Familial Aggregation of Atrial Fibrillation
A Study in Danish Twins

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Background—Heritability may play a role in nonfamilial atrial fibrillation (AF). We hypothesized that a monozygotic (MZ) twin whose co-twin was diagnosed with AF would have an increased risk of the disease compared with a dizygotic (DZ) twin in the same situation.

Methods and Results—A sample of 1137 same-sex twin pairs (356 MZ and 781 DZ pairs) in which one or both members were diagnosed with AF were identified in The Danish Twin Registry. Concordance rates were twice as high for MZ pairs than for DZ pairs regardless of sex (22.0% versus 11.6%, $P<0.0001$). In a Cox regression of event-free survival times, we compared the time span between occurrences of disease in MZ and DZ twins. The unaffected twin was included when his or her twin-sibling (the index twin) was diagnosed with AF. After adjustment for age at entry, MZ twins had a significantly shorter event-free survival time (hazard ratio, 2.0; 95% CI, 1.3 to 3.0), thereby indicating a genetic component. Using biometric models, we estimated the heritability of AF to be 62% (55% to 68%), due to additive genetics. There were no significant differences across sexes.

Conclusions—All the analyses of twin similarities in the present study indicate that genetic factors play a substantial role in the risk of AF for both sexes. The recurrence risk for co-twins (12% to 22%) is clinically relevant and suggests that co-twins of AF-affected twins belong to a high-risk group for AF. **(*Circ Arrhythmia Electrophysiol*. 2009;2:378-383.)**

Key Words: atrial fibrillation ■ arrhythmia ■ risk factors ■ twin study ■ genetics

Atrial fibrillation (AF) is a common type of arrhythmia, currently affecting more than 5% of the Western population over 65 years of age.[1] AF is associated with risk of thromboembolic complications, heart failure, and death.[2] It is more common in men than women and in those with heart failure, valvular heart disease, hypertension, diabetes, and with increasing age.[3,4] In approximately 12% (to 30%) of AF patients, no concomitant heart disease is present, a condition known as "lone AF."[5,6] Although AF is a common disease and constitutes a major problem in public health,[7] current treatment methods for AF are far from satisfactory. Various treatment strategies are currently used, but the recurrence rate is high, and many patients eventually have development of permanent AF refractory to any attempt to obtain sinus rhythm (SR), including electric cardioversion. This lack of true success in treatment of AF is partly explained by the scarce knowledge of the pathogenesis of AF.

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It is not known why the majority of individuals with hypertension or valvular or structural heart disease remain in SR even in an advanced age, whereas others have AF in the absence of these or any other known risk factors. These facts make it reasonable to consider AF a multifactorial disease in which genetic factors may play an important role in defining the risk for the development of the disease.

In 1947, Wolff[8] described 3 brothers who all were diagnosed with AF at a young age, and since then there has been a debate about the heritability of this arrhythmia. From kindreds with familial AF, we know that certain mutations can cause the disease, but until now only private mutations not found outside the actual family have been described.[9–11] On the other hand, common polymorphisms have been shown to associate with the risk of AF in patients with nonfamilial AF and in the general population at large.[12–16] These findings indicate that AF to some degree is a polygenetic disease. An attempt to estimate the heritability of AF in the general population has been done with data from the Framingham Heart Study, showing that parental AF is a risk factor for AF in offspring.[12] Likewise, a study of the general population in Iceland demonstrated that Icelandic patients with AF are more closely related to each other than the rest of the population, suggesting a significant degree of heritability in nonfamilial AF.[17]

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No relatives are genetically closer to each other than monozygotic twins. When twin populations are sampled and followed, it is possible to collect epidemiological data concerning more common diseases, their distribution, incidence, and prevalence, and their relation to sex, age, zygosity, and so forth. The classic comparisons between monozygotic (MZ) twins (with completely identical genes) and dizygotic (DZ) twins (with no more genes in common than ordinary sib pairs), can provide estimates of heritability, that is, the extent to which the variation in a given population with respect to a certain trait is gene dependent.[18] In the present study, we investigated the incidence of AF among Danish twins whose twin-sibling (ie, index twin) already had the disease, and, from calculations of concordance rates and hazard ratios, we aimed at estimating the co-twin risk of being diagnosed with AF during follow-up and the heritability of nonfamilial AF.

