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EDITORIAL COMMENT

Bridging Atrial and Ventricular Failure Through Biomarkers

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Auricular fibrillation frequently complicates severe heart conditions, potentially leading to heart failure or even death if not promptly treated.

—Paul Dudley, 1937[1]

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia worldwide. Its incidence is steadily increasing, with a significant impact on public health and health care costs. AF is not an isolated condition; rather, it is a manifestation of cardiac disease that often involves the atria and typically includes 1 or more valves, diastolic and/or systolic dysfunction, and structural atrial disease in various combinations. AF and heart failure (HF) frequently coexist, a connection that has been recognized for nearly a century.[1] However, their relationship is complex, making it challenging to determine when/whether HF is a cause or a consequence of AF.

AF can worsen HF by promoting electrophysiological remodeling, fibrosis, and tachycardia-induced cardiomyopathy, which lead to ventricular dilation, decreased contractility, and persistent diastolic dysfunction. Conversely, HF exacerbates AF through neurohormonal activation, structural remodeling and mitral valve regurgitation, increased atrial fibrosis, and altered ionic currents, all of which promote AF maintenance. Both conditions contribute to a vicious cycle, where each exacerbates the other, complicating patient management and underscoring the necessity for effective risk stratification. Circulating biomarkers could be crucial in unraveling this cycle, especially in patients with diagnosed AF, by revealing underlying cardiac structural and functional pathways and highlighting the increased risk of HF.[2]

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In this issue of *JACC*, Haller et al[3] investigated the incremental prognostic performance of 3 biomarkers, each released through a different mechanism, for HF risk stratification in patients with AF. The study pooled individual patient data from 3 major randomized trials (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], and RE-LY [Randomized Evaluation of Long-Term Anticoagulation Therapy]) within the COMBINE-AF (A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation) cohort. The objective was to evaluate the prognostic utility of N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hs-cTnT), and growth-differentiation factor (GDF)-15 in predicting HF-related outcomes in AF patients. The primary composite endpoint was hospitalization for heart failure (HHF) or cardiovascular death, with secondary endpoint combining HHF and HF-related death. The study included 32,041 patients with a median follow-up of 27 months. Given the intricate relationship between AF and HF, it is not surprising that a significant proportion of patients

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with AF have a previous history of HF, namely 42% in this cohort, and 31% present with an ejection fraction of <50%. Elevated levels of NT-proBNP, hs-cTnT, and GDF-15 were independently associated with increased risks of cardiovascular death/HHF, HHF, and HF-related death. Specifically, the HR values per each SD increase for NT-proBNP, hs-cTnT, and GDF-15 were, respectively, 1.68 (95% CI: 1.59-1.77), 1.39 (95% CI: 1.33-1.44), and 1.20 (95% CI: 1.15-1.25). The addition of these biomarkers to clinical models significantly improved risk prediction, with the C-index for the primary endpoint increasing from 0.70 to 0.77 ($P < 0.001$). Weighted quantile sum regression indicated that NT-proBNP and hs-cTnT contributed equally to risk assessment (38% and 41%, respectively), whereas GDF-15 provided a lesser but still significant contribution (21%).[3]

The study strengths include the large cohort size and the robust statistical methods used to validate the findings. The pooling of data from 3 large-scale trials enhances the generalizability of the results. On the other hand, the observational nature of the analysis within randomized trials introduces potential biases, and the lack of external validation cohorts means that the findings need replication in other populations. Additionally, whereas biomarkers provide valuable prognostic information, their utility in guiding specific therapeutic interventions requires further exploration. Moreover, the absence of soluble suppression of tumorigenicity 2, an established predictor of death or HF in patients with AF irrespective of history of HF or NT-proBNP levels, is a possible limitation. Indeed, soluble suppression of tumorigenicity 2 was shown to predict outcomes in HF patients beyond established biomarkers, such as NT-proBNP and hs-cTnT.[4] Finally, the proposed cutoffs for the 3 biomarkers, derived from previous studies, remain debatable. Elevated natriuretic peptide levels are observed in about 20% to 30% of individuals with AF. Consequently, the diagnostic criteria for HF and biomarkers' cutoffs in patients with AF should differ from those applied to patients without AF.[2]

