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Clinical, biomarker, and genetic predictors of specific types of atrial fibrillation in a community-based cohort: data of the PREVEND study

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Aims Atrial fibrillation (AF) may present variously in time, and AF may progress from self-terminating to non-self-terminating AF, and is associated with impaired prognosis. However, predictors of AF types are largely unexplored. We investigate the clinical, biomarker, and genetic predictors of development of specific types of AF in a community-based cohort.

Methods We included 8042 individuals (319 with incident AF) of the PREVEND study. Types of AF were compared, and multivariate multinomial regression analysis determined associations with specific types of AF.

Results Mean age was 48.5 ± 12.4 years and 50% were men. The types of incident AF were ascertained based on electrocardiograms; 103(32%) were classified as AF without 2-year recurrence, 158(50%) as self-terminating AF, and 58(18%) as non-self-terminating AF. With multivariate multinomial logistic regression analysis, advancing age ($P < 0.001$ for all three types) was associated with all AF types, male sex was associated with AF without 2-year recurrence and self-terminating AF ($P = 0.031$ and $P = 0.008$, respectively). Increasing body mass index and MR-proANP were associated with both self-terminating ($P = 0.009$ and $P < 0.001$) and non-self-terminating AF ($P = 0.003$ and $P < 0.001$). The only predictor associated with solely self-terminating AF is prescribed anti-hypertensive treatment ($P = 0.019$). The following predictors were associated with non-self-terminating AF; lower heart rate ($P = 0.018$), lipid-lowering treatment prescribed ($P = 0.009$), and eGFR <60 mL/min/1.73 m^2 ($P = 0.006$). Three known AF-genetic variants (rs6666258, rs6817105, and rs10821415) were associated with self-terminating AF.

Conclusions We found clinical, biomarker and genetic predictors of specific types of incident AF in a community-based cohort. The genetic background seems to play a more important role than modifiable risk factors in self-terminating AF.

Keywords Arrhythmia • Atrial fibrillation • Risk factors • Epidemiology • Genes • Biomarkers

Introduction

Nowadays, atrial fibrillation (AF) is one of the cardiovascular epidemics in Europe and the USA, and increases risk of stroke, heart failure, and death.[1,2] As a consequence, AF has extensive impact on public health. The toll of AF is expected to increase in the years to come.[3]

After a first episode of AF, rates of AF recurrences are extremely high, >90%.[4] Atrial fibrillation may have various presentations; AF may manifest as self-terminating episodes of AF, or more sustained forms of AF. Clinical risk factors of incident AF are well known, and include advancing age, male sex, hypertension, obesity, diabetes, heart failure, and valvular disease.[5,6] Data regarding risk factors for specific AF types are sparse.[7] Recent data suggest that more sustained forms of AF are at higher risk of vascular events, heart failure, and death.[4,8] Rates of AF progression vary between 5 and 15% per year depending on the population studied.[9–11] Recent studies identified risk factors for AF progression including advancing age,

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What's new?

- We studied predictors of specific types of incident AF (AF without 2-year recurrence, self-terminating, and non-self-terminating AF) in a community-based cohort.
- Clinical, biomarker, and genetic predictors of specific types of incident AF in a community-based cohort were found.
- The balance between the genetic background and modifiable risk factors of AF seems different in self-terminating vs. non-self-terminating AF.

hypertension, heart failure, stroke, and chronic obstructive pulmonary disease.[8,11] Still, a large part of the risk of AF progression to non-self-terminating AF is unexplained.[6,12] Recently, 10 genetic variants have been discovered associated with AF;[13] however, no data are available regarding the association of these genetic variants with specific AF types.

We now investigate the clinical, biomarker, and genetic predictors of specific AF types, in a well-characterized community-based cohort, the Dutch Prevention of Renal and Vascular End-stage Disease (PREVEND) study.

