Relations of Liver Fat With Prevalent and Incident Atrial Fibrillation in the Framingham Heart Study

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Background—Obesity is an important risk factor for nonalcoholic fatty liver disease and atrial fibrillation (AF). Less is known about the relations between nonalcoholic fatty liver disease and AF. We sought to evaluate the association between fatty liver and prevalent and incident AF in the community.

Methods and Results—We examined Framingham Heart Study participants who underwent a study-directed computed tomography scan, had hepatic steatosis (HS) evaluated, and did not report heavy alcohol use between 2002 and 2005. We evaluated cross-sectional associations between liver fat and prevalent AF with logistic regression models. We assessed the relations between liver fat and incident AF during 12-year follow-up with Cox proportional hazards models. Of 2122 participants (53% women; mean age, 59.0±9.6 years), 20% had HS. AF prevalence (n=62) among individuals with HS was 4% compared to 3% among those without HS. There was no significant association between HS (measured as continuous or dichotomous variables) and prevalent AF in age- and sex-adjusted or multivariable-adjusted models. Incidence of AF (n=153) among participants with and without HS was 8.7 cases and 7.8 cases per 1000 person-years, respectively. In age- and sex-adjusted and multivariable-adjusted models, there were no significant associations between continuous or dichotomous measures of HS and incident AF.

Conclusions—In our community-based, longitudinal cohort study, liver fat by computed tomography scan was not significantly associated with increased prevalence or incidence of AF over 12 years of follow-up. (***J Am Heart Assoc***. 2017;6: e005227. DOI: 10.1161/JAHA.116.005227.)

Key Words: atrial fibrillation • epidemiology • liver • nonalcoholic fatty liver disease • obesity • observational studies

Nonalcoholic fatty liver disease (NAFLD), which is associated with obesity, is now the most common chronic liver disease in the United States.[1] The liver damage associated with NAFLD ranges from hepatic steatosis (HS) to fibrosis in the absence of excessive alcohol intake; however, the leading cause of death in patients with NAFLD is ischemic heart disease.[2–4] NAFLD is associated with an increased risk for cardiovascular disease, particularly among those with diabetes mellitus.[4] Previous studies have demonstrated that patients with NAFLD have altered cardiac function and structure, which may predispose to heart failure and atrial fibrillation (AF).[5–7] Whereas obesity is considered an important risk factor for AF,[8] less is known about whether NAFLD is associated with AF after accounting for obesity.

There are several mechanisms that could potentially link NAFLD and AF beyond shared risk factors. First, NAFLD may contribute to increased systemic inflammation,[9] which may trigger AF.[10,11] Second, participants with NAFLD may have

left ventricular diastolic dysfunction,[5–7] which also could predispose to AF.[12] Individuals with NAFLD have an increased risk of ischemic heart disease,[4] which is an established risk factor for AF. Additionally, intermittent hypoxia from sleep apnea is associated with an increased severity of NAFLD[13] and with increased atrial arrhythmogenicity and AF.[14] Finally, NAFLD is associated with autonomic dysfunction[15,16] that may impact cardiac remodeling and play an important role in both initiating and maintaining AF.[17]

Only a limited number of previous studies have related NAFLD, as defined on computed tomography (CT) or ultrasound, with prevalent or incident AF. The results of previous studies have been conflicting, with some studies identifying an association between elevated liver enzymes, but not imaging-defined NAFLD, with AF, whereas others reported that imaging-defined NAFLD was a predictor of AF in select cohorts.[18–22] Methods to prevent AF are incompletely understood,[23] and there are data to suggest that weight loss is associated with a reduced risk of AF.[24,25] It is not known whether methods aimed at reducing hepatic fat may impact incident AF. Though the interactions between obesity, hepatic fat, and cardiovascular disease are complex, more studies are needed to better define the relations between HS and AF. Thus, we hypothesize that HS is associated with both prevalent AF and incident AF over up to 12 years of follow-up in Framingham Heart Study (FHS) Offspring and Third Generation cohort participants, after accounting for known AF risk factors.

