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Blood Lipids and the Incidence of Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis and the Framingham Heart Study

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Background—Dyslipidemia is a major contributor to the development of atherosclerosis and coronary disease. Its role in the etiology of atrial fibrillation (AF) is uncertain.

Methods and Results—We studied 7142 men and women from the Multi-Ethnic Study of Atherosclerosis (MESA) and the Framingham Heart Study who did not have prevalent AF at baseline and were not on lipid-lowering medications. Total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, and triglycerides were measured using standard procedures. Incident AF during follow-up was identified from hospital discharge codes; review of medical charts; study electrocardiograms; and, in MESA only, Medicare claims. Multivariable Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals of AF by clinical categories of blood lipids in each cohort. Study-specific results were meta-analyzed using inverse of variance weighting. During 9.6 years of mean follow-up, 480 AF cases were identified. In a combined analysis of multivariable-adjusted results from both cohorts, high levels of high-density lipoprotein cholesterol were associated with lower AF risk (hazard ratio 0.64, 95% CI 0.48 to 0.87 in those with levels ≥60 mg/dL versus <40 mg/dL), whereas high triglycerides were associated with higher risk of AF (hazard ratio 1.60, 95% CI 1.25 to 2.05 in those with levels ≥200 mg/dL versus <150 mg/dL). Total cholesterol and low-density lipoprotein cholesterol were not associated with the risk of AF.

Conclusion—In these 2 community-based cohorts, high-density lipoprotein cholesterol and triglycerides but not low-density lipoprotein cholesterol or total cholesterol were associated with the risk of AF, accounting for other cardiometabolic risk factors. (*J Am Heart Assoc*. 2014;3:e001211 doi: 10.1161/JAHA.114.001211)

Key Words: atrial fibrillation • cholesterol • epidemiology • lipids • risk factors

Dyslipidemia is a major contributor to the development of atherosclerosis and coronary heart disease. High levels of low-density lipoprotein cholesterol (LDLc), and low levels of high-density lipoprotein cholesterol (HDLc) have been consistently associated with increased risk of coronary heart disease.[1] In addition, lowering of LDLc and total cholesterol

with statins reduces the risk of coronary events.[2] The role of dyslipidemia as a risk factor for other cardiac conditions, including atrial fibrillation (AF), is less clear. Prevalence and severity of atherosclerosis have been associated with the risk of AF,[3] but the few published studies exploring the link between blood lipids and AF have yielded inconsistent and paradoxical results. In contrast with the association observed with coronary heart disease, high levels of LDLc and total cholesterol were unexpectedly associated with lower risk of AF in some community-based studies.[4–8] With the general aim of clarifying the role of blood lipids as risk factors for AF, we analyzed data from the Multi-Ethnic Study of Atherosclerosis (MESA) and the Framingham Heart Study (FHS), 2 community-based studies in the United States that have collected extensive information on cardiovascular risk factors including blood lipids.

Methods

Study Cohorts

MESA is a racially diverse, community-based, prospective cohort study designed to investigate the prevalence, progression, and risk factors of subclinical cardiovascular disease (CVD) in the general population. Details of the overall design, recruitment, and methods have been published elsewhere.[9] Briefly, 6814 men and women aged 45 to 84 years and without known CVD were recruited in 2000–2002 from 6 US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York City, NY; and Saint Paul, MN).

The FHS is a prospective, community-based investigation of the epidemiology of CVD. The study began in 1948 with the enrollment of the original cohort. In the early 1970s, offspring and spouses of the original cohort were recruited into the Framingham Offspring Study and examined every 4 to 8 years

afterward.[10] In the present analysis, we included 3532 participants attending the sixth examination cycle of the Framingham Offspring Study (1995–1998; age range: 30 to 87 years), considered baseline for this analysis.

For the primary analysis, we excluded participants with prevalent AF at baseline, those taking lipid-lowering medications, and those with missing values for any relevant covariates (Figure 1). Participants with prevalent myocardial infarction or heart failure in the FHS were also excluded (by design, MESA participants were free of clinical CVD at baseline). After applying exclusion criteria, 4534 participants in MESA and 2608 in the FHS were eligible. The study was approved by institutional review boards at participating institutions. All participants provided written informed consent.

Measurement of Lipid Levels

In MESA and the FHS, fasting blood samples were collected at baseline, processed, and stored at -70°C. Total cholesterol, HDLc, and triglycerides were measured using standard methods.[11,12] LDLc was calculated using the Friedewald equation (all values in mg/dL): LDLc$=$total cholesterol$-$HDLc$-$triglycerides$\times 0.2$.[13]

Ascertainment of Atrial Fibrillation

Incident cases of AF during follow-up in MESA were identified through MESA event surveillance and, for participants enrolled in fee-for-service Medicare, from inpatient Medicare claims data. As part of standard event surveillance procedures in the MESA cohort, all hospitalizations are identified every 9 to 12 months during follow-up calls to study participants or a proxy. Discharge diagnostic and procedure codes from those hospitalizations are abstracted. AF was considered to be present if an International Classification of Diseases, Ninth
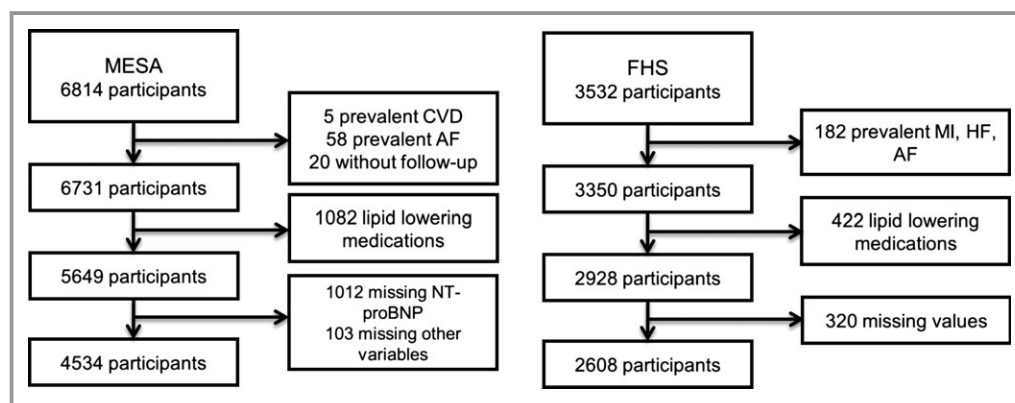
Figure 1. Flowchart of study participants: MESA, 2000–2002, and the FHS, 1995–1998. AF indicates atrial fibrillation; CVD, cardiovascular disease; FHS, Framingham Heart Study; HF, heart failure; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

Revision, Clinical Modification code 427.31 or 427.32 was present in any position. AF hospitalizations associated with open cardiac surgery were excluded. Similarly, in Medicare claims, AF was defined as the presence of an International Classification of Diseases, Ninth Revision, Clinical Modification code 427.31 or 427.32 in any position in any inpatient claim during 1999–2010. If the first AF claim occurred before the baseline MESA exam, the participant was considered to have prevalent AF and thus was excluded from the analysis.