Methods

Population

This study was performed using data from individuals participating in the PREVEND study, founded in 1997 in Groningen, The Netherlands. A detailed description of this study has been previously described.[14] In total, 8592 individuals were included and followed at 3-year intervals. AF assessment has been described in detail previously.[14] In brief, all electrocardiograms (ECGs) made at PREVEND screenings visits, hospital visits, or hospital admissions were screened. For present analysis, we excluded 248 individuals without any ECG. Of the 8344 individuals, 621 were diagnosed with AF. We excluded 79 individuals with prevalent AF. Of the 542 individuals with incident AF, we excluded those with <2 follow-up ECGs in the first 2 years after initial AF ($n = 137$). Additionally, we excluded those with <90 days between first and last available ECG ($n = 82$), and those with insufficient ECG quality to determine the rhythm ($n = 4$), leaving 319 individuals with incident AF for analysis (Supplementary material online, *Figure S1*). The PREVEND study was approved by the institutional medical Ethics Committee and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Atrial fibrillation definitions

Incident AF was assessed if either atrial flutter or AF was present on a 12-lead ECG at one of the three follow-up visits, or at an outpatient visit or hospital admission in the two hospitals in the city of Groningen (University Medical Center Groningen and Martini Hospital).[14] Based on all subsequent ECGs made in the first 2 years after initial AF detection, individuals were classified. If >1 ECG was performed on the same day, the ECG with AF was counted. Atrial fibrillation was classified as (i) AF without 2-year recurrence when AF was present on the initial ECG, but no AF was seen on all subsequent ECGs during 2-years after initial AF, (ii) self-terminating AF when AF was present on the initial ECG and on follow-up ECGs, but AF was seen on fewer than 90% of all follow-up ECGs, and (iii) non-self-terminating AF when AF was present on the initial ECG and on $>90\%$ of all follow-up ECGs.

Covariate definitions

Systolic and diastolic blood pressures were calculated as the mean of the last two measurements of the two visits, using an automatic Dinamap XL Model 9300 series device. Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure <90 mmHg, or self-reported use of anti-hypertensive drugs. Anti-hypertensive drugs were defined as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, or calcium antagonists as a marker of hypertension.[14] Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m^2), and obesity was defined as a BMI $>$ 30 kg/m^2. Diabetes was defined as a fasting plasma glucose $\geq$7.0 mmol/L (126 mg/dL), or a non-fasting plasma glucose $\geq$11.1 mmol/L, or use of anti-diabetic drugs. Hypercholesterolaemia was defined as total serum cholesterol >6.5 mmol/L (251 mg/dL) or a serum cholesterol >5.0 mmol/L (193 mg/dL) if a history of myocardial infarction was present or use of lipid-lowering drugs. Smoking was defined as nicotine use in the last 5 years. Previous myocardial infarction or stroke was defined as participant-reported hospitalization for at least 3 days as a result of this condition. Heart failure was ascertained by an expert panel as described in detail before.[15]

Laboratory testing

Fasting blood samples were obtained during the morning, and 24-h urine collections were obtained. The details on the laboratory measurements have been published previously.[16,17] Urinary albumin excretion was measured in the first morning void. The glomerular filtration rate was calculated using the simplified modification of diet formula.[18]

Genetic variants

Genotyping was performed using the Illumina CytoSNP12 v2 chip as previously described.[19] The single nucleotide polymorphisms (SNPs) from each of the 10 AF susceptibility loci identified by prior genome wide association studies[13] were selected for association testing. When the AF-related SNP was not directly genotyped on the Illumina CytoSNP12 v2 chip, imputed data was used (additional information in Supplementary material online, *Table S1*). Genotype data were only available for a subset of the included individuals (3419 individuals [42.5%]).

Statistical analysis

To adjust for the overselecting of individuals with microalbuminuria at study start, we added urine-albumin excretion as covariate in all regression analysis. Characteristics of the AF without 2-year recurrence, self-terminating, non-self-terminating AF, and no AF groups were presented as mean $\pm$ standard deviation or median (interquartile range) for continuous variables and counts with percentages for categorical variables. Comparisons between the specific AF types and the no AF group were evaluated using the *t*-test or

the analysis of variance or the Wilcoxon rank test or Kruskal test, depending on normality of the data, for continuous data. For categorical data, the Fisher exact test (in case of binomial proportions) was used predominantly, and in the case of >2 response categories, the χ^2 test was used. We examined associations between AF-related SNPs and AF types using multinomial logistic regression analysis. We performed multivariate multinomial logistic regression analysis to assess the clinical, biomarker, and genetic predictors of specific types of AF (AF without 2-year recurrence, self-terminating, and non-self-terminating AF). In multinomial logistic regression, the different AF types are compared with the no AF group as reference. Covariates (except the genetic variants) with $P < 0.05$ in a urine-albumin excretion adjusted model were stepwise incorporated in a multivariable-adjusted model. The final multivariable model included all covariates with $P < 0.05$. Finally, interactions in the multivariate model were investigated. All analysis were performed using R package (version 3.0.3), and a *P*-value of <0.05 was considered statistically significant (*Figure 1*).