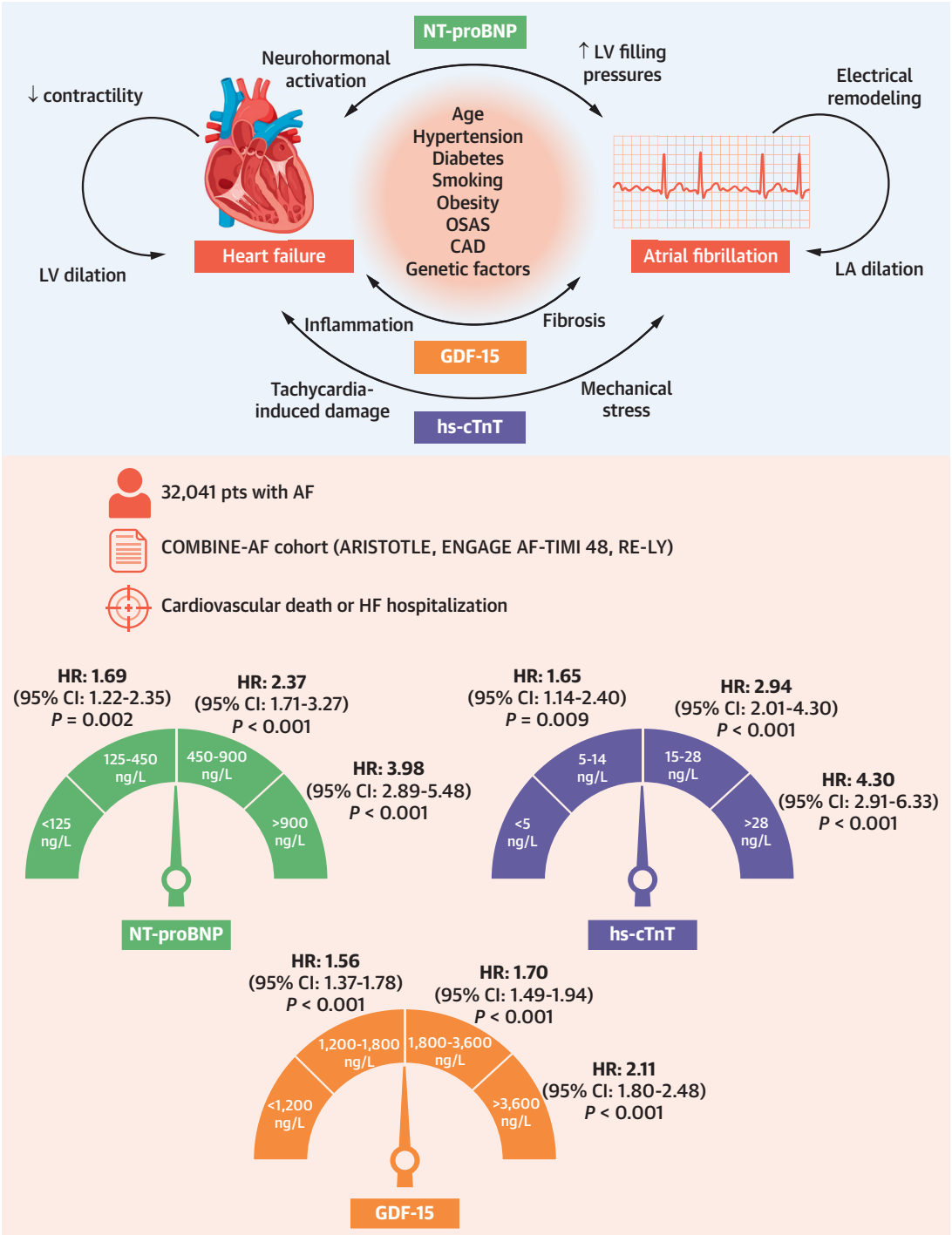
This study further shows how AF and HF are linked through a complex interplay of mechanisms. AF worsens cardiac function and promotes adverse remodeling, whereas the severity of the underlying cardiac disease correlates with the persistence and severity of AF. NT-proBNP, hs-cTnT, and GDF-15 can provide crucial insights into this complex relationship (**Figure 1**). NT-proBNP, which is elevated in response to cardiac stress and volume overload, reflects the severity of HF and the impact of AF on cardiac function and filling pressures. hs-cTnT, being associated with myocardial injury, highlights the damage inflicted by both AF and HF. Furthermore, GDF-15, linked to inflammation and tissue remodeling, underscores the shared inflammatory and fibrotic pathways contributing to both conditions. These biomarkers have already exhibited strong additive and independent prognostic value in different contexts, such as acute and chronic HF, cardiomyopathies, and congenital heart diseases.[2]

The ability to stratify accurately HF risk in patients with AF using these biomarkers allows for more tailored management strategies. In particular, NT-proBNP and hs-cTnT could be integrated into routine clinical assessment, guiding decisions on aggressive risk factor management, prompting the ruling-out of an underlying structural heart disease, supporting an early initiation of HF therapies, and a closer monitoring of high-risk patients. The 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines already emphasize the importance of managing patients without HF, but with risk factors and elevated biomarkers (stage B HF). For patients with AF, this involves lifestyle modifications and treatment of exacerbating conditions such as obesity and obstructive sleep apnea.[5]

Patients with AF and a higher risk of HF might also benefit from closer follow-up and expedited introduction of cardioprotective drugs such as mineralocorticoid receptor antagonists or sodium-glucose cotransporter 2 inhibitors, where indicated. For example, the sodium-glucose cotransporter 2 inhibitor empagliflozin has recently shown to exhibit atrial antiarrhythmic effects in patients with HF with preserved ejection fraction by inhibiting Na increased influx and late I_{Na}.[6] Patients with a history of HF would particularly benefit from carefully titrated cardioactive medications and, in the case of HF with preserved ejection fraction, even drugs with less robust evidence.

Future research should focus on validating these findings in diverse populations and developing biomarker-based HF risk stratification in patients with AF into clinical practice. Randomized controlled trials are needed to assess whether biomarker-guided therapy can improve outcomes in patients with AF at high risk for HF. Moreover, the exploration of novel biomarkers and the

FIGURE 1 **Biomarkers for Risk Prediction of Heart Failure in Patients With Atrial Fibrillation: Pathophysiological Rationale and Results From the COMBINE-AF Cohort**



See text for details. AF = atrial fibrillation; ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CAD = coronary artery disease; COMBINE-AF = A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation; ENGAGE AF-TIMI 48 = Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48; GDF = growth-derived factor; HF = heart failure; hs-cTnT = high-sensitivity cardiac troponin T; LA = left atrium; LV = left ventricle; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OSAS = obstructive sleep apnea syndrome; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy.

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development of multimarker panels could further refine risk prediction models.

In conclusion, the study by Haller et al[3] highlights that NT-proBNP, hs-cTnT, and, to a lesser extent, GDF-15 are powerful tools for refining HF risk assessment in patients with AF. Nonetheless, their current clinical value is more about shaping follow-up intensity and risk factor management than steering precise