INVITED COMMENTARY

Global Arrhythmia Burden: The Public Health Implications of the Rise in Atrial Fibrillation

Several recent studies have noted a rise in the prevalence and incidence of atrial fibrillation (AF). The population burden of AF is expected to double over the next 40 years and will likely affect between 6 to 12 million Americans by 2050.[1-3] In this issue of the *Archives*, Wong and colleagues[4] confirm that this phenomenon is not limited to the United States. Using administrative data, these investigators demonstrate that the number of hospitalizations for AF in Australia tripled over a 15-year period between 1993 and 2007. In comparison, the number of hospitalizations for myocardial infarction and heart failure increased only modestly during this time.

What accounts for this rise in AF? As Wong and colleagues[4] propose, an increasing population of older patients may explain part of this trend. Patients with coronary artery disease and congestive heart failure are surviving longer and contributing to the growing population at risk for AF. Increasing age is associated with other comorbidities, including valvular heart disease, diabetes mellitus, hypertension, and peripheral arterial disease, all of which are risk factors not only for the development of AF but also for AF-associated thromboembolic complications. Increasing use of ambulatory electrocardiography devices and implantable arrhythmia devices such as pacemakers, defibrillators, and cardiac resynchronization therapy devices have likely enhanced detection of asymptomatic and minimally symptomatic arrhythmias. These possibilities, however, likely explain only a part of the increase in AF hospitalizations.

A larger and older population with AF will increase the burden of morbidity and mortality associated with AF. Even with appropriate risk stratification and anticoagulation, the risk of thromboembolic stroke is increased in AF, especially among patients with risk factors.[5] Even brief, asymptomatic episodes of AF that are detected incidentally in patients with implantable arrhythmia devices are associated with ischemic strokes or peripheral emboli.[6] More ominously, incident AF is associated with an increased risk of all-cause mortality in health care professionals[7] and other cohorts.[8,9] These findings portend a potentially dramatic rise in hospitalizations, stroke, and AF-associated mortality by 2050 unless our therapeutic options evolve adequately to counter these challenges.

Unfortunately, no single therapeutic breakthrough alone is likely to mitigate the rising burden of AF. Although all AF is characterized by chaotic atrial electrical activity, the arrhythmia is a final common pathway of multiple heterogeneous conditions, including electrical triggers (especially in the pulmonary veins), underlying structural heart disease, long-standing hypertension, genetic disorders, cardiomyopathies, and, almost certainly, other conditions we do not yet understand. Currently, guideline-based treatment strategies for AF begin with assessment and appropriate reduction of stroke risk (with aspirin, warfarin, or other anticoagulants) followed by treatment of AF-associated symptoms beginning first with control of the ventricular response to AF. If a rate control strategy fails or is otherwise unacceptable to the patient, efforts to achieve and maintain normal sinus rhythm can include cardioversion, antiarrhythmic drugs, and/or ablation by either catheter-based or surgical approaches. Unfortunately, patients continue to be hospitalized with poor ventricular rate control despite the use of rate controlling drugs. Furthermore, even when control of the rhythm is desired, antiarrhythmic drugs have both incomplete efficacy and substantive toxicities. Although promising in some, catheter ablation in the best candidates has both nontrivial procedural risk and a likelihood of success for a first procedure on the order of 60% to 85%, even with concomitant antiarrhythmic drug therapy.[10] At a fundamental level, all of these treatments address a condition that has already afflicted the heart without addressing the upstream causes.

Clearly, both in the United States and abroad, the public health burden of AF is increasing. The good news is that anticoagulation with warfarin in appropriately risk-stratified patients has reduced (but not eliminated) stroke risk, and recent randomized trials suggest that simpler regimens with new anticoagulants are as efficacious as warfarin. Better insights into the mechanisms of AF have identified patients with structurally normal hearts and pulmonary venous atrial tachycardia triggers as particularly good candidates for AF ablation. Unfortunately, though, the burden of AF is increasing despite these and other advances.

We must do better—even greater support for scientific discovery may lead to better understanding of the mechanisms leading to AF and novel therapeutic approaches. Hopefully, new strategies with better profiles of safety and efficacy than those of our current therapeutic arsenal will mitigate the future symptoms and risks of adverse AF-associated outcomes. We are even more hopeful that other strategies may eventually emerge to prevent AF. Without such advances, the burden of AF will weigh heavily on our world in the coming decades.