Results

Individuals' characteristics

We included 8042 individuals (319 with incident AF) in our analysis. The mean age was 48.5 ± 12.4 years and 49.5% were men. In *Table 1*, the clinical risk factors, cardiovascular diseases, and biomarkers at study start are depicted according to the types of incident AF. Of all included incident AF cases, 103 (32%) were classified as AF without 2-year recurrence, 158 (50%) as self-terminating AF, 58 (18%) as non-self-terminating AF. The median number of ECGs per individual was 15 (interquartile range 9–27). Age was significantly higher in each specific AF type group when compared with the no AF group. Sex differences were observed in all three AF type groups compared with no AF (49% men); 66% of AF without 2-year recurrence ($P < 0.001$), 63% of self-terminating AF ($P < 0.001$) and 74% of non-self-terminating AF ($P < 0.001$) individuals were men. Body mass index, systolic and diastolic blood pressure were significantly higher in each specific AF type group when compared with the no AF group. Hypertension, previous myocardial infarction, and diabetes were more common in each specific AF type group when compared with the no AF group. Heart rate was higher in the self-terminating and non-self-terminating AF group when compared with the no AF group. All measured biomarkers were significantly higher in each specific AF type group when compared with the no AF group.

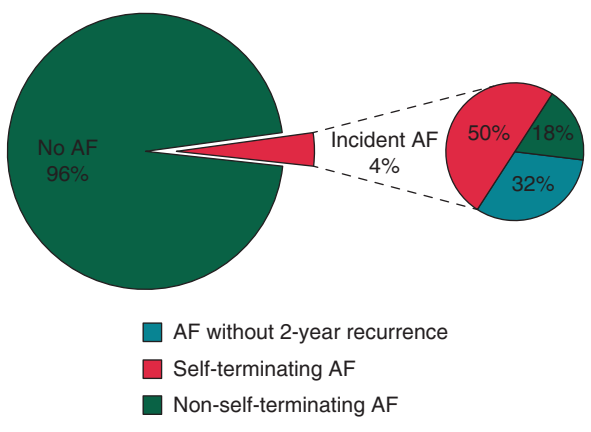

Figure 1 Representative Figure Specific types of atrial fibrillation. In present study, individuals with incident Atrial fibrillation were ascertained based on electrocardiogramavailability; 103(32%) were classified as AF without 2-year recurrence, 158(50%) as self-terminating AF, and 58(18%) as non-self-terminating AF.

Common genetic variants

With multinomial logistic regression analysis, and the no AF group as reference, rs6666258, on chromosome 1q21, in the *KCNN3/PMVK* locus [relative risk ratio (RRR) 1.58, 95% confidence interval (CI) 1.12–2.23, $P = 0.009$), rs6817105, on chromosome 4q25 near the *PITX2* locus (RRR 1.74, 95% CI 1.12–2.68, $P = 0.013$), and rs10821415, on chromosome 9q22, in the *C9orf3* locus (RRR 1.49, 95% CI 1.07–2.08, $P = 0.019$) were associated with self-terminating AF, and not with the other AF types (*Table 2*).

Predictors of specific atrial fibrillation types

With multivariate multinomial logistic regression analysis, advancing age ($P < 0.001$ for all AF types, *Table 3*) was associated with AF without 2-year recurrence, self-terminating, and non-self-terminating AF. Male sex was associated with AF without 2-year recurrence and self-terminating AF ($P = 0.031$ and $P = 0.008$). Increasing BMI and higher concentrations of mid-regional prohormone atrial natriuretic peptide (MR-proANP) were associated with both self-terminating ($P = 0.009$ and $P < 0.001$, respectively) and non-self-terminating AF ($P = 0.003$ and $P < 0.001$, respectively). Prescribed anti-hypertensive treatment ($P = 0.016$) was only associated with self-terminating AF. The following covariates were associated with non-self-terminating AF; lower heart rate ($P = 0.018$), lipid-lowering treatment prescribed ($P = 0.012$), and eGFR < 60 mL/min/1.73 m^2 ($P = 0.007$) (Supplementary material online, *Figure S2*).

