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 United States and an incremental national cost of $26 billion.\textsuperscript{1,2} The prevalence of AF is increasing; it is projected that, by 2050, AF will affect 6 to 12 million Americans.\textsuperscript{3,4} The growing burden of AF has far-reaching public health implications because of the association of AF with an increased risk of stroke, heart failure, and mortality.\textsuperscript{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.\textsuperscript{7-10} In our brief review, we describe the most recently discovered AF-related prognostic factors,\textsuperscript{11} discuss some new prognostic algorithms for estimating the risk from AF and its complications,\textsuperscript{12} and highlight that additional efforts are needed to prevent AF-related cardiovascular morbidity and mortality.

AF and Risk for Stroke

Nonrheumatic AF is a major contributor to increased mortality rates\textsuperscript{5} and an independent risk factor predisposing to stroke.\textsuperscript{13,14} In community-dwelling individuals, the odds of developing a stroke is almost 5-fold higher in patients with known AF than in those who do not have clinically apparent AF.\textsuperscript{14} In the United States, the proportion of Americans aged ≥65 years is increasing and is estimated to reach 19.6% in 2030.\textsuperscript{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% to 18% of those aged 80 years.\textsuperscript{16} AF accounts for almost 1 in 4 strokes in patients aged ≥80 years.\textsuperscript{14} Furthermore, strokes from AF are associated with a 50% increased risk of serious disability and 60% increased risk of death at 3 months in comparison with strokes from other causes.\textsuperscript{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, and (4) the established associations between AF and proinflammatory and hypercoagulable states.\textsuperscript{19,20}

Previous 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.\textsuperscript{21} Although paroxysmal AF episodes lasting <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.\textsuperscript{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 AF

It has been demonstrated that >60% of strokes could be prevented by anticoagulation with warfarin.\textsuperscript{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.\textsuperscript{25} The Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled; CHADS\textsubscript{2}) risk-scoring system is the most widely used algorithm to predict stroke.\textsuperscript{26} Recently, the Cardiac failure or dysfunction, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled)-Vascular disease, Age 65 to 74, and Sex category (Female) (CHA\textsubscript{2}DS\textsubscript{2}-VASc) risk score was developed to incorporate both major clinical risk factors (eg, previous stroke/transient ischemic attack and age ≥75 years) and clinically relevant nonmajor risk factors (eg, 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\textsubscript{2}DS\textsubscript{2}-VASc (C statistic, 0.67; 95% confidence interval [CI], 0.67–0.68) exhibited slightly better performance than the CHADS\textsubscript{2} (C statistic, 0.66; 95% CI, 0.65–0.66) with respect to thromboembolic event prediction.\textsuperscript{12} Conducting a net reclassification improvement analysis of data from >57 000 participants with AF, Friberg et al\textsuperscript{27} showed that 1 of 10 patients would have
been upgraded to a more accurate high-risk category by using the CHA₂DS₂-VASc in comparison with the CHADS₂ scoring system. Also, in the Swedish Atrial Fibrillation study, 2 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.\textsuperscript{12,28}\n\nNotably, 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 the lowest risk (CHA₂DS₂-VASc score=0).\textsuperscript{29}\n
**Prognostic Importance of AF Complicating Cardiac Surgery**\n\nNew-onset AF is common after cardiac surgery, affecting 20% to 40% of individuals hospitalized for coronary artery bypass grafting procedures, but postoperative AF has previously been considered to be of minimal long-term prognostic importance.\textsuperscript{30} However, a recent study involving >16,000 patients who underwent coronary artery bypass graft procedures reported that postoperative AF was associated with higher long-term, all-cause mortality (hazard ratio [HR], 1.21; 95% CI, 1.12–1.32) during a mean follow-up of 6 years (range, 0–12.5 years) in comparison with patients not experiencing this arrhythmia.\textsuperscript{31} The association between postoperative 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.\textsuperscript{32} Investigations have suggested that agents such as amiodarone or colchicine also may be useful to prevent AF after cardiac surgery.\textsuperscript{33} In light of the prognostic significance of postoperative AF, further studies into strategies to prevent AF after cardiac surgery are also needed.

