Published in final edited form as:
Circulation. 2012 September 4; 126(10): e143–e146. doi:10.1161/CIRCULATIONAHA.112.129759.

An Update on the Prognosis of Patients with Atrial Fibrillation

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Atrial fibrillation (AF) is a highly prevalent and costly health problem, with an estimated incidence of 28 per 1000 person-years in the U.S. and an incremental national cost of $26 billion.[1,2] The prevalence of AF is increasing; it is projected that by 2050, AF will affect 6–12 million Americans.[3,4] The growing burden of AF has far-reaching public health implications due to the association of AF with an increased risk of stroke, heart failure, and mortality.[3,5,6] In recent years, the prognosis of patients with AF in certain at-risk subgroups, including those with heart failure, myocardial infarction, and chronic kidney disease, has been studied.[7–10] In our brief review, we describe the most recently discovered AF-related prognostic factors,[11] some new prognostic algorithms for estimating the risk from AF and its complications,[12] and highlight that additional efforts are needed to prevent AF-related cardiovascular morbidity and mortality.

Atrial Fibrillation and Risk for Stroke

Non-rheumatic AF is a major contributor to increased mortality rates[5] and an independent risk factor predisposing to stroke.[13,14] In community-dwelling individuals, the odds of developing a stroke is almost 5-fold higher in patients with known AF as compared with those who do not have clinically apparent AF.[14] In the U.S., the proportion of Americans aged 65 years or older is increasing and is estimated to reach 19.6% in 2030.[15] These changing demographics suggest that rates of thromboembolic stroke may rise in the near future for several major reasons. The prevalence of AF increases dramatically with advancing age and it is present in 9–18% of individuals by the age of 80 years.[16] AF accounts for almost 1 in 4 strokes in patients aged 80 years or older.[14] Furthermore, strokes from AF are associated with a 50% increased risk of serious disability and 60% increased risk of death at 3-months compared with strokes from other causes.[17,18] The high degree of morbidity from strokes secondary to AF likely relates to 4 factors: 1) the thromboembolic nature of AF-related cerebrovascular events; 2) the association between AF and other cardiovascular diseases; 3) the predilection for strokes from AF to involve the anterior circulation or lead to multiple ischemic foci; 4) and the established associations between AF and pro-inflammatory and hypercoagulable states.[19,20]

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Prior estimates associating AF with increased risk for stroke may not fully capture risk from AF because AF is often asymptomatic and paroxysmal. Recent studies, in some cases using implantable electrocardiographic monitors, have emphasized that up to 21% of patients with stroke or transient ischemic attacks have undiagnosed AF.[21] Although paroxysmal AF episodes lasting less than 30 seconds have traditionally been considered of little prognostic importance, a recent study showed that even high atrial rates of short duration are associated with higher risk for acute and chronic brain infarcts.[22,23] AF may have an even stronger relation with stroke than was previously appreciated. Clearly, further research into the prognostic importance of brief episodes of AF in the community is needed to help guide stroke prevention in patients with short episodes.

An Update on Stroke Risk Prediction in Patients with Atrial Fibrillation

It has been demonstrated that more than 60% of strokes could be prevented by anticoagulation with warfarin.[24] However, not all patients with AF are at sufficient risk for developing a stroke to justify long-term anticoagulation, especially given the higher risk for major bleeding associated with anticoagulant use.[25] The Cardiac failure, Hypertension, Age, Diabetes, Stroke [Doubled; $CHADS_2$] risk scoring system is the most widely used algorithm to predict stroke.[26] Recently, the Cardiac failure or dysfunction, Hypertension, Age≥75 [Doubled], Diabetes, Stroke [Doubled]-Vascular disease, Age 65–74, and Sex category [Female] (CHA_2DS_2-VASc) risk score was developed to incorporate both “major” clinical risk factors (e.g., previous stroke/transient ischemic attack and age≥75 years) and “clinically relevant non-major” risk factors (e.g., heart failure, hypertension, diabetes, female sex, age 65–75 years, and atherosclerotic vascular disease) into an updated clinical stroke risk prediction schema. In the Swedish Atrial Fibrillation cohort study, the CHA_2DS_2-VASc [C-statistic, 0.67; 95% Confidence Interval (CI), 0.67–0.68] exhibited slightly better performance than the $CHADS_2$ (C statistic, 0.66; 95% CI, 0.65–0.66) with respect to thromboembolic event prediction.[12] Conducting a net reclassification improvement analysis of data from over 57,000 participants with AF, Friberg et al. showed that 1 of 10 patients would have been upgraded to a more accurate high-risk category using the CHA_2DS_2-VASc as compared with the $CHADS_2$ scoring system.[27] Also in the Swedish Atrial Fibrillation study, two recently developed schemas [HEMORR(2)HAGES and the HAS-BLED, C-statistic for both ~0.6] were compared and exhibited similar, albeit modest, ability to predict major bleeding events.[12, 28] Notably, analysis of the net clinical benefit of anticoagulant treatment in the Swedish Atrial Fibrillation study shows that the risk of stroke in patients with AF not treated with anticoagulants is higher than the risk of intracranial bleeding in treated patients in all but those at lowest risk (CHA_2DS_2-VASc score =0).[29]

