Association Between Familial Atrial Fibrillation and Risk of New-Onset Atrial Fibrillation

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A HERITABLE COMPONENT UN-derlying atrial fibrillation (AF) has been well demon-strated,[1-6] and it is now evi-dent that genetic variants are associ-ated with AF risk.[7-10] However, the role of familial occurrence across and within generations has received little attention.

Several gaps in knowledge exist regarding the association between familial AF and AF risk. Although AF risk appears greater with younger age of AF onset in relatives,[1,2] the magnitude of risk attributable to familial AF has not been characterized across a wide range of AF onset ages in family members. Whereas occurrence of AF in a first-degree relative is associated with new-onset AF, only parental AF has been demonstrated to confer risk independent of other AF risk factors.[1] The association between sibling AF and AF risk after accounting for parental disease has not been examined. Importantly, the extent to which risk conferred by familial AF is mediated by

Context Although the heritability of atrial fibrillation (AF) is established, the contribution of familial AF to predicting new-onset AF remains unknown.

Objective To determine whether familial occurrence of AF is associated with new-onset AF beyond established risk factors.

Design, Setting, and Participants The Framingham Heart Study, a prospective community-based cohort study started in 1948. Original and Offspring Cohort participants were aged at least 30 years, were free of AF at the baseline examination, and had at least 1 parent or sibling enrolled in the study. The 4421 participants in this analysis (mean age, 54 [SD, 13] years; 54% women) were followed up through December 31, 2007.

Main Outcome Measures Incremental predictive value of incorporating different features of familial AF (any familial AF, premature familial AF [onset ≤65 years old], number of affected relatives, and youngest age of onset in a relative) into a risk model for new-onset AF.

Results Across 11 971 examinations during the period 1968-2007, 440 participants developed AF. Familial AF occurred among 1185 participants (26.8%) and premature familial AF occurred among 351 participants (7.9%). Atrial fibrillation occurred more frequently among participants with familial AF than without familial AF (unadjusted absolute event rates of 5.8% and 3.1%, respectively). The association was not attenuated by adjustment for AF risk factors (multivariable-adjusted hazard ratio, 1.40; 95% confidence interval [CI], 1.13-1.74) or reported AF-related genetic variants. Among the different features of familial AF examined, premature familial AF was associated with improved discrimination beyond traditional risk factors to the greatest extent (traditional risk factors, C statistic, 0.842 [95% CI, 0.826-0.858]; premature familial AF, C statistic, 0.846 [95% CI, 0.831-0.862]; $P=.004$). Modest changes in integrated discrimination improvement were observed with premature familial AF (2.1%). Net reclassification improvement (assessed using 8-year risk thresholds of <5%, 5%-10%, and >10%) did not change significantly with premature familial AF (index statistic, 0.011; 95% CI, −0.021 to 0.042; $P=.51$), although categoryless net reclassification was improved (index statistic, 0.127; 95% CI, 0.064-0.189; $P=.009$).

Conclusions In this cohort, familial AF was associated with an increased risk of AF that was not attenuated by adjustment for AF risk factors including genetic variants. Assessment of premature familial AF was associated with a very slight increase in predictive accuracy compared with traditional risk factors.

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common AF susceptibility loci identified in genome-wide association studies on chromosomes 4q25, 16q22, and 1q21[7-10] is unknown.

Furthermore, familial AF has not been formally examined as a risk factor for AF using conventional metrics that assess discrimination and risk reclassification. Investigators from the Framingham Heart Study recently developed a clinical risk score for predicting AF,[11] but familial AF was not assessed as a potential risk factor. We examined the association between AF occurrence in a first-degree relative and AF risk and hypothesized that considering familial AF would enhance prediction of new-onset AF.

METHODS
Participants

We identified participants from the Framingham Heart Study who were aged at least 30 years and free of AF at 1 or more of the following examinations: Original Cohort[12] cycles 11 (1968-1971; n=934), 18 (1983-1985; n=621), 22 (1990-1994; n=353), and 26 (1999-2001; n=148) and Offspring Cohort[13] cycles 1 (1971-1975; n=2326), 3 (1984-1987; n=2622), 5 (1991-1995; n=2600), and 7 (1998-2001; n=2367). All included participants had at least 1 parent or sibling enrolled in the study. Because examinations were conducted 2 to 8 years apart, we examined the 8-year occurrence of AF. Participants in this analysis were followed up through December 31, 2007. Study protocols for examination cycles received ethics approval from the Boston University Medical Center Institutional Review Board, and participants signed consent forms.

