of the cases were confirmed in a physician review of discharge summaries from 125 possible AF cases.³ AF cases were also identified if ICD-9 code 427.3 or *International Statistical Classification of Diseases, 10th Revision* (ICD-10) code I48 was listed as a cause of death. Most incident AF cases ($>98\%$)

in this analysis were identified from hospital discharge codes. In this analysis, the incidence date of AF was defined as the date for the first ECG showing AF, the first hospital discharge coded as AF, or when AF was listed as a cause of death, whichever occurred earlier.

Assessment of Lipid Levels

Blood samples were collected at each visit after a fast of at least 8 hours and sent to the ARIC Central Lipid Laboratory for processing. Detailed procedures are available elsewhere.^{23,24} Briefly, total plasma cholesterol and triglycerides were determined by enzymatic methods, HDLc was measured after dextran-magnesium precipitation, and LDLc was calculated by the Friedewald equation²⁵ in those with triglyceride levels <4.52 mmol/L.

Assessment of Lipid-Lowering Medication Use

The use of lipid-lowering medications was self-reported and confirmed by checks on medications brought to each visit by the patient. Lipid medications were divided into 2 categories: statins and other lipid medications. Included in the "other" category were niacin (vitamin B3), bile sequestrants, fibrates, and other antihyperlipidemics. Participants taking both statins and another type of lipid-lowering medication were considered to be in the statin category.

Measurement of Other Covariates

At each study visit, participants underwent a physical examination and provided self-reported information. Detailed procedures on covariate measurements are available elsewhere.²³ At each visit, prevalent HF was defined as the reported use of HF medication in the previous 2 weeks, the presence of HF according to the Gothenburg criteria (only at the baseline visit), or having developed incident HF from the previous visit.²⁶ Incident HF was defined as the presence of ICD-9 code 428 in any hospitalization during follow-up.²⁷ Prevalent CHD was defined as prior cardiovascular revascularization, physician-diagnosed myocardial infarction, or presence of a previous myocardial infarction by ECG. Incident CHD was ascertained by the ARIC Morbidity and Mortality Classification Committee using data from follow-up calls, hospitalization records, and death certificates.²⁸ Prevalent stroke was defined as the self-reported physician diagnosis of a stroke before visit 1, and after visit 1, it was adjudicated from diagnosis codes indicative of cerebrovascular disease.²⁹ Incident stroke was defined as the first probable or definite hospitalized stroke occurring in a participant free of a history of diagnosed stroke at baseline.

Statistical Analysis

Inclusion/Exclusion Criteria

Of the 15 792 participants who attended visit 1 in the ARIC study, we excluded individuals who were of a racial/ethnic group other than white or African American and nonwhites in the Minneapolis and Washington County field centers ($n=103$), those with prevalent AF at visit 1 ($n=37$), those with a low-quality or missing ECG ($n=309$), those missing lipid levels ($n=395$), those nonfasting ($n=558$), and those missing covariates ($n=14$). For analysis of lipid levels, those taking cholesterol medications at visit 1 were also excluded ($n=407$; 20% statins). The final sample for lipid-level analysis included 13 969 participants (25% African American, 45% male). The association of use of cholesterol-lowering medications with AF was estimated in 13 044 ARIC participants using visit 2 as baseline and similar exclusion criteria. Beginning follow-up at visit 2 allowed us to adjust for lipid levels and covariates from visit 1 as potential confounders.

