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Novel Risk Factors for Atrial Fibrillation: Useful for Risk Prediction and Clinical Decision-Making?

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Atrial fibrillation (AF) is the most common cardiac arrhythmia; the lifetime risk is 1 in 4 for persons over the age of 40 years in the United States.¹ AF is associated with an increased risk of death, dementia, heart failure and stroke.^{2–5} AF leads to high healthcare system utilization rates.⁶ Based on current US age- and sex-specific prevalence data, the national incremental AF cost in 2010 is estimated to range from \$6.0 to \$26.0 billion.⁷

Risk factors for AF are diverse,⁸ and include advancing age, male sex, diabetes, hypertension, valvular disease, myocardial infarction, heart failure, obesity, elevated inflammatory marker concentrations, and PR-interval prolongation, as recently reviewed elsewhere.⁹ Risk-prediction models are important to define individual risk for AF, to identify novel risk factors for AF, to identify and assess potential targets of therapy, and to enhance the cost-effective implementation of therapies for both primary and secondary prevention of AF.¹⁰ A recently published risk score for the development of AF based on the established cardiovascular risk factors accounted for only part of the AF risk (C-statistic 0.76).¹¹ Thus, although many risk factors for AF have been described, a substantial proportion of AF risk still remains unexplained.

In the past years, multiple novel AF risk factors have been studied. In the present review, we aim to describe recently described risk factors, and will underscore that substantial efforts are needed to incorporate novel markers of AF into risk-prediction models. Efforts to optimize risk prediction models and prevention algorithms are useful for risk communication, patient motivation, and clinical decision-making.¹⁰

Familial Aggregation, Ethnic Differences and Genetics of AF

Familial Aggregation

In recent years, increasing data have been reported supporting the notion that AF in the general population is heritable. Diverse population-based studies have demonstrated that

familial clustering of AF is common. In one such study, Framingham Heart Study investigators reported that a parental history of AF doubled the risk of AF in offspring,¹² and that a family history of AF improved risk prediction of AF.¹³ An analysis of 1137 same-sex twin pairs (356 monozygotic and 781 dizygotic pairs) in which one or both members were diagnosed with AF from the Danish Twin Registry found that concordance rates were twice as high for monozygotic pairs than for dizygotic pairs (22.0% versus 11.6%, $P<0.0001$).¹⁴

Ethnic Differences

Despite having a higher burden of traditional AF risk factors, African Americans appear to be at lower risk of AF than whites.¹⁵ To determine whether genetic differences were responsible, Marcus et al. investigated European ancestry as an independent risk factor for AF.¹⁶ The authors compared AF risk in whites ($n=4543$) and African Americans ($n=822$) in the Cardiovascular Health Study as well as in whites ($n=10\,902$) and African Americans ($n=3517$) in the Atherosclerosis Risk in Communities Study. Percent European ancestry in African Americans was estimated with ancestry informative markers from the two different genetic analysis arrays. After adjustment for potential confounders, European ancestry remained a predictor of incident AF in each cohort alone, with a combined estimated hazard ratio (HR) for AF of 1.17 (95% confidence interval [CI], 1.07 to 1.29; $P=0.001$) for each 10% increase in European ancestry.¹⁶

Common Genetic Variants

Building upon data showing that AF was heritable, several published investigations have convincingly demonstrated a genetic component to AF. Before high-throughput genotyping techniques and genome-wide association studies (GWAS), candidate-gene studies screened genes for causative mutations based on assumptions regarding their pathophysiological role and found several single-nucleotide-polymorphisms (SNPs) in ion channels, gap junction proteins, atrial natriuretic peptide, inflammatory mediators, and renin-angiotensin-aldosterone system genes that appeared to relate to AF. Perhaps due to the relatively small sample sizes and heterogeneous nature of the candidate gene studies, only a few of the SNPs associated with AF in candidate-gene studies could be replicated in additional independent cohorts.^{17,18}