Assessment of AF

At each Framingham Heart Study clinic examination, participants' medical histories, physical examinations, and electrocardiograms were obtained to ascertain symptoms and findings suggestive of cardiovascular disease. Records of all interim hospitalizations for cardiovascular disease were sought for review.

Participants were classified as having AF if either atrial flutter or atrial fibrillation was found on an electrocardiogram obtained at a Framingham Heart Study clinic visit, on an electrocardiogram during an encounter with an external clinician, or by Holter monitoring or was noted in hospital records.[14] Familial AF was defined as occurrence of AF in a first-degree relative prior to an examination commencing an 8-year follow-up period. Since participants could be eligible for examination on multiple occasions in the Framingham Heart Study, examinations commencing an 8-year follow-up period were denoted as baseline examinations, in contrast to the initial study examination. A priori, we defined familial AF as premature when the first-detected occurrence was at age 65 years or younger in a first-degree relative in keeping with prior analyses of early-onset AF.[4,10] Two physicians unaware of familial AF status (D.L. and E.J.B.) adjudicated AF events.

Statistical Analysis

Participant characteristics were ascertained at Framingham Heart Study clinic examinations. Potential risk factors for AF other than familial AF were derived from a published prediction model and included age, sex, body mass index, systolic blood pressure, treatment for hypertension, PR interval, significant heart murmur (at least grade 3 of 6 systolic or any diastolic), and heart failure (eAppendix; available at http://www.jama.com).[11] In 477 participants from the Original Cohort, neither treatment for hypertension nor heart murmur was available at examination 11 (1968-1971), and both were carried forward from examination cycle 10 (1966-1970). Heart murmur status was not measured in 148 Original Cohort participants who attended examination 26 (1999-2001) and was carried over from earlier examinations.

We examined associations between risk factors and incident AF using proportional hazards regression with robust variance estimators to account for relatedness among participants.[15] We

restricted our model to risk factors with multivariable-adjusted 2-sided $P<.05$ in our sample and forced in treatment for hypertension (eAppendix).[11] Follow-up began at baseline examinations and participants were censored at death, loss to follow-up, or the earliest of either the next baseline examination or 8 years. Follow-up windows were pooled.[16] Proportional hazards assumptions were verified with multiplicative interaction terms between covariates and survival time. To account for potentially differing baseline hazards of AF during different cohorts and eras, we stratified models by cohort and examination.

We estimated the cumulative incidence of AF among those with or without familial AF using the Kaplan-Meier method, adjusting for the competing risk of death.[17] We calculated unadjusted absolute event rates by dividing the number of events by the number of person-examinations, where the total number of person-examinations is the sum of the number of baseline examinations that all participants attended. We modeled familial AF in several ways, including treating the presence of familial AF as a dichotomous variable, treating the number of first-degree relatives with AF as a continuous dosage, and introducing separate indicators for AF in fathers, mothers, and siblings. Since the number of informative family members differs across participants, we explored associations between familial and incident AF in models stratified by family size; presence of fathers, mothers, or siblings in the study; presence of any parent vs sibling in the study; and in nonstratified models. In models that included terms for maternal, paternal, and sibling AF, we used contrasts among estimated regression coefficients to test equality of effects among different sources of familial AF with the Wald χ^2 statistic.

We examined whether the effect estimate for familial AF differed according to participant age by modeling AF risk in different participant age groups (30-49, 50-59, 60-69, 70-79, and 80-99 years). We also examined the relation-

ships between age at AF onset in the youngest affected relative and incident AF compared with participants without familial AF by including indicators for familial AF and familial age at AF onset in the same model. We examined linearity of the association with a restricted cubic spline model among those with familial AF (knots at 50, 60, 70, 80, and 90 years).[18,19]

In a subset of genotyped participants, we assessed the degree to which risk associated with familial AF was mediated by AF-associated genetic loci by examining the change in effect estimate for familial AF after adjusting for genotypes of 4 common single-nucleotide polymorphisms (SNPs) tagging validated genome-wide significant ($P < 5 \times 10^{-8}$) AF susceptibility signals (chromosomal loci 4q25 [rs2200733] and 4q25 [rs10033464][7] [$r^2 = 0.015$ in HapMap phase 3 CEU sample[20]]; 16q22 [rs2106261][8,9]; and 1q21 [rs13376333][10]). The eAppendix contains genotyping and imputation details. Minor alleles for SNPs were modeled assuming an additive genetic effect.