Lipid-Level Analysis

We categorized individuals by lipid levels according to clinical categories outlined in the National Cholesterol Education Program Adult Treatment Panel III guidelines: HDLc, <1.04 , 1.04 to 1.54, and ≥ 1.55 mmol/L (<40 , 40 to 59, and ≥ 60 mg/dL); LDLc, 2.59 to 4.13, and ≥ 4.14 mmol/dL (<100 , 100 to 159, and ≥ 160 mg/dL); total cholesterol, <5.18 , 5.18 to 6.21, and ≥ 6.22 mmol/L (<200 , 200 to 239, and ≥ 240 mg/dL); triglycerides, <1.70 , 1.70 to

2.25 and ≥ 2.26 (<150, 150 to 199, and ≥ 200 mg/dL).³⁰ For the analysis with lipid levels as a time-dependent exposure (see later), a measurement of 1-SD increment of each lipid level was used to allow comparisons among different blood lipid levels: HDLc: 0.44 mmol/L (17 mg/dL); LDLc: 1.01 mmol/L (39.1 mg/dL); total cholesterol: 1.07 mmol/L (41.3 mg/dL); triglycerides: 0.73 mmol/L (64.3 mg/dL). In an additional analysis, we examined the association of changes in LDLc levels from visit 1 to visit 4 with AF risk, adjusting for covariates from both visits, along with baseline LDLc levels. *P* values for trend were calculated, including lipid levels as continuous variables in the models.

We estimated the association of baseline (visit 1) lipid levels with the incidence of AF using Cox proportional hazards models with time to AF as the main outcome variable. *Follow-up time* was defined as the time elapsed between baseline and date of AF incidence, death, loss to follow-up, or December 31, 2007, whichever came earlier. The rate of AF was modeled using a Cox proportional hazards model with lipid levels as time-varying covariates. Models were adjusted for baseline covariates, including age, sex, race, study site, education (less than completed high school, high school diploma, or at least some college), income (<\$16 000, \$16 000-<\$35 000, \$35 000-<\$50 000, or \geq \$50 000), and height (continuous). They were also adjusted for the following time-varying covariates: smoking (never, former, or current), alcohol drinking (never, former, or current), body mass index (continuous), diabetes (dichotomous), systolic blood pressure (continuous), diastolic blood pressure (continuous), use of antihypertensive medications, use of cholesterol-lowering medications, prevalent stroke, prevalent HF, and prevalent CHD. An additional model was performed, also adjusting for incident stroke, incident HF, and incident CHD as time-varying covariates. The proportional hazards assumption was tested using time interaction terms and inspection of log-negative log-survival curves.

Because most AF events were identified from hospitalizations, we conducted 2 additional analyses to evaluate whether associations between lipid levels and AF risk would be biased because of the method of event ascertainment. First, we determined whether lipid levels were associated with incidence of any hospitalization, and compared those results with the association of lipids and AF. Second, we included any hospitalization as a time-dependent covariate in the models, to determine whether hospitalizations mediated any observed association between lipid levels and AF.

Lipid-Lowering Medication Analysis

To measure the association between lipid medication use and the incidence of AF, visit 2 was used as baseline. The models were adjusted for covariates of interest from visit 1, using similar models as previously stated and additionally adjusting for LDLc and triglycerides measured at the previous visit. The association between lipid medication use and incidence of AF was assessed using Cox proportional hazards models with time-varying medication use (visits 2, 3, and 4) and covariates to account for changes in medication use over time.

In addition to the standard multivariable analyses for lipid medications, we conducted a secondary analysis using a propensity score approach.³¹ First, we calculated an estimated propensity score as the probability of receiving treatment at visit 2 given covariates (previously mentioned) using a logistic model. Second, we performed 2 different analyses: (1) a standard Cox model adjusting for the propensity score and (2) a model in which treated and untreated were matched on their continuous propensity score at a 4:1 ratio, with nearest neighbor matching and no replacement for prior matched control, analyzed in a Cox model. Follow-up for this analysis also started at visit 2 to adjust for other covariates measured in the previous visit, including LDLc and triglyceride levels.

We conducted stratified analyses by age and race categories in all lipid levels. Effect measure modification was formally tested, including an interaction term between age and race variables and levels of each lipid measurement. All statistical analyses were performed with SAS version 9.2 (SAS Inc; Cary, NC).