GWAS have, successfully identified 3 genetic loci (4q25 near transcription factor *PITX2*,^{19,20} and 16q22 near *ZFHX3*,²¹ and 1q21 at the small-conductance calcium-activated potassium channel *KCNN3*²²), all pointing toward novel pathways not previously known to be involved in AF. The *PITX2* locus encodes a homeobox transcription factor of the paired type, previously identified to be of importance for the formation of embryonic pulmonary myocardial cells, necessary for pulmonary myocardial sleeves development, and for the formation of a sinus node in the left atrium.^{23,24}

As follow-up of GWAS, Lubitz and colleagues did fine mapping of the 4q25 locus near *PITX2* and genotyped 34 haplotype-tagging single-nucleotide polymorphisms (SNPs) in 790 case and 1177 control subjects from Massachusetts General Hospital and tested for association with AF.²⁵ Results were replicated in 5066 cases and 30661 controls from the German Competence Network for Atrial Fibrillation, Atherosclerosis Risk In Communities Study, Cleveland Clinic Lone AF Study, Cardiovascular Health Study, and Rotterdam Study. Lubitz et al. found 2 novel AF susceptibility signals on chromosome 4q25. Considering the multiple susceptibility signals at the chromosome 4q25 locus identified individuals with increased risk of AF.²⁵

In the last two years, experimental and human studies have increased the understanding of *PITX2* in adult hearts and its relation with AF. Wang et al. studied postnatal mice and found that *PITX2c* is expressed in left atria, pulmonary veins, and right ventricles and that *PITX2c* deficient mice are predisposed to atrial arrhythmias.²⁶ Kirchhof et al. studied human atrial tissues and found higher *PITX2* expression levels in the left atrium compared to the right atrium or ventricles.²⁷ Compared with the wild type *PITX2c* heterozygous 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 were observed.²⁷ Chinchilla et al. used atrial tissue samples of 47 permanent AF patients, and 100 controls undergoing cardiac surgery, and found *PITX2c* expression significantly decreased in human patients with permanent AF.²⁸ Additional characterization of chamber-specific *Pitx2* conditional mouse mutants, displaying a ~60% reduction of *Pitx2* expression, provided an illuminating experimental model of *Pitx2* insufficiency. Studies using this mouse model revealed that atrial, but not ventricular, chamber-specific deletion of *Pitx2* results in differences in the action potential amplitude and resting membrane potential in the adult heart as well as ECG characteristics consistent with atrioventricular block. Lack of *Pitx2* in atrial myocardium impairs sodium channel and potassium channel expression, mediated in part by miRNA misexpression.²⁸

Experimental analysis of the small-conductance calcium-activated potassium channels, previously not considered as important cardiac ion channels, demonstrated that these channels are expressed in human hearts and are more important in atria than in ventricles.²⁹ Previous investigations suggested that the small-conductance calcium-activated potassium channels are of importance for atrial repolarization and AF.³⁰ Diness and colleagues demonstrated that using 3 different inhibitors of the small-conductance calcium-activated potassium channels prolongs atrial effective refractory period without affecting QT interval and prevents and terminates AF in both ex vivo and in vivo experiments.³¹

Early-Life Antecedents of AF

Birthweight

Early-life antecedents such as low birth weight³² and childhood socioeconomic status³³ have been related to hypertension, diabetes, obesity, heart failure, coronary artery disease, stroke, and overall mortality. A recent analysis of the Women's Health Study included 27982 healthy women.³⁴ Information on birth weight was categorized into 5 different categories. They observed that increasing birth weight category was significantly associated with incident AF.³⁴

Subclinical Risk Factors for AF

Pericardial Fat

Obesity is an important risk factor for AF. Pericardial fat is an ectopic fat deposit in close proximity of the heart and shares blood supply with the cardiac microcirculation.³⁵ Pericardial fat is highly metabolically active³⁶ and may be a pathway by which obesity increases the risk of AF. Framingham Heart Study investigators studied 3217 participants with multislice computed tomography and quantified adipose tissue volumes.³⁷ Pericardial fat, in contrast to intrathoracic or visceral abdominal fat, was associated with prevalent AF, even after adjustment for AF risk factors, including body mass index.³⁷ Batal and colleagues specifically studied left atrium epicardial fat pad thickness by multislice computed tomography in 73 individuals without AF, 60 with paroxysmal AF, and 36 with persistent AF.³⁸ They reported that increased posterior left atrial fat thickness appears to be associated with AF burden independent of age, body mass index, or left atrial area.³⁸