In the FHS, AF was diagnosed if AF or atrial flutter were present on an ECG obtained from a Framingham clinic visit, outpatient clinical visit, inpatient hospitalization, or Holter monitor. All potential AF cases were adjudicated by an FHS cardiologist.[14]

Assessment of Other Covariates

In both MESA and the FHS, information on cardiovascular risk factors and other variables was collected during the baseline examination following standardized protocols. Education, smoking history, alcohol intake, and use of medications were assessed through questionnaires. Physical activity was assessed by an activity questionnaire adapted from the Cross-Cultural Activity Participation Study (in MESA)[15] and by asking how many times per week the participant engaged in intense physical activity (in the FHS). Resting blood pressure, height, and weight were measured with the participant in light clothing. Body mass index was calculated as the weight in kilograms divided by height in square meters. Fasting blood glucose and high-sensitivity C-reactive protein were measured using comparable methods in both cohorts.[16,17] Diabetes was defined based on having fasting blood glucose >125 mg/dL or a history of medical treatment for diabetes. B-type natriuretic peptide (BNP) was measured in FHS participants using a high-sensitivity immunoradiometric assay (Shionogi), and N-terminal prohormone of BNP (NT-proBNP) was measured in MESA using a commercially available immunoassay (Roche Diagnostic Elecsys proBNP assay) on the Elecsys 2010 instrument.

Statistical Analysis

Separate analyses were conducted with MESA and FHS data. We examined the association of baseline blood lipid levels with AF incidence calculating hazard ratios (HRs) and 95% CIs from Cox proportional hazard models. Initially, we conducted analyses using established clinical cut points: <200, 200 to 239, and ≥240 mg/dL for total cholesterol; <100, 100 to 129, 130 to 159, and ≥160 mg/dL for LDLc; <40, 40 to 59, and ≥60 mg/dL for HDLc; and <150, 150 to 199, and ≥200 mg/dL for triglycerides.[18] In additional models, we included lipid levels as continuous variables scaled to approximately 1SD increments, using the same values in

both cohorts. Models were initially adjusted for age; sex; and, in MESA only, race or ethnicity. In a second model, we adjusted for other potential confounders, including study site (in MESA), education, body mass index, height, smoking, alcohol intake, systolic and diastolic blood pressure, use of antihypertensive medications, diabetes, C-reactive protein, and $\log_e$-transformed NT-proBNP (in MESA) or BNP (in the FHS). Participants with NT-proBNP or BNP levels below the limit of detection were assigned the detection limit value (n=289 in MESA, n=844 in the FHS). Finally, we ran a model additionally adjusting for incident heart failure and myocardial infarction as time-dependent covariates to determine whether associations between blood lipids and AF incidence were mediated by incident cardiac disease. Heart failure and myocardial infarction events diagnosed on the same date as AF cases were considered interim events for this analysis. The proportional hazards assumption was assessed including interaction terms between time and the independent variable of interest and exploring log(-log) survival curves. No violations of the assumption were found. We examined interactions between lipid levels and age, sex, race or ethnicity, and obesity status including multiplicative terms in the Cox models. Results from MESA and the FHS were combined using fixed-effects meta-analysis. Between-study heterogeneity was assessed using Cochran's Q statistic and I^2.[19,20]

Four additional analyses were conducted in the MESA cohort only. First, we evaluated the impact of excluding participants taking lipid-lowering medications in the primary analysis. Specifically, for participants taking lipid-lowering medications at baseline and without missing covariates (n=860), we imputed the underlying untreated levels of total cholesterol based on their observed values under treatment and the observed changes in lipid levels associated with treatment among other MESA cohort members who started lipid-lowering therapy during cohort follow-up, as described previously.[21] In a second sensitivity analysis in MESA, we determined the impact of AF case-ascertainment method on the estimates of association, repeating the analysis and excluding events identified only through Medicare claims. Because Medicare claims were available only from participants aged 65 years or older enrolled in fee-for-service Medicare, differential outcome misclassification could occur if lipid levels were associated with Medicare enrollment. Third, we conducted an analysis additionally adjusting for health insurance status (no insurance, private insurance, Medicare, Medicaid, military or US Department of Veterans Affairs sponsored, other type of health insurance) and annual income (<$20 000, $20 000 to <$50 000, $50 000 or more) to account for the impact of access to health care in the ascertainment of AF. Finally, because NT-proBNP was missing for a sizable proportion of MESA participants, we used multiple imputation to create 30 data sets including the

following variables: age, sex, race or ethnicity, study site, education, height, body mass index, smoking status, alcohol drinking, physical activity, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, C-reactive protein, end point status, and the Nelson–Aalen estimate of the baseline cumulative hazard, as recommended elsewhere.[22]

Results

In MESA, over a mean follow-up of 8.2 years (median 8.7 years), 221 incident AF cases were identified among 4534 eligible participants, whereas in the FHS, 259 incident AF cases occurred in 2608 participants during a mean follow-up of 11.9 years (median 12.7 years). Table 1 provides baseline characteristics by cohort. With the exception of the racial and ethnic distribution, the 2 cohorts had similar cardiovascular risk profiles.

The associations between blood lipid levels and AF incidence are presented in Table 2. Because no evidence of between-cohort heterogeneity existed, combined results are presented. Cohort-specific results are provided in supplementary Table S1. In age, sex, and race-adjusted models, total cholesterol was not associated with AF risk, whereas high levels of HDLc and LDLc and low levels of triglycerides were associated with lower risk of AF. After adjustment for potential confounders, total cholesterol and LDLc were not associated with lower risk of AF. In contrast, higher HDLc remained associated with lower AF risk (HR 0.64, 95% CI 0.48 to 0.87 comparing HDLc levels ≥60 mg/dL and <40 mg/dL), whereas risk of AF was elevated in those with higher triglycerides (HR 1.60, 95% CI 1.25 to 2.05 comparing triglyceride levels ≥200 mg/dL and <150 mg/dL) (Table 2, Model 2). The associations of HDLc and triglycerides with AF were slightly attenuated after adjustment for incident heart failure and myocardial infarction as time-dependent

Table 1. Baseline Characteristics by Cohort: MESA, 2000–2002, and the FHS, 1995–1998