Methods

Study Sample

Participants were drawn from the FHS Offspring and Third Generation cohorts who underwent measurement of liver fat by abdominal multi-detector computed tomography (MDCT) scan between 2002 and 2005 as a part of a substudy (Figure 1).[26–28] Of the 3475 participants with adequate measures of liver fat on the MDCT study, we excluded participants for the following indications: 50 for missing covariates, 97 for missing serum alanine aminotransferase (ALT) or aspartate aminotransferase levels (AST), 39 for history of self-reported heavy alcohol use (defined as >14 drinks per week for women and >21 drinks per week for men),[29] and 1167 for age ≤45 years, given that the incidence of AF is low among younger adults.[30] The final sample included 2122 individuals. For the analysis of incident AF, we additionally excluded those with prevalent AF (n=62). The institutional review boards of Boston University Medical Center and Massachusetts General Hospital approved of the protocol. All participants provided written informed consent.
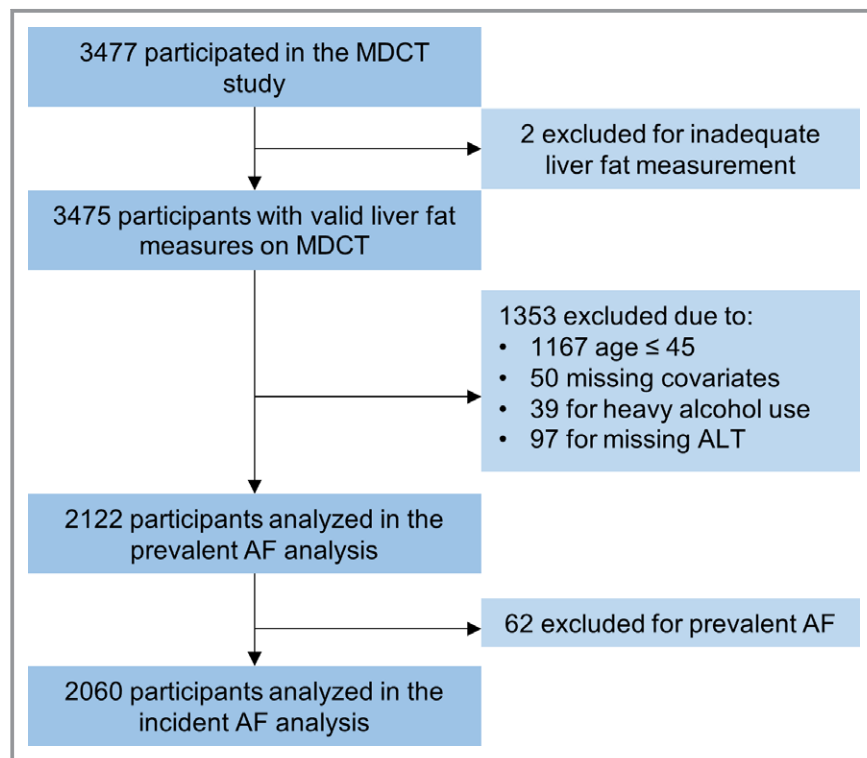
Figure 1. Study sample in the analyses of liver fat with prevalent and incident atrial fibrillation. AF indicates atrial fibrillation; ALT, alanine aminotransferase; MDCT, multidetector computed tomography.

MDCT Protocol and Measurement of Liver Fat

The MDCT substudy has been described in detail previously.[27] Briefly, participants underwent abdominal imaging (Light-Speed Ultra; General Electric, Milwaukee, WI) in the supine position with 25 contiguous 5-mm slices (120 kVp, 400 mA; gantry rotation time, 500 ms; table feed, 3:1) starting at the upper edge of S1. A radiopaque phantom (Image Analysis, Lexington, KY) was placed under each participant and visualized on each image obtained.

We obtained the mean MDCT Hounsfield units (HU) from 3 areas of the liver to determine the average liver HU. We calculated the liver phantom ratio (LPR) as the ratio between the average liver HU and the phantom HU as previously described.[31] As the LPR decreases, the amount of fat in the liver increases. We defined HS by an LPR $\leq$0.33, which was shown in our previous work to be highly sensitive and specific for detecting liver fat.[32]

Assessment of AF

All FHS participants underwent an electrocardiogram (ECG) at each FHS study visit. We also obtained ECGs and Holter monitor reports from physician offices and hospital records. Prevalent AF was defined by the presence of any episode of confirmed atrial flutter or AF on an ECG or Holter monitor report before the MDCT substudy. Biennial health history updates included a question on occurrence of AF. All prevalent and incident AF cases underwent adjudication by at least 2 FHS cardiologists.[33]