Table 1. Baseline Characteristics of ARIC Participants by Total Cholesterol Levels, ARIC, 1987–1989

Characteristics	Total Cholesterol Level, mmol/L (mg/dL)		
	<5.18 (<200)	5.18–6.21 (200–239)	≥ 6.22 (≥ 240)
No. of participants	5458	5246	3265
Age, y	53.2 (5.8)	54.4 (5.7)	55.3 (5.6)
Male sex, %	48.1	44.3	39.1
African American, %	26.5	22.3	27.9
High school degree, %	78.7	77.4	74.5
Income \geq \$50 000, %	26.7	24.0	19.4
Current smoker, %	26.7	24.4	26.6
Current alcohol use, %	57.6	56.9	55.1
BMI, kg/m ²	27.4 (5.5)	27.6 (5.4)	27.9 (5.0)
Height, cm	169.4 (9.3)	168.4 (9.3)	167.0 (9.2)
Diabetes, %	8.6	9.8	12.2
Systolic blood pressure, mm Hg	119.2 (18.4)	121.3 (18.6)	123.3 (19.2)
Diastolic blood pressure, mm Hg	73.0 (11.3)	73.7 (11.1)	74.6 (11.2)
Antihypertensive medications, %	26.3	29.0	32.9
Prevalent coronary heart disease, %	3.4	4.5	5.1
Prevalent stroke, %	1.6	1.9	1.6
Prevalent heart failure, %	3.9	4.3	4.2

Values correspond to mean (SD) unless otherwise indicated.

ARIC indicates Atherosclerosis Risk in Communities; BMI, body mass index.

Results

Selected characteristics for ARIC participants by categories of total cholesterol are shown in Table 1. Older participants, women, African Americans, and those with less education and income were more likely to have higher levels of total cholesterol. Diabetes, hypertension, prevalent CHD, and prevalent HF were also associated with higher cholesterol.

Blood Lipids and AF Risk

During a median follow-up of 18.7 years, we identified 1433 incident AF cases. After adjustment for potential confounders and intermediates, there was no significant association between baseline levels of HDLc and triglycerides with incident AF (Table 2). Higher levels of LDLc and total cholesterol at baseline were associated with a lower risk of incident AF. Compared to those with LDLc levels <2.59 mmol/L, the hazard ratios (HRs) and 95% CIs of AF in individuals with an LDLc of 2.59–4.13 mmol/L was 0.84 (0.72–0.97); and in those with an LDLc ≥ 4.14 mmol/L, 0.85 (0.72–1.01) (*P*=0.06 for trend). Compared with those with total cholesterol levels <5.18 mmol/L, the HR (95% CI) of AF was 0.88 (0.76–1.01) in those with levels ≥ 6.22 mmol/L (*P*=0.03 for trend). Models not adjusting for prevalent stroke, HF, and CHD and also models additionally adjusting for incident stroke, HF, and CHD produced similar results.

Results of the association between incident AF and each lipid level measurement at visits 2 to 4 were similar and are shown in Figure 1. A significant inverse association was seen between LDLc and total cholesterol and incident AF in most visits, with

Table 2. Hazard Ratios (95% CIs) of AF by Baseline Levels of Blood Lipids, Categorized by Clinically Relevant Categories, ARIC, 1987–2007