Methods

The Danish Twin Registry is a nationwide and population-based registry, established in 1954. The registry contains information about twins born between 1870 and 2004 and identified through church records or through the Central Office of Civil Registration. The registry currently holds data of more than 75 000 Danish twin pairs. All twins in the registry are ascertained independently of any disease. Zygosity is self-reported and established through a questionnaire with questions on the degree of similarity between twins in a pair.[19,20] Validity of this kind of classification has been evaluated through blood samples and misclassification found to be less than 5% of cases.[21]

Information on diagnosis (World Health Organization; International Classification of Diseases, 8th edition: code 427.4; 10th edition: code I48.9) was collected from The Danish National Patient Registry. This registry contains information about all patient contacts with all Danish Hospitals since 1977, including the specific hospital and department, admission and discharge dates, and diagnoses (www.sst.dk).

Through merging information from the 2 registries, all twin pairs in which at least 1 of the twins was diagnosed with AF were identified. For all twins identified, the following information was sampled: zygosity, sex, time of birth, vital status, time of death or emigration, and time of first diagnosis of AF. From the initial data set, twins born earlier than January 1, 1912, were excluded to avoid misclassification due to diagnosis not registered in The Danish National Patient Registry. Twins with unknown zygosity and twin pairs with information only on 1 twin were also excluded from the dataset. Opposite sex twin pairs were excluded because data on opposite twin pairs are only available for a fraction of the cohorts under study.[20] Furthermore, before entering the Cox proportional hazards model, twin pairs in which the co-twin was lost to follow-up before diagnosis of the index twin were excluded. Finally, 1 pair of twins was excluded due to doubt of diagnosis as the index twin apparently was diagnosed at the age of 7.

Statistical Analysis

Analysis of Proband-Wise Concordance Rates

The proband-wise concordance rate is the probability that a twin gets the disease given that his or her twin partner already has the disease. Concordant twin-pairs are defined as pairs in which both twins have been diagnosed with AF and discordant twin-pairs as pairs in which only 1 twin has the diagnosis. The proband-wise concordance rate is preferred to other types of concordance rates because it does not vary with the ascertainment probability and is found to equal on average the population case-wise rate.[22]

Because MZ twins are completely identical for all genetic factors and DZ twins share on average 50% of their genes, higher concordance rates among MZ twins are interpreted to be caused by genetic factors. Differences between concordance rates for MZ and DZ twins are tested with the χ^2 test with 1 degree of freedom. The concordance rates were calculated manually, using the formula for proband-wise concordance rates.

Cox Proportional Hazards Model

The genetic effect was explored using survival analysis in the Cox proportional hazards model. The diagnosis-free time after diagnosis of the index twin was compared between MZ and DZ twins. The index twin is defined as the twin first diagnosed with AF within a twin pair. The co-twin is defined as the twin who is the twin-sibling of the index twin.

A shorter time span between occurrences of disease in MZ twins would be indicative of a genetic effect. Thus, for each twin pair, we calculated the time span from diagnosis of the index twin to diagnosis of the co-twin. For some pairs this time was right-censored because of end of follow-up or death. In a Cox model, the relation between time from diagnoses and zygosity, sex, and age was assessed. In further analysis, we included an interaction term between sex and zygosity to assess whether the genetic effect is dependent on sex. To investigate the genetic effect in younger twins, we analyzed the twins divided into 2 strata defined as $\geq$65 years and $<$65 years. Results are given as hazard ratios with 95% confidence limits. Cumulative incidence curve was constructed from Kaplan-Meier coordinates and differences between strata (zygosity) evaluated by log-rank test. We used SAS version 9.1 and the procedure "proc phreg," calculating the Cox proportional hazards model.