Covariates and Baseline Measurements

Covariates and baseline measurements were assessed at the seventh examination (1998–2001) for the FHS Offspring Cohort and at the first examination (2002–2005) for the FHS Third Generation Cohort. Alcohol use and smoking status were assessed on the basis of physician-administered questionnaires. Self-reported alcohol use was recorded as drinks per week or drinks per month. Participants were considered current smokers if they had smoked at least 1 cigarette per day in the year preceding the FHS examination. Plasma glucose and serum AST and ALT were obtained from fasting morning samples using an automated Roche method (Roche Cobas 501; Roche, Indianapolis, IN). Using standard protocols, trained technicians measured heart rate, blood pressure, height, and weight in all participants. Body mass index (BMI) was defined as weight (kg)/height^2 (m^2). Diabetes mellitus was defined as fasting plasma glucose $\geq$126 mg/dL or treatment with a hypoglycemic agent or insulin. Heart failure and myocardial infarction (MI) events were noted at the FHS clinical encounter with a study physician and from available medical records. All heart failure and MI events were adjudicated by a committee of 3 FHS investigators.

Statistical Analysis

For the analysis of the association between liver fat and prevalent AF, we constructed multiple logistic regression models adjusting for covariates. We evaluated liver fat as a continuous variable using the −LPR (given that LPR decreases with increasing liver fat) and as a dichotomous value with an LPR $\leq$0.33 defined as HS. The base model was adjusted for age and sex alone. The multivariable model adjusted for age and sex and known risk factors for AF,[30] including current smoking, alcohol use, systolic blood pressure, diastolic blood pressure, antihypertensive medication use, diabetes mellitus, history of heart failure, and history of MI. Because liver fat is weakly correlated with BMI (r=0.25),[32] we included a third model, which added adjustment of BMI to the multivariable model. Results are reported as odds ratios (ORs) with 95% CIs. All logistic regression models were checked for goodness of fit using the Hosmer–Lemeshow goodness-of-fit test, and there was no evidence of lack of fit (P>0.05).

For the analysis of the association between liver fat and incident AF, we excluded any participant with diagnosed prevalent AF at baseline assessment. We constructed multivariable Cox (proportional hazards) regression models to assess the relationship between liver fat and incident AF over up to 12 years of follow-up. Censoring occurred at the time of death or end of follow-up. As with the prevalent AF analysis above, we evaluated liver fat as a continuous and dichotomous variable. We also evaluated the incidence of AF among those with HS (LPR $\leq$0.33) and increased ALT (defined as >19 U/L for women and >30 U/L for men)[34] at baseline. The multivariable models were adjusted for covariates in the same manner as in the prevalent AF analysis. We assessed the assumption of proportional hazards by calculating a supremum test on the basis of the cumulative sums of Martingale-based residuals. Results are reported as hazard ratios (HRs) with 95% CI. Age- and sex-adjusted cumulative AF incidence curves by HS status were generated for the graphical representation of data. Cumulative incidence curves were calculated and adjusted using the corrected group prognostic method.[35] The log-rank test was used to compare the AF cumulative incidence curves among those with and without HS at baseline.

Given that we had 153 incident AF cases, a post-hoc power calculation revealed that we had 80% power to discover an adjusted HR of 1.27 or larger per presence versus absence of NAFLD at a 0.05 significance level. Analyses were performed in SAS software (version 9.3; SAS Institute Inc., Cary, NC). A 2-tailed probability value of <0.05 was considered statistically significant.

Results

Study Sample Characteristics

We present the baseline characteristics of the study sample (n=2122) in Table 1. The sample included 1120 (53%) women, and the mean age was 59.0±9.6 years. Overall, 20% of participants had HS on MDCT (defined by LPR). Those with HS had similar ages, but were less often women compared to those without HS. In general, compared to those without MDCT HS, individuals with HS had a higher prevalence of cardiovascular disease risk factors, including higher mean BMI ≥30 kg/m^2 and blood pressure, and higher percentages with hypertension, diabetes mellitus, and history of heart failure or

past MI. Prevalence of AF among those with HS was 4% compared to 3% among those without HS.

