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Stroke and Death Prediction with the Impact of Vascular Disease in Patients with Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia encountered in the U.S. and the growing burden of AF has profound health implications due to the association of AF with an increased risk of stroke, heart failure, and mortality. AF is a significant risk factor for thromboembolic stroke; and also independently increases total mortality in patients with and without cardiovascular disease. Various risk stratification schemes such as $CHADS_2$ and CHA_2DS_2-VASc have been implemented in clinical practice to determine the risk of cardio-embolic stroke, and need for thrombo-prophylaxis in patients with AF. AF is also closely related to the pathophysiology of other cardiovascular and peripheral vascular disease. Many patients with AF have associated atherosclerosis given that many risk factors for atherosclerosis also predispose to AF. Myocardial infarction (MI) is also closely related to AF and its clinical course is affected by new onset AF. This review elucidates the impact of AF on major adverse cardiovascular events and mortality outcomes in relation to stroke, coronary artery disease and peripheral vascular disease.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia requiring treatment encountered in the U.S. and the growing burden of AF has profound health implications due to the association of AF with an increased risk of stroke, heart failure, and mortality.[1-4] AF carries an increased risk of arterial thrombo-embolism and ischemic stroke because of embolization of thrombi that form within the left atrium and left atrial appendage.[4] Strokes in patients with AF are associated with higher mortality, morbidity, and longer hospital stays than those without AF.[5] AF is also closely inter-related with other comorbid conditions such as coronary artery disease (CAD), myocardial infarction (MI), and peripheral arterial disease (PAD). The prevalence of AF is influenced by age, gender, cardiovascular disease (CVD) and cardiovascular risk factors such as hypertension, diabetes, obesity and insulin resistance.[6-8] AF is also closely associated with MI. The incidence of new onset AF in the setting of acute MI has been reported to be between 4-18 % in various studies.[9-11] AF has also been suggested as a predictive marker of increased mortality in patients with acute MI. This review elucidates the impact of AF on major adverse cardiovascular events and mortality outcomes in relation to stroke, coronary artery disease and peripheral vascular disease.

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Methods

We performed a comprehensive literature search in the PubMed database using medical subject headings (MeSH) terms for 'Atrial Fibrillation', 'Stroke', 'Coronary Artery Disease', and 'Peripheral Arterial Diseases'. Original and clinical studies describing atrial fibrillation and its impact on epidemiology and outcomes of comorbid conditions such as CAD, MI and PAD were included. We also included clinical studies describing the impact of AF on overall mortality.

Atrial Fibrillation and Stroke

In patients with AF, the fibrillating atria results in decreased atrial transport, increased atrial pressure, atrial stretch and dilation which results in blood stasis and thrombus formation.[12-14] Atrial stretch also leads to increased production of atrial natriuretic peptide which may lead to hemoconcentration within the atria.[15] AF is associated with abnormalities of hemostasis, platelet activation and endothelial dysfunction adding to the risk of thrombus formation.[16-18] The left atrium and particularly the left atrial appendage are the sources of cardio-embolic events in about 70 - 90 % of the cases of AF-associated thromboembolism.[19]
Ischemic strokes in patients with AF have worse outcomes following stroke with greater disability and mortality as compared to patients without AF.[20] Thrombo-prophylaxis with anticoagulation agents has been the key for prevention of stroke in patients with AF. Randomized clinical trials have shown that warfarin, aspirin (to a lesser degree) and newer anticoagulants such as dabigatran, apixaban and rivaroxaban reduce the risk of stroke in patients with AF.[21,22] The risk of stroke and thrombo-embolism in AF is not homogeneous, and several risk stratification schemes have been developed to quantify the risk of stroke, and guide the thrombo-prophylaxis for stroke prevention.[23] One of the widely used scheme is the $CHADS_2$ score (acronym for Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, and prior stroke or transient ischemic attack [TIA]).[24] Pre-admission $CHADS_2$ score has also been shown to be a predictor of increased mortality, increased severity and poor functional outcome following a stroke.[25,26]