Biometric Models

Biometric models were used to estimate the heritability. The relative importance of genetic factors is assessed by the liability approach. Liability is based on threshold models, reflecting prevalence on a latent distribution of liability. Individuals above this threshold are assumed to have the trait of interest, whereas individuals under the threshold are assumed not to have the trait.[23]

The correlation between relatives—in the present study, MZ and DZ twins—is used to partition the correlation into components attributable to shared genes and environments, to estimate heritability. The correlation coefficients rMZ and rDZ calculated for MZ and DZ twins, respectively, provides information of genetic as well as environmental influences, and, assuming equal environments, differences in the 2 correlation coefficients will represent the influence of genetic factors. The following relations are the standard assumptions about the quantitative genetics:

$$r_{MZ}=a^2+d^2+c^2,\ r_{DZ}=0.5\ a^2+0.25\ d^2+c^2,$$

$$\text{and } 1=a^2+d^2+c^2+e^2$$

where a^2 corresponds to the proportion of the total variance associated with additive genetic effects (A), d^2 with dominant genetic effects (D), c^2 with shared environmental effects (C), and e^2 with nonshared environmental effects (E). All components are assumed to be independent. Different genetic models can be tested combining these elements, but no more than 3 components can be simultaneously represented in a model for MZ and DZ twins reared together. An ADE model refers to decomposition of frailty Z=A+D+E, an AE model refers to Z=A+E, and so on. Dominant and shared environmental factors cannot be represented simultaneously because of confounding of the two in a study of twins reared together. The model assumes no epistasis, no gene-environment interaction, and no assortative mating. Selection of the best-fitted model is based on Akaike information criterion (AIC=χ^2-2 df). We used Mx software[24] for the estimation procedures, and all models were fitted to contingency tables separately for men and women.

Subanalysis of Early Onset AF

To study the effect of zygosity and sex in the younger age groups, we used a cutoff age of 65 years at the time of diagnosis of proband. This value was chosen as a compromise to define a population as young as possible without loosing the possibility to perform the

Table 1. Baseline Characteristics of Participants by Zygosity and Diagnostic Status at Inclusion

	All	Female	Male
Discordant pairs			
No. of pairs	1045	453	592
Age, y	68.2 (13.2)	71.7 (11.8)	65.5 (13.5)
Zygosity (MZ)	312 (30%)*	125 (28%)†	187 (32%)‡
Concordant pairs			
No. of individuals	92	40	52
Age, y	67.7 (11.1)	71.8 (9.3)	64.5 (11.5)
Zygosity (MZ)	44 (48%)*	19 (48%)†	25 (48%)‡

Continuous variables are mean (SD).

*$P<0.001$, †$P<0.05$, ‡$P<0.01$, by Student t test for continuous values or χ^2 for categorical values comparing discordant and concordant pairs.

analysis at all due to too low number of events. The estimates were calculated as odds ratios with 95% confidence limits from a 2×2 table using the χ^2 and Fisher exact test.

Results

A total of 1137 twin pairs were identified, 356 MZ and 781 DZ pairs. Of these 1137 pairs, 92 were concordant and 1045 were discordant pairs. Mean age of the concordant pairs at inclusion (time of first diagnosis) was 68.2 years and for the discordant pairs, 67.7 years (Table 1).

Concordance Rates

Proband-wise concordance rates are shown in Table 2. Analyzing all 1137 twins in 1 group regardless of sex showed concordance rate for MZ twins approximately twice the rate for DZ twins: 22.0% versus 11.6% ($P<0.0001$). Stratifying for sex did not change these figures significantly: 23.3% versus 11.4% ($P<0.001$) for women and 21.1% versus 11.7% ($P=0.001$) for men.