Prognostic Importance of Atrial Fibrillation Complicating Cardiac Surgery

New-onset AF is common after cardiac surgery, affecting 20–40% of individuals hospitalized for coronary artery bypass grafting procedures, but post-operative AF has previously been considered to be of minimal long-term prognostic importance.[30] However, a recent study involving over 16,000 patients who underwent coronary artery bypass graft procedures reported that post-operative AF was associated with higher long-term, all-cause mortality [hazard ratio (HR), 1.21; 95% CI, 1.12 to 1.32] during a mean follow-up of 6 years (range 0 to 12.5 years) when compared to patients not experiencing this arrhythmia.[31] The association between post-operative AF and risk for dying was attenuated when patients were prescribed warfarin, suggesting that postoperative AF was associated with subsequent thromboembolic complications secondary to episodes of AF.[32] Investigations have suggested that agents such as amiodarone or colchicine also may be useful to prevent AF after cardiac surgery.[33] In light of the prognostic significance of post-operative AF, further studies into strategies to prevent AF post-cardiac surgery are also needed.

Prognostic Importance of Pre-operative Atrial Fibrillation in Patients Undergoing Non-Cardiac Surgery

Current perioperative risk prediction tools[34] place a high emphasis on history of cardiovascular diseases such as coronary artery disease but do not incorporate information about AF status. A recent study by van Diepen et al. involving over 38,000 patients showed that 6.4% of patients with AF who underwent a non-cardiac surgical procedure died within 30 days of their operation and that patients with AF had a 69% higher risk for post-operative mortality than patients with coronary heart disease (odds ratio, 1.69; 95% CI, 1.34 to 2.14).[35] These data suggest that preoperative AF may be a useful predictor of adverse in-hospital and short-term outcomes after non-cardiac surgery and that risk prediction tools incorporating AF should be developed in order to better identify patients at risk for post-surgery stroke, rehospitalization, and death.

Prognosis from AF Select Patient Subgroups

AF in Patients with Heart Failure

Chronic heart failure and AF often coexist, share risk factors, and each condition strongly predisposes to the other.[36,37] Women and men with AF have an 11- and 3-fold higher risk, respectively, of developing heart failure and dying when compared with those with no AF.[4,38] In a prior study involving Framingham Heart Study participants, the combination of AF and heart failure carried a worse prognosis than either condition in isolation [in subjects with heart failure, development of AF was associated with increased mortality [men: HR, 1.6; 95% CI, 1.2 to 2.1; women: HR, 2.7; 95% CI, 2.0 to 3.6].[10] Another recent study of 99,810 patients hospitalized with heart failure and enrolled in the Get With the Guidelines-Heart Failure program between 2005 and 2010 showed that AF was present in 1/3 of heart failure cases and that AF was associated with adverse hospital outcomes, longer length of stay, and higher in-hospital death rates (4.0% versus 2.6%, $P<0.001$).[39] Two recent meta-analyses have summarized the published literature on the risk of death in patients with heart failure with AF compared to those with heart failure alone. The results of these analyses show that the coexistence of AF in HF patients increases the odds of death from 14%–57% in comparison to isolated HF.[40]

The findings of a recent community-based study involving 1664 individuals with heart failure showed not only that the presence of AF was associated with a greater than 2-fold higher risk of death compared to those with heart failure alone, but also that patients with AF developing after heart failure were at greater risk for dying than patients with pre-existing AF at the time of heart failure diagnosis.[7] These findings are consistent with those of multiple heart failure trials, which reproducibly demonstrate that AF is associated with higher long-term morbidity and mortality in heart failure patients.[41] The association between new-onset AF, heart failure progression, and increased mortality does not prove causality. In contradistinction, AF may be a marker for the intensity or duration of exposure to common risk factors, severity of hemodynamic perturbation, or neurohormonal dysregulation in heart failure. Nevertheless, the pathophysiological relations between AF and heart failure are of great clinical and public health importance in light of the growing numbers of older patients with both heart failure and AF.