One major limitation of the $CHADS_2$ stratification is that it is derived from pooled data based on stroke risk factors derived from non-vitamin K antagonists (VKA) arms of trial cohorts, which does not account for all potential risk factors for stroke, such as MI and PAD. In order to further improve the risk stratification $CHA2DS_2$-VASc score was introduced recently.[27] This risk scheme takes into account the presence of peripheral vascular disease as well as greater age stratification as well as female gender as risk factors for stroke. The presence of AF in association with PAD is associated with substantial increases in morbidity and mortality. In relation to concurrent atherothrombotic disease; the presence of complex aortic plaque on the descending aorta has been shown to be an independent predictor of thrombo-embolism and stroke in AF.[28,29] The potential usefulness of CHA_2DS_2-VASc is also supported by the finding that oral anticoagulation with VKAs is much more effective than aspirin in an elderly population.[30] It has also been shown elderly patients, despite being at a higher risk of cerebrovascular events, have been undertreated with oral anticoagulants.[31]

The consideration of these additional factors and a better estimation of the age effect in the CHA_2DS_2-VASc score provides some improvement in prediction of thrombo-embolism over the $CHADS_2$ scheme. It also led to a low event rate for stroke in low risk patients and the classification of only a small proportion of patients into the intermediate risk category.[27]

Criticism of these predictive scores

Although these risk stratifications are simple to apply and successfully identify patients at relatively low risk of stroke, variation exists in their predictive accuracy. The level of consensus regarding the classification of patients into moderate risk and high risk is poor. In the future, stroke risk may be more accurately predicted by considering additional risk factors. For example, left ventricular systolic dysfunction detected by echocardiography is an independent risk factor for stroke in AF.[29,32] Studies have also shown that AF is an independent predictor of clinical outcomes even after controlling for $CHADS_2$ score and oth-

er variables.[33] A retrospective study has proposed that integration of AF duration and burden has the potential to contribute to an improved risk stratification and its aid to clinical decision making should be tested prospectively in future.[34]

Atrial Fibrillation and Myocardial Infarction

Pathophysiology

AF often coexists with CAD and MI. The incidence of new-onset AF is reported to be about 10% in the setting of acute MI.[35-37] The causal etiologies of AF in the setting of MI include atrial ischemia, pericardial inflammation, acute hypoxia, electrolyte-metabolic imbalance, elevated atrial pressures and hemodynamic impairment secondary to left ventricular dysfunction.[11,38,39] A canine study has demonstrated that chronic atrial ischemia creates substrates for both spontaneous ectopy (Ca^{2+} release events, increased Na^{+} - Ca^{2+} exchange current) and sustained re-entry, thereby leading to both AF triggering and maintenance.[40] Acute left atrial ischemia has been demonstrated to be the predominant mechanism responsible for early onset AF in patients with MI.[41] A case- control study demonstrated that CAD involving atrial branches of the coronary circulation is an independent predictor of new onset AF after a MI.[42]

Impact of Atrial Fibrillation on outcomes in MI

A recently published study by Jabre et al demonstrated that the occurrence of new onset AF after MI was associated with a marked increase in mortality. This increased mortality risk imparted by AF varies markedly according to its timing, with the highest risk of death observed for new onset AF occurring >30 days after the incident MI.[43] Another meta-analysis with a sample size of more than 120,566 patients showed that AF was independently predictive of both short- and long-term clinical outcomes in patients with MI. This increased risk of mortality could also be due to the fact that AF is a surrogate marker for heart failure, atrial volume overload and elevated filling pressure. Older age, hypertension, prior MI and advanced Killip class of congestive heart failure were found to be predictors of new onset AF in the setting of MI.[44,45]

Another study also implicated AF as a predictor of worse outcomes following MI. In this study patients with AF had significantly worse outcomes (prolonged hospital stay, development of congestive heart failure, reinfarction, cerebrovascular accident), and higher in- hospital, 30-day and 1-year mortality. Patients developing AF during their hospitalization for MI had higher in-hospital and 30-day mortality rates as compared to those with existing pre- admission AF and those without AF.[41] However it is unclear whether AF is a risk marker or a causal mediator of increased mortality after MI. While studies consistently indicate that new-onset AF is associated with unfavorable outcomes, whether new onset AF is an independent predictor of short-term and long-term outcomes remains debatable.[46,47]