After exploring the relationships between familial AF and AF risk, we assessed model fit statistics with the addition of various features of familial AF in an AF prediction model. For discrimination and reclassification analyses, we estimated risk at 8 years. We examined the incremental utility of each of the tested features of familial AF by assessing discrimination using the C statistic for time-to-event data[21] and reclassification of predicted AF risk with integrated discrimination and net reclassification improvement indexes.[22] We used risk thresholds of less than 5%, 5% to 10%, and greater than 10%[11] for the net reclassification improvement index. We also assessed "categoryless" net reclassification improvement, which assesses any upward or downward reclassification; values greater than 0 correspond to improved reclassification (eAppendix).[23] The a priori significance threshold was $P < .05$ using 2-sided tests. Model calibration was assessed with the Hosmer-Lemeshow χ^2 statistic. Statistical analy-

ses were performed using SAS software, version 9.2.[15]

RESULTS

Eight-year windows from 4455 participants were pooled. After excluding 156 baseline examinations with incomplete covariate data, 4421 participants with 11 971 baseline examinations remained for analysis. The average age at examination was 53.9 (SD, 13.3) years, and 54% were female participants (TABLE 1). Atrial fibrillation developed in 440 participants during 8-year follow-up windows.

The number of first-degree relatives analyzed per participant varied from 1 to 10 (median, 3). Familial AF occurred among 1185 participants (26.8%) and premature familial AF occurred among 351 participants (7.9%). Of the 2393 baseline examinations at which familial AF was present, sources included fathers (n=1163), mothers (n=1068), and siblings (n=404). The sum exceeds the number of participants with familial AF because multiple affected relatives could contribute to familial AF for any given individual. Among participants with familial AF, the number of affected relatives ranged from 1 to 5 (median, 1). Approximately 98% of participants with familial AF had 2 or fewer affected relatives.

Association Between Familial AF and Incident AF

The cumulative incidence of AF according to presence of familial AF, accounting for competing risk, is plotted in FIGURE 1. The unadjusted absolute event rates among participants with and without familial AF were 5.8% (139 events in 2393 person-examinations) and 3.1% (301 events in 9578 person-examinations), respectively. Familial AF was associated with new-onset AF in age- and sex-adjusted models (hazard ratio [HR], 1.39; 95% confidence interval

Table 1. Characteristics of Participants at the 11 971 Baseline Examinations Included in the Analysis[a]
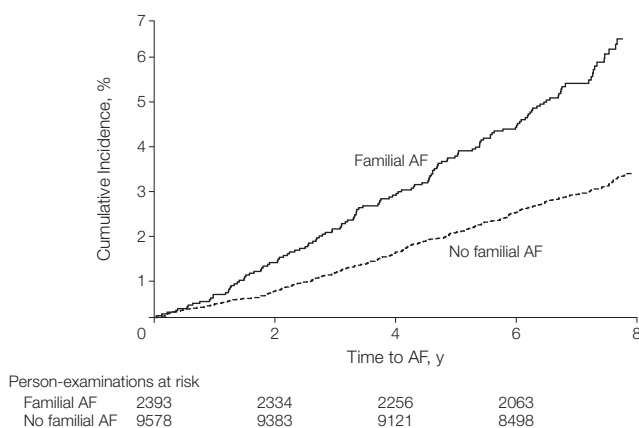
Characteristics	No. (%) of Participants[b]
Age, mean (SD), y	53.9 (13.3)
Women	6476 (54)
Body mass index, mean (SD)[c]	26.9 (4.9)
Systolic blood pressure, mean (SD), mm Hg	128 (19)
Antihypertensive therapy	2394 (20)
PR interval duration, mean (SD), ms	163 (24)
Heart murmur	359 (3)
Heart failure	72 (<1)

[a] The 11 971 baseline examinations correspond to pooled examinations from 4421 unique individuals.
[b] Data are presented as No. (%) of participants unless otherwise indicated.
[c] Body mass index is calculated as weight in kilograms divided by height in meters squared.

