Trends in Cardiovascular Medicine ▮ (2016) ▮▮▮–▮▮▮

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Update on atrial fibrillation

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ABSTRACT

Atrial fibrillation (AF) is the most common arrhythmia with a substantial effect on individual morbidity and mortality as well as healthcare expenditure. The management of AF is complex and fraught with many uncertain and contentious issues. We have seen substantial progress in AF management in the last two decades including better understanding of the epidemiology, genomics, monitoring, drug and non-pharmacological treatment of the arrhythmia, its complications and stroke risk reduction. In this review, we present a comprehensive discussion on AF with emphasis on most recent updates.

Key words: Atrial fibrillation, Antiarrythmic drugs, Ablation, Stroke risk, Anticoagulation.

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Current and future incidence and prevalence of atrial fibrillation

Atrial fibrillation (AF) is the most common arrhythmia and accounts for one-third of hospitalizations for rhythm disorders in the United States [1]. Atrial fibrillation is of public health importance and profoundly increases morbidity, mortality, and health-related expenditures. Morbidities include outcomes such as heart failure, stroke, and the deleterious effects on quality of life (QOL), functional status, and cognition. In the United States and Western Europe, the aging population and the accompanying rise in the prevalence of AF have magnified its toll on morbidity and healthcare costs. The estimated US prevalence of 2.7–6.1 million is expected to increase to 5.6–12.1 million by the middle of this century [2,3].

Cumulative lifetime risk estimates indicate that AF is largely a disease of aging. In the United States and European community-based cohort studies, the lifetime risk of AF is 22–26% in men and 22–23% in women by 80 years of age [3,4]. AF risk doubles in each decade of age; less than 1% in individuals 50–59 years of age are affected, whereas 10% of those 80–84 years and 11–18% of those more than 85 years of age have AF [5]. A recent analysis of medical costs associated with AF in 38 million individuals in the United States demonstrated that individuals with AF had 73% higher medical costs compared with matched control subjects. The incremental cost was $8075 per individual with AF in the United States, resulting in a total national incremental expenditure of $26.0 billion dollars [6] in 2008.

There remains a paucity of epidemiological data on AF from many parts of the world, including Eastern Europe, Africa, and South America. Racial differences in AF remain poorly understood as well. Overall, blacks have a higher prevalence of multiple AF risk factors (obesity, diabetes mellitus, hypertension, and heart failure), yet a lower incidence of AF. In the ARIC study, the cumulative risk of AF at 80 years of age reached 21% in white men and 17% in white women, but was only 11% in black men and women [7].

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The authors have indicated that there are no conflicts of interest.

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http://dx.doi.org/10.1016/j.tcm.2016.06.007
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The contrasting burden of risk factors with decreased AF incidence has been called a "racial paradox" [8].

AF has a profound clinical and public health burden, which has grown over the last several decades. Epidemiological approaches have delineated the major clinical risk factors, but there are large areas of uncertainty. We hope that a better understanding of AF risk factors and risk stratification will facilitate prevention.

Risk factors for AF

The past few decades have seen a concerted effort to reduce the population-wide impact of atherosclerosis and cardiovascular disease, for example, by the use of statin therapy, control of hypertension, and attempts to reduce smoking. Despite reduced risk for arteriosclerosis and coronary artery disease, the incidence of AF continues to increase, indicating that the control of traditional risk factors for cardiovascular disease may not reduce AF to a similar extent.

There are well-established risk factors specifically for AF. These are age, arterial hypertension, congestive heart failure, including heart failure with impaired or preserved left ventricular systolic function [9], as well as myocardial infarction, valvular heart disease, and diabetes mellitus [10]. Identification of these risk factors may be followed by early intervention and appropriate treatment to prevent disease progression. There are emerging risk factors for AF, which have received much less attention and may provide additional leverage to decrease the incidence of AF. Subclinical hyperthyroidism, obesity, chronic kidney disease, obstructive sleep apnea, heavy alcohol use, and even high-level endurance training associated with an increased risk of AF, although their evidence is lacking that eliminating one or more of these risk factors is protective against recurrence [11,12].

Biomarkers in atrial fibrillation

Despite years of research and advances in catheter-based therapies for AF, we are still striving to understand the reasons for the development of AF and the mechanisms underlying the structural abnormalities observed in patients with AF. Various mechanisms including atrial fibrosis, myocyte damage, electric remodeling, atrial dilatation, prothrombotic state have been proposed. Biological substances, enzymes, hormones, and other markers of stress and malfunction, collectively referred to as biomarkers, appear to have clinical importance. Biomarkers derived from the blood, such as markers of inflammation, coagulation, renal function, myocardial injury, and cardiovascular stress, have been associated with clinical events. 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. Some markers appear to reflect the pathophysiologic process for development of AF, while others may simply be suited as markers of risk for future cardiovascular events. Biomarkers that reflect different pathophysiological mechanisms are shown in Fig. 1.

The importance of troponin and Nt-pro BNP in an AF population was first reported from the randomized evaluation of long-term anticoagulant therapy (RE-LY) biomarker substudy performed in 6189 patients with AF and treated with either warfarin or dabigatran because of an increased risk of stroke [14]. The results from the larger ARISTOTLE [15] biomarker study verified and extended the role of NT-pro BNP. This study demonstrated a strong association between elevated risk of ischemic stroke and rising NT-pro BNP levels. Both of these biomarkers have been linked to myocardial cell stress.

Reduced renal function with low GFR has been associated with an increased risk of stroke. Cystatin C, a small protein, is minimally influenced by disease states, and is therefore believed to be a better endogenous marker of GFR than creatinine [16]. The significance of cystatin C as a risk marker in an AF population was also reported from the ARISTOTLE and RE-LY biomarker substudies [17,18]. Rising cystatin C levels were independently associated with increased rates of stroke or systemic embolism, mortality, and major bleeding.

In addition to cystatin C, the RE-LY biomarker study described a significant association between baseline D-dimer levels and the risk of stroke, cardiovascular death, and major bleeding outcomes independent of established risk factors including the CHADS2 variables [19]. Also, markers of inflammation including C-reactive protein and IL-6 have been independently associated with AF in the above studies. Recently, higher levels of adiponectin were associated with atrial fibrillation [20].

Schnabel et al. [21] chose a panel of 10 candidate AF biomarkers aiming to represent distinct pathophysiological pathways, including inflammation (C-reactive protein and fibrinogen), neurohormonal activation (BNP and N-terminal natriuretic peptide), 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 stepwise-selection models, log-transformed BNP (HR per SD = 1.62; 95% CI: 1.41–1.85; $P < 0.0001$) and C-reactive protein (HR = 1.25; 95% CI: 1.07–1.45; $P = 0.004$) remained associated with AF occurrence 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.

Emerging role of genetics

The familial nature of AF was reported as early as 6 decades ago. There have been infrequent reports of families with an apparent Mendelian inheritance of AF. In 1997, Brugada et al. [22] described the first genetic locus for AF; however, the causative gene at the locus remains elusive. Multiple mutations have been identified in potassium and sodium channels, gap junction proteins, and signaling molecules.

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