Heart Failure in Atrial Fibrillation
— An Update on Clinical and Echocardiographic Implications —

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Atrial fibrillation (AF) is the most common sustained arrhythmia in adults and has unfavorable consequences such as stroke, heart failure (HF), and death. HF is the most common adverse event following AF and the leading cause of death. Therefore, identifying the association between AF and HF is important to establish risk stratification for HF in AF. Recent studies suggested that left atrial and ventricular fibrosis is an important link between AF and HF, and the prognostic impact may differ with respect to HF subtype, stratified with left ventricular ejection fraction (EF). Mortality risk in patients with concurrent AF and HF with reduced EF (HFrEF) appears slightly higher compared with those with concurrent AF and HF with preserved EF (HFpEF). On the other hand, the prognostic impact of HF in AF is similar between HFrEF and HFpEF. Further, left atrial size, as well as left atrial and left ventricular functional assessment, are reported to be useful for the prediction of HF in AF, incremental to the conventional risk factors. In this review, we focus on the epidemiological, pathophysiological, and prognostic associations between AF and HF, and review the clinical and echocardiographic predictors for HF in AF.

**Key Words:** Atrial fibrillation; Echocardiography; Heart failure; Mortality; Risk factors

**Epidemiology of HF and AF**
AF and HF frequently coexist, and each condition promotes the other. Among patients with AF, the incident risk of HF is 2- to 5-fold higher than among those without AF. A recent study has reported that more than one-third of the patients with new AF had HF, and more than half with new HF had AF. In Japan, the incidence rate of HF after the diagnosis of AF has been reported to be approximately 1.5–2% per year. The cumulative incidence rate of HF in AF is reported as 20% at 5 years, which is higher than the risk of stroke. Of note, the incident risk of HF appears higher in the early phase after AF diagnosis.

Regarding HF subtype, stratified by left ventricular ejection fraction (LVEF), HF with preserved EF (HFpEF) is more prevalent in AF patients than HF with reduced EF (HFrEF). Similarly, AF is more likely to occur in patients with HFpEF than in those with HFrEF. According to recent data from the Swedish Heart Failure Registry, the prevalence of AF was 65%, 60%, and 53% in HFrEF, respectively. The cumulative incidence of AF in HF is reported as 20% at 5 years, which is higher than the risk of stroke.

**Prognostic Association Between AF and HF**
Patients with concurrent HF and AF have a significantly worse prognosis compared with those with only 1 of the 2 conditions. The Framingham Heart Study demonstrated that subsequent HF in AF is associated with an increased risk of death with a hazard ratio (HR) of 2.7 in men and 3.1 in women. Similarly, another study...
demonstrated that subsequent HF in AF is associated with a 3.4-fold higher risk of death compared with no evidence of HF. Furthermore, cardiovascular death, including HF, was reported as the leading cause of death among AF patients in some recent studies. Data from a meta-analysis including 71,683 patients showed that cardiovascular death accounted for 46% of all-cause deaths in AF patients, whereas stroke accounted for only 5.7% of all deaths. In the recent prospective substudy of the Effective Anticoagulation with Factor Xa Next Generation in AF-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48), which included 971 patients with a CHADS2 score ≥2 demonstrated that hospitalization for HF was more common than for thromboembolic events (9.6% vs. 4.9%), and cardiovascular death was the most common cause of death (71.9%) in AF patients.

Notably, the impact of AF and HF on death may differ according to their temporal association. In a recent study investigating patients with AF or HF, the subsequent development of the other was associated with increased risk of death, and, also, preexisting HF negatively affected survival in patients with AF; however, preexisting AF did not have an impact on survival in patients with HF. Similarly, other studies have identified that the prognostic impact of AF in HF appears stronger for new-onset AF compared with concurrent or preexisting AF (Figure A). A study in Olmsted County including 3,292 patients demonstrated that patients who developed HF after AF exhibited >2-fold increased risk of death, whereas those with AF prior to HF had a 29% increased risk of death.