**Prognostic Importance of Preoperative AF in Patients Undergoing Noncardiac Surgery**\n\nCurrent perioperative risk prediction tools\textsuperscript{34} place a high emphasis on history of cardiovascular diseases such as coronary heart disease but do not incorporate information about AF status. A recent study by van Diepen et al\textsuperscript{35} involving >38,000 patients showed that 6.4% of patients with AF who underwent a noncardiac surgical procedure died within 30 days of their operation and that patients with AF had a 69% higher risk for postoperative mortality than patients with coronary heart disease (odds ratio, 1.69; 95% CI, 1.34–2.14). These data suggest that preoperative AF may be a useful predictor of adverse in-hospital and short-term outcomes after noncardiac surgery and that risk prediction tools incorporating AF should be developed to better identify patients at risk for postsurgery stroke, rehospitalization, and death.

**Prognosis From AF Select Patient Subgroups**\n
**AF in Patients With Heart Failure**\n\nChronic heart failure and AF often coexist and share risk factors, and each condition strongly predisposes to the other.\textsuperscript{36,37} Women and men with AF have an 11- and 3-fold higher risk, respectively, of developing heart failure and dying in comparison with those with no AF.\textsuperscript{4,38} In a previous 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, 1.2–2.1; women: HR, 2.7; 95% CI, 2.0–3.6]).\textsuperscript{39} 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 one third 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).\textsuperscript{39} Two recent meta-analyses have summarized the published literature on the risk of death in patients with heart failure with AF in comparison with 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% to 40% in comparison with isolated HF.\textsuperscript{40,41}\n
The findings of a recent community-based study involving 16,644 individuals with heart failure showed not only that the presence of AF was associated with a >2-fold higher risk of death in comparison with those with heart failure alone, but also that patients with AF that develops after heart failure were at greater risk for dying than patients with preexisting AF at the time of heart failure diagnosis.\textsuperscript{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 patients with heart failure.\textsuperscript{42} 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**\n\nAtrial 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.\textsuperscript{43} A recent community-based cohort study confirmed the findings of several previous investigations,\textsuperscript{43} showing that AF was associated with a 4-fold higher risk for death in patients with myocardial infarction in comparison with those with no AF (HR, 3.77; 95% CI, 3.37–4.21), even after adjustment for the clinical characteristics of participants.\textsuperscript{43} Notably, the timing of AF postinfarction appears to be of importance, with the highest risk for death observed among study participants developing AF >1 month after their infarction (in comparison with no AF, HR, 2.58; 95% CI, 2.21–3.00) and a lower risk for death seen in individuals with AF occurring during the first 2 days after infarction (in comparison with no AF, HR, 1.63; 95% CI, 1.37–1.93). Another meta-analysis of 43 studies including >250,000 subjects revealed that AF was associated with an almost 50% higher odds of death (odds ratio 1.46; 95% CI, 1.35–1.58).\textsuperscript{44} 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, and a risk for stroke, as well. As shown in the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, proteinuria was associated with an >50% increased risk of thromboembolism (relative risk, 1.54; 95% CI, 1.29–1.85), and there was an inverse relation observed between risk of stroke and estimated glomerular filtration rate (expressed in mL · min⁻¹ · 1.73 m⁻²). In comparison with an estimated glomerular filtration rate ≥60, the relative risk was 1.16 (95% CI, 0.95–1.40) for an estimated glomerular filtration rate of 45 to 59, and 1.39 (95% CI, 1.13–1.71) for an estimated glomerular filtration rate <45 (P=0.008 for trend). 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 AF**

High-sensitivity C-reactive protein (hs-CRP) has been identified as a marker for increased risk of adverse cardiovascular events, including death. Recently, an analysis of data from 293 participants in the Atherosclerosis Risk In Communities study with AF and hs-CRP data were conducted to address the prognostic value of this biomarker in AF. Over a 9-year follow-up period, hs-CRP was associated with higher all-cause mortality after adjustment (HR, 2.52; 95% CI, 1.49–4.25). 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 because of its association with an increased level of systemic inflammation, endothelial dysfunction, and risk for thromboembolic complications, 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 are frequently elevated in individuals with AF and improve thromboembolic risk prediction over risk prediction instruments by using only clinical variables (increased the C statistic from 0.68 to 0.72, P<0.0001). On the basis of these data, the authors conclude that troponin I and N-terminal pro-B-type natriuretic peptide may be useful for predicting adverse outcomes in AF.

**Conclusions**

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. 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 those who have undergone 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.

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**Disclosures**

None.

**References**


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