Discussion

In our contemporary community-based cohort, we determined clinical, biomarker, and genetic predictors of specific types of incident AF; AF without 2-year recurrence, self-terminating, and non-self-terminating AF.

Types of atrial fibrillation

A first episode of AF is always followed by a recurrence of AF, however the timing of recurrence maybe highly variable.[4] Different types of AF are described.[6,12] The most widely used classification system for temporal patterns of AF is the 3-P classification; paroxysmal, persistent, and permanent AF.[1] When AF terminates spontaneously it is called paroxysmal AF, when AF continues beyond 7 days, it is called persistent AF, when cardioversions of longstanding persistent AF are deemed unnecessary or have failed, it is called permanent AF.

Table 1 Clinical and biomarker profile, according to type of incident AF

Clinical profile	No. of AF (n = 7723)	AF without 2-year recurrence (n = 103)	*P*-value	Self-terminating AF (n = 158)	*P*-value	Non-self-terminating AF (n = 58)	*P*-value
Age (years)	48 ± 12	59 ± 10	<0.001	59 ± 9	<0.001	62 ± 9	<0.001
Male sex	3770 (49%)	68 (66%)	<0.001	100 (63%)	<0.001	43 (74%)	<0.001
Caucasian	7322 (95%)	97 (94%)	0.657	155 (98%)	0.067	56 (97%)	0.769
BMI (kg/m^2)	26.0 ± 4.2	27.3 ± 3.6	<0.001	28.2 ± 4.6	<0.001	28.0 ± 3.7	<0.001
Obesity	1154 (15%)	26 (25%)	0.008	45 (29%)	<0.001	10 (17%)	0.585
systolic blood pressure (mmHg)	128 ± 20	138 ± 22	<0.001	144 ± 23	<0.001	148 ± 21	<0.001
Diastolic blood pressure (mmHg)	74 ± 10	78 ± 9	<0.001	79 ± 9	<0.001	79 ± 10	<0.001
Heart rate(bpm)	69 ± 10	68 ± 11	0.278	68 ± 11	0.045	66 ± 11	0.018
Anti-hypertensive treatment prescribed	912 (14%)	33 (35%)	<0.001	51 (36%)	<0.001	25 (53%)	<0.001
Hypertension	1944 (26%)	41 (41%)	0.001	91 (59%)	<0.001	38 (67%)	<0.001
Previous myocardial infarction	184 (2%)	11 (11%)	<0.001	17 (11%)	<0.001	10 (18%)	<0.001
Heart failure	12 (0.2%)	0 (0%)	1.000	1 (0.6%)	0.232	3 (5.2%)	<0.001
Glucose lowering treatment prescribed	97 (2%)	4 (4%)	0.058	6 (4%)	0.024	2 (4%)	0.165
Diabetes mellitus	259 (3%)	10 (10%)	0.003	13 (9%)	0.003	8 (14%)	<0.001
Previous stroke	48 (0.6%)	3 (3%)	0.029	4 (2.6%)	0.020	1 (1.8%)	0.307
Smoking	3451 (45%)	47 (46%)	0.842	69 (44%)	0.871	22 (38%)	0.354
Lipid-lowering treatment prescribed	272 (4%)	10 (11%)	0.007	19 (14%)	<0.001	8 (17%)	<0.001
Biomarker profile							
Glucose (mmol/L)	4.7 (4.3–5.1)	4.9 (4.5–5.3)	<0.001	5.0 (4.6–5.6)	<0.001	4.9 (4.5–5.7)	0.008
eGFR(mL/min/1.73 m^2)	80.5 (71.7–89.8)	75.7 (65.8–88.0)	0.006	75.2 (70.0–86.2)	0.002	75.8 (66.6–82.9)	0.020
eGFR ≤ 60–mL/min/1.73 m^2	414 (5%)	11 (11%)	0.028	12 (8%)	0.210	5 (9%)	0.236
Urinary albumin concentration (mg/L)	11.8 (6.9–7.5)	13.5 (10.2–25.2)	0.009	15.8 (10.9–25.8)	<0.001	16.3 (10.1–54.7)	0.002
Creatinine(μmol/L)	82.0 (73.0–91.0)	86 (75–99)	0.005	85 (75–97)	0.009	89 (80–96)	0.001
Cystatine C(mg/L)	0.77 (0.68–0.87)	0.84 (0.73–0.95)	<0.001	0.87 (0.75–0.98)	<0.001	0.91 (0.82–1.02)	<0.001
NT-proBNP (ng/L)	35.1 (15.9–68.0)	74.1 (36.1–122.1)	<0.001	68.6 (30.7–153.4)	<0.001	123.2 (63.6–270.1)	<0.001
MR-proANP (ng/L)	46.7 (34.0–63.5)	64.0 (48.4–90.5)	<0.001	64.9 (46.2–95.2)	<0.001	83.3 (55.8–120.1)	<0.001
Highly sensitive-C-reactive protein (mg/L)	1.23 (0.54–2.85)	1.64 (0.83–3.83)	0.006	2.13 (0.86–4.04)	<0.001	2.11 (1.23–5.42)	<0.001