Variable	HDLc, mmol/L (mg/dL)			P Value for Trend
	<1.04 (<40)	1.04–1.54 (40–59)	≥1.55 (≥60)	
AF cases	485	665	283	...
Person-years	58 815	111 506	66 320	...
AF incidence*	6.03	4.83	3.89	...
Model 1	1 (Ref)	0.78 (0.69–0.88)	0.63 (0.53–0.74)	<0.0001
Model 2	1 (Ref)	0.97 (0.85–1.09)	1.00 (0.84–1.19)	0.56
Variable	LDLc, mmol/L (mg/dL)			P Value for Trend
	<2.59 (<100)	2.59–4.13 (100–159)	≥4.14 (≥160)	
AF cases	217	825	391	...
Person-years	38 202	138 779	59 659	...
AF incidence*	5.15	4.53	4.60	...
Model 1	1 (Ref)	0.87 (0.75–1.01)	0.88 (0.74–1.04)	0.15
Model 2	1 (Ref)	0.84 (0.72–0.97)	0.85 (0.72–1.01)	0.06
Variable	Total Cholesterol, mmol/L (mg/dL)			P Value for Trend
	<5.18 (200)	5.18–6.21 (200–239)	≥6.22 (≥240)	
AF cases	547	553	333	...
Person-years	92 693	88 838	55 110	...
AF incidence*	4.87	4.68	4.36	...
Model 1	1 (Ref)	0.96 (0.85–1.08)	0.89 (0.77–1.02)	0.03
Model 2	1 (Ref)	0.95 (0.84–1.07)	0.88 (0.76–1.01)	0.03
Variable	Triglycerides, mmol/L (mg/dL)			P Value for Trend
	<1.70 (<150)	1.70 (150–199)	≥2.26 (≥200)	
AF cases	977	228	228	...
Person-years	177 413	33 456	25 771	...
AF incidence*	4.41	4.73	6.04	...
Model 1	1 (Ref)	1.08 (0.93–1.24)	1.40 (1.21–1.62)	<0.0001
Model 2	1 (Ref)	0.87 (0.75–1.00)	1.02 (0.88–1.18)	0.52

The *P* value for trend is the association with linear continuous levels. Model 1, Cox proportional hazard model adjusted for age, sex, and race. Model 2, model 1, additionally adjusted for study site, education, income, height, smoking status, drinking status, body mass index, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, diabetes, prevalent stroke, prevalent heart failure, and prevalent coronary heart disease.

AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; Ref, reference.

*Per 1000 person-years. Adjusted for age, sex, and race.

stronger associations in later visits. Results were comparable when we considered lipid levels as time-dependent exposures, also shown in Figure 1. The HRs (95% CIs) of AF by 1-SD increment in time-varying HDLc and triglyceride measurements were 0.97 (0.91–1.04) and 1.00 (0.96–1.04), respectively. The HR (95% CI) in time-varying LDLc measurements was 0.90 (0.85–0.96); and in total cholesterol, 0.89 (0.84–0.95). In analyses including only AF events identified in study ECGs (*n*=117), the HR (95% CI) of AF per 1 SD increment was 0.79 (0.63–0.98) for LDLc and 0.75 (0.60–0.93) for total cholesterol. Adjustment for exercise in the models did not change the significance of the association. An additional analysis was performed examining the change in LDLc from visit 1 to visit 4. After excluding those taking cholesterol medications, and after adjustment for visit 1 and visit 4 covariates and baseline LDLc levels, the HR (95% CI) for a 1-mmol/L (38.6 mg/dL) change of

LDLc was 0.79 (0.69–0.90). These results indicate that the larger the decrease in LDLc from visit 1 to visit 4, the lower the risk of AF. LDLc was not associated with overall risk of hospitalizations (HR, 0.98 [95% CI, 0.96–1.00] for a 1-SD increment), and adjustment for hospitalizations as a time-dependent covariate did not change the association between LDLc and AF risk (HR, 0.91 [95% CI, 0.86–0.97] for a 1-SD LDLc increment as a time-dependent covariate).

AF-free survival curves from visits 1 and 4 by LDLc levels are shown in Figure 2, with higher survival in those with higher LDLc. There was no significant age or race interaction between HDLc, LDLc, and total cholesterol levels. However, the association of triglyceride levels with AF risk varied by race (*P*=0.02), with a stronger association in African Americans compared with whites (HR [95% CI], 1.14 [1.03–1.26] versus 0.99 [0.94–1.03], respectively).

