Atrial fibrillation (AF) is a global public health problem characterized by dramatically increasing prevalence, significantly associated morbidity and mortality, and ominously spiraling healthcare costs. Thus, the lifetime risk for AF in individuals over the age of 40 in the United States is \( \approx 1/4 \) and the risk of stroke, heart failure, and death is increased in affected individuals.\(^1\)\(^-\)\(^3\) Although currently estimated to be present in \( \approx 2 \) million persons, it is expected that as many as 12 million people will have AF by 2050.\(^4\) Not surprisingly, AF is responsible for significant US healthcare costs, which are estimated to exceed 6 billion dollars annually.\(^5\) Accordingly, identifying the risk factors for the development of AF and strategies to reduce risk and, thereby prevent AF is a high priority of the American Heart Association.\(^6\)

The established modifiable risk factors for AF include hypertension, diabetes mellitus, previous cardiovascular disease, obesity, and cigarette smoking.\(^7\) However, after considering these risk factors, considerable residual risk remains. In the Framingham cohort, hypertension, prevalent heart disease, diabetes mellitus, and cigarette smoking accounted for 44% of the risk in men and 58% of the risk in women.\(^8\) In the Atherosclerosis Risk in Communities (ARIC) study, 57% of incident AF cases during a 17-year follow-up could be explained by having at least 1 borderline or elevated risk factor (hypertension, obesity, diabetes mellitus, cigarette smoking, and previous heart disease); the most important contributor was hypertension, which accounted for approximately a quarter of the AF burden.\(^9\)

A heritable component undoubtedly accounts for some of the residual risk. AF in a parent doubles the risk of AF in offspring,\(^10\) and a positive family history improves risk prediction of AF.\(^11\) Genome-wide association studies have identified unanticipated polymorphisms that are genetic risk factors for AF. For example, expression of the homeobox transcription factor, Pitx2, in atrial tissue is reduced when compared with controls in humans with permanent AF,\(^12\) and mice deficient in Pitx2 are prone to atrial arrhythmia.\(^13\)

A variety of novel risk factors for AF have been studied, notably atrial remodeling, which itself is associated with numerous factors (demographic, anthropomorphic, behavioral, classical cardiovascular risk factors, pulmonary disease, and hyperthyroidism) that interact with AF in a complex fashion.\(^14\) Other novel risk factors include the biomarkers brain natriuretic peptide, C-reactive protein, and long-chain n-3 polyunsaturated fatty acids; and subclinical factors, such as pericardial fat, systolic blood pressure within the normal range, left ventricular (LV) diastolic function, and subclinical coronary artery disease.\(^15\) However, it is unclear whether these novel risk factors improve risk prediction models, such as the community-based Framingham Risk Score.\(^16\) The latter was improved only minimally (ie, net risk reclassification was not statistically significant) after incorporating the standard M-mode echocardiographic variables, left atrial diameter, LV wall thickness, and fractional shortening; however, the authors acknowledged that more sophisticated echo measures may improve risk prediction.\(^17\)