Atrial Fibrillation and Peripheral Vascular Disease

Pathophysiology

Both AF and peripheral vascular disease contribute to increased risk of stroke and thrombo-embolism. Many patients with AF have associated atherothrombosis given that various risk factors for atherosclerosis also predispose to AF. In a sub-analysis of SPAF-III (Stroke Prevention in Atrial Fibrillation) trial, complex atherosclerotic plaque was detected in 25% of patients with AF independent of sex and serum cholesterol levels.[48] Pre-clinical studies have shown that several biomarkers of platelet activation and endothelial damage/dysfunction such as plasma P- selectin and von-Willebrand factor are associated with AF. New onset AF has been shown to induce local platelet activation and increased thrombin generation.[49-51] Flow-mediated dilatation (FMD), a marker of pre-clinical atherosclerosis and a predictor of vascular outcomes has also been shown to be impaired in AF.[52] However, it remains unclear if FMD is impaired because of underlying rhythm irregularity or presence of concomitant risk factors for atherosclerosis.[52,53]

Clinical aspects

Observational studies consistently show that

AF and atherosclerosis share common risk factors such as hypertension, obesity and age.[54,55] Increasing age is an independent predictor of AF and its associated complications.[56] A population-based prospective cohort study examined the association between atherosclerosis and AF by measuring the intima- media thickness (IMT) of common carotid artery and carotid plaque in 4,407 subjects with clinically insignificant atherosclerosis, and related vascular complications. During the follow-up period of this study, 269 cases of new-onset AF were identified, with the risk of AF being independently associated with IMT and carotid plaque severity, although this relationship was only statistically significant in women.[57,58] Based on this study, it could be concluded that subclinical atherosclerosis is associated with new onset AF in subjects without a history of CAD. One possible explanation for this observation could be that atherosclerosis gradually or abruptly reduces the blood supply to the sinus node and the atrial tissues that affect the conduction of electrical impulse through the atria. Also, reduced blood supply leads to microscopic scarring of the atrial wall leading to impaired conduction.[59]

Inflammation and Atrial Fibrillation

Pathophysiology

Inflammation is known to play an important role in the pathogenesis of several cardiovascular diseases.[63-66] Evidence supports a key role for inflammation in all phases of the atherosclerotic process, from endothelial dysfunction and plaque formation through progression ultimately leading to thrombotic complications. There is growing evidence for a possible role of inflammation in the pathogenesis of AF and in particular its thrombotic complications.[67-70]

Histologic studies of atrial tissue in patients with AF has revealed leukocyte infiltration and increased levels of 3-nitrotyrosine and protein carbonyls which are considered to be inflammatory markers.[71,72] Inflammation is a crucial initiator of atrial fibrosis because inflammatory stimuli such as NADPH-oxidase-derived ROS and cytokines, growth factors, angiotensin II and other hormones, as well as mechanical stretch lead to fibroblast proliferation and differentiation into myofibroblasts which contribute to impaired conduction in atrial tissue.[73-75]

A study by Bruins and colleagues demonstrated that following coronary artery bypass grafting, elevated levels of high-sensitivity C-reactive protein (hsCRP) were found to be associated with occurrence of AF.[76] Besides CRP, specific cytokines such as IL-6 and TNF-α have also been linked to AF.[77,78] In particular, IL-6 has emerged as an independent predictor of stroke and overall mortality in patients with AF, underlining that inflammation in AF might further worsen patient prognosis.[79,80]

Clinical Aspects of Inflammation and AF

An analysis of the JUPITER trial revealed that in subjects without established cardiovascular disease, elevated baseline levels of hsCRP were found to be associated with development of AF. In this study rosuvastatin 20 mg daily was found to reduce the incidence of AF.[81] A recently published analysis of the Framingham study observed that, after adjusting for standard risk factors for AF such as age, hypertension and previous myocardial infarction, elevated white cell count was associated with development of new onset AF.[82] The relationship between elevated hsCRP and white cell count with incident AF suggests that further studies investigating the role of inflammatory pathways and pathogenesis of AF may lead to new insights.