### Differences in Prognostic Significance Between HF Subtypes

Recent studies have investigated the difference in prognostic significance based on HF subtype. There is compelling evidence of which HF subtype is the major driver for death. A study that investigated Framingham Heart Study participants between 1980 and 2012 identified a higher mortality rate in patients with concurrent AF and HFrEF than in those with concurrent AF and HFrEF (Figure B). Similarly, in a systematic review of AF and HF, patients with concurrent AF and HFrEF had a higher mortality risk than patients with concurrent AF and HFrEF (Figure B). However, analyses of patients with AF demonstrated that new-onset HFpEF and HFrEF appeared to have similar adverse associations with death (Figure C). On the other hand, a meta-analysis of 152,306 HF patients reported that the increment risk of AF for death in HF was significantly higher in HFpEF compared with HFrEF (HR: 1.21 vs. 1.09) (Figure D). In the Swedish Heat Failure Registry, AF was associated with a similar increased risk of death in HFpEF, HFmrEF, and HFrEF, with HRs of 1.11, 1.22, and 1.17, respectively. More recently, interesting results have been shown in a study using the registry of the European Society of Cardiology. In that study, the prognostic impact of AF for combined of all-cause death or HF hospitalization was significant in patients with HFpEF (HR: 1.365, P<0.001) and HFmrEF (HR: 1.302, P=0.014), but not in patients with HFrEF (P=0.502) (Figure D); however, the survival or event-free survival rate was similar in patients with concurrent AF and HFpEF and those with concurrent AF and HFrEF, or slightly worse in those with concurrent AF and HFrEF (Figure B). It is assumed that the hemodynamic consequences of AF in HFpEF may be more significant because it is associated with increased myocardial wall stress compared with HFrEF. Further studies are warranted to clarify the temporal interaction between AF and HF with regard to HF subtype.

### Underlying Pathophysiology of AF and HF

HF and AF share common risk factors such as age, hypertension, chronic obstructive pulmonary disease, overweight, and diabetes. Although the underlying mechanism is rather complicated, left atrial (LA) structural, electrical, and neurohormonal remodeling is reported to be associated with AF development. Recent studies consider LA...
Indeed, the presence and severity of diastolic dysfunction are substrates for the development of HF. Ventricular stiffness, and elevated LV filling pressure, which are likely caused by LV diastolic dysfunction, LV myocardial fibrosis may represent a potential link between AF-mediated cardiomyopathy, is related to lower LVEF. Indeed, among patients with AF and HFrEF, there is a significant number of cases of LVEF improvement after recovery of sinus rhythm by ablation therapy. The CASTLE-AF trial, which investigated patients with AF and EF ≤35% who underwent ablation therapy, demonstrated a 40% reduction in the risk of HF hospitalization and death after ablation therapy.

**Clinical Risk Factors for HF Development in AF**

In previous studies, conventional risk factors for HF in the general population such as advancing age, LV hypertrophy, obesity, hypertension, diabetes, structural heart disease, and history of myocardial infarction have been shown as significant predictors for HF development in patients with AF. A prospective study in Japan including 1,942 AF patients demonstrated that organic heart disease, anemia, renal dysfunction, and diabetes mellitus were independently associated with incident HF. Additionally, it was demonstrated that a new scoring system, the HARRDD score (organic heart disease: 2 points, anemia: 1 point, renal dysfunction: 1 point, diabetes: 1 point, and diuretic use: 1 point; range: 0–6 points) stratified patients’ risk for HF development (HF incidence of patients scoring 0 points: 0.2%, vs. 6 points: 40.8%), with a high predictive ability (area under the curve=0.840). However, this score has yet to be externally validated.

Although data regarding the relationship of the type of fibrotic changes as a hallmark of LA structural remodeling. Indeed, the presence and severity of diastolic dysfunction are predictive of incident AF. Further, LA fibrosis is likely caused by LV diastolic dysfunction, LV myocardial stiffness, and elevated LV filling pressure, which are important substrates for the development of HF. Therefore, myocardial fibrosis may represent a potential link between AF and HF. It is easy to speculate that in patients with significant diastolic dysfunction, who depend largely on the atrial contribution to ventricular filling, the loss of atrial function may diminish cardiac output leading to HF. Nakatani et al reported that 55% of patients with AF and preserved LVEF have reduced stroke volume index (<33 mL/m²), and persistent AF patients, who may have worse diastolic function, have a greater increment in the stroke volume index after ablation therapy than do paroxysmal AF patients. However, no data are available comparing prognostic significance in patients with AF and HFrEF on outcomes with or without ablation therapy.

In patients with HFrEF, the AF burden is suggested to be different from that of HFrEF patients. It has been indicated that AF promotes LA and LV fibrosis, and may lead to perpetuation of AF and worsening of HF. In fact, LV fibrotic change is more pronounced in patients with persistent AF compared with those with paroxysmal AF or sinus rhythm. Furthermore, it has been demonstrated that long-standing AF, which may partly include patients with AF-mediated cardiomyopathy, is related to lower LVEF. Indeed, among patients with AF and HFrEF, there is a significant number of cases of LVEF improvement after recovery of sinus rhythm by ablation therapy. The CASTLE-AF trial, which investigated patients with AF and EF ≤35% who underwent ablation therapy, demonstrated a 40% reduction in the risk of HF hospitalization and death after ablation therapy.

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AF to the incidence of HF remain scarce, it is common that persistent AF is more predictive of incident HF compared with paroxysmal AF. The AF population study in the Outcome Registry for Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry demonstrated that permanent AF, which was compared with paroxysmal AF, and elevated baseline heart rate were risks for incident HF, independent of conventional risk factors. In a Japanese community-based prospective survey, the Fushimi AF Registry, sustained AF was associated with a higher incidence of the composite outcome of cardiac death and HF hospitalization compared with paroxysmal AF. Interestingly, this association was only observed in the younger AF population (age ≤74 years), and not in the older group. In the HFpEF population-based study, it was also demonstrated that persistent AF is independently associated with worse HF hospitalization-free survival, but not paroxysmal AF.