	MESA	FHS
n	4534	2608
Age, y	62 (10)	58 (10)
Female, %	52	56
Race or ethnicity, %		
White	39	100
Black	24	0
Hispanic	24	0
Chinese American	14	0
Completed high school, %	82	95
Body mass index, kg/m^2	28 (6)	28 (5)
Height, cm	167 (10)	168 (9)
Current smoker, %	13	15
Current alcohol drinker, %	56	62
Systolic BP, mm Hg	126 (21)	127 (18)
Diastolic BP, mm Hg	72 (10)	75 (9)
Hypertension medications, %	32	23
Diabetes, %	11	8
C-reactive protein, mg/L	3.8 (5.9)	4.4 (10.0)
NT-proBNP, pg/mL	99 (200)	—
BNP, pg/mL	—	14 (18)
Total cholesterol, mg/dL	196 (35)	207 (37)
HDLc, mg/dL	51 (15)	53 (16)
LDLc, mg/dL	120 (31)	129 (34)
Triglycerides, mg/dL	126 (66)	126 (65)

Values correspond to mean (SD) or percentage. BNP indicates B-type natriuretic peptide; BP, blood pressure; FHS, Framingham Heart Study; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; NT-proBNP, N-terminal prohormone of BNP.

Table 2. Hazard Ratios and 95% CIs of AF by Categories of Blood Lipids

Total Cholesterol, mg/dL	<200		200 to 239	≥240
AF events, no.	240		172	68
Person-years	34 004		23 980	9410
Incidence rate*	7.1		7.2	7.2
Model 1[†]	1 (Ref)		0.98 (0.81 to 1.20)	0.94 (0.71 to 1.24)
Model 2[‡]	1 (Ref)		1.14 (0.93 to 1.40)	1.20 (0.90 to 1.60)
Model 3[§]	1 (Ref)		1.13 (0.92 to 1.39)	1.23 (0.92 to 1.64)
HDLc, mg/dL	<40		40 to 59	≥60
AF events, no.	139		237	104
Person-years	14 261		34 439	18 693
Incidence rate*	9.7		6.9	5.6
Model 1[†]	1 (Ref)		0.75 (0.60 to 0.93)	0.60 (0.45 to 0.79)
Model 2[‡]	1 (Ref)		0.76 (0.59 to 0.98)	0.64 (0.48 to 0.87)
Model 3[§]	1 (Ref)		0.80 (0.64 to 1.00)	0.66 (0.50 to 0.91)

LDLc, mg/dL	<100	100 to 129	130 to 159	≥160
AF events, no.	109	185	125	61
Person-years	15 221	24 681	18 504	8987
Incidence rate*	7.2	7.5	6.8	6.8
Model 1[†]	1 (Ref)	0.93 (0.74 to 1.18)	0.83 (0.64 to 1.07)	0.82 (0.59 to 1.13)
Model 2[‡]	1 (Ref)	0.95 (0.75 to 1.20)	0.96 (0.73 to 1.25)	1.03 (0.74 to 1.43)
Model 3[§]	1 (Ref)	0.98 (0.77 to 1.25)	0.95 (0.73 to 1.24)	1.06 (0.76 to 1.47)

Triglycerides, mg/dL	<150		150 to 199	≥200
AF events, n	316		76	88
Person-years	48 361		10 013	9019
Incidence rate*	6.5		7.6	9.8
Model 1[†]	1 (Ref)		1.11 (0.86, 1.42)	1.56 (1.23, 1.99)
Model 2[‡]	1 (Ref)		1.10 (0.86, 1.43)	1.60 (1.25, 2.05)
Model 3[§]	1 (Ref)		1.05 (0.81, 1.36)	1.54 (1.20, 1.97)

Combined results from MESA, 2000–2010, and the FHS, 1995–2010. AF indicates atrial fibrillation; BNP, B-type natriuretic peptide; FHS, Framingham Heart Study; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol MESA, Multi-Ethnic Study of Atherosclerosis; NT-proBNP, N-terminal prohormone of BNP; Ref, reference.
*Per 1000 person-years.
[†]Model 1: Cox proportional hazards model adjusted for age, sex, and race or ethnicity (only in MESA).
[‡]Model 2: As Model 1, additionally adjusted for study site (only in MESA), education, height, body mass index, smoking status, alcohol drinking, physical activity, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, C-reactive protein, and $\log_e$(NT-proBNP) (in MESA) or $\log_e$(BNP) (in the FHS).
[§]Model 3: As Model 2, additionally adjusted for incident myocardial infarction and incident heart failure as time-dependent covariates.

covariates (Table 2, Model 3). Similar associations were observed using blood lipids as continuous instead of categorical variables (Figure 2) and when only MESA white participants were combined with FHS participants (Table S2). Cohort-specific Kaplan–Meier survival curves are presented in Figure 3 (HDLc, triglycerides) and Figure S1 (total cholesterol, LDLc). Age, sex, race or ethnicity, and obesity status did not significantly modify the association of lipid levels with AF incidence (Table 3; Tables S2 to S5).