Crude Incidence of AF by HS Status

Mean follow-up duration was 9.3 years in 19 235 person-years of observation. During up to 12 years follow-up, 153 participants developed AF (Table 2). The overall incidence of AF was 7.95 cases per 1000 person-years. Incidence of AF among participants with HS on MDCT was 8.7 cases per 1000 person-years, whereas incidence of AF among participants without HS on MDCT was 7.8 cases per 1000 person-years.

Association Between Liver Fat and Prevalent AF

There was no significant association between fatty liver (measured as a continuous or dichotomous variable) and prevalent AF in age- and sex-adjusted or multivariable-adjusted models (Table 3). Also, those participants with HS on MDCT and elevated ALT did not have an increased prevalence of AF compared to those without both HS and an elevated ALT.

Association Between Liver Fat and Incident AF

In age- and sex-adjusted and multivariable-adjusted models, there were no significant associations between continuous or dichotomous measures of HS and incident AF (Table 4). Additionally, participants with both HS and elevated ALT did not demonstrate an increased incidence of AF in adjusted models compared to those without both HS and an elevated ALT. Cumulative hazard curves illustrate incidence of AF for participants with HS (LPR ≤0.33) compared to those without HS (LPR >0.33; Figure 2).

Discussion

Principal Findings

In our community-based, longitudinal cohort study, we did not observe a statistically significant association between liver fat

Table 1. Clinical Characteristics at Baseline in the Overall Sample (n=2122), by HS Status

Clinical Characteristics	Total Sample	HS (LPR ≤0.33)	No HS (LPR >0.33)
n	2122	423 (20%)	1699 (80%)
Age, y	59.0±9.6	59.2±9.3	58.9±9.7
Women	1120 (53%)	194 (46%)	926 (55%)
Offspring	1244 (59%)	250 (59%)	994 (59%)
Current smoking	221 (10%)	49 (12%)	172 (10%)
Alcohol, drinks/week	2.6±3.6	3.1±4.3	2.5±3.4
Weight, kg	80±18	90±18	78±17
Height, cm	169±10	169±9	169±10
BMI, kg/m^2	28.0±5.3	31.3±5.7	27.2±4.8
Systolic blood pressure, mm Hg	124±17	129±15	123±17
Diastolic blood pressure, mm Hg	76±9	79±10	75±9
Hypertension treatment	554 (26%)	171 (40%)	383 (23%)
Diabetes mellitus	155 (7%)	53 (13%)	102 (6%)
History of heart failure	15 (0.7%)	6 (1.4%)	9 (0.5%)
History of MI	67 (3%)	18 (4%)	49 (3%)
Prevalent AF	62 (3%)	17 (4%)	45 (3%)
ALT, U/L	27.1±18.9	34.3±24.2	25.2±16.8
Elevated ALT*	962 (45%)	259 (61%)	703 (41%)
AST, U/L	25.5±14.6	29.3±23.4	24.5±11.2
LPR	0.36±0.05	0.27±0.06	0.38±0.02

Data are expressed as means±SD or as number (percentage). AF indicates atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HS, hepatic steatosis; LPR, liver phantom ratio; MI, myocardial infarction.
*Elevated ALT is defined as ALT >19 U/L for women and >30 U/L for men.

Table 2. Incidence of AF, by Presence of HS

	Total Sample	HS (LPR ≤0.33)	No HS (LPR >0.33)	P Value*
Events	153	33	120	
Total	2060	406	1654	
Person-years	19 235	3801	15 434	
AF incidence/1000 person-years	8.0	8.7	7.8	0.56

AF indicates atrial fibrillation; HS, hepatic steatosis; LPR, liver phantom ratio.
*P value describes the differences between those with and without HS.