Echocardiographic Prediction of HF Development in AF

In patients with AF, echocardiography plays a central role in screening, management, and follow-up. In addition, echocardiographic evaluation is useful for the prediction of future HF events in patients with AF, incremental to conventional clinical risk factors. However, it is generally challenging to determine the representative heart beat for measurement of echocardiographic parameters in such patients because of the irregular heart rhythm. A guideline of the American Society of Echocardiography recommends that measurements obtained from a minimum of 5 consecutive cardiac cycles should be averaged in patients with AF. Also, previous studies have demonstrated an index beat that has similar R-R intervals in the preceding and preceeding heart beats is an accurate and easy to perform echocardiographic assessment in patients with AF.

During ventricular diastole, the LA is directly exposed to LV pressure through the open mitral valve. Therefore, in patients with sinus rhythm, and without mitral valve disease or left-to-right shunts, LA size has been demonstrated as a marker of elevated LV filling pressure and the severity of LV diastolic dysfunction and is a well-known predictor of HF development. However, in a previous study by Tsang et al, indexed LA volume was not a significant predictor of future cardiovascular events in AF patients, despite it being a strong predictor in sinus rhythm. On the other hand, recent studies have shown conflicting results. Potpara et al demonstrated that LA dimensions and low-normal LV EF (50–54%) were significant predictors for incident HF in patients with first-diagnosed AF and a structurally normal heart. In our recent study, which investigated a larger cohort of AF patients with a longer mean follow-up period, indexed LA volume was a significant predictor for HF development, independent of age, LV EF, and LV mass. In this study, the estimated 8-year HF event-free survival rates of each group stratified by indexed LA volume (<40 mL/m², 40–60 mL/m², >60 mL/m²) were 87%, 80%, 67%, respectively. Although the process of LA enlargement in AF may be more complicated than in sinus rhythm, because the LA in the AF population is commonly enlarged, and AF itself causes LA remodeling, the degree of LA enlargement may represent a susceptibility to HF development. LA size has been used as a common echocardiographic parameter and may be useful for risk stratification, but the appropriate cutoff value and clinical utility of LA volume has not been validated in AF patients, and further studies are needed.

It is suggested that LA dysfunction or LA fibrosis antedate LA enlargement, and the prognostic utility of LA function has also been investigated. In a study of the ENGAGE AF-TIMI 48 study, LA dysfunction assessed by LA emptying fraction [100% (LA maximal volume − LA minimal volume)/LA maximal volume] and LA expansion index [(LA maximal volume − LA minimal volume)/LA minimal volume] were significantly associated with an increased risk for cardiovascular death, HF hospitalization, or both, with an intraobserver intraclass correlation coefficient of 0.95 (range: 0.91–0.99) and an interobserver intraclass correlation coefficient of 0.84 (range: 0.75–0.93). In that study, LA functional impairment was demonstrated as more predictive of these outcomes than LA size. The usefulness of other myocardial functional assessments beyond LVEF to predict cardiovascular outcomes in AF patients has been also investigated, and the results are summarized in the Table. A cohort study of 190 persistent AF patients reported that a combination index using transmitral flow E and LA strain (E/LA strain) was a predictor of cardiovascular events including cardiovascular death, HF hospitalization, myocardial infarction, and stroke although they did not demonstrate intra- and interobserver reliability of E/LA strain. Su et al also demonstrated that worsening global LV longitudinal strain was independently associated with an increased risk of cardiovascular events in AF, with intra- and interobserver mean percent errors for measurement of 5.3±3.5% and 6.2±3.8%, respectively. Of note, global LV longitudinal strain was still a significant predictor in the subgroup of patients with preserved EF.

From this viewpoint, LA size or LA function, as well as LV function, may add significant incremental prognostic value for HF events beyond the conventional clinical and LV parameters. However, the clinical utility of these parameters has not been well validated, and there are limited data available about which parameter is appropriate for risk assessment in AF patients. Therefore, larger-scale studies, which investigate and compare these parameters, as well as taking HF subtype into consideration, are needed to establish risk stratification of patients with AF.

Conclusions

In patients with AF, HF is the most common adverse consequence, with a significantly worse prognosis. LV and LA fibrotic change is demonstrated as an important link between AF and HF, and clinical and echocardiographic risk assessment for HF is of particular interest in AF. Further studies are needed for the characterization of these prognostic factors with respect to the temporal relationship of AF and HF, as well as HF subtype, and may lead to improve AF management strategies and prognostic outcomes.

Disclosure

The authors have no conflicts of interest to disclose.

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