Figure 1. Cumulative AF Incidence by Presence or Absence of Antecedent AF in a First-Degree Relative Accounting for Competing Risk of Death

Person-examinations at risk				
Familial AF	2393	2334	2256	2063
No familial AF	9578	9383	9121	8498

AF indicates atrial fibrillation. Person-examinations at risk at 8 years are not shown because 8-year follow-up windows were pooled and the majority of censored person-examinations at 8 years contributed to a subsequent risk pool at 0 years.

[CI], 1.12-1.73; P=.003) and remained associated after multivariable adjustment (HR, 1.40; 95% CI, 1.13-1.74; P=.002) (**TABLE 2**). Removing from the model the PR interval, a variable that is genetically related to AF[24,25] and that may not always be available in the clinical setting, did not substantively alter the association of familial AF (Table 2). Similarly, the effect estimate for familial AF was not materially altered when the original AF risk prediction model and coefficients[11] were used or when diabetes mellitus, another heritable condition[26] associated with AF,[27,28] was included in the model (eTable 1).

Atrial fibrillation risk was associated with increasing number of affected first-degree relatives (HR, 1.24; 95% CI, 1.05-1.46 per affected member) (Table 2). The association was not substantially affected by adjustment for family size (eTable 2).

Effect estimates for familial AF were similar in subsets of participants with parent(s) only, sibling(s) only, and both parent(s) and sibling(s) in the study; little heterogeneity was seen in the risk conferred by familial AF across sources (eTable 3). Sibling AF was associated with AF risk after adjusting for maternal and paternal AF (HR, 1.39; 95% CI, 1.02-1.91; P=.04). We did not observe a difference in AF risk according to familial relationship when maternal, paternal, and sibling AF were included in the same model (HRs, 1.37, 1.15, and 1.39, respectively; χ_2^2=0.66; P=.72).

Relationships of Participant Age and Familial Age at AF Onset

The risk of new-onset AF associated with familial AF may vary in a nonlinear fashion with increasing participant age at examination (**FIGURE 2**A).
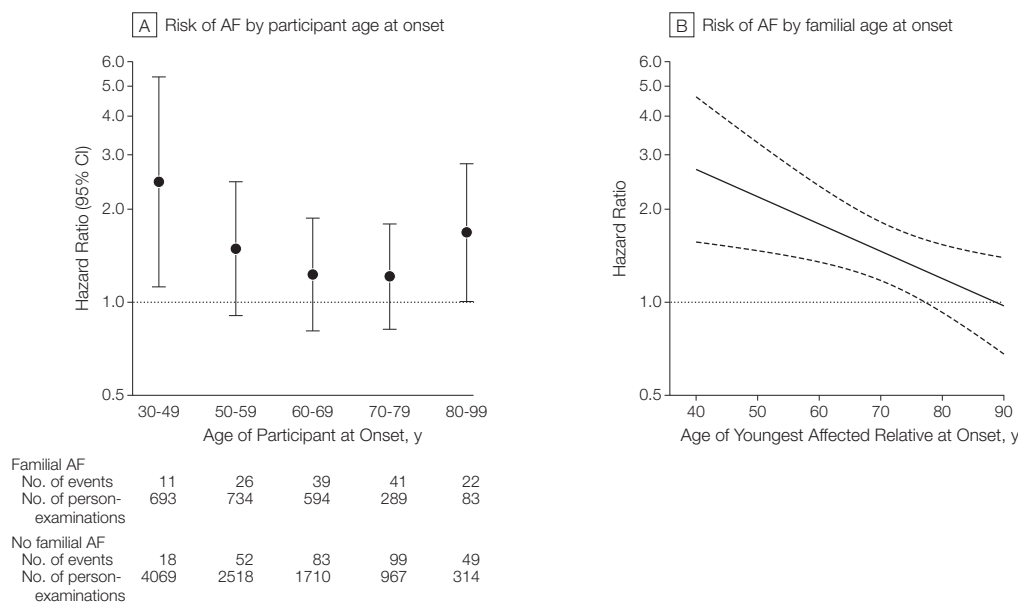
Table 2. Association Between First-Degree Familial AF and Incident AF[a]