Data are expressed as mean ± SD, median (interquartile range), or numbers (%). Each AF group is compared with the no AF group.
AF, atrial fibrillation; BMI, body mass index; eGFR, estimated glomular filtration rate; MR-proANP, Mid-regional prohormone of the atrial natriuretic peptide; NT-proBNP, N-terminal prohormone of the brain natriuretic peptide.

Table 2 Distribution of common AF-related genetic variants associated with type of incident AF

Genetic variants			AF type					
			AF without 2-year recurrence (n = 103)		Self-terminating AF (n = 158)		Non-self-terminating AF (n = 58)	
AF SNP	Chromosome	Closest gene	RRR (95% CI)	*P*-value	RRR (95% CI)	*P*-value	RRR (95% CI)	*P*-value
rs6666258	1q21	*KCNN3-PMVK*	0.94 (0.57–1.54)	0.795	1.58 (1.12–2.23)	0.009	1.11 (0.63–1.95)	0.715
rs3903239	1q24	*PRRX1*	1.04 (0.66–1.65)	0.860	1.33 (0.95–1.85)	0.094	1.27 (0.75–2.16)	0.369
rs6817105	4q25	*PITX2*	1.73 (0.96–3.13)	0.068	1.74 (1.12–2.68)	0.013	1.27 (0.59–2.70)	0.539
rs2040862	5q31	*WNT8A*	1.12 (0.62–2.01)	0.703	1.07 (0.70–1.66)	0.747	0.97 (0.48–1.96)	0.931
rs3807989	7q31	*CAV1*	0.90 (0.58–1.41)	0.656	1.08 (0.77–1.50)	0.666	0.72 (0.43–1.21)	0.218
rs10821415	9q22	*C9orf3*	1.14 (0.72–1.79)	0.571	1.49 (1.07–2.08)	0.019	0.93 (0.55–1.59)	0.798
rs10824026	10q22	*SYNPO2L*	1.32 (0.68–2.56)	0.406	1.04 (0.67–1.62)	0.862	1.22 (0.58–2.55)	0.604
rs1152591	14q23	*SYNE2*	1.01 (0.64–1.59)	0.956	1.09 (0.78–1.51)	0.626	0.72 (0.43–1.23)	0.229
rs7164883	15q24	*HCN4*	1.33 (0.76–2.33)	0.313	0.83 (0.51–1.35)	0.455	0.53 (0.21–1.33)	0.175
rs2106261	16q22	*ZFHX3*	1.00 (0.57–1.74)	0.987	1.30 (0.89–1.90)	0.177	1.72 (0.98–3.01)	0.060

In multinomial logistic regression, the AF groups are compared with the no AF group (n = 7723), which act as a reference. Adjusted for urinary albumin concentration (mg/L).
AF, atrial fibrillation; CI, confidence interval; RRR, relative risk ratio; SNP, single nucleotide polymorphism.

