REVIEW

Biomarkers and the prediction of atrial fibrillation: state of the art

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Abstract: Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice, and it places a substantial burden on the health care system. Despite improvements in our understanding of AF pathophysiology, we have yet to develop targeted preventive therapies. Recently, numerous biological markers have been identified to aid in the prediction of future AF events. Subclinical markers of atrial stress, inflammation, endothelial dysfunction, kidney dysfunction, and atherosclerosis have been linked to AF. The connection between these markers and AF is the identification of subclinical states in which AF propagation is likely to occur, as these conditions are associated with abnormal atrial remodeling and fibrosis. Additionally, several risk scores have been developed to aid in the identification of at-risk patients. The practicing clinician should be aware of these subclinical markers, as several of these markers improve the predictive abilities of current AF risk scores. Knowledge of these subclinical markers also provides clinicians with a better understanding of AF risk factors, and the opportunity to reduce the occurrence of AF by incorporating well-known cardiovascular disease risk factor modification strategies. In this review, we highlight several novel biological markers that have improved our understanding of AF pathophysiology and appraise the utility of these markers to improve our ability to predict future AF events.

Keywords: biological markers, prediction, atrial fibrillation

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice, affecting nearly 3 million Americans.[1,2] Risk factors include diabetes, hypertension, and coronary heart disease.[3,4] AF is associated with the development of several cardiovascular outcomes, including stroke, congestive heart failure, and myocardial infarction.[5–11] Additionally, the arrhythmia is associated with an increased risk of mortality.[12–15]

AF places a significant burden on the United States health care system, with national incremental costs between $6 and $26 billion.[16] These estimates likely will increase in the coming decades and parallel the growth in individuals older than 65 years of age, as the prevalence of AF increases dramatically with age.[1,17] Therefore, preventive strategies with aims to identify those who are at risk for AF development are of paramount importance for public health officials in order to reduce the current and future burden of this arrhythmia and its well-known complications.

Numerous biological markers, either measured in blood or by noninvasive techniques, have been identified to predict the development of future AF events.

These markers have enhanced our understanding of AF pathophysiology by identifying several processes that facilitate the initiation and perpetuation of the arrhythmia. These markers also provide important prognostic information, especially when faced with the decision to initiate risk factor modification strategies with aims to reduce AF development.

Although several reviews have been written regarding the usefulness of biomarkers in AF,[18,19] none have focused on the ability of these markers to improve the prediction of incident AF. In this review, we examine several recent biological markers that have improved our understanding of AF pathophysiology and appraise the clinical utility of these markers to predict future AF events (Figure 1).

Markers of atrial stress

Enlargement of the left atrium is thought to contribute to the abnormal conductive properties observed in AF.[20] Therefore, markers that detect elevated atrial filling pressures and early atrial hypertension are excellent indicators of abnormal atrial remodeling in which AF development is likely.

B-type natriuretic peptide (BNP) and the stable N-terminal portion of the prohormone, pro-BNP (NT-proBNP), are peptides synthesized by cardiac myocytes in response to elevated pressure and resultant myocardial stretch.[21] Although commonly thought of as a marker of volume overload and left ventricular dysfunction, direct increases in atrial pressure and stretch have been shown to induce the synthesis and secretion of BNP.[22]

A report from the Cardiovascular Health Study and Malmö Diet and Cancer Study demonstrated that NT-proBNP was significantly associated with incident AF events after adjustment for common risk factors.[23,24] Data from the Multi-Ethnic Study of Atherosclerosis found NT-proBNP to be a robust predictor of incident AF in a diverse cohort of racially/ethnically diverse males and females.[25] Additionally, BNP was shown to predict incident AF in the Framingham Heart Study and this marker improved the predictive ability of the AF risk score developed in this cohort.[26] BNP also was found to improve the predictive ability of the Cohorts for Heart and Aging Research in Genomic Epidemiology AF consortium (CHARGE-AF) risk score for AF.[27]

Markers of inflammation

Inflammation has been implicated in the pathophysiology of AF,[28] and C-reactive protein (CRP) has been the most widely studied proinflammatory marker regarding AF risk. This acute-phase reactant produced in the liver is thought to promote arrhythmiogenesis through atrial remodeling and increasing atrial ectopy, suggesting a link between inflammation and arrhythmiogenesis.[29]