In a sensitivity analysis in the MESA cohort, we excluded 54 AF events identified from Medicare claims only to avoid differential outcome misclassification. Results did not appreciably change (Table S6). In addition, we conducted an analysis including participants using lipid-lowering medications at baseline, implementing multiple imputation to adjust their total cholesterol levels based on medication type and dosage. This analysis included 5394 eligible participants and 272 AF events. The multivariable-adjusted HR of AF associated with a 1SD difference in total cholesterol was 1.06 (95% CI 0.92 to 1.21), very similar to the model not including lipid-lowering medication users (Table 4). Finally, associations remained unchanged after additional adjustment for health
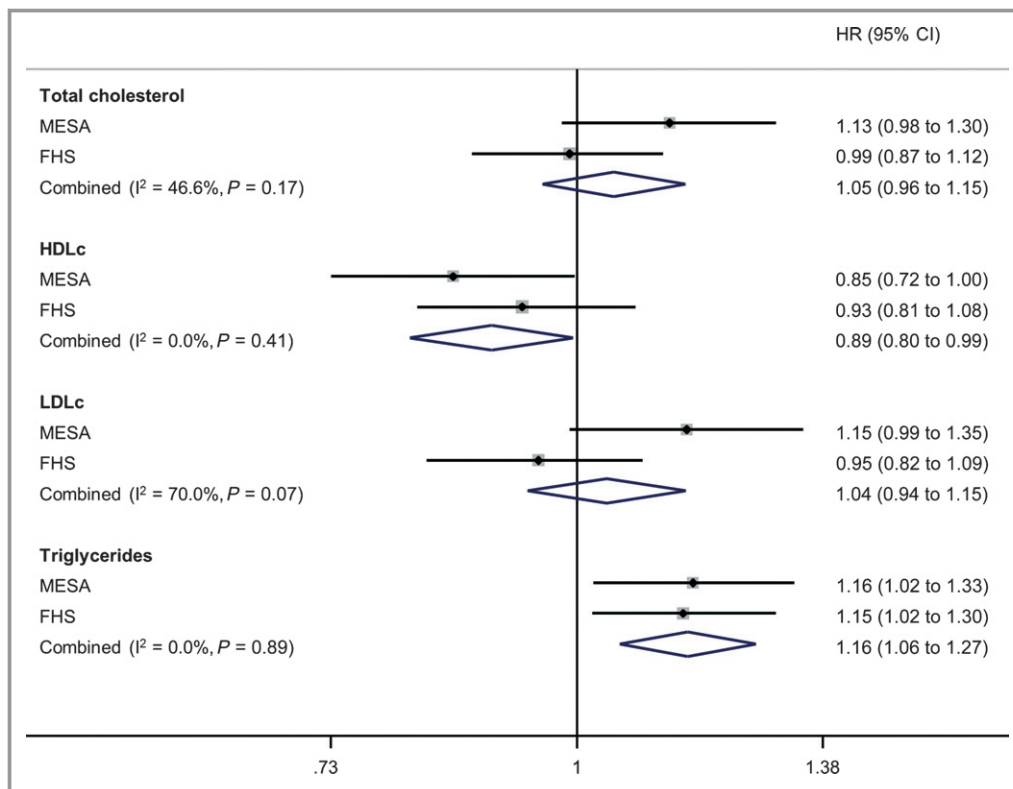
Figure 2. Association of blood lipids with AF. Cohort-specific and combined HRs and 95% CIs associated with a 1SD increment in blood lipids (total cholesterol: 35 mg/dL; HDLc: 15 mg/dL; LDLc: 35 mg/dL; triglycerides: 65 mg/dL). *P* values are from heterogeneity tests. Cohort-specific estimates are combined using fixed-effects meta-analysis. Results from Cox proportional hazards models adjusted for age, sex, race or ethnicity (only in MESA), study site (only in MESA), education, height, body mass index, smoking status, alcohol drinking, physical activity, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, C-reactive protein, and log_e(N-terminal prohormone of B-type natriuretic peptide) (in MESA) or log_e(B-type natriuretic peptide) (in the FHS). FHS indicates Framingham Heart Study; HDLc, high-density lipoprotein cholesterol; HR, hazard ratio; LDLc, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis.

insurance status and income at baseline (Table S7) or after imputing log_e(NT-proBNP values) using multiple imputation (Table S8).

Discussion

In 2 large community-based cohorts, high triglycerides and low HDLc were associated with a higher risk of AF after accounting for relevant clinical risk factors and biomarkers. In contrast to previously published studies, LDLc and total cholesterol were not associated with AF incidence. Results were similar in both MESA and FHS data and robust in several sensitivity analyses. The observed associations were consistent across age, sex, and race and ethnicity groups.

The association between blood lipids and AF risk has been studied in several previous publications, which have offered inconsistent results. Similar to our observations, a post hoc analysis of the Antihypertensive and Lipid Lowering Treatment

to Prevent Heart Attack (ALLHAT) trial found that lower levels of baseline HDLc were associated with an increased risk of AF.[23] Associations with total cholesterol, LDLc, or triglycerides were not reported. In contrast, a previous publication from the ARIC study found high LDLc and total cholesterol to be associated with a lower risk of AF, whereas HDLc and triglycerides were not related to AF risk.[5] In 2 Japanese cohorts, high total cholesterol, HDLc, and LDLc were associated with lower AF risk, but triglycerides were not associated with AF.[4,7] Similar inverse association between LDLc and AF risk was recently reported in the Women's Health Study.[8] The Cardiovascular Health Study also reported lower risk of AF among participants with higher total cholesterol.[6] Lack of adjustment for important confounders may partly explain inconsistencies between studies. In the present analysis, high LDLc was associated with lower risk of AF in minimally adjusted models but not after multivariable adjustment. Adjustment for levels of natriuretic peptides (NT-proBNP or
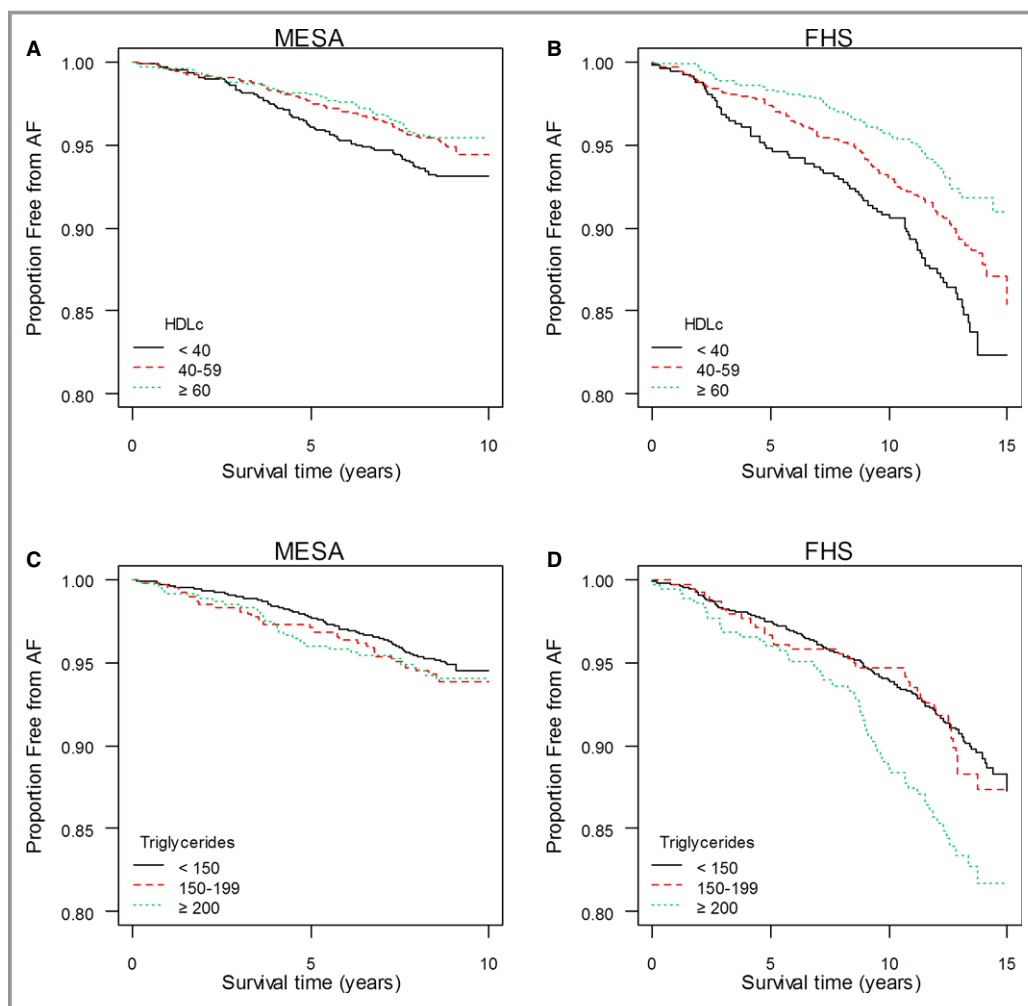
Figure 3. Kaplan–Meier curves presenting AF-free survival probabilities by categories of HDLc and triglycerides in the MESA and FHS studies. A, HDLc in MESA. B, HDLc in FHS. C, triglycerides in MESA. D, triglycerides in FHS. AF indicates atrial fibrillation; FHS, Framingham Heart Study; HDLc, high-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis.