Model	No. of Events/Person-Examinations		Hazard Ratio (95% Confidence Interval)	P Value
	Familial AF	No Familial AF		
Presence of any first-degree familial AF				
Age- and sex-adjusted			1.39 (1.12-1.73)	.003
Multivariable-adjusted[b]	139/2393	301/9578	1.40 (1.13-1.74)	.002
Multivariable-adjusted without PR[b]			1.40 (1.13-1.74)	.002
Premature first-degree familial AF (onset ≤ age 65 y), multivariable-adjusted[b]	55/789	385/11 182	2.01 (1.49-2.71)	<.001
No. of first-degree relatives with AF, risk per each additional affected family member[b]			1.24 (1.05-1.46)	.01

[a] Models stratified by cohort and examination.
[b] Adjusted for age, sex, body mass index, systolic blood pressure, treatment for hypertension, PR interval, heart murmur, heart failure, age × heart murmur, and age × heart failure.

Figure 2. Association Between Familial AF and AF Risk According to Participant Age or Familial Age at AF Onset

A Risk of AF by participant age at onset

	30-49	50-59	60-69	70-79	80-99
Familial AF					
No. of events	11	26	39	41	22
No. of person-examinations	693	734	594	289	83
No familial AF					
No. of events	18	52	83	99	49
No. of person-examinations	4069	2518	1710	967	314

B Risk of AF by familial age at onset

AF indicates atrial fibrillation. A, The multivariable-adjusted hazard for AF among participants with familial AF, compared with those without familial AF, is shown by participant age strata. Error bars indicate 95% confidence intervals (CIs). B, The multivariable-adjusted hazard for AF among participants with familial AF, compared with those without familial AF, is shown according to the age at onset of the youngest first-degree relative with AF. The solid line is the risk estimate and the dashed lines indicate the 95% CI. Among participants with familial AF, the risk of AF increased with decreasing age at AF onset in the youngest affected relative (hazard ratio, 1.32; 95% CI, 1.12-1.56; P<.001). The age of the youngest affected relative ranged from 37 to 102 years. Data were plotted based on a multivariable regression model that included both familial AF and youngest affected relative's age at onset, in which a constant value for youngest affected relative's age at onset (eg, 0) was assigned to participants without familial AF. The hazard ratios and 95% CIs were calculated based on the linear combinations of β estimates and variance-covariance between these predictors. The estimated hazard ratios and 95% CIs do not rely on the constant value assigned.

The relationships between familial age at AF onset and AF risk are shown in Figure 2B. Among participants with familial AF, we observed a log-linear increase in AF risk as the age of the youngest affected relative decreased (HR for each decreasing decade of age, 1.32; 95% CI, 1.12-1.56; $P < .001$). In the subset of participants aged 65 years or younger at a baseline examination, the unadjusted absolute event rate among individuals with premature familial AF was 4.3% (27 events in 630 person-examinations), whereas the rate among participants without premature familial AF (either no familial AF or familial AF >65 years) was 1.2% (105 events in 8848 person-examinations). Premature familial AF was associated with premature AF onset after multivariable adjustment (HR, 3.03; 95% CI, 1.90-4.83; $P < .001$).

Adjustment for Genetic AF Susceptibility Loci

In a subset of 2861 previously genotyped participants, familial AF was associated with increased risk of AF similar to that observed in the full sample, with unadjusted absolute event rates of 5.8% (116 events in 2005 person-examinations) and 2.3% (207 events in 7168 person-examinations) for those with and without familial AF, respectively (multivariable-adjusted HR, 1.43; 95% CI, 1.13-1.83; $P = .003$). After further adjustment for genotypes of 4 SNPs tagging AF susceptibility loci, the effect estimate for familial AF remained essentially unchanged (HR, 1.38; 95% CI, 1.08-1.75; $P = .01$) (eTable 4).

Incremental Utility of Familial AF for AF Risk Prediction

Each of the assessed features of familial AF improved model fit beyond traditional risk factors alone (TABLE 3). The C statistic indicated slightly improved discrimination with each familial AF feature. The largest improvement was observed with premature familial AF (traditional risk factors, C statistic, 0.842 [95% CI, 0.826-0.858]; premature familial AF, C statistic, 0.846 [95% CI, 0.831-0.862]; $P = .004$).

Integrated discrimination improvement estimates were similar for each familial AF feature, though the standard errors and, hence, P values differed (Table 3). The relative integrated discrimination improvement values (1.0%-2.1%) indicate weaker performance of each familial AF feature than the mean of variables already in the model.