There is growing interest and evidence for the role of molecular biomarkers in new onset AF and its recurrence after cardioversion and catheter ablation. Inflammatory markers such as IL-6, CRP and CD40 L are being investigated for a link between systemic inflammation and AF. A recent study demonstrated that elevated levels of IL-6 were associated with early AF recurrence after electrical or chemical cardioversion.[83] These studies suggest that anti-inflammatory therapies such as statins and corticosteroids could play a key role in prevention of AF recurrence and its progression. A

population based cohort study investigated the association between elevated levels of inflammation- sensitive proteins (ISPs) and incident AF. In a patient pool of 6,031 men without history of MI, stroke, heart failure or cancer, plasma levels of 5 ISPs (fibrinogen, haptoglobin, ceruloplasmin, α (1)- antitrypsin and orosomucoid) were measured. After a mean follow up period of 25 years, baseline levels of ceruloplasmin were found to be significantly increased in men with new onset AF. A composite score of five ISPs was also found to be significantly associated with AF.[84] Ceruloplasmin has been shown to play a key role in oxidative stress and its elevated levels could suggest a role of oxidative pathways in remodeling of atria, this could also be a possible link between ceruloplasmin and incidence of AF.[85]

Molecular Markers in Atrial Fibrillation

Von-Willebrand factor (vWF) has been proposed as a biomarker of endothelial damage and dysfunction because increased plasma levels have been found in inflammatory and atherosclerotic vascular disease in which the endothelium is likely to be damaged.[86] Circulating levels of vWF have also been found to be a marker of structural damage to the left atrial endocardium. Data from the SPAF III trial showed that there is an independent association between vWF levels and clinical risk for stroke in AF patients.[87] In a recently published prospective study of 829 patients, high levels of plasma vWF (>221 IU/dl) was found to be an independent risk factor for adverse events (thrombotic, overall mortality and bleeding) in anticoagulated patients with long-standing persistent AF.[88] A possible mechanism by which elevated levels of vWF could be associated with increased stroke risk and overall poor prognosis is through generation of a prothrombotic state due to increased expression of factor VIII and accelerated platelet activation and adhesion.[89] Based on these molecular and clinical studies vWF could be a potential novel therapeutic target for reducing stroke risk, although it remains unclear whether vWF directly increases stroke risk, or is simply a marker for increased risk.

Various other molecular markers such as CD40 L P- selectin, IL-6, and recently micro- RNA have generated great interest in their respective roles in AF pathophysiology. A study on 231 patients by Ferro and colleagues reported that the incidence of vascular events was significantly higher in patients with elevated levels of CD40 L.[90] Soluble P-selectin (sP-sel) is a marker of platelet activation which seems to play a key role in thrombogenesis in patients with AF. A study by Fu et al demonstrated that patients with idiopathic AF and lone AF had increased levels of sP-sel as compared to healthy controls.[91]

IL-6 has been implicated in the inflammatory pathways responsible for AF initiation and propagation and is believed to play an important role in post-operative AF.[92] In an analysis of the GISSI-AF trial, patients with AF were found to have significantly elevated levels of IL-6 as compared with healthy controls. Further studies are warranted to elucidate the role of IL-6 in the pathogenesis and as therapeutic target in patients with AF.[93]

Future Directions

AF is a global public health problem leading to increased morbidity, prolonged hospital stay and overall mortality. There is an increasing understanding of the relationship between AF, vascular disease and clinical outcomes such as stroke. Further studies are needed to further refine risk stratification for stroke in patients with AF. Molecular studies have identified numerous biological pathways and potential novel therapeutic targets for prevention and optimal management of both AF and vascular disease.

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