Table 3. Hazard Ratios and 95% CIs of AF Per 1SD* Increment in Blood Lipids by Sex: MESA, 2000–2010, and the FHS, 1995–2010

	MESA			FHS		
	Women	Men	P for Interaction	Women	Men	P for Interaction
AF events, no.	81	140		119	140	
Person-years	19 007	17 389		17 587	13 411	
Total cholesterol†	1.09 (0.86 to 1.39)	1.15 (0.96 to 1.38)	0.42	0.99 (0.83 to 1.19)	0.97 (0.81 to 1.16)	0.43
HDLc†	0.81 (0.63 to 1.04)	0.88 (0.71 to 1.10)	0.69	0.95 (0.79 to 1.16)	0.93 (0.75 to 1.15)	0.69
LDLc†	1.24 (0.96 to 1.60)	1.11 (0.91 to 1.36)	0.94	0.94 (0.78 to 1.15)	0.93 (0.88 to 1.23)	0.56
Triglycerides†	1.00 (0.77 to 1.29)	1.23 (1.05 to 1.44)	0.17	1.20 (0.99 to 1.45)	1.11 (0.95 to 1.31)	0.45

AF indicates atrial fibrillation; FHS, Framingham Heart Study; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis.

*SD values: total cholesterol: 35 mg/dL; HDLc: 15 mg/dL; LDLc: 35 mg/dL; triglycerides: 65 mg/dL.

†Cox proportional hazards model adjusted for age, race or ethnicity (only in MESA), study site (only in MESA), education, height, body mass index, smoking status, alcohol drinking, physical activity, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, C-reactive protein, and $\log_e$(N-terminal prohormone of B-type natriuretic peptide) (in MESA) or $\log_e$(B-type natriuretic peptide) (in the FHS).

Table 4. Hazard Ratios (95% CIs) of Atrial Fibrillation by Total Cholesterol Categories, Including Primary Study Sample and Imputed Cholesterol for 860 Participants Using Lipid-Lowering Medication at Baseline and Without Missing Covariates: Multi-Ethnic Study of Atherosclerosis, 2000–2010

	Total Cholesterol Categories, mg/dL			Continuous	
	<200	200 to 239	≥240	1SD Difference*	P Value
AF events, no.	169	81	22	272	
Person-years	25 567	13 728	4049	43 344	
Incidence rate[†]	6.6	5.9	5.4	6.3	
Model 1[‡]	1 (Ref.)	1.01 (0.76, 1.34)	0.92 (0.62, 1.38)	0.97 (0.85, 1.10)	0.60
Model 2[§]	1 (Ref.)	1.16 (0.86, 1.56)	1.15 (0.76, 1.73)	1.06 (0.92, 1.21)	0.44

AF indicates atrial fibrillation.
*1SD for total cholesterol: 35 mg/dL.
[†]Per 1000 person-years.
[‡]Model 1: Cox proportional hazards model adjusted for age, sex, and race or ethnicity.
[§]Model 2: Cox proportional hazards model adjusted for age, sex, race or ethnicity, study site, education, height, body mass index, smoking status, alcohol drinking, physical activity, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, C-reactive protein, and $\log_e$(N-terminal prohormone of B-type natriuretic peptide).

BNP) may be particularly important because an inverse association between LDLc levels and NT-proBNP has been described previously,[24] and natriuretic peptides are strong predictors of AF risk.[25–27] Consequently, these biomarkers might have confounded associations in the previous studies. Other reasons for inconsistencies between studies could be differences in the age distribution and racial composition of the populations; prevalence of effect modifiers and confounders, including obesity and other cardiometabolic risk factors; AF ascertainment methods; and length of follow-up.

The observed inverse association between HDLc and AF risk observed in the MESA and FHS cohorts may be explained by different mechanisms. High HDLc may reduce risk of AF indirectly through the prevention of coronary heart disease and heart failure,[1,28] which are established risk factors for AF.[29] In our analyses, we observed a small attenuation of the association between HDLc and AF after adjustment for interim cardiovascular events, partly supporting this hypothesis. Besides, HDLc has anti-inflammatory and antioxidant properties,[30] potentially inhibiting 2 pathophysiological pathways in AF.[31,32] Even though we adjusted for numerous potential confounders, residual confounding by lifestyles such as physical activity, which is associated with higher HDLc and possibly lower AF risk, could also explain the observed results. The association of higher triglycerides with an increased risk of AF may also be explained by increased risk of overall CVD. As we observed for HDLc, the association of triglycerides with AF incidence was partly attenuated after adjustment for incident CVD. In addition, higher triglycerides are a component of the metabolic syndrome, which has been associated with the incidence of AF in community-based cohorts.[33,34] Finally, both high triglycerides and low HDLc are associated with the presence of microvascular disease,[35]

although the role played by microvascular disease in AF pathogenesis is not known.

For the present analysis, we excluded participants using lipid-lowering medications to avoid the potential confounding effect that these drugs, particularly statins, could have. In small clinical trials, statins have been associated with reduced risk of AF, although large trials have failed to support this effect.[36] Exclusion of lipid-lowering medication users, however, could have eliminated those with the highest underlying levels of LDLc and total cholesterol, obscuring a potential association with AF incidence. Nonetheless, in a sensitivity analysis in the MESA cohort, we showed that excluding users of lipid-lowering medication at baseline did not have a meaningful impact on the association of total cholesterol with AF incidence.