Data from the Cardiovascular Health Study, a population-based cohort in Norway, and the Malmö Diet and Cancer Study have demonstrated that higher levels of CRP are associated with an increased risk of AF.[24,30,31] An examination of participants from the Copenhagen City Heart Study observed an increased risk of AF with higher levels of CRP.[32] CRP also has been shown to predict AF after acute myocardial infarction.[33] Although CRP has been associated with an increased risk for AF, the addition of this inflammatory marker did not improve the predictive abilities of the Framingham Heart Study or CHARGE-AF risk scores for incident AF.[26,27] Data from the Malmö Diet and Cancer Study also failed to show improvement in the prediction for future AF events beyond traditional risk factors with CRP.[24]
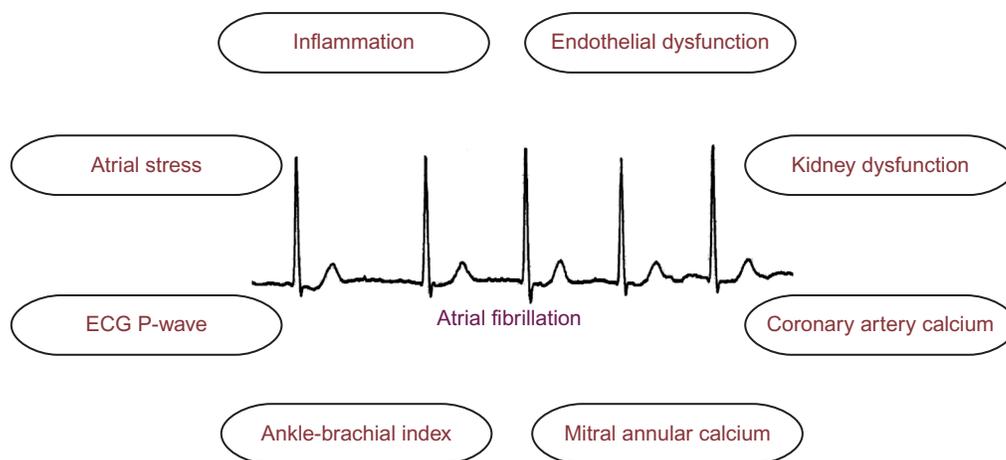

Figure 1 Biomarkers implicated in the prediction of incident atrial fibrillation.
Abbreviation: ECG, electrocardiogram.

Endothelial dysfunction

Markers of endothelial dysfunction have been linked to AF. Arterial flow-mediated dilation (FMD) is an indirect measurement of endothelial nitric oxide (NO) release,[34] and abnormalities in this process have been linked to AF through atrial remodeling and increased atrial ectopy.[35,36]

A study of patients with chronic AF showed that abnormal FMD measurements are significantly impaired compared with sinus rhythm controls.[37] Another case-control study showed that participants with persistent AF have impaired FMD, and that FMD improves after restoration of sinus rhythm.[38] Only one report from the Multi-Ethnic Study of Atherosclerosis has demonstrated that abnormal FMD measurements precede the development of AF, suggesting a role for endothelial dysfunction in the pathogenesis of AF.[39] Although abnormal endothelial dysfunction predisposes to AF, no studies have assessed the ability of this marker to improve the discriminatory capacity of current AF risk scores. Additionally, the use of FMD as an indirect measurement of NO has not been widely adopted as a biological marker for the prediction of arrhythmias.

Markers of kidney dysfunction

Elevations in serum creatinine and reductions in glomerular filtration rate (GFR) are associated with hypertension, higher levels of inflammation, and cardiovascular disease.[40] These common comorbid conditions are well-known risk factors for AF development.

Reductions in GFR, as measured by cystatin C, and the presence of albuminuria were associated with an increased risk for incident AF in the Atherosclerosis Risk In Communities study.[41] Similar results were obtained for GFR measured by serum creatinine, although not as robust as cystatin C.[41] The association between reductions in GFR by serum creatinine and incident AF also was observed in a prospective community-based observational cohort study in Japan,[42] and in a cohort of hypertensive patients.[43] Markers of inflammation have been shown to predict incident AF in patients with chronic kidney disease (CKD),[44] providing evidence that the proinflammatory state of CKD promotes the development of AF. However, no reports have explored the ability of CKD markers to improve the prediction of incident AF events beyond traditional risk factors.