Cox Proportional Hazards Model

From the original total number of 1137 twin pairs, we identified 806 pairs, 255 MZ and 551 DZ pairs, in which the co-twins were alive after the diagnosis of the index twin and thus fitted into a Cox proportional hazard model. The risk of AF was significantly associated with monozygosity (hazard ratio [HR], 2.0; 95% CI, 1.3 to 3.0; $P=0.0009$). The disease rate is twice as high in MZ twins compared with DZ twins (Figure), and this difference is clearly statistically significant,

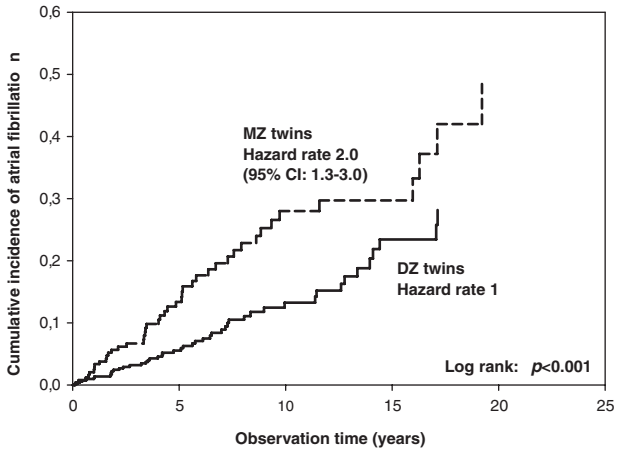

Figure. Plot of cumulative incidence of AF as a function of zygosity for both sexes analyzed together.

indicating that AF has a genetic component. As expected, entry age had a strong effect on AF risk (HR, 1.5; 95% CI, 1.2 to 1.9) for each 10-year increase $P<0.0001$). Disease rate was 30% higher in men but not statistically different from the female rate (HR, 1.3; 95% CI, 0.84 to 2.0; $P=0.24$). When analyzing 2 age groups separately, we find a stronger genetic effect of zygosity in twins <65 years than in twins ≥65 years (HR, 2.9; $P=0.0036$ versus HR, 1,65; $P=0.0514$); the difference is not statistically significant ($P=0.21$). This effect was expected, as we see a tendency for the time to diagnosis of the co-twin to decrease as a function of the age of the index twin at time of his or her diagnosis. The effects of age as an independent risk factor play a role.

In the analysis allowing for a sex-dependent effect of zygosity, this appeared to be stronger for women (HR, 2.1; 95% CI, 1.2 to 4.0; $P=0.017$) than for men (HR, 1.9; 95% CI, 1.1 to 3.3; $P=0.021$), but the difference between the sexes was not statistically significant ($P=0.78$). This difference was even more pronounced though still not statistically significant when analyzed for the younger age groups. Analyzing only patients younger than 65 years at time of diagnosis of proband showed the odds ratio for women at 5.2 (95% CI, 1.2 to 23.1; $P=0.034$) and for men, 2.7 (95% CI, 1.1 to 6.7; $P=0.020$) (Table 3).

Biometric Models

Contingency tables along with prevalence for AF divided into sex and zygosity groups are shown in Table 4. Tetrachoric

Table 2. Number of Concordant and Discordant Twin Pairs and Proband-Wise Concordance Rates for AF by Sex and Zygosity

	Both Sexes		Women		Men	
Zygosity	MZ	DZ	MZ	DZ	MZ	DZ
Total No. of AF twin pairs	356	781	144	349	212	432
Concordant pairs	44	48	19	21	25	27
Discordant pairs	312	733	125	328	187	405
Proband-wise concordance rate, %	22.0*	11.6*	23.3†	11.4†	21.1‡	11.7‡

Concordant pairs are pairs in which both twins have the disease; discordant pairs are pairs in which only 1 twin has the disease. Concordance rate is the probability that an affected twin has a co-twin who is also affected. Differences between proband-wise concordance rates (in percentages) in MZ and DZ twins are statistically significant.

