ORIGINAL RESEARCH

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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.
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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

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Accompanying Tables S1 through S8 and Figure S1 are available at http://jaha.ahajournals.org/content/3/5/ e001211/suppl/DC1

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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×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

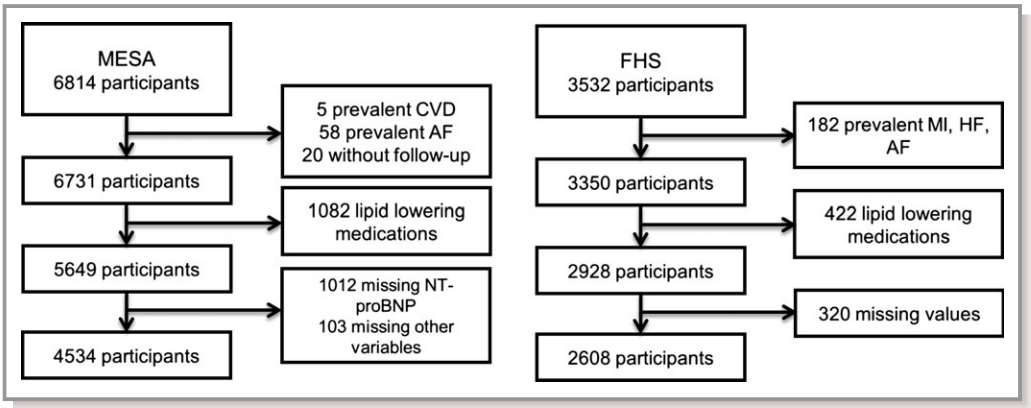

Figure 1. Flowchart of study participants: MESA, 2000–2002, and the FHS, 1995–1998. AF indicates atrial fibrillation; CVD, cardiovascular disease; FHS, Framingham Heart Study; HF, heart failure; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; NT-proBNP, N-terminal prohormone of 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

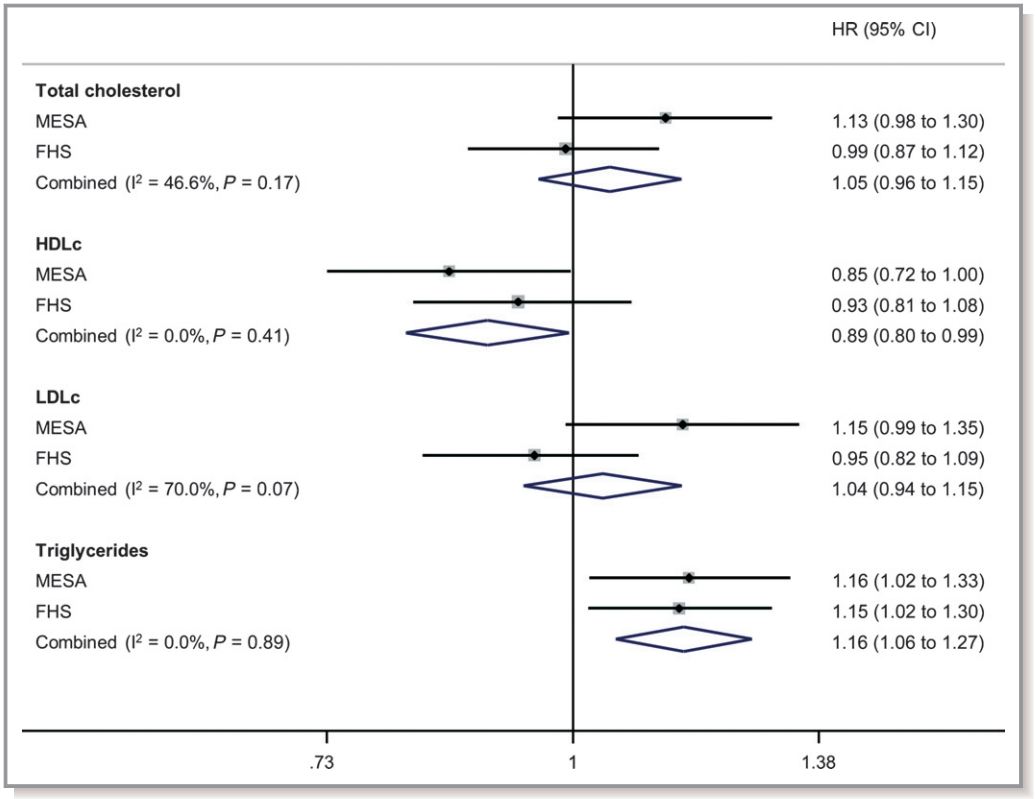

Figure 2. Association of blood lipids with AF. Cohort-specific and combined HRs and 95% CIs associated with a 1SD increment in blood lipids (total cholesterol: 35 mg/dL; HDLc: 15 mg/dL; LDLc: 35 mg/dL; triglycerides: 65 mg/dL). *P* values are from heterogeneity tests. Cohort-specific estimates are combined 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