Table 3. Logistic Regression Models for the Association Between Liver Fat (LPR) and Prevalent AF

Adjustment	Continuous Liver Fat (−LPR)		HS (LPR ≤0.33)		HS (LPR ≤0.33) and Elevated ALT	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Age and sex	1.08 (0.84–1.38)	0.56	1.52 (0.85–2.73)	0.16	0.77 (0.30–1.96)	0.58
Multivariable*	1.01 (0.76–1.33)	0.94	1.29 (0.68–2.42)	0.43	0.83 (0.32–2.16)	0.70
Multivariable*+BMI	0.95 (0.71–1.27)	0.71	1.12 (0.58–2.18)	0.74	0.76 (0.29–1.99)	0.57

Data are shown as odds ratios (95% CIs) per SD decrease of the liver phantom ratio (increasing liver fat). AF indicates atrial fibrillation; ALT, alanine aminotransferase; BMI, body mass index; HS, hepatic steatosis; LPR, liver phantom ratio; MV, multivariable; OR, odds ratio.
*Multivariable adjustment included sex, age, systolic blood pressure, diastolic blood pressure, current smoking, use of antihypertensive medication, prevalent diabetes mellitus, history of heart failure, and history of myocardial infarction.

and prevalent or incident AF after over 19 000 person-years of observation.

In the Context of the Previous Literature

Previous studies evaluating the association between liver fat and AF have mostly relied on blood-based surrogate markers of liver fat, including serum ALT, AST, or gamma glutamyl transpeptidase (GGT) levels.[19,20,36] GGT, a liver enzyme, was found to be associated with incident AF in the Atherosclerosis Risk in Communities study.[36] In a previous investigation of the FHS Original and Offspring cohorts, elevated ALT and AST were associated with increased incidence of AF, over 10 years of follow-up, adjusting for alcohol use.[20] There are several potential explanations for why we did not confirm the previous findings. In the previous FHS study, mean age of participants was 65±10 years and those that developed AF were, on average, 6.8 years older at baseline compared to those who remained free of AF during the observation period. The incident rate of AF was 13.2 cases per 1000 person-years. Our study cohort was derived from the younger FHS participants in the Offspring and Third Generation cohorts who participated in the MDCT substudy. Though we excluded participants aged ≤45 years, the mean age of our sample was still relatively young at just under 60 years of age. Additionally, increases in ALT, AST, and GGT are not specific for liver fat. Elevated levels may be found in other conditions related to AF, such as alcohol use or heart failure, so it is possible that the previously reported associations between ALT, AST, or GGT and AF were driven by residual confounding from alcohol or comorbid medical conditions. Additional studies are required in older participants to examine how generalizable our findings are across age categories.

Few studies have assessed the association between radiographically defined liver fat and AF. In a previous FHS investigation, there was no association observed between visceral abdominal fat and prevalent AF in multivariable-adjusted models, but liver fat was not examined.[37] In a German cohort study including community-dwelling individuals, elevated liver enzymes, but not ultrasound-defined HS, was associated with prevalent AF, which is in line with the findings of our study.[19] An investigation conducted using data from a Finnish registry of individuals with hypertension as well as age- and sex-matched controls showed that ultrasound-defined HS was associated with a higher odds of incident AF.[18]

In our community-based cohort study, we did not demonstrate a significant association between liver fat and incident AF. There are a number of possible explanations for why our results differ from those observing an association between liver fat and AF. First, given that 51% of the participants in the Finnish study had hypertension, the results may not be generalizable to community-based samples with lower rates of

Table 4. Cox Proportional-Hazards Models Relating Liver Fat (LPR) to Incidence of AF

Models	Continuous Liver Fat (−LPR)		HS (LPR ≤0.33)		HS (LPR ≤0.33) and Elevated ALT	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Age- and sex-adjusted	1.08 (0.93–1.26)	0.31	1.10 (0.75–1.62)	0.62	1.16 (0.71–1.87)	0.56
MV* adjusted	1.05 (0.90–1.23)	0.54	1.04 (0.70–1.53)	0.86	1.10 (0.67–1.80)	0.70
MV*+BMI adjusted	1.02 (0.87–1.20)	0.78	0.96 (0.64–1.45)	0.86	1.06 (0.65–1.74)	0.81

Data are shown as hazard ratios (95% CIs) per SD decrease of the liver phantom ratio (increasing liver fat). AF indicates atrial fibrillation; ALT, alanine aminotransferase; BMI, body mass index; HR, hazard ratio; HS, hepatic steatosis; LPR, liver phantom ratio; MV, multivariable.
*Multivariable adjustment included sex, age, systolic blood pressure, diastolic blood pressure, current smoking, use of antihypertensive medication, prevalent diabetes mellitus, history of heart failure, and history of myocardial infarction.
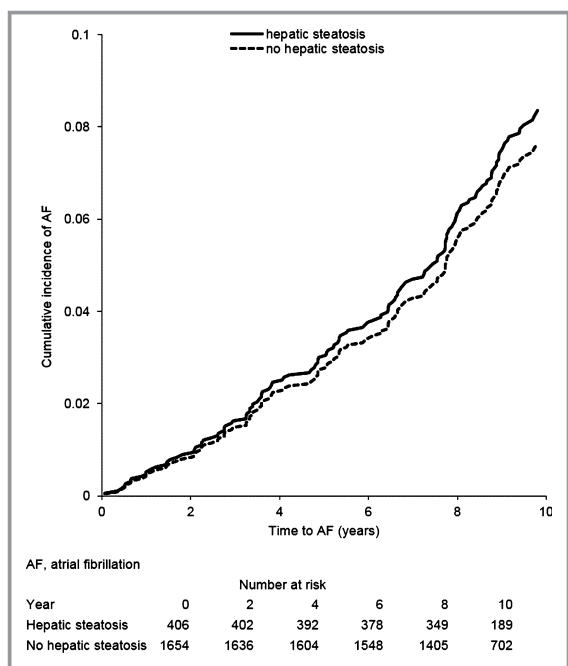
Figure 2. Age- and sex-adjusted cumulative incidence curves for incident atrial fibrillation (AF) by presence or absence of hepatic steatosis. Participants with nonalcoholic fatty liver disease had a higher cumulative incidence of AF during follow-up, though results were not statistically significant (log-rank test, *P*=0.55).

prevalent hypertension or other cardiovascular risk factors. Second, in contrast to our method of defining AF, in the Finnish study, AF was defined based on hospital discharge diagnoses. As such, it is possible that individuals with HS were more likely to be hospitalized for AF compared to those without HS, which may have introduced a systematic bias. Indeed, those with HS also tended to have a higher burden of comorbid cardiovascular disease, which may complicate the management of AF and require hospitalization instead of outpatient management. Importantly, there were only 153 incident cases of AF noted over 12 years of follow-up in our study. As such, we may not have had sufficient power to detect modest associations between liver fat and AF.

Strengths and Limitations

The major strengths of our investigation include the use of a well-phenotyped, community-dwelling sample within the context of a longitudinal cohort study with systematic follow-up procedures and detailed outcome ascertainment. However, a number of limitations are important to consider. First, MDCT is most sensitive and specific for moderate-to-severe liver fat and we cannot comment on the association between mild liver fat or more-severe forms of NAFLD, including steatohepatitis or liver fibrosis, and AF. Second, our sample was

constituted middle-aged to older adults, largely of European descent. The generalizability of our findings to different races or ethnicities or older or younger age individuals is not known. Also, because the prevalence of AF is low, we had limited power. Finally, because AF is often asymptomatic, it is possible we missed AF during case ascertainment despite a careful assessment for outcomes.

Conclusion

Our findings, if confirmed, suggest that liver fat is not associated with AF over and above traditional AF risk factors in middle-aged to older, community-dwelling adults. Although FHS participants with increased liver fat had a higher burden of adverse cardiovascular traits, they did not have an increased prevalence of AF and were not at substantively increased risk for developing AF over a 12-year period. Additional prospective studies are needed to validate our findings.

Sources of Funding

Author Contributions

Study concept and design (Long, Chung, Benjamin); acquisition of data (Hoffmann, Benjamin); Analysis and interpretation of data (Long, Yin, Larson, Hoffmann, Ellinor, Lubitz, McManus, Magnani, Staerk, Ko, Helm, Chung, Benjamin); drafting of the manuscript (Long); critical revision of the manuscript for important intellectual content (Yin, Ellinor, Lubitz, McManus, Magnani, Staerk, Ko, Helm, Hoffmann, Chung, Benjamin); statistical analysis (Yin, Larson); administrative, technical, or material support (Hoffmann); study supervision (Benjamin). All authors approved the final version of the manuscript.

Disclosures

Ellinor is the PI on a grant from Bayer HealthCare to the Broad Institute focused on the genetics and therapeutics of AF. McManus has consulted and/or received grant funding from Bristol-Meyers Squibb, Sanofi Aventis, Philips Healthcare, Biotronik Inc., and Pfizer for work related to AF. He is an equity stakeholder in MobileSense Technologies, LLC. The other authors have no conflicts to report.

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