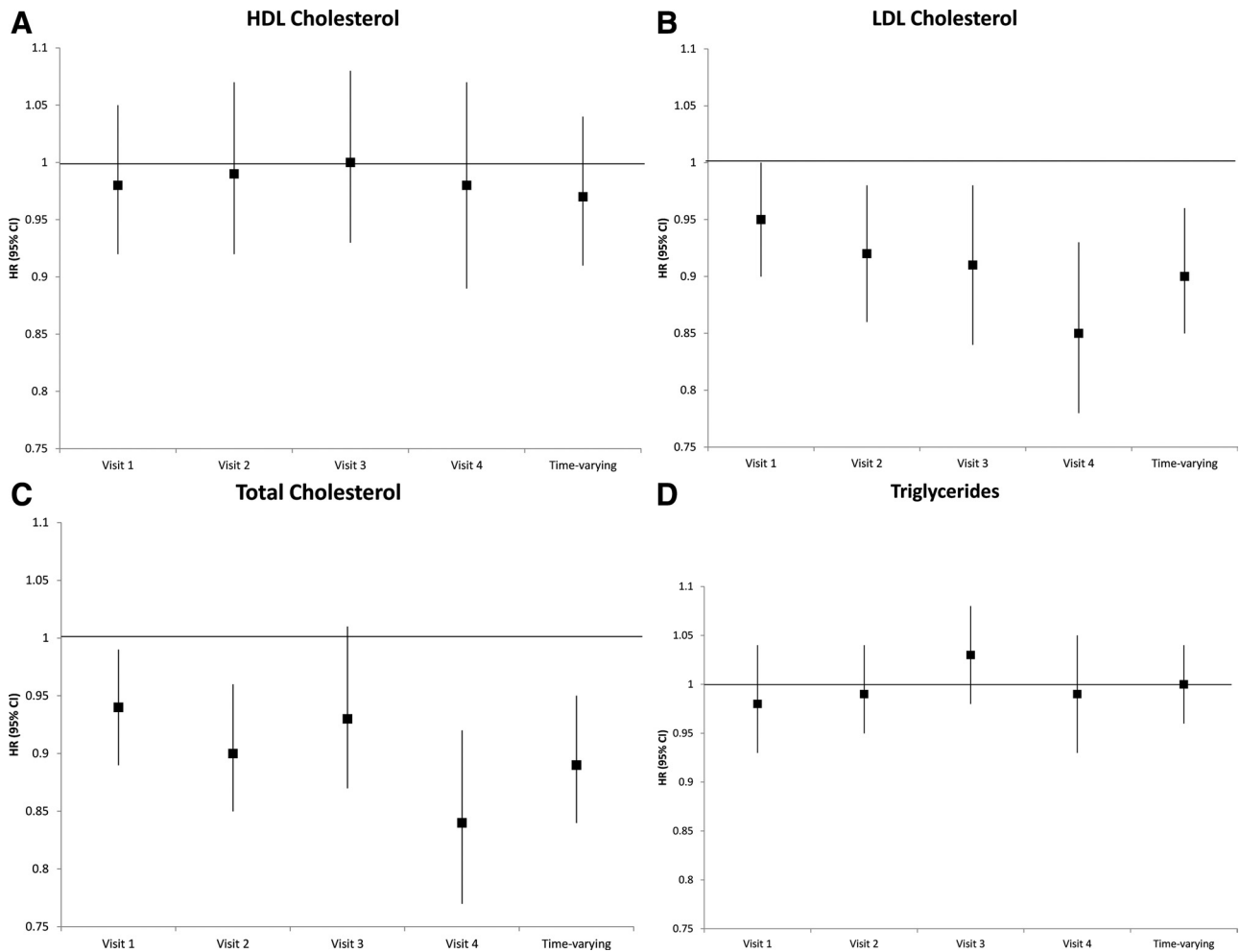


Figure 1. Hazard ratios and 95% CIs of atrial fibrillation, according to lipid-level measurements (**A**: HDLc; **B**: LDLc; **C**: Total cholesterol; **D**: Triglycerides) at each visit, and as a time-varying variable, Atherosclerosis Risk in Communities (ARIC), 1987 to 2007. Results from separate Cox proportional hazard models, adjusted for age, sex, race, study site, education, income, height, smoking status, drinking status, body mass index, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, diabetes, prevalent stroke, prevalent heart failure, prevalent coronary heart disease, and use of cholesterol medications.