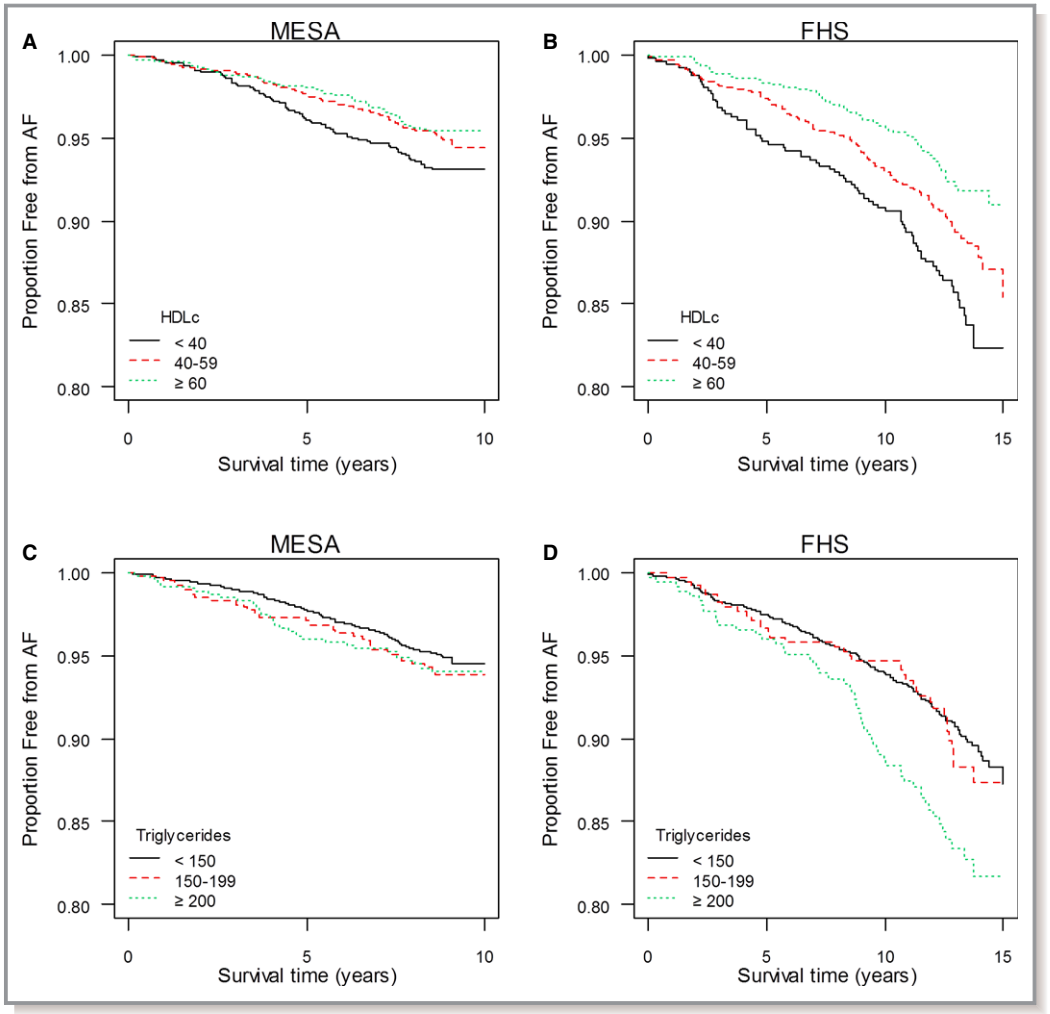

Figure 3. Kaplan–Meier curves presenting AF-free survival probabilities by categories of HDLc and triglycerides in the MESA and FHS studies. A, HDLc in MESA. B, HDLc in FHS. C, triglycerides in MESA. D, triglycerides in FHS. AF indicates atrial fibrillation; FHS, Framingham Heart Study; HDLc, high-density 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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References

1. Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302:1993–2000.
2. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA*. 1999;282:2340–2346.
3. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Rooij FJ, Lip GY, Witteman JC. Subclinical atherosclerosis and risk of atrial fibrillation: the Rotterdam Study. *Arch Intern Med*. 2007;167:382–387.
4. Watanabe H, Tanabe N, Yagihara N, Watanabe T, Aizawa Y, Kodama M. Association between lipid profile and risk of atrial fibrillation. *Circ J*. 2011;75:2767–2774.
5. Lopez FL, Agarwal SK, MacLehose RF, Soliman EZ, Sharrett AR, Huxley RR, Konety S, Ballantyne CM, Alonso A. Blood lipid levels, lipid-lowering medications, and the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities Study. *Circ Arrhythm Electrophysiol*. 2012;5:155–162.
6. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg C, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96:2455–2461.
7. Iguchi Y, Kimura K, Shibazaki K, Aoki J, Kobayashi K, Sakai K, Sakamoto Y. Annual incidence of atrial fibrillation and related factors in adults. *Am J Cardiol*. 2010;106:1129–1133.
8. Mora S, Akinkuolie AO, Sandhu RK, Conen D, Albert CM. Paradoxical association of lipoprotein measures with incident atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2014;7:612–619.
9. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacobs DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol*. 2002;156:871–881.
10. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. *Prev Med*. 1975;4:518–525.
11. Holvoet P, Jenny NS, Schreiner PJ, Tracy RP, Jacobs DR. The relationship between oxidized LDL and other cardiovascular risk factors and subclinical CVD in different ethnic groups: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2007;194:245–252.
12. Ingelsson E, Massaro JM, Sutherland P, Jacques PF, Levy D, D'Agostino RB, Vasan RS, Robins SJ. Contemporary trends in dyslipidemia in the Framingham Heart Study. *Arch Intern Med*. 2009;169:279–286.
13. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
14. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994;271:840–844.
15. Irwin ML, Mayer-Davis EJ, Addy CL, Pate RR, Durstine JL, Stolarczyk LM, Ainsworth BE. Moderate-intensity physical activity and fasting insulin levels in women: the Cross-Cultural Activity Participation Study. *Diabetes Care*. 2000;23:449–454.
16. Lutsey PL, Jacobs DR Jr, Kori S, Mayer-Davis EJ, Shea S, Steffen LM, Szklo M, Tracey R. Whole grain intake and its cross-sectional association with obesity, insulin resistance, inflammation, diabetes and subclinical CVD: the MESA Study. *Br J Nutr*. 2007;98:397–405.
17. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D'Agostino RB, Vasan RS. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med*. 2006;355:2631–2639.
18. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
19. Cochran WG. The combination of estimates from different experiments. *Biometrics*. 1954;10:101–129.
20. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
21. McClelland RL, Kronmal RA, Haessler J, Blumenthal RS, Godd DC Jr. Estimation of risk factor associations when the response is influenced by medication use: an imputation approach. *Stat Med*. 2008;27:5039–5053.
22. White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med*. 2009;28:1982–1998.
23. Haywood LJ, Ford CE, Crow RS, Davis BR, Massie BM, Einhorn PT, Williard A; for the ALLHAT Collaborative Research Group. Atrial fibrillation at baseline and during follow-up in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). *J Am Coll Cardiol*. 2009;54:2023–2031.