In this issue of Circulation: Cardiovascular Imaging, Russo et al\(^18\) examined the ability of speckle-tracking echo LV global longitudinal strain (GLS) to predict new-onset AF during a 5-year follow-up in 675 participants over the age of 50 years enrolled in the community-based Cardiac Abnormalities and Brain Lesions/Northern Manhattan Study. A lower GLS and an increased real-time 3-dimensional left atrial volume index (LAVI) was associated with incident AF, whereas LV ejection fraction was not. Both abnormal GLS and LAVI were associated with a 28% increase in AF compared with normal GLS and LAVI (2%) and an intermediate risk if one or the other was abnormal. The risk associated with GLS was incremental to LAVI and other risk factors, and resulted in an increase in the net reclassification improvement index (a statistic used to measure the improvement in prediction performance gained by adding a marker to a set of baseline variables for predicting a binary outcome.) The authors conclude that being a powerful and independent risk factor for new-onset AF, GLS may improve AF risk stratification and guide different treatment and monitoring strategies. The mechanism of the association between GLS and incident AF is not clear, but as the authors note, it may result from subclinical LV dysfunction, that is, a more advanced disease process; its association with other risk factors independent of LV systolic function, such as vascular disease; undiagnosed paroxysmal AF, which is known to decrease GLS and recover after successful ablation; and perhaps most intriguingly, abnormal atrial reservoir function. The latter is an attractive hypothesis since by first principles, LV longitudinal function is an important determinant of atrial remodeling.
reservoir function, which itself is a powerful predictor of new-onset AF. For example, LA emptying fraction (a measure of reservoir function) was associated with increased risk of AF and flutter after adjustment for baseline clinical risk factors, LV ejection fraction, LV diastolic functional grade, and LA volume. Patients at highest risk were those with both reduced LA emptying fraction (<49%) and increased LA VI (≥238 mL/m²). In another study, there was a strong association between peak atrial longitudinal strain (global PALS, an accurate measure of reservoir function) and cardiovascular events after similar adjustments; both LA emptying fraction and global PALS were superior and incremental to LA VI, suggesting that impaired reservoir function of the LA represents a more advanced state and a more sensitive indicator of left atrial remodeling. Assessment of LA function has been useful in secondary prevention of AF as it has been shown that the magnitude and timing of atrial deformation consistently predicts recurrences of AF after cardioversion or AF ablation. Moreover, using delayed enhancement cardiac magnetic resonance imaging, reservoir strain has been related to atrial structural remodeling and fibrosis.

Several studies suggest that atrial booster pump function also identifies cardiovascular risk in the general population. For example, a low transmitral Doppler atrial filling fraction (and increased E/A vti) predicted a new-onset AF in 942 subjects of the Framingham Study independent of left atrial size; thus a 1 SD decrease in the atrial filling fraction was associated with a 28% higher risk of AF, suggesting that decreased booster pump function predates atrial arrhythmia.

Although a large body of data support the use of the maximum LA volume for predicting cardiovascular risk, as did the study by Russo et al, theoretical considerations about atrial function and loading, and mounting evidence suggest that minimum LA volume may be a more important prognostic indicator. Although minimum LA volume (measured at end-diastole) is exposed to LV diastolic pressure and is influenced by atrial booster pump function, LA maximal volume is primarily because of increased atrial pressure and volume. Interestingly, minimal LA volume correlates better with LV filling pressures than does maximum LA volume and predicts more accurately the 3-year risk of developing first AF or flutter, independent of maximal LAV, clinical variables, body mass index, and LV diastolic dysfunction. Whether LV GLS would add incremental predictive ability to risk models that include global PALS and minimum LAV is a hypothesis worth testing.

Identifying and targeting individuals at high risk for AF may provide a cost-effective primary prevention strategy. Nonspacing, nonelectrophysiological (eg, P-wave morphology, heart rate variability, and recurrence plots of R–R intervals) AF prevention approaches that have shown promise include the use of statins, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, omega-3 fatty acids, and colchicine for postoperative AF; unfortunately, these agents have all shown mixed results and there is currently an insufficient evidence base to recommend their use. Atrial-specific ion channels and atrial fibrosis are promising pharmacological targets for AF prevention and treatment, but clinical trials are lacking.

Risk stratification as achieved by Russo et al using sensitive indices that detect subclinical disease will facilitate the development of robust risk prediction models and enable more personalized and targeted AF risk reduction. However, data from large ethnically diverse populations are needed to confirm the incremental predictive ability of chamber-specific deformational indices. Although equipment and analytic techniques are becoming increasingly standardized, the development of age- and sex-adjusted normal reference and partition values on a larger scale will be needed to predict and ultimately prevent the development of AF.

Disclosures

None.

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Brian D. Hoit

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