Lipid-Lowering Medication Use and AF Risk

We assessed the association of use of cholesterol medications with AF risk, considering visit 2 as baseline, while adjusting for covariates from the previous visit. Among the 13 044 eligible participants, 2102 were taking some cholesterol-lowering medication at 1 or more visits, with 68% of those taking statins at some point (39% at visit 2, 59% at visit 3, and 80% at visit 4). There were 1311 incident AF cases identified, and of those occurring in cholesterol medication users (278 events), 68% occurred in those taking statins. After multivariable adjustment, there was no association between time-varying cholesterol medication use across visits and the incidence of AF, with an HR (95% CI) of 0.96 (0.82–1.13), compared with those not taking cholesterol-lowering medications (Table 3). There was also no association with AF risk between those taking statins and in those taking other cholesterol medications: HR (95% CI), 0.91 (0.66–1.25). Models not adjusting for prevalent stroke, heart disease, and CHD, and models additionally adjusting for incident stroke, heart disease, and CHD, produced similar results.

A secondary analysis was performed using propensity scores calculated at visit 2. In a standard Cox model, the

propensity score–adjusted HR (95% CI) was 1.09 (0.88–1.34) when comparing lipid-lowering medication use with nonuse. When matched 4:1 (not treated/treated) by propensity score, results were similar: HR (95% CI), 1.03 (0.89–1.20).

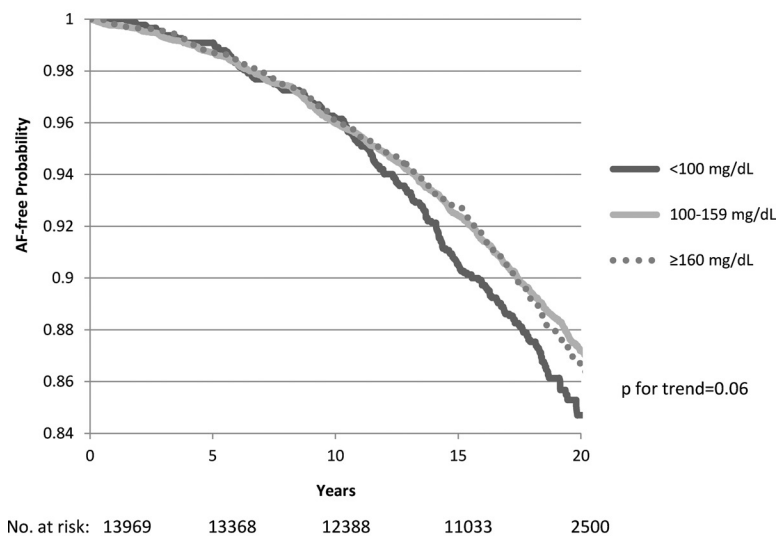
Discussion

In this population-based prospective study, we found no independent association between HDLc or triglycerides and incidence of AF, whereas lower levels of LDLc and total cholesterol were associated with a higher AF risk. We also found no independent association between lipid-lowering medications, including statins, and the risk of AF. These associations were independent of lifestyle factors, clinical factors, and cardiovascular disease, and were similar in whites and African Americans.