AF in Patients with Coronary Heart Disease

Atrial fibrillation is often observed in patients with coronary heart disease and is a common consequence of the acute coronary events, yet until recently evidence was conflicting with respect to its prognostic significance.[42] A recent community-based cohort study confirmed the findings of several prior investigations,[43] showing that AF was associated with a four-

fold higher risk for death in patients with myocardial infarction when compared to those with no AF (HR, 3.77; 95% CI, 3.37 to 4.21), even after adjustment for the clinical characteristics of participants.[43] Notably, the timing of AF post-infarction appears to be of importance, with the highest risk for death observed among study participants developing AF more than 1 month after their infarction (compared to no AF, HR, 2.58; 95% CI, 2.21 to 3.00) and a lower risk for death seen in individuals with AF occurring during the first 2 days after infarction (compared to no AF, HR, 1.63; 95% CI, 1.37 to 1.93). Another meta-analysis of 43 studies including over 250,000 subjects with revealed that AF was associated with an almost 50% higher odds of death (odds ratio 1.46; 95% CI, 1.35 to 1.58).[42] This worse prognosis persisted irrespective of when AF occurred relative to the acute coronary event. These data convincingly demonstrate that AF should be considered a significant clinical event during acute myocardial infarction.

AF in Patients with Chronic Kidney Disease

Chronic kidney disease is both a major risk factor for the development of AF[44] as well as risk for stroke.[45] As shown in the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study,[8] proteinuria was associated with an over 50% increased risk of thromboembolism (relative risk, 1.54; 95% CI, 1.29 to 1.85), and there was an inverse relation observed between risk of stroke and estimated glomerular filtration rate (eGFR expressed in $mL \times min^{-1} \times 1.73\ m^{\#x2212;2}$). Compared with an eGFR ≥ 60, the relative risk (RR) was 1.16 (95% CI, 0.95 to 1.40) for an eGFR of 45 to 59, and 1.39 (95% CI, 1.13 to 1.71) for an eGFR<45 (P=0.008 for trend).[8] These findings demonstrate that chronic kidney disease is associated with a higher risk of thromboembolic events in AF after adjustment for other relevant risk factors. Further efforts to incorporate information about kidney function into stroke risk prediction schema appear warranted.

Risk Factors associated with Prognosis from Atrial Fibrillation

High sensitivity C-reactive protein (hs-CRP) has been identified as a marker for increased risk of adverse cardiovascular events, including death.[11,46,47] Recently, an analysis of data from 293 participants in the Atherosclerosis Risk In Communities study with AF and hs-CRP data was conducted in order to address the prognostic value of this biomarker in AF.[11] Over a 9-year follow-up period, hs-CRP was associated with higher all-cause mortality after adjustment (HR, 2.52; 95% CI, 1.49 to 4.25). Moreover, adding hs-CRP to a risk prediction schema that included clinical prognostic factors improved the C-statistic for all-cause (from 0.627 to 0.677) and cardiovascular mortality (from 0.700 to 0.718). Perhaps due to its association with an increased level of systemic inflammation, endothelial dysfunction, and/or risk for thromboembolic complications,[48,49] hs-CRP may be an important prognostic marker in patients with AF.

A recent analysis of data from the Randomized Evaluation of Long-Term Anticoagulation Therapy study reported that serum levels of troponin I and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are frequently elevated in individuals with AF and improve thromboembolic risk prediction over risk prediction instruments using only clinical variables (increased the C-statistic from 0.68 to 0.72, $p < 0.0001$).[50] On the basis of these data, the authors conclude that troponin I and NT-proBNP may be useful for predicting adverse outcomes in AF.

Conclusions and future directions

In the absence of proven effective therapies for the primary prevention of AF, contemporary AF treatment focuses on thromboembolic risk assessment and risk-appropriate anticoagulation, rhythm control in some symptomatic individuals, and aggressive

cardiovascular risk factor modification. The prognosis of patients with AF, particularly the increasing number of individuals with both AF and heart failure, remains poor despite advances in the treatment of AF.[51] Further efforts are needed to better understand the longitudinal course of AF among older adults, and the long-term prognosis of patients with AF and comorbid cardiovascular diseases and surgeries. It is also clear that the associations between AF and adverse outcomes are stronger in subgroups with comorbidities such as those with heart failure and after cardiac surgery than in healthier populations. Future research is needed to determine whether targeting of primary and secondary prevention interventions on such patients, perhaps through the use of prognostic markers, improves prognosis from AF.[52,53]

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