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RESEARCH LETTER

Genetic Polymorphisms for Estimating Risk of Atrial Fibrillation in the General Population: A Prospective Study

Atrial fibrillation (AF) is a common cardiac disease and major risk factor for stroke, heart failure, and death. Tools for prediction of AF have been developed to identify individuals who might benefit from preventive therapies, incorporating conventional cardiovascular risk factors, and the effects of such risk factors have been evaluated across several cohorts.[1,2] Recently, a heritable component to AF has been reported, and polymorphisms in 3 genetic regions have been reproducibly associated with AF: chromosome 4q25, located 150 kb from the closest gene—a transcription factor (*PITX2*) involved in cardiac development; chromosome 16q22, intronic to another transcription factor of unknown function, expressed in cardiac tissue (*ZFHX3*); and an amino acid–altering variant in *KCNH2*, one of the major cardiac voltage-gated potassium channels.[3-5] Rare genetic variants segregating with AF are typically exclusive to individual families and unlikely to contribute to AF prediction at the population level, but genetic polymorphisms could provide important predictive information.

Methods. The single nucleotide polymorphism (SNP) with the strongest association at each of the 3 genetic regions reproducibly associated with AF in genome-wide[3,4] or candidate gene studies[5] was genotyped in a large population-based cohort of middle-aged participants from southern Sweden (Malmö Diet and Cancer study[6]). Data collection and clinical definitions have been described previously.[6] Briefly, 30 447 randomly selected individuals (born 1923-1950) attended a baseline examination between 1991 and 1996 with (1) sampling of venous blood, (2) measurement of blood pressure and anthropometric measures, and (3) completion of a questionnaire. Cardiac disease end points were ascertained from national registers (Swedish Cause of Death Register and Swedish Hospital Discharge Register).[6] Follow-up for AF extended through January 1, 2009.

DNA extracted from peripheral blood cells was assigned to batches without regard to AF status or personal identity. The batches were genotyped with the same set of reagents using real-time polymerase chain reaction with 2.5 ng of DNA as the polymerase chain reaction template for allelic discrimination (ABI 7900HT; Life Technologies). Genotype calls were obtained using SDS version 2.3 software (Life Technologies) and fluorescence intensity plots curated manually.

Association of genotype with AF was studied using both cross-sectional and prospective study designs. In cross-sectional analyses, the association of SNPs with AF diagnosed before baseline was examined using logistic regression analysis. In prospective analyses, the association of SNPs with incident AF during follow-up was examined in individuals free of AF at baseline using Cox proportional hazards models with censoring at death, emigration, or end of follow-up. Kaplan-Meier estimates of absolute AF risk per genotype were calculated. The proportionality of hazards assumption was confirmed using a Schoenfeld global test.

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Polymorphisms associated with AF were assessed for predictive discrimination using the Harrell concordance (C) statistic, a generalization of the area under the receiver operating characteristic curve, with confidence interval estimates using a jackknife resampling method in the Stata package Somers D (Stata Corp). Model calibration was evaluated using the Gronnesby-Borgan test implemented in the Stata package stcoxgof (Stata Corp). All analyses were performed using SAS version 9.2 (SAS Institute) or Stata version 11.1 (Stata Corp).

Informed consent was obtained from all participants, and the study was approved by the ethics committee of Lund University, Lund, Sweden. The study protocol is consistent with the principles of the Declaration of Helsinki.

Results. Baseline characteristics for the Malmö Diet and Cancer study cohort have been published previously.[6] Clinical data were available for 28 473 individuals, 26 946 of whom had DNA available. The mean (SD) age was 58.1 (7.6) years, and the majority were women (60.6%). At baseline, 287 individuals had been diagnosed as having AF (prevalence, 1.0%). During a follow-up period of up to 17.8 years (median follow-up, 14.1 years; interquartile range, 12.9-15.7 years), 2050 individuals developed AF. The Kaplan-Meier estimate of cumulative AF incidence was 11.9% (95% CI, 10.7%-13.3%).

The call rate was higher than 95% for all 3 SNPs. Minor allele frequencies (MAFs) were similar to those in previous studies and the European panel of the HapMap project (4q25: *T* allele, MAF 10.1%; 16q22: *A* allele, MAF

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