*$P<0.0001$, †$P<0.001$, ‡$P=0.001$.

Table 3. Distribution of Events Stratified for Sex and Zygosity and With Age at Diagnosis of Index Twin <65 Years (n=391)

	Women		Men	
	MZ	DZ	MZ	DZ
No event	15 (79%)	78 (95%)	67 (85%)	155 (94%)
AF	4 (21%)	4 (5%)	12 (15%)	10 (6%)
Total	19 (100%)	82 (100%)	79 (100%)	165 (100%)
Odds ratio (95% CI)	5.2 (1.2–23.1)		2.7 (1.1–6.7)	

Distribution of events differed significantly between MZ and DZ twins for both sexes; χ^2 and Fisher exact test (P=0.034 for women; P=0.020 for men).

correlations for men and women are given in Table 5 together with probability values for test of homogeneity of thresholds across zygosity groups. Women show significantly different thresholds (P<0.01) caused by differing prevalence in the zygosity groups, whereas there is no difference for men (P=0.08). Assuming the same thresholds across zygosity groups, within the sexes there is a significant difference in thresholds (and thereby prevalence) between men and women (P<0.001). Model-fit statistics for the biometric models are shown in Table 6; the AE model provided the best-fitting model (lowest AIC) for both men and women. The heritability of AF was estimated to be 67% (95% CI, 57% to 76%) among women and 59% (95% CI, 49% to 67%) among men because of additive genetic effects (Table 7). The difference in heritability of men and women was not statistically significant, and the common estimate is 62% (95% CI, 55% to 68%).

Discussion

In the present study of Danish twins with AF, we demonstrate that once a twin is diagnosed with AF, the probability of his or her co-twin getting the disease is associated with zygosity. Two studies have previously addressed the heritability of nonfamilial AF or AF in the general population, concluding that risk of AF to some extent is a heritable condition,[12,17] but these studies have not been able to disentangle the effect of common familial environment and genetic factors. Because

Table 4. Contingency Tables and Prevalence of AF Among Danish Twins Subdivided Into Sex and Zygosity Groups

		MZ Twin 2		DZ Twin 2	
	Twin 1	+AF	−AF	+AF	−AF
Women	+AF	19	63	21	164
	−AF	63	5.001	164	7.916
Prevalence (95% CI), %		1.58 (1.35–1.84)		2.24 (2.02–2.48)	
Men	+AF	25	93	27	203
	−AF	93	4.821	203	8.542
Prevalence (95% CI), %		2.35 (2.07–2.67)		2.56 (2.33–2.80)	
Both sexes	+AF	44	156	48	367
	−AF	156	9.822	367	16.458
Prevalence (95% CI), %		1.97 (1.78–2.17)		2.41 (2.25–2.57)	

Table 5. Tetrachoric Correlations

	r_{MZ} (95% CI)	r_{DZ} (95% CI)	*P* Value*
Women	0.66 (0.54–0.75)	0.36 (0.25–0.46)	<0.01
Men	0.56 (0.45–0.65)	0.35 (0.25–0.45)	0.08

r_{MZ} indicates correlation coefficient for MZ twins; r_{DZ}, correlation coefficient for DZ twins.

*Test for equal threshold for MZ and DZ.

MZ twins have completely identical genes, no relatives are genetically closer to each other than they, and we assume that any variation in concordance rates of AF between MZ and DZ twins will be gene dependent.

Comparisons of concordance rates as well as analysis of twin similarities indicate that genetic effects play a significant role for the risk of AF for both sexes. Concordance rates for MZ twins are more than twice the rates for DZ twins when both sexes are analyzed in 1 group, 22.0% versus 11.6%, and this difference is highly significant (P<0.0001) Analyzing both sexes separately did not change these figures (Table 2). The analysis of twin similarities further supports this by estimating the heritance of AF to be 62% due to additive genetic factors (ie, the effect of the genetic factors are acting additively and not primarily as gene-gene interaction, which would have been reflected in a more than factor 2 difference in the correlation for MZ and DZ twins) (Table 7).