Table 3 Multivariate multinomial logistic regression comparing type of AF to no AF

Covariate	AF type					
	AF without 2-year recurrence (n = 103)		Self-terminating AF (n = 158)		Non-self-terminating AF (n = 58)	
	RRR (95% CI)	*P*-value	RRR (95% CI)	*P*-value	RRR (95% CI)	*P*-value
Age (per 10 years)	1.70 (1.37–2.13)	<0.001	2.14 (1.48–3.07)	<0.001	1.84 (1.51–2.24)	<0.001
Male sex	1.66 (1.05–2.62)	0.031	2.82 (1.32–6.02)	0.008	1.47 (0.99–2.18)	0.053
Anti-hypertensive treatment prescribed	1.50 (0.88–2.56)	0.135	2.52 (1.19–5.33)	0.016	1.33 (0.85–2.08)	0.213
BMI (per 5 kg/m^2)	1.25 (0.94–1.66)	0.126	1.77 (1.15–2.71)	0.009	1.41 (1.12–1.78)	0.003
Heart rate (per 5bpm)	0.96 (0.86–1.07)	0.464	0.86 (0.73–1.01)	0.074	0.89 (0.80–0.98)	0.018
Lipid-lowering treatment prescribed	1.54 (0.76–3.14)	0.234	2.25 (0.96–5.26)	0.063	2.04 (1.17–3.56)	0.012
MR-proANP (per 50 ng/L)	1.33 (1.00–1.77)	0.051	1.78 (1.31–2.43)	<0.001	1.48 (1.19–1.84)	<0.001
eGFR $\leq$ 60 mL/min/1.73 m^2	0.92 (0.43–1.96)	0.828	0.62 (0.20–1.97)	0.416	0.33 (0.15–0.74)	0.007

In multinomial logistic regression, the AF groups are compared with the no AF group (n = 7723), which act as a reference. Adjusted for urinary albumine concentration.
AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; eGFR, estimated glomular filtration rate; MR-proANP, Mid-regional prohormone of the atrial natriuretic peptide; RRR, relative risk ratio.

The designation of paroxysmal and persistent AF is not changed when the arrhythmia is terminated by pharmacological or electrical cardioversion.[1] However, above classification system is not ideal for several reasons. First, the categories of this classification are not mutually exclusive, and may differ within the same individual. Secondly, in daily clinical practice and in both hospital- and population-based studies, most often there is no continuous rhythm monitoring available and asymptomatic AF may be overlooked. Thirdly, the preferences of the individual having AF and the treating physician may influence the applied therapy and thereby the type of AF. This has led to the use of various classification systems in different studies.[4,9] In present study, we tried to use an intuitive classification system based on the availability of ECGs, with the AF without 2-year recurrence as AF once detected, and not found on subsequent ECGs within 2 years after AF detection, self-limiting AF as AF present on fewer than 90% of all available follow-up ECGs, and non-self-terminating AF as AF present on >90% of all follow-up ECGs. A third of the incident AF individuals had AF without 2-year recurrence, half of the individuals presented with self-terminating AF, and a minority of 18% had non-self-terminating AF as first presentation.

Clinical and biomarker predictors of specific atrial fibrillation types

Atrial fibrillation may progress from self-terminating to non-self-terminating forms, and relates to more cardiovascular morbidity and mortality,[11,20] whereby the rates of progression vary between 5 and 15% per year,[9–11] In hospital-based cohorts, a wide range

of clinical predictors was found related to AF progression; advancing age, larger atrial size, heart failure valvular disease, hypertension, higher body mass index, chronic obstructive pulmonary disease, and prior stroke.[10,11,20] However, it remains difficult to define the individual risk of non-self-terminating AF and AF progression. In PREVEND, we studied the clinical predictors of the individuals with different types of AF, and largely similar groups. Only distinct differences in age, male sex, anti-hypertensive treatment prescribed, BMI, heart rate, lipid-lowering treatment prescribed, MR-ANP, and eGFR $\leq$ 60 mL/min/1.73 m^2 were found as predictors of specific AF types.