Our results add to the growing literature on blood lipids and AF. This literature, however, is inconsistent, and the exact role of blood lipids in the development of AF, if any, remains to be determined. Future studies using Mendelian randomization (ie, using gene variants known to affect blood lipid levels as an instrumental variable) may shed new light on the causal relationships between blood lipids and AF, as they have done for coronary heart disease.[37] Moreover, whether lipid-lowering drugs could be used for the primary prevention of AF is uncertain.[38]

Some limitations of our study include the between-cohort heterogeneity in AF event ascertainment and the measurement of some covariates (eg, natriuretic peptides) and our inability to identify participants with asymptomatic paroxysmal AF. In addition, most AF cases in the MESA cohort were identified through hospital discharge codes. Consequently, differential bias with regard to the outcome ascertainment may have occurred if participants who were more likely to be hospitalized for dyslipidemia-related conditions (eg, coronary

heart disease) were also more likely to be diagnosed with AF. Nonetheless, the consistent results observed in both cohorts, the presence of associations after adjustment for incident CVD during the follow-up, and the robustness of our results with additional adjustment for health insurance status and extensive measures of socioeconomic status suggest that the impact of differences and shortcomings in end point ascertainment was probably limited. Despite the extensive adjustment for risk factors and biomarkers of AF, residual confounding may have affected the results. Finally, exclusion of participants due to missing data may limit the generalizability of our findings and potentially bias the results. Nonetheless, this study has major strengths, including the combination of 2 different cohorts; use of a racially diverse sample; the detailed assessment of cardiovascular risk factors; and, in the FHS, the use of physician-adjudicated AF events.

In conclusion, we found in 2 distinct and well-characterized community-based cohorts that lower blood levels of HDLc and higher levels of triglycerides were associated with an increased risk of AF. No associations were observed between total cholesterol or LDLc and AF risk. Future research should address the clinical significance of these associations, explore underlying mechanisms, and assess the impact of modification of lipid levels in the development of AF.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Hazard ratios (HR) and 95% confidence intervals (CI) of atrial fibrillation by categories of blood lipids, cohort-specific results. MESA, 2000-2010, and FHS, 1995-2010

	MESA				FHS			
	Total cholesterol (mg/dL)							
	<200	200-239	≥240		<200	200-239	≥240	
AF events, n	127	74	20		113	98	48	
Person-years	20524	12174	3698		13480	11806	5712	
Model 1†	1 (Ref.)	1.10 (0.82, 1.48)	1.00 (0.62, 1.61)		1 (Ref.)	0.89 (0.68, 1.17)	0.91 (0.65, 1.29)	
Model 2‡	1 (Ref.)	1.37 (1.01, 1.85)	1.28 (0.78, 2.08)		1 (Ref.)	0.98 (0.75, 1.30)	1.16 (0.82, 1.66)	
Model 3	1 (Ref.)	1.31 (0.96, 1.78)	1.32 (0.81, 2.17)		1 (Ref.)	1.00 (0.75, 1.32)	1.18 (0.83, 1.69)	
	HDLc (mg/dL)							
	<40	40-59	≥60		<40	40-59	≥60	
AF events, n	62	112	47		77	125	57	
Person-years	7776	19657	8963		6485	14782	9730	
Model 1	1 (Ref.)	0.74 (0.54, 1.02)	0.67 (0.44, 1.01)		1 (Ref.)	0.75 (0.56, 1.01)	0.55 (0.38, 0.81)	
Model 2	1 (Ref.)	0.75 (0.54, 1.04)	0.60 (0.39, 0.93)		1 (Ref.)	0.78 (0.53, 1.14)	0.68 (0.45, 1.01)	
Model 3	1 (Ref.)	0.80 (0.57, 1.11)	0.67 (0.43, 1.05)		1 (Ref.)	0.80 (0.59, 1.08)	0.68 (0.45, 1.02)	
	LDLc (mg/dL)							
	<100	100-129	130-159	≥160	<100	100-129	130-159	≥160
AF events, n	58	92	50	21	51	93	75	40
Person-years	9250	14251	9208	3687	5971	10430	9296	5300
Model 1	1 (Ref.)	1.01 (0.72, 1.40)	0.92 (0.63, 1.34)	1.02 (0.62, 1.69)	1 (Ref.)	0.86 (0.61, 1.21)	0.75 (0.52, 1.06)	0.70 (0.46, 1.06)
Model 2	1 (Ref.)	1.07 (0.77, 1.50)	1.21 (0.82, 1.79)	1.39 (0.83, 2.33)	1 (Ref.)	0.83 (0.59, 1.17)	0.78 (0.54, 1.12)	0.84 (0.55, 1.28)
Model 3	1 (Ref.)	1.15 (0.82, 1.62)	1.20 (0.81, 1.78)	1.47 (0.87, 2.47)	1 (Ref.)	0.83 (0.59, 1.18)	0.78 (0.55, 1.13)	0.85 (0.56, 1.31)
	Triglycerides (mg/dL)							
	<150	150-199	≥200		<150	150-199	≥200	
AF events, n	149	38	34		167	38	54	
Person-years	26068	5421	4907		22293	4592	4112	
Model 1	1 (Ref.)	1.28 (0.89, 1.83)	1.43 (0.98, 2.08)		1 (Ref.)	0.96 (0.67, 1.36)	1.66 (1.22, 2.26)	
Model 2	1 (Ref.)	1.33 (0.92, 1.91)	1.58 (1.06, 2.34)		1 (Ref.)	0.92 (0.64, 1.32)	1.61 (1.17, 2.22)	
Model 3	1 (Ref.)	1.17 (0.80, 1.70)	1.46 (0.98, 2.18)		1 (Ref.)	0.95 (0.66, 1.36)	1.59 (1.16, 2.19)	

Model 1: Cox proportional hazards model adjusted for age, sex, and race/ethnicity (only in MESA)

Model 2: As Model 1, additionally adjusted for study site (only in MESA), education, height, body mass index, smoking status, alcohol drinking, physical activity, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, C-reactive protein, and log(NT-proBNP) (MESA) or log(BNP) (FHS).

Model 3: As Model 2, additionally adjusted for incident myocardial infarction and incident heart failure as time-dependent covariates

Table S2. Hazard ratios and 95% confidence intervals of atrial fibrillation per 1-standard deviation increment in blood lipids (total cholesterol: 35 mg/dL, HDLc: 15 mg/dL, LDLc: 35 mg/dL, triglycerides: 65 mg/dL) by race/ethnicity, MESA 2000-2010

	MESA					Combined MESA whites + FHS
	White	Black	Hispanic	Chinese-American	P for interaction	
AF events, n	125	43	41	12		
Person-years	14251	8739	8319	5088		
Total cholesterol HR (95%CI) [a]	0.99 (0.81, 1.20)	1.21 (0.88, 1.68)	1.19 (0.89, 1.59)	1.33 (0.65, 2.70)	0.73	0.99 (0.89, 1.10)
HDLc HR (95%CI) [a]	0.84 (0.68, 1.04)	0.82 (0.58, 1.16)	0.79 (0.49, 1.27)	0.79 (0.34, 1.80)	0.74	0.90 (0.80, 1.01)
LDLc HR (95%CI) [a]	1.05 (0.85, 1.31)	1.21 (0.85, 1.71)	1.19 (0.86, 1.65)	1.39 (0.62, 3.15)	0.88	0.98 (0.87, 1.10)
Triglycerides HR (95%CI) [a]	1.04 (0.86, 1.26)	1.43 (1.03, 1.98)	1.23 (0.92, 1.63)	1.23 (0.67, 2.28)	0.27	1.12 (1.01, 1.24)

[a] Cox proportional hazards model adjusted for age, sex, education, height, body mass index, smoking status, alcohol drinking, physical activity, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, C-reactive protein, and log(NT-proBNP)

Table S3. Hazard ratios and 95% confidence intervals of atrial fibrillation by categories of HDLc by sex, MESA 2000-2010 and FHS 1995-2010.