Blood Pressure in Non-Hypertensive Range

Hypertension, defined as use of antihypertensive medication or blood pressures above 140/90 mmHg, is the most prevalent risk factor for AF, but data regarding the risk of AF at lower blood pressure levels are sparse. An analysis of 34221 women participating in the Women's Health Study showed that blood pressure was strongly associated with incident AF, and systolic blood pressure was more strongly related to AF incidence than diastolic blood pressure.³⁹ Systolic blood pressure levels within the non-hypertensive range were associated with incident AF, even after accounting for blood pressure changes over time.³⁹

Left Ventricular Diastolic Dysfunction

Atrial fibrillation and left ventricular diastolic dysfunction share multiple risk factors, including aging and hypertension.⁴⁰ Since diastolic dysfunction causes atrial pressure and volume overload, atrial structural remodeling is common among patients with abnormal diastolic parameters. An early Framingham Heart Study report demonstrated that the ratio of echocardiographically measured velocity-time integrals of the Doppler mitral valve inflow early (E-wave) and late (A-wave) diastolic filling waves, and the E-wave deceleration time, were markers of increased risk of AF.⁴¹ More recently, investigators of the Cardiovascular Health Study examined echocardiographic parameters of diastolic function in 4480 older adults, and reported that Doppler peak E-wave velocity and left atrial diameter were positively and nonlinearly associated, and Doppler A-wave velocity time integral displayed a U-shaped relationship with the risk of AF.⁴² Vogel et al. described the natural history of 388 participants of the Rochester Epidemiology Project with diastolic dysfunction without signs or symptoms of heart failure. Over the course mean 3.9 years, 52 participants developed AF.⁴³

Subclinical Coronary Artery Disease

Myocardial infarction is a risk factor for AF. Diagnosis of coronary artery disease is generally based on the presence or history of acute coronary syndrome or myocardial infarction. Nucifora et al., however, used multislice computed tomography to detect asymptomatic coronary artery disease.⁴⁴ They compared 150 patients with AF without known coronary artery disease to 148 patients without AF but with similar demographic and clinical characteristics, including pretest likelihood for coronary artery disease. Eighteen percent of patients with AF were classified as having no coronary artery disease by multislice computed tomography, whereas 41% showed nonobstructive coronary artery disease, and the remaining 41% had obstructive coronary artery disease ($P=0.01$ compared with patients without AF).⁴⁴

Clinical Risk Factors for AF

Physical Activity

Regular physical activity is well known to have a beneficial effect on many cardiovascular risk factors. Physical activity is associated with a 3 to 5 mmHg reduction in systolic blood pressure,⁴⁵ a reduction in body weight and body mass index,⁴⁶ and the prevention of coronary heart disease,⁴⁷ suggesting that exercise may reduce the incidence of AF. On the other hand, data suggest that excessive exercise may increase the risk for AF.⁴⁸ Investigators from the Women's Health Study followed 34759 women who reported their leisure-time physical activity for the occurrence of AF. They found that women who achieved the federal government's recommendation of 7.5 metabolic equivalent-hour/week of physical activity were at reduced risk of AF compared with those who did not (HR 0.86; CI 0.75 to 0.98; $P=0.03$), but this association was attenuated by body mass index.⁴⁹ Comparable results were published by the Cardiovascular Health study in older adults.⁵⁰

Chronic Kidney Disease

Patients with chronic kidney disease are at higher risk for coronary heart disease and heart failure.⁵¹ Chronic kidney disease is associated hypertension, left ventricular hypertrophy, and systemic inflammation.⁵¹ Since many of these cardiovascular risk factors and diseases have been associated with AF, Alonso et al. sought to examine the risk between chronic kidney disease and AF in 10328 men and women from the Atherosclerosis Risk in Communities study. They found that reduced kidney function and presence of albuminuria were strongly associated with the incidence of AF, during 10 years follow-up, accounting for other risk factors.⁵² Baber et al. followed 26917 participants in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study and found similar results; regardless of severity, chronic kidney disease was associated with an increased prevalence of AF.⁵³