24. Sanchez OA, Duprez DA, Bahrami H, Daniels LB, Folsom AR, Lima JA, Maisel A, Peralta CA, Jacobs DR Jr. The associations between metabolic variables and NT-proBNP are blunted at pathological ranges: the Multi-Ethnic Study of Atherosclerosis. *Metabolism*. 2014;63:475–483.
25. Patton KK, Heckbert SR, Alonso A, Bahrami H, Lima JA, Burke G, Kronmal RA. N-terminal pro-B-type natriuretic peptide as a predictor of incident atrial fibrillation in the Multi-Ethnic Study of Atherosclerosis: the effects of age, sex, and ethnicity. *Heart*. 2013;99:1832–1836.
26. Schnabel RB, Larson MG, Yamamoto JF, Sullivan LM, Pencina MJ, Meigs JB, Tofler GH, Selhub J, Jacques PF, Wolf PA, Magnani JW, Ellinor PT, Wang TJ, Levy D, Vasan RS, Benjamin EJ. Relations of biomarkers of distinct pathophysiological pathways and atrial fibrillation incidence in the community. *Circulation*. 2010;121:200–207.
27. Sinner MF, Stepas KA, Moser CB, Krijthe BP, Aspelund T, Sotoodehnia N, Fontes JD, Janssens ACJW, Kronmal RA, Magnani JW, Witteman JC, Chamberlain AM, Lubitz SA, Schnabel RB, Vasan RS, Wang TJ, Agarwal SK, McManus DD, Franco OH, Yin X, Larson MG, Burke GL, Launer LJ, Hofman A, Levy D, Gottdiener JS, Kaab S, Couper D, Harris TB, Astor BC, Ballantyne CM, Hoogeveen RC, Arai AE, Soliman EZ, Ellinor PT, Stricker BHC, Gudnason V, Heckbert SR, Pencina MJ, Benjamin EJ, Alonso A. B-type natriuretic peptide and C-reactive protein in the prediction of atrial fibrillation risk: the CHARGE-AF Consortium of community-based cohort studies. *Europace*. 2014;16:1426–1433.
28. Velagaleti RS, Massaro J, Vasan RS, Robins SJ, Kannel WB, Levy D. Relations of lipid concentrations to heart failure incidence: the Framingham Heart Study. *Circulation*. 2009;120:2345–2351.
29. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, Sinner MF, Sotoodehnia N, Fontes JoD, Janssens ACJW, Kronmal RA, Magnani JW, Witteman JC, Chamberlain AM, Lubitz SA, Schnabel RB, Agarwal SK, McManus DD, Ellinor PT, Larson MG, Burke GL, Launer LJ, Hofman A, Levy D, Gottdiener JS, Kääb S, Couper D, Harris TB, Soliman EZ, Stricker BHC, Gudnason V, Heckbert SR, Benjamin EJ. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc*. 2013;2:e000102.
30. Rye K-A, Barter PJ. Cardioprotective functions of HDLs. *J Lipid Res*. 2014;55:168–179.
31. Guo Y, Lip GYH, Apostolakis S. Inflammation in atrial fibrillation. *J Am Coll Cardiol*. 2012;60:2263–2270.
32. Yang K-C, Dudley SC. Oxidative stress and atrial fibrillation: finding a missing piece to the puzzle. *Circulation*. 2013;128:1724–1726.
33. Watanabe H, Tanabe N, Watanabe T, Darbar D, Roden DM, Sasaki S, Aizawa Y. Metabolic syndrome and risk of development of atrial fibrillation: the Niigata preventive medicine study. *Circulation*. 2008;117:1255–1260.
34. Chamberlain AM, Agarwal SK, Ambrose M, Folsom AR, Soliman EZ, Alonso A. Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J*. 2010;159:850–856.
35. Sacks FM, Hermans MP, Fioretto P, Valensi P, Davis T, Horton E, Wanner C, Al-Rubeaan K, Aronson R, Barzon I, Bishop L, Bonora E, Bunnag P, Chuang L-M, Deerochanawong C, Goldenberg R, Harshfield B, Hernández C, Herzlinger-Botein S, Itoh H, Jia W, Jiang Y-D, Kadowaki T, Laranjo N, Leiter L, Miwa T, Odawara M, Ohashi K, Ohno A, Pan C, Pan J, Pedro-Botet J, Reiner Z, Rotella CM, Simo R, Tanaka M, Tedeschi-Reiner E, Twum-Barima D, Zoppini G, Carey VJ. Association between plasma triglycerides and high-density lipoprotein cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes mellitus: a global case–control study in 13 countries. *Circulation*. 2014;129:999–1008.
36. Rahimi K, Emberson J, McGale P, Majoni W, Merhi A, Asselbergs FW, Krane V, Macfarlane PW; on behalf of the PROSPER Executive. Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials. *BMJ*. 2011;342:d1250.
37. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hólm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart AFR, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett M-S, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki M-L, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PIW, Klungel OH, Maitland-van der Zee A-H, Peters BJM, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VHM, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WMM, Boer JMA, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a Mendelian randomisation study. *Lancet*. 2012;380:572–580.
38. January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC, Cigarroa JE, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. [published online before print March 28, 2014]. *Circulation*. 2014. Available at: http://circ.ahajournals.org/content/early/2014/04/10/CIR.0000000000000041. Accessed August 28, 2014.