	MESA			FHS		
Women	<40	40-59	≥60	<40	40-59	≥60
AF events, n	9	43	29	15	60	44
Person-years	1779	10133	7094	1506	7899	8181
HR (95%CI) [a]	1 (ref.)	0.74 (0.34, 1.60)	0.54 (0.23, 1.23)	1 (ref.)	0.73 (0.40, 1.31)	0.62 (0.33, 1.17)
Men						
AF events, n	53	69	18	62	65	13
Person-years	5997	9523	1868	4977	580	1549
HR (95%CI) [a]	1 (ref.)	0.76 (0.52, 1.12)	0.67 (0.37, 1.19)	1 (ref.)	0.85 (0.60, 1.22)	0.75 (0.40, 1.40)

[a] Cox proportional hazards model adjusted for age, race/ethnicity (only in MESA), study site (only in MESA), education, height, body mass index, smoking status, alcohol drinking, physical activity, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, C-reactive protein, and log(NT-proBNP) (in MESA) or log(BNP) in FHS.

Table S4. Hazard ratios and 95% confidence intervals of atrial fibrillation per 1-standard deviation increment in blood lipids (total cholesterol: 35 mg/dL, HDLc: 15 mg/dL, LDLc: 35 mg/dL, triglycerides: 65 mg/dL) by age, MESA 2000-2010 and FHS 1995-2010.

| | MESA | | | FHS | | |
	<65	≥65	P for interaction	<65	≥65	P for interaction
AF events, n	41	180		124	135	
Person-years	22110	14286		23897	7100	
Total cholesterol HR (95%CI) [a]	1.23 (0.95, 1.60)	1.08 (0.92, 1.27)	0.31	1.01 (0.83, 1.21)	0.95 (0.80, 1.14)	0.30
HDLc HR (95%CI) [a, b]	1.12 (0.79, 1.60)	0.80 (0.66, 0.95)	0.04	1.03 (0.83, 1.27)	0.89 (0.72, 1.09)	0.48
LDLc HR (95%CI) [a]	1.18 (0.89, 1.58)	1.14 (0.95, 1.35)	0.81	0.92 (0.75, 1.12)	0.95 (0.78, 1.15)	0.35
Triglycerides HR (95%CI) [a]	1.16 (0.85, 1.60)	1.14 (0.99, 1.32)	0.85	1.17 (1.00, 1.38)	1.11 (0.92, 1.33)	0.22

[a] Cox proportional hazards model adjusted for sex, race/ethnicity (only in MESA), study site (only in MESA), education, height, body mass index, smoking status, alcohol drinking, physical activity, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, C-reactive protein, and log(NT-proBNP) (in MESA) or log(BNP) in FHS.

[b] Combined results from MESA and FHS were 1.05 (95%CI 0.88, 1.26) for those <65 years old and 0.84 (95%CI 0.73, 0.96) for those 65 and older (p for interaction = 0.06)

Table S5. Hazard ratios and 95% confidence intervals of atrial fibrillation per 1-standard deviation increment in blood lipids (total cholesterol: 35 mg/dL, HDLc: 15 mg/dL, LDLc: 35 mg/dL, triglycerides: 65 mg/dL) by obesity status, MESA 2000-2010 and FHS 1995-2010.

| | MESA | | | FHS | | |
	Non-obese (BMI<30)	Obese (BMI≥30)	P for interaction	Non-obese (BMI<30)	Obese (BMI≥30)	P for interaction
AF events, n	151	70		171	88	
Person-years	25415	10981		23073	7925	
Total cholesterol						
HR (95%CI) [a]	1.17 (0.99, 1.38)	1.02 (0.78, 1.35)	0.89	1.00 (0.86, 1.16)	0.99 (0.77, 1.24)	0.91
HDLc						
HR (95%CI) [a]	0.92 (0.77, 1.10)	0.61 (0.42, 0.87)	0.43	0.96 (0.81, 1.14)	0.87 (0.66, 1.16)	0.92
LDLc						
HR (95%CI) [a]	1.17 (0.97, 1.40)	1.15 (0.85, 1.56)	0.93	0.99 (0.84, 1.17)	0.85 (0.65, 1.11)	0.84
Triglycerides						
HR (95%CI) [a]	1.17 (0.99, 1.37)	1.15 (0.92, 1.45)	0.82	1.07 (0.91, 1.26)	1.33 (1.10, 1.60)	0.35

[a] Cox proportional hazards model adjusted for age, sex, race/ethnicity (only in MESA), study site (only in MESA), education, height, smoking status, alcohol drinking, physical activity, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, C-reactive protein, and log(NT-proBNP) (in MESA) or log(BNP) in FHS.

Table S6. Hazard ratios (HR) and 95% confidence intervals (CI) of atrial fibrillation by categories of blood lipids excluding AF cases identified from Medicare claims. MESA, 2000-2010

	Total cholesterol (mg/dL)			
	<200	200-239	≥240	
AF events, n	99	54	14	
Person-years	19645	11689	3538	
Model 1†	1 (Ref.)	0.99 (0.70, 1.38)	0.84 (0.48, 1.49)	
Model 2‡	1 (Ref.)	1.22 (0.86, 1.73)	1.16 (0.65, 2.08)	
	HDLc (mg/dL)			
	<40	40-59	≥60	
AF events, n	53	81	33	
Person-years	7462	18796	8615	
Model 1	1 (Ref.)	0.62 (0.43, 0.89)	0.51 (0.31, 0.82)	
Model 2	1 (Ref.)	0.62 (0.43, 0.90)	0.45 (0.27, 0.75)	
	LDLc (mg/dL)			
	<100	100-129	130-159	≥160
AF events, n	49	63	40	15
Person-years	8854	13662	8808	3548
Model 1	1 (Ref.)	0.80 (0.55, 1.16)	0.85 (0.56, 1.29)	0.83 (0.46, 1.48)
Model 2	1 (Ref.)	0.84 (0.57, 1.22)	1.14 (0.74, 1.75)	1.17 (0.65, 2.13)
	Triglycerides (mg/dL)			
	<150	150-199	≥200	
AF events, n	108	32	27	
Person-years	25009	5183	4681	
Model 1	1 (Ref.)	1.47 (0.99, 2.19)	1.51 (0.98, 2.31)	
Model 2	1 (Ref.)	1.53 (1.02, 2.28)	1.66 (1.06, 2.60)	

Model 1: Cox proportional hazards model adjusted for age, sex, and race/ethnicity

Model 2: As Model 1, additionally adjusted for study site, education, height, body mass index, smoking status, alcohol drinking, physical activity, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, C-reactive protein, and log(NT-proBNP).