Biomarkers of AF

Biomarkers are potential novel instruments to enhance AF risk prediction and to provide insights into the pathophysiology of the disease, and may help to identify novel targets for therapy. Recently, B-type natriuretic peptide (BNP) was investigated as a biomarker for incident AF. Although most widely used as a marker of heart failure, elevated BNP levels have been reported in patients with AF.^{54,55} In the Cardiovascular Health Study, a community-based population of 5445 older adults, NT-proBNP was a strong predictor of incident AF, adjusting for other risk factor (adjusted HR, 4.0; 95% CI, 3.2 to 5.0; $P<0.001$).⁵⁶

Previously, multiple biomarkers have been studied in relation to AF, but their predictive ability remains uncertain. Schnabel et al.⁵⁷ chose a panel of 10 candidate AF biomarkers aiming to represent distinct pathophysiological pathways, including inflammation (C-reactive protein [CRP] and fibrinogen), neurohormonal activation (B-type natriuretic peptide [BNP] and N-terminal proatrial natriuretic peptide [N-ANP]), oxidative stress and endothelial dysfunction (homocysteine), the renin-angiotensin-aldosterone system (renin and aldosterone), thrombosis and endothelial function (D-dimer and plasminogen activator inhibitor type 1), and microvascular damage (urinary albumin excretion). In 3120 Framingham Heart Study participants, they found that the biomarker panel was associated with incident AF ($P<0.0001$). In stepwise-selection models, log-transformed BNP (HR per SD, 1.62, 95% CI, 1.41 to 1.85, $P<0.0001$) and C-reactive protein (HR, 1.25, 95% CI, 1.07 to 1.45, $P=0.004$) remained associated with AF after multivariable adjustment. Adding BNP and C-reactive protein, separately and together, to an AF risk score based on clinical covariates revealed that only BNP improved risk stratification beyond well-established clinical risk factors.⁵⁷

Blood lipids are established risk factors for coronary artery disease, which may precede incident AF. Limited and inconsistent data exist on the association of triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDLc) and high-density lipoprotein cholesterol (HDLc) with incident AF. Recently investigators of the Atherosclerosis Risk in Communities study reported that higher concentrations of LDLc and total cholesterol were associated with a lower incidence of AF; though the mechanisms linking lipids to AF remain uncertain. No association between HDLc and triglycerides with incident AF was found.⁵⁸

Long-chain n-3 polyunsaturated fatty acids (n-3 PUFAs) may reduce the risk of AF as was previously shown in experimental studies. Prior human studies evaluating fish or n-3 PUFA consumption from dietary questionnaires and incident AF have reported conflicting results. The Cardiovascular Health Study investigated the association of circulating levels of n-3

PUFAs (eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid) and incident AF. They found that higher circulating total long-chain n-3 PUFA and docosahexaenoic acid levels were associated with lower risk of incident AF.⁵⁹

Conclusions

As with other forms of cardiovascular disease, more than half of the AF burden is potentially preventable.⁶⁰ Adequate risk assessment is therefore of utmost importance to improve primary and secondary prevention of AF and its consequences.⁶¹ However, the traditional risk factors for AF do not explain all cases of AF. Present risk stratification tools for AF are an important step forward, however are far from optimal. In recent years, investigators have learned more about the pathophysiology of AF, and multiple studies have demonstrated a role for heritability and genetics, early-antecedents, pre-clinical risk factors, and circulating biomarkers in the development of AF. Future research is needed to determine the extent to which novel risk factors are associated with AF in racial and ethnic minorities. Data are also needed as to the extent to which novel risk factors improve existing AF risk prediction models over traditional CVD risk factors, in order to better identify patients at risk for AF to target for disease prevention.⁶² We are embarking on an exciting chapter in AF risk prediction and prevention as novel AF biomarkers better identify patients at risk for AF and identify potential targets of therapy, enabling more personalized and targeted AF risk reduction.¹⁰

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