Cox proportional hazard regression models with age and sex as covariates showed a hazard ratio of 2.0 for development of AF for an MZ twin once his or her twin-sibling had developed the disease. Analyzing twins younger than and older than 65 years separately showed that this effect is even stronger in the younger twins (HR, 2.9; P=0.0036 versus HR, 1.65; P=0.0514), although the difference is not statistically significant. We had expected that AF in the younger twins would be more genetic, because they do not have the same degree of concomitant diseases that increases the risk of AF. Age and sex are known to be strongly associated with risk of AF with male sex and increasing age as predictors of increasing risk, but in our model only age and zygosity was significantly associated with risk for AF. Furthermore, the increase in risk associated to zygosity was higher than that associated with a 10-year increase in age. Testing the distribution of events stratified for sex and zygosity in the age groups younger than 65 years showed an odds ratio for AF of 5.2 for women and 2.7 for men (Table 3), suggesting a stronger association between zygosity and AF for women than for men in the younger age groups, although the difference between the 2 groups were nonsignificant. This finding is in accordance with data from the Framingham Heart Study,[12] in which female AF had a stronger association with risk of AF in offspring than in male AF. In the present analysis, this trend increased with decreasing age, and we speculate whether the explanation may be that female AF in the younger age groups is more likely to be "lone AF" and therefore more genetic in nature. This would imply that AF in the older age groups to a higher degree is associated with concomitant conditions such as hypertension, ischemic heart disease, diabetes, and obesity—all conditions with a male predominance. Disorders with a genetic predisposition often

Table 6. Model-Fit Statistics for Biometric Models

	Women					Men				
Model	AIC	vs	Δdf	$\Delta\chi^2$	*P* Value	AIC	vs	Δdf	$\Delta\chi^2$	*P* Value
ACE	6.08					−2.53				
ADE	6.34					5.70				
AE	4.34	ACE	1	0.26	0.61	−3.45	ACE	1	1.08	0.30
CE	17.3	ACE	1	13.3	<0.001	4.24	ACE	1	8.77	<0.01
DE	15.3	ADE	1	10.9	<0.01	29.1	ADE	1	25.4	<0.001
E	117	AE	1	115	<0.001	109	AE	1	115	<0.001

A indicates additive genetic effects; D, dominant genetic effects; E, shared environmental effects; C, nonshared environmental effects; AIC, Akaike Information Criterion; Δdf, difference in degrees of freedom; $\Delta\chi^2$, difference in χ^2.

occur at a younger age. As mentioned, AF primarily is a disease of the elderly, but occasionally patients as young as in their early 20s are seen. The younger the patients are, the more likely they will present with AF in the absence of major predisposing conditions and therefore presumably with AF of a more genetic nature. Although we see a trend toward this conclusion in claiming that young female participants in our study present the strongest association between zygosity and AF, the present data suggest that AF in all age groups has a considerable genetic component.

This study provides estimates of the sources of the variability in AF occurrence. Currently, a number of loci that confer increased vulnerability to AF and variance in candidate genes have been found both through linkage studies and genome-wide association studies. Association between loci on chromosome 10[25] and 6[26] have been reported, and the list of candidate genes is currently expanding: KCNQ1,[9] KCNJ2,[10] KCNE5,[14] KCNE2,[11] and the genes behind the renin-angiotensin system[15] and PITX2.[16] The heritability estimates give a very helpful overall estimate of the influence of genetic factors and can give us information about the prospect of identifying further genetic variants of importance for AF.

Conclusion

Monozygosity associates with increased risk of AF for twins whose twin-sibling has been diagnosed with AF. Assuming that the major difference between MZ and DZ twins is the degree of genetic similarity, we interpret this difference in risk of AF to be caused by genetic factors, and biometric models suggest a degree of heritability in AF as high as 62%.