Net reclassification improvement using 8-year risk thresholds of less than 5%, 5% to 10%, and greater than 10% was not enhanced by familial AF (premature familial AF, index statistic, 0.011 [95% CI, −0.021 to 0.042]; $P = .51$; any familial AF, index statistic, −0.029 [95% CI, −0.057 to 0.000]; $P = .05$) (Table 3 and eTable 5). Notably, only 12% of our sample had predicted 8-year risks that exceeded 10%. In contrast, categoryless net reclassification improvement indicated weak to moderate improvement in risk reclassification with premature familial AF (index statistic, 0.127; 95% CI, 0.064-0.189; $P = .009$) and any familial AF (index statistic, 0.253; 95% CI, 0.164-0.341; $P < .001$). The significant improvement in categoryless net reclassification was driven by the downward classification of nonevents (94% correctly classified downward for premature AF and 80% for any familial AF).

The Hosmer-Lemeshow statistic indicated adequate calibration between observed and predicted AF risk in models without familial AF ($\chi_9^2 = 14.9$; $P = .11$) and with familial AF ($\chi_9^2 = 16.1$; $P = .08$).

COMMENT

Herein, we report an association between the occurrence of AF in a first-degree relative and risk of new-onset AF

Table 3. Models Assessed for Discrimination and Risk Reclassification

Model	AIC[a]	C Statistic		Integrated Discrimination Improvement Index			Net Reclassification Improvement Index[b]		Categoryless Net Reclassification Improvement Index	
		Statistic (95% CI)	P Value[c]	Statistic (95% CI)	Relative Value, %	P Value[c]	Statistic (95% CI)	P Value[c]	Statistic (95% CI)	P Value[c]
Base model[d]	5797	0.842 (0.826 to 0.858)								
Base model + No. of first-degree relatives with AF	5792	0.844 (0.828 to 0.860)	.02	0.001 (−0.001 to 0.003)	1.0	.21	−0.022 (−0.046 to 0.003)	.09	0.014 (−0.076 to 0.103)	.78
Base model + familial AF	5789	0.844 (0.828 to 0.860)	.06	0.003 (0.000 to 0.005)	2.1	.05	−0.029 (−0.057 to 0.000)	.05	0.253 (0.164 to 0.341)	<.001
Base model + familial AF + age at onset of youngest affected relative	5783	0.846 (0.830 to 0.862)	.005	0.002 (−0.001 to 0.005)	1.9	.14	−0.010 (−0.041 to 0.021)	.52	0.189 (0.105 to 0.272)	<.001
Base model + premature familial AF	5779	0.846 (0.831 to 0.862)	.004	0.003 (−0.001 to 0.006)	2.1	.14	0.011 (−0.021 to 0.042)	.51	0.127 (0.064 to 0.189)	.009

Abbreviations: AIC, Akaike information criterion; CI, confidence interval.
[a] Lower values indicate better model fit.
[b] Corresponds to 8-year risk thresholds of less than 5%, 5% to 10%, and greater than 10%.
[c] Compared with base model.
[d] Base model includes age, sex, body mass index, systolic blood pressure, treatment for hypertension, PR interval, heart murmur, heart failure, age × heart murmur, and age × heart failure.

in 4421 individuals of European descent. Familial AF was associated with incident AF after multivariable adjustment for commonly accepted AF risk factors, including genetic variants at AF susceptibility loci. Consideration of familial AF, particularly when premature in onset, slightly improved prediction of new-onset AF beyond conventional AF risk factors.

Our findings support and extend previous reports of AF heritability.[1-6] The observation that AF risk is inversely related to the age at which a first-degree relative develops AF is consistent with reports of an increased risk of AF in individuals with relatives affected before age 60 years[2] or parents before age 75 years.[1] We further demonstrate that the estimated hazard of AF diminishes loglinearly with increasing age of an affected family member. We also found that AF risk is associated with an increasing number of affected first-degree relatives. Sibling AF conferred a similar magnitude of risk as parental AF and was informative even after considering parental AF status, similar to observations of risk in cardiovascular disease.[29]

Unexpectedly, the magnitude of risk associated with familial AF varied by participant age in a nonlinear fashion. Our precision to determine the nature of the relationship was limited owing to the small number of person-examinations and events in each stratum of participant age. Future investigation of the observed U-shaped relationship between an individual's age and the association between familial AF and risk of AF will require larger samples.