Blood Lipid Levels and AF

The relationship between lipid levels and AF risk has not been extensively addressed. Previous publications reported that low HDLc levels were associated with a 20% to 40%

A Survival Curves by LDL Cholesterol, 1987-2007



B Survival Curves by LDL Cholesterol, 1996-2007

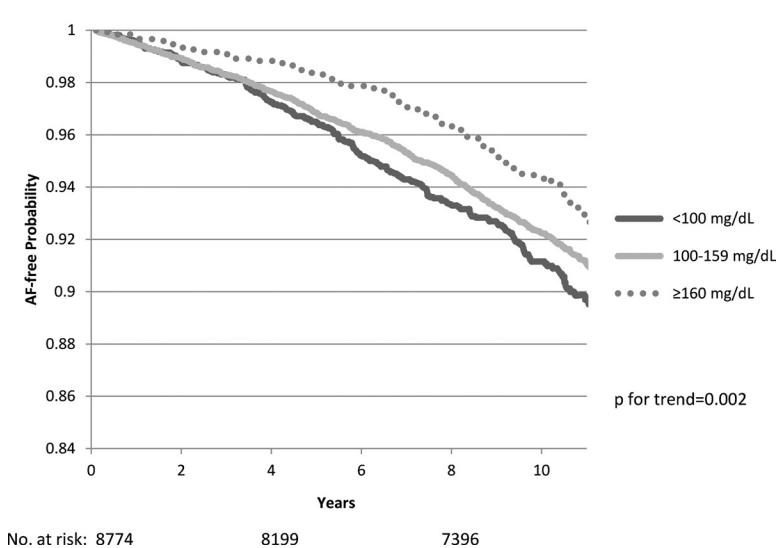


Figure 2. Kaplan-Meier survival curves for atrial fibrillation (AF) by categories of low-density lipoprotein cholesterol (LDLc; <100, 100–159, and \geq 160 mg/dL) from baseline (**A**: top panel) and from visit 4 (**B**: bottom panel), Atherosclerosis Risk in Communities (ARIC), 1987–2007 and 1996–2007, respectively. Cox proportional hazards model excluding those taking cholesterol-lowering medications at baseline, and adjusted for age, sex, study site, education, income, height, smoking status, drinking status, body mass index, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, diabetes, prevalent stroke, prevalent heart failure, and prevalent coronary heart disease. The *P* value for trend is considered across categories. The number of subjects at risk throughout the duration of the study follow-up is shown on the x axis.

higher risk of AF^{7–9}; however, residual confounding could have been responsible for that association. In our analysis, an initial association between HDLc and AF risk disappeared after adjustment for a wide selection of potential confounders. Similar results were observed for triglycerides.

The inverse association of LDLc and total cholesterol with AF risk is intriguing, and has been previously seen in an analysis of the Cardiovascular Health Study, which included individuals aged \geq 65 years.¹¹ Similar results were found in 2 Japanese populations, in which individuals with hypercholesterolemia had a 25% lower odds of developing AF and an 8% reduction in AF risk with each 10% increase in LDLc.^{9,32} Notably, this association was stronger in older individuals, consistent with our results of stronger inverse associations in later ARIC visits. However, no clear mechanism exists to explain this association. Subclinical hyperthyroidism might be potentially responsible, because hyperthyroidism reduces levels of total cholesterol and LDLc,³³ and is associated with increased

risk of AF.³⁴ Unfortunately, we do not have information on thyroid profiles in ARIC participants. Blood lipids could also affect the composition of cell membranes, which is a major determinant of cell excitability. In vitro studies have shown that cholesterol modulates the distribution and function of some ion channels potentially involved in the occurrence of AF, such as the Kv1.5 potassium channel.^{35,36} Whether this mechanism explains the observed association is hypothetical and requires further research.

Lipid-Lowering Medications and AF

Published reports addressing the relationship between statins and AF have provided inconsistent results, and the conclusions tend to be different based on clinical trials (no association) or observational studies (reduced AF risk).²¹ This study provided results consistent with those seen in most randomized clinical trials and indicated no relationship between statin use or any lipid-lowering medication use and the risk of AF. During the years the ARIC visits were conducted (1987–1998), statins were

Table 3. Hazard Ratios (95% CIs) of AF by Lipid Medication Use Over Time, ARIC, 1990–2007

Variable	No Cholesterol Medications	Any Cholesterol Medications
No. of participants	10 942	2102
AF cases	1033	278
Hazard ratio (95% CI)*	1 (Ref)	0.96 (0.82–1.13)
	Other Cholesterol Medications	Statins
No. of participants	666	1436
AF cases	89	189
Hazard ratio (95% CI)*	1 (Ref)	0.91 (0.66–1.25)

AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; Ref, reference.

