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EDITORIAL COMMENT

Oral Anticoagulant Agents in Patients With Atrial Fibrillation and Heart Failure

Does Heart Failure Status Influence Efficacy and Safety?*

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Atrial fibrillation (AF) is the most common sustained heart rhythm disorder and confers a ≥5-fold risk for stroke (1). AF and heart failure (HF) frequently coexist, sharing risk factors and pathophysiological mechanisms (2-4). Approximately 30% of patients with AF also have HF, and more severe HF symptoms lead to further symptomatic deterioration, hospitalizations, embolic events, and death (4-10). In patients with severely symptomatic HF with concomitant AF, coagulation control with vitamin K antagonists is more difficult to attain because of frequent drug interactions and possibly congestive liver dysfunction (11).

The advent of non-vitamin K antagonist oral anticoagulant agents (NOACs) is dramatically changing the way patients with AF are treated. These drugs (dabigatran, rivaroxaban, apixaban, and edoxaban) do not require monitoring and have been shown to be at least noninferior (11-14) or even superior (12,13) to warfarin for thromboprophylaxis in patients with AF and to produce less intracranial bleeding. A recent meta-analysis of the 4 main randomized trials of NOACs in AF (RE-LY [Randomized Evaluation of Long Term Anticoagulant Therapy], ROCKET-AF [Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation], ARISTOTLE [Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation], and ENGAGE AF-TIMI 48 [Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48]) found no treatment differences regarding efficacy and safety in patients classified as having HF compared with those without HF diagnosis. In other words, NOACs were overall effective and likely safer (fewer intracranial hemorrhages) in patients with AF regardless of the reported HF status (15). In the absence of a dedicated randomized trial of NOACs specifically targeting HF populations, meta-analyses including "aggregate trial-level data" (not patient-level data) provide some reassurance regarding the use of these drugs in patients with HF. However, despite the consistent treatment benefits across the pre-specified subgroup analyses within the trials, these may be underpowered to detect significant differences between groups, such as patients with HF versus those without HF. In a recent extensive review, several challenges for future studies were highlighted (16).

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In this issue of *JACC: Heart Failure*, Savarese et al. (17) present a comprehensive meta-analysis of the efficacy and safety of NOACs in patients with AF with and without HF. The results are overall confirmatory and nicely complement the previously published results by Xiong et al. (15), adding the more recent data from ENGAGE AF-TIMI 48. Overall, compared with warfarin, the efficacy of NOACs in reducing the rates of stroke and systemic embolism did not differ between patients with and those

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without HF. Interestingly, there were lower major bleeding rates, particularly regarding intracranial bleeding with the use of NOACs, but the p value for HF status interaction was >0.05 for all efficacy and safety endpoints.

Are these findings sufficient evidence to support the use of NOACs in patients with HF? Several limitations preclude the rapid generalization of this treatment to all HF populations. Generally, patients with HF have higher cardiovascular event rates compared with patients without HF (as also demonstrated in the present study), and enrolling patients with HF in AF trials provides a "risk enrichment" that may strengthen the power to detect treatment effect. Actually, it is worth mentioning that HF is a major determinant of the calculated "thromboembolic risk score" used to support the decision to initiate anticoagulation therapy, although the definition of HF varies within the various thromboembolic risk scores, and thromboembolic risk varies greatly across HF presentation and severity profiles (18). For example, the ATRIA and $CHADS_2$ risk scores include decompensated HF, whereas the "C" in CHA_2DS_2-VASc refers to recently decompensated HF (irrespective of ejection fraction) or moderate to severe systolic dysfunction on imaging methods (even in asymptomatic patients). The use of a consistent and reliable HF definition across NOAC trials could improve the predictive value of these risk scores. However, HF is not incorporated in contemporary bleeding risk scores (16). Importantly, the definition of baseline HF status in AF trials has been inconsistent and subjective. Essentially, in NOACs trials, HF definition was based on symptoms reported by the site investigator or on left ventricular ejection fraction (assessed by any methods, which were not consistently reported). Moreover, in almost all AF NOAC trials, data regarding HF etiology, baseline loop diuretic dose, previous HF hospitalizations, and natriuretic peptide levels were not documented. Therefore, HF versus no-HF subgroups could have been frequently misassigned (19). In addition, no stratification at randomization was performed on the basis of HF status, and the HF subgroups were not powered to reach definitive conclusions in the subgroup analyses. Finally, in most trials, patients with severely impaired renal function and very old patients were excluded (20). Patients with creatinine clearance lower than 30 ml/min were excluded from all NOAC trials (lower than 25 ml/min in ARISTOTLE), and only <20% of patients in all these trials had creatinine clearance <50 ml/min. These exclusions likely decrease the prevalence and severity of patients with HF in most NOAC AF trials, which is a serious limitation for the generalizability of the results of these trials so far to all patients with HF. On the safety side, because renal function impairment increases the risk for bleeding (16), the current trials can misleadingly underestimate the safety of NOACs in real-world patients with HF. Hence, the results of HF subgroup analyses derived from these trials may not reflect the real risk-to-benefit ratio in HF populations with AF and can hardly be extended to all such patients.

Furthermore, hospitalizations for worsening HF were not considered as endpoints in AF trials. These may be related to pulmonary embolism, which may mimic HF worsening, and HF hospitalization may be due to or associated with rhythm disturbances, events that may be influenced by NOAC therapy and not accounted for in NOAC AF trials. Antithrombotic benefits of oral anticoagulant therapy in patients with HF may exceed benefits limited to stroke and systemic embolism events and include venous thrombotic events. HF endpoint are important to consider in AF trials, not only for monitoring treatment efficacy and safety but also to assess potential treatment interactions (16) (**Table 1**).

TABLE 1 Definition of Heart Failure in Atrial Fibrillation Non-Vitamin K Antagonist Oral Anticoagulant Agent Trials and Potential for Improvement

Trial	HF Definition	HHF Endpoints	HF Stratification	Severe Renal Impairment	Potential for Improvement
RE-LY	NYHA class ≥II LVEF	No	No	Excluded	• HF etiology • HF treatment
ROCKET-HF	HF history LVEF <40%	No	No	Excluded	• Volume status • Loop diuretic dose
ENGAGE AF-TIMI 48	HF history NYHA class	No	No	Excluded	• Previous HF hospitalizations • IV loop diuretic agents during index hospitalization
ARISTOTLE	HF history LVEF <40%	No	No	Excluded	• Natriuretic peptide levels • Concomitant antiplatelet agents

ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ENGAGE AF-TIMI 48 = Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48; HF = heart failure; HHF = heart failure hospitalization; IV = intravenous; LVEF = left ventricular ejection fraction; NOAC = non-vitamin K antagonist anticoagulant agent; NYHA = New York Heart Association; RE-LY = Randomized Evaluation of Long Term Anticoagulant Therapy; ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.