Coronary artery calcium

Coronary artery calcium (CAC) measured by cardiac computed tomography (CT) provides an estimate of coronary plaque burden.[45] This technique largely has been used to detect obstructive coronary artery disease, but recent reports have demonstrated that CAC predicts events that are not limited to the coronary arteries, including stroke.[46] Given that coronary heart disease is a well-known risk factor for AF,[3,4] several reports have explored the utility of CAC measurements to predict AF events.

An examination of 6,641 participants with baseline CAC measurements from the Multi-Ethnic Study of Atherosclerosis has shown that higher levels of coronary calcium predict incident AF.[47] Additionally, a follow-up study from the same cohort demonstrated that the relationship between CAC and AF depends on the extent of CAC progression over time.[48] Highly calcified coronary arteries are associated with larger pulmonary veins and left atrial enlargement,[49] suggesting that the presence of CAC identifies individuals who have the abnormal substrate for AF propagation. The inclusion of CAC in the Framingham Heart Study and CHARGE AF risk scores for AF also was shown to improve the predictive abilities of both scores.[47]

Mitral annular calcium

Mitral annular calcification (MAC) is a chronic degenerative process that affects the base of the mitral valve. Several AF risk factors, such as diabetes and hypertension, have been associated with the presence of MAC.[50,51] The presence of MAC has been associated with left atrial enlargement,[52] suggesting that persons with MAC are likely to have the necessary substrate for AF development.

In the Framingham Heart Study, MAC, detected by echocardiography, was associated with the development of AF.[53] A report from the Multi-Ethnic Study of Atherosclerosis also demonstrated that MAC, detected by CT, was associated with an increased risk of AF and this risk was greater with higher levels of MAC.[54] Additionally, MAC was shown to improve discrimination beyond variables included in the Framingham Heart Study and CHARGE-AF risk scores for AF.

Ankle-brachial index

The ankle-brachial index (ABI) has been widely accepted as a diagnostic tool to detect the presence of peripheral artery disease, and abnormalities in this measurement are associated with well-known AF risk factors, such as diabetes and smoking.[55,56] This tool has been suggested to be a unique biological marker as it has the ability to detect pathology before clinical symptoms are evident, and provides physicians with an opportunity to implement preventive strategies before cardiovascular disease events ensue.[57]

Data from the Multi-Ethnic Study of Atherosclerosis have demonstrated that abnormal ABI measurements (ie, <1.0 or >1.4) are associated with an increased risk for AF development.[58] Similar results were reported from the Cardiovascular Health Study.[59] Abnormal ABI values and AF are associated with proinflammatory markers and poor cardiovascular risk factor profiles in which each condition likely influences the other.[3,30,55] Although this measure has not been incorporated into recently developed AF risk scores, abnormalities in the ABI are able to detect persons in whom AF is likely to develop.

Electrocardiographic P-wave

The P-wave on the resting 12-lead electrocardiogram (ECG) is a representation of atrial electrophysiology. Abnormalities of this marker are thought to represent delayed atrial depolarization due to underlying atrial fibrosis, dilation, and elevated filling pressure.[60,61] These markers detect abnormal atrial substrate, which allows for AF propagation.

P-wave terminal force in lead V_1 ($PTFV_1$) is one of the best-known left atrial abnormalities, and this metric is highly correlated with left atrial pressure and size.[62,63] $PTFV_1$ was associated with incident AF in the Atherosclerosis Risk In Communities study.[64] Additionally, prolonged P-wave duration was predictive of incident AF in the same cohort,[64] the Framingham Heart Study,[65] and the Copenhagen ECG Study.[66] The relationship between P-wave duration and AF was nonlinear, with shortened P-wave duration being predictive of incident AF in the Copenhagen ECG Study.[66] Similarly, inconsistencies were reported for PR interval, with some studies showing an association between prolonged PR interval and AF,[64,67–69] and others demonstrating an increased AF risk with short PR interval.[69,70] Prolonged PR interval was included as a covariate in the Framingham Heart Study risk score for AF,[71] and P-wave duration was incorporated into the AF risk score developed in the Atherosclerosis Risk In Communities study.[72] Both reports demonstrate that the ECG is able to improve our ability to predict AF. However, the ability of other P-wave markers to improve AF prediction has not been explored. Nonetheless, these findings implicate the ECG as a cost-effective biological marker of AF risk due to its low-cost and widespread availability.

Current atrial fibrillation risk scores

To date, three scoring systems have been developed to predict incident AF. These risk scores were developed from community-based studies in which the identification of cardiovascular disease risk factors was the primary focus.