Table S7. Hazard ratios (HR) and 95% confidence intervals (CI) of atrial fibrillation by categories of blood lipids adjusting for health insurance status and income at baseline (N = 4408; 213 AF cases). MESA, 2000-2010

	Main model	Additionally adjusted for health insurance status and income
Total cholesterol	1.13 (0.98, 1.30)	1.13 (0.98, 1.31)
HDLc	0.85 (0.71, 1.00)	0.82 (0.70, 0.97)
LDLc	1.15 (0.99, 1.35)	1.16 (0.99, 1.36)
Triglycerides	1.16 (1.02, 1.33)	1.17 (1.03, 1.34)

Main model: Cox proportional hazards model adjusted for age, sex, race/ethnicity, study site, education, height, body mass index, smoking status, alcohol drinking, physical activity, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, C-reactive protein, and log(NT-proBNP).

Table S8. Hazard ratios (HR) and 95% confidence intervals (CI) of atrial fibrillation by categories of blood lipids with multiple imputation of log(NT-proBNP) concentrations. MESA, 2000-2010

	Main model*	Multiple imputation	P-value**
Total cholesterol	1.13 (0.98, 1.30)	1.08 (0.94, 1.23)	0.65
HDLc	0.85 (0.71, 1.00)	0.88 (0.76, 1.03)	0.77
LDLc	1.15 (0.99, 1.35)	1.09 (0.94, 1.26)	0.62
Triglycerides	1.16 (1.02, 1.33)	1.08 (0.99, 1.19)	0.39

*Main model: Cox proportional hazards model adjusted for age, sex, race/ethnicity, study site, education, height, body mass index, smoking status, alcohol drinking, physical activity, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, C-reactive protein, and log(NT-proBNP).

**P-value for the comparison of hazard ratios in the main analysis and in the analysis imputing log(NT-proBNP)

Figure S1. Kaplan-Meier curves presenting AF-free survival probabilities by categories of total cholesterol and LDLc in the MESA and FHS studies. (a) Total cholesterol in MESA; (b) Total cholesterol in FHS; (c) LDLc in MESA; (d) LDLc in FHS
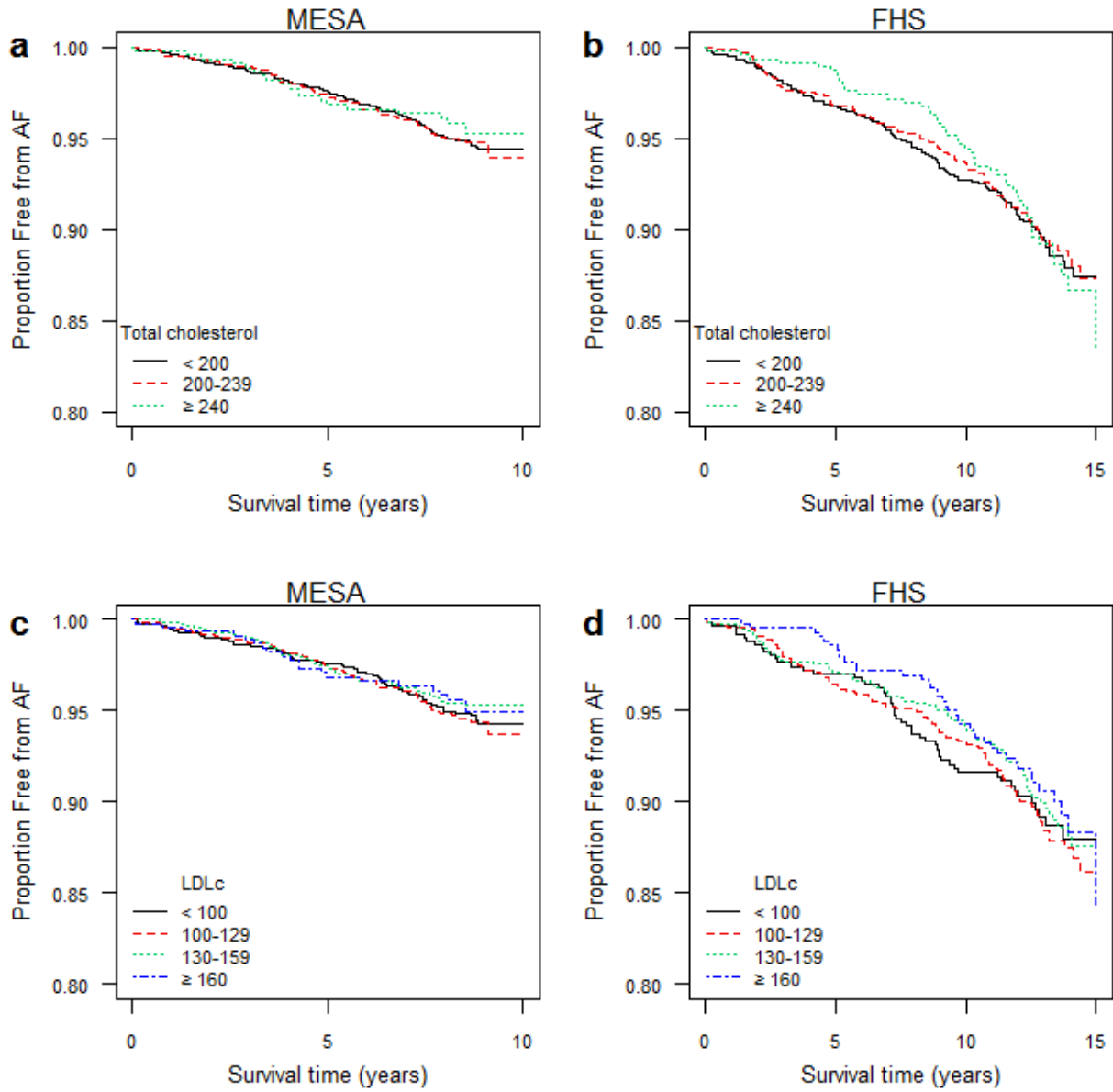
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