In a recent analysis, comparing paroxysmal and non-paroxysmal AF in the community-based Women's Health Study differences were found in higher age and body mass index, but not in hypertension between both types of AF.[7] In an analysis of the aspirin-treated AF patients, included in hospital-based AF Clopidogrel Trial with Irbesartan for prevention of Vascular Events-Aspirin and Apixaban vs. acetylsalicylic acid to prevent stroke in AF patients who have failed or are unsuitable for vitamin K antagonist treatment trials, the clinical profile according to AF type was presented; and multiple differences were present. Patients with permanent AF were older, more men, and a greater cardiovascular disease burden.[8] Importantly, patients in those studies had AF at inclusion, whereas we studied the predictors of those at risk for a specific type of incident AF. Furthermore, the applied definitions were different, the cohort origin (hospital based vs. community based), and the selection of participants (AF patients vs. healthy population).

Genetic variants and specific atrial fibrillation types

We found a different distribution of risk alleles of three common AF-associated genetic variants for each AF type; all three associated with self-terminating AF, and not with AF without 2-year recurrence and non-self-terminating AF. Although it is not completely understood how these genetic variants increase the risk of (a specific type of) AF, the observed differences may support the idea that individuals may be susceptible to AF and even specific type of AF. The first genetic variant rs6666258 at chromosome 1q21 lies within a gene called *KCNN3* that encodes for a voltage-independent calcium-activated potassium channel.[21] In human and mouse cardiac repolarization models, KCNN3 channels are of importance during the late phase of cardiac action potential. In atrial myocytes of *KCNN3* knockout mice it has been observed that the action potential duration was prolonged, the number of early depolarizations was increased, and pacing-induced atrial arrhythmias were common.[22] The SNPs from each of the 10 AF susceptibility loci were identified by prior genome wide association studies.[13] The second genetic variant rs6817105 at chromosome 4q25 lies near a gene called *PITX2* that encodes for the paired-like homeodomain transcription factor 2.[21] *PITX2c*$^{-/-}$ predisposes mice to atrial arrhythmia.[23] Similarly, in human atrial tissue, *PITX2* expression levels were found $\sim$2 times higher in the left atrium compared with the right atrium or the ventricles. *PITX2c* heterozygote mice had shorter atrial action potential durations compared with the wild type and were susceptible to AF induced by pacing, whereas no differences in cardiac morphology, including interstitial fibrosis and function, were observed.[24] The third genetic variant rs10821415 at chromosome 9q22 is located in an open reading frame C9orf3, also known as AP-O, encoding aminopeptidase O, which is expressed in the heart, and involved in cleavage of angiotensin subtypes.[25] No reports regarding its pathophysiological role in AF are available. The reported differences in genotypes found in those with self-terminating AF are intriguing, and suggest that there may be differences in pathophysiological pathways underlying the AF types. One may speculate that the genetic background is of relative more importance in those at risk for self-terminating AF, where the cardiovascular risk factors and disease are of relative more importance in those at risk for non-self-terminating AF. However, further studies are warranted to uncover the genetic contribution of specific AF types.

Strengths and limitations

Strengths of our analysis are the well-characterized cohort, the prospective design, long-term follow-up, and rigorous ascertainment of AF. The study also had potential limitations largely because of the observational study design. First, our AF ascertainment strategy may have been insensitive to asymptomatic paroxysms of AF, so asymptomatic AF may have been overlooked. Secondly, the number of ECGs per individual was highly variable especially in those with the minimum number of three ECGs in 2 years. In total, 61 (19%) individuals with incident AF had $<$5 ECGs; therefore, misclassification may have occurred. However, the total number of ECGs made in PREVEND participants was over 40,000. Thirdly, we were not informed about the treatment of AF, which may have impact the classification of AF. Information on rate- or rhythm control treatment was not available. Also, it is plausible that we may have been underpowered to study small size effects between the AF types, since numbers of individuals in each AF type were modest. Therefore, joint analyses in genetic consortia are necessary to increase statistical power, and extent present findings. Fourthly, since the majority of individuals included were of European ancestry, results cannot be extended to other ethnicities. Finally, by design, our cohort was enriched for microalbuminuria, and although we adjusted for microalbuminuria in all regression analysis, we cannot exclude the possibility that it has impacted our results.

Conclusions

We found clinical, biomarker, and genetic predictors of specific types of incident AF in a community-based cohort. The genetic background seems to play a more important role than modifiable risk factors in self-terminating AF.

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