Study Limitations

The quality of the diagnoses in The Danish National Patient Registry is a topic for discussion. In a former validation of the registry, review of 116 medical records by a cardiologist confirmed the diagnoses in 112 cases.[27] Twins diagnosed with AF before 1977 and not on any later occasion will not be registered in The Danish National Patient Registry. This potential misclassification was minimized by only including twins older than 65 years at the time of start of the registry.

Misclassification regarding the diagnosis is most likely independent of zygosity and will make the concordance rates smaller in both groups of twins, thus making the groups more similar and increasing the probability of the null hypothesis. Despite this fact, we have found a strong heritability estimate.

We make the assumption that any differences in concordance rates between MZ and DZ twins is due to the difference in their degree of genetic relatedness. This is standard twin methodology, and all twin heritability estimates are made under the "equal environment assumption," that is, the degree of intrapair similarity due to the common environment is equal in monozygotic and dizygotic twins. This assumption has been much debated and investigated, and it has generally been shown to be a valid and robust assumption.[28]

The majority of excluded twins were excluded because of lack of follow-up information about the co-twin. This was most frequent among the older twin pairs, thus reflecting differences in data handling and collection over time and not differential reporting depending on zygosity or disease status. Regarding the group of twins born before 1912, 27 twin pairs that otherwise qualified for inclusion were excluded: 17 DZ (same sex) and 10 MZ pairs. None of these pairs were concordant with respect to disease. From the population in the analysis, the expected distribution of zygosity and concordance in a group of 27 twin pairs would be 19 DZ (same sex) and 8 MZ pairs, and of these, 2 pairs would be concordant. It is therefore not likely that any significant bias is introduced by this exclusion.

General practitioners in Denmark do not register ICD diagnoses in the NPR. Therefore, affected twins who have not been hospitalized but only diagnosed by their general practitioner will not be included in this study. This means that the actual number of both MZ and DZ twins with AF may be higher. Certain clinical conditions, such as hypertension, ischemic heart disease, diabetes, and hyperthyroidism, are strong risk factors for AF. Our study design unfortunately did not give us the opportunity to assess the distribution of these risk factors among our twin population. Because these conditions also are suspected to be at least to some degree heritable, this may be a potential bias.

Monozygotic twins know that they share most of their phenotypic traits because they are "identical twins," as opposed to dizygotic twins, who may not resemble each other

Table 7. Variance Components for AE Models

	Both Sexes	Women	Men
a^2 (95% CI)	0.62 (0.55–0.68)	0.67 (0.57–0.76)	0.59 (0.49–0.67)
e^2 (95%CI)	0.38 (0.32–0.45)	0.33 (0.24–0.43)	0.41 (0.33–0.51)

a^2 indicates additive genetic effects; e^2, nonshared environmental effects.

either physically or psychologically. A monozygotic twin with a twin-sibling diagnosed with AF may therefore be more eligible to seek a physician to be examined for this same disease than a dizygotic twin with a co-twin diagnosed with AF. This will overestimate monozygotic concordance rates.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. Familial clustering of AF has been known for more than 70 years. In population studies, children of parents with AF have a nearly double or even greater risk of AF. Mutations and polymorphisms in genes coding for ion channels involved in cardiac repolarization and connexins may be involved in promoting AF. The present twin study confirms the basic notion that inherited factors play a role in the development of AF and suggests that the importance of heritable factors may be greater than previously suggested. We find that monozygotic twins have twice the concordance rate for AF as dizygotic twins. A monozygotic twin has twice the risk of AF if his or her co-twin is diagnosed with AF, as compared with a dizygotic twin in the same situation. We estimate the heritability of AF to be as high as 67%. Family history is an important factor to take into consideration in the evaluation of patients at risk for development of AF. Understanding the genetic components and how they contribute to the pathophysiology leading to AF may lead to new approaches in diagnosis, prevention, and treatment of this common cardiac arrhythmia.

Familial Aggregation of Atrial Fibrillation: A Study in Danish Twins

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