The Framingham Heart Study was one of these cohorts, in which the following clinical characteristics were incorporated into the risk score for AF: age, sex, body mass index, systolic blood pressure, treatment of hypertension, PR interval duration, clinically significant cardiac murmur, and heart failure.[71] Additionally, a score was developed from the Atherosclerosis Risk In Communities study in which age, race, height, smoking, systolic blood pressure, treatment of hypertension, cardiac murmur, ECG left ventricular hypertrophy, prolonged P-wave duration, diabetes, coronary heart disease, and heart failure were incorporated to develop a 10-year risk score for AF.[72] The most recent risk score was developed from cohort studies participating in CHARGE-AF.[70] In this risk score, individual participant data was used from the Framingham Heart Study, the Cardiovascular Health Study, and the Atherosclerosis Risk In Communities study to derive a 5-year predictive model including the following characteristics: age, race, height, weight, systolic and diastolic blood pressure, current smoking, treatment of hypertension, diabetes, and history of myocardial infarction and heart failure.[70]

From these reports, it is evident that a poor cardiovascular risk factor profile portends an increased risk for AF development. However, the risk scores developed from the Framingham Heart Study and the Atherosclerosis Risk In Communities study demonstrate that ECG markers of the left atrium are important predictors of AF. Although PR interval did not improve the CHARGE-AF risk score's ability to predict future AF events,[70] the aforementioned findings provide evidence that ECG-based markers of atrial pathology are important for AF prediction in certain populations. Additionally, the addition of BNP to the Framingham Heart Study risk score improved the predictive ability of the model.[26] CAC and MAC also were able to improve discrimination in the Framingham Heart Study and CHARGE-AF risk scores for AF,[47,54] but modest improvements were noted compared with the reclassification statistics reported for BNP.[26] Overall, these findings support a role for biological markers to improve the prediction of AF events.

Discussion

In this review, we have identified several biomarkers that predict incident AF. The link between these biological markers and AF is the identification of subclinical states in which AF propagation is likely to occur after an inciting trigger. For example, elevations in BNP detect underlying atrial stretch, which increase one's risk for AF. Similarly, markers of inflammation, endothelial dysfunction, and kidney dysfunction identify those who likely have abnormal atrial remodeling.

Persons with higher levels of CAC and MAC, and persons with abnormal ABI measurements and P-wave indices also have these abnormal atrial properties. If these processes are not corrected, myocardial fibrosis ensues and results in the abnormal electrophysiological properties in which AF development is probable.[73] Therefore, each marker explored represents a potential area for preventive intervention.

Due to the current and future burden that AF will place on the health care system, adequate risk assessment is crucial to prevent the development of this common arrhythmia. The aforementioned reports have undoubtedly improved our understanding of AF pathophysiology, and provided clinicians with important information with which to incorporate preventive measures. The practicing clinician should be aware of conditions associated with each of the markers discussed, as they also are associated with an increased risk for cardiovascular disease. An example would be the appropriate treatment of hypertension to reduce cardiovascular disease risk. By appropriately treating this condition, reductions in atrial pressure and atrial remodeling will simultaneously decrease the occurrence of AF.[74–76] The reduction of subclinical atherosclerosis (ie, coronary calcification) with lipid-lowering therapies is another example to possibly reduce AF risk by decreasing the development of the necessary substrate for arrhythmia propagation.[77] Also, the identification of abnormal P-wave indices on routine ECG measurement should alert providers to an increased risk for AF development and prompt the implementation of cardiovascular risk factor modification strategies.

From these reports, it is apparent that biomarkers provide important prognostic information regarding AF risk, and potentially have the ability to improve the prediction of this common arrhythmia. Additionally, appropriate risk stratification is needed to identify populations in which targeted preventive therapies will be most beneficial. Further studies are needed to determine if many of the newer biological markers identified in this review are able to refine the predictive abilities of current AF risk scores. Also, the biological markers discussed often represent distinct subclinical states associated with a single comorbid condition. It is possible that multiple biomarkers encompassing several subclinical states will provide a unique profile in which AF risk prediction is possible before the development of clinically apparent disease, and this hypothesis should be explored.

Overall, the identification of biological markers has improved our understanding of AF pathophysiology and demonstrated an ability to improve AF risk prediction. Further research in this area will allow for more precise and personalized strategies to ultimately prevent AF.

Disclosure

The authors report no conflicts of interest in this work.

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