*Cox proportional hazard model with time-varying medication use and adjusted for age, sex, race, study site, education, income, and time-varying (from the previous visit) height, smoking status, drinking status, body mass index, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, diabetes, prevalent stroke, prevalent heart failure, prevalent coronary heart disease, and low-density lipoprotein cholesterol and triglyceride levels.

gaining in popularity, and that, combined with the participants getting older, meant most statin users were not taking them until around visit 4 (1996–1998). There have been no study visits since 1998, so we were unable to determine how many of the participants with incident AF were receiving statins or lipid-lowering medications in the years between visit 4 and the year in which their AF occurred.

Strengths and Limitations

Some other study limitations should be noted. Asymptomatic AF and AF managed exclusively in an outpatient setting could not be identified, because most of our incident AF cases were ascertained from hospitalization discharge records. However, the incidence rates of AF in the ARIC study are consistent with other population-based studies, and the validity of AF ascertainment using hospitalizations is acceptable.³ In a subanalysis in this study comparing AF ascertained from hospital records with AF from study ECGs, there was an even stronger inverse association seen between LDLc (HR, 0.79 for ECGs and 0.90 for hospital records) and total cholesterol (HR, 0.75 for ECGs and 0.89 for hospital records) and incident AF in the ECG group, thus supporting evidence that AF ascertained from hospitalizations is acceptable. Also, LDLc levels were not associated with the risk of hospitalization, and adjustment for incident hospitalizations before AF incidence or censoring did not change the association between LDLc and AF. There is also the possibility that those with dyslipidemia have more paroxysmal AF that was not captured by our AF ascertainment process. Other limitations include the possible misclassification of exposures, both lipid levels and lipid-lowering medications, because of unmeasured changes between visits. Along with no data on thyroid hormones, which might confound our results, the ARIC study also does not contain information on the dose of statins or other lipid medications. Higher doses have a stronger effect on cholesterol levels and other processes (eg, inflammation in

the case of statins) and, therefore, different doses may differentially affect the incidence of AF. Also, we cannot determine the impact of lifestyle changes a patient may incorporate to become healthier after discovering he or she has high cholesterol. Despite these limitations, our study has important strengths, including a large sample size, a long follow-up, an elevated number of AF events, a biracial sample, and an extensive list of measured covariates.

Conclusions

In conclusion, we found that higher levels of LDLc and total cholesterol were associated with a lower incidence of AF independently of other risk factors. HDLc and triglycerides, however, were not independently associated with AF incidence after multivariable adjustment. Future research should replicate these results and study potential mechanisms. In addition, no association was found between lipid-lowering medication, including statins, and the incidence of AF. At present, there are still insufficient data to recommend the use of statins solely for AF prevention.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Limited data exist on the association between blood lipid levels and the risk of atrial fibrillation (AF), despite blood lipid levels being established risk factors for coronary heart disease. Similarly, data on the effectiveness of lipid-lowering medications, including statins, for the prevention of AF development in otherwise healthy populations have been inconsistent. This study tested the association between blood lipid levels, lipid-lowering medication use, and the risk of AF in a large, biracial, prospective cohort. After multivariable adjustment, we found no independent association between high-density lipoprotein cholesterol and triglycerides and AF incidence. Likewise, the use of lipid-lowering medications was not associated with incident AF. We found, however, that higher levels of low-density lipoprotein and total cholesterol were significantly associated with a lower incidence of AF. No convincing explanation exists for this inverse association at this time; however, comparable observations have been made in similar studies, particularly in older individuals. Future research should replicate our results and study potential mechanisms. At present, data to recommend the use of statins solely for AF prevention are insufficient.