The estimated 40% increase in the hazard for new-onset AF associated with familial AF was not attenuated by adjustment for traditional AF risk factors or genetic variants at AF susceptibility loci, demonstrating that risk associated with familial AF was not substantially mediated by known risk factors in our sample. The concept of "missing heritability" has received much attention in the current era of genome-wide association studies.[30] Our results justify future efforts to identify novel genetic variants, unmeasured environmental factors, and potential joint effects of genetic and environmental factors involved in the pathogenesis of AF.

We demonstrated that consideration of easily ascertained clinical factors at the bedside results in excellent discrimination of AF risk. Familial AF improves discrimination, particularly when familial AF is premature or when familial age at AF onset is taken into account. Premature familial AF discriminates AF risk better than considering any occurrence of familial AF, perhaps because premature AF is a less heterogeneous disorder. The small magnitude of improvement in discrimination attributable to different familial AF variables is consistent with reports in which family history was examined in the context of cardiovascular disease[31,32] and reflects the difficulty of assessing novel risk factors for incremental benefit beyond established risk factors.

The absence of significant benefit with the category-based net reclassification improvement may have arisen because few participants in our sample were in the highest category of predicted AF risk and because clinically meaningful risk thresholds for AF are uncertain. The fact that categoryless net reclassification improvement with premature familial AF was driven by correct downward classification of individuals who did not develop AF may provide reassurance to patients without familial AF. Generally, the small magnitude of improvement in the C statistic, integrated discrimination improvement, and categoryless net reclassification improvement indexes with each of the assessed features of familial AF suggest that meaningful enhancement of AF prediction beyond traditional risk factors by considering familial AF may require large samples. Assessment of familial AF in larger samples might lead to improved prediction of AF risk in more individuals in absolute terms but may not be expected to enhance the magnitudes of effect we observed in our sample.

Our selected age threshold of 65 years or younger may not be the optimal cutoff for defining premature familial AF, and the number of participants with premature familial AF was limited. We submit that a systematic analysis of various definitions of premature familial AF based on different age thresholds, as well as potential variation by sex, is warranted in larger samples. Indeed, the association between parental myocardial infarction and offspring cardiovascular disease risk has been shown to differ according to parental age and sex.[33]

Strengths of our study include the multigenerational nature of the Framingham Heart Study, which allowed us to examine documented and adjudicated occurrences of AF within families. In contrast, self-reported AF or family history of AF would likely result in less robust results because of the inherent inaccuracy of such information. Other strengths include that physicians without knowledge of familial occurrence status adjudicated AF events and that risk factors were systematically and routinely ascertained.

Our study has several limitations. First, our analysis was limited to a single sample of European ancestry and the results may not be generalizable to other populations. Second, not all family members participated in the Framingham Heart Study. Such family members were not included in our analysis and may bias our results. However, we assume that nonparticipation is random and unlikely to result in meaningful bias. Third, we acknowledge that there may be other genetic susceptibility loci for AF that mediate the risk conferred by familial AF.[24,25] We included only replicated loci that were beyond genome-wide significance. Fourth, we had low power to detect differences in the magnitude of risk conferred by maternal and paternal AF. Larger samples will be necessary to examine whether these associations differ and, perhaps, whether specific parent-of-origin allelic effects modify associations between genetic variants and AF. Fifth, the occurrence of AF beyond first-degree relatives is associated with AF risk[2,4] and may be clinically informative. However, we submit that ascertainment of first-degree rather than extended family history information is most

practical in the clinical setting. Sixth, although our risk model included systolic blood pressure and treatment for hypertension, it is not clear to what extent successful treatment of blood pressure during follow-up may affect AF risk. Moreover, whereas heart murmur data were ascertained routinely at Framingham Heart Study examinations, there are insufficient echocardiographic data in our sample to determine the effect of echocardiographic valvular disease on the risk of familial AF or to compare the reliability of heart murmur with echocardiography.

CONCLUSION

In our population, occurrence of AF in first-degree relatives was associated with AF risk after adjustment for established AF risk factors and AF-related genetic variants. Assessment of familial AF enhanced risk prediction slightly beyond traditional risk factors, particularly when familial AF occurred prematurely. Future efforts should attempt to discern the factors that mediate the association between familial AF and AF risk, further explore the relationships between premature familial AF and risk prediction, and determine whether incorporating genetic variants into an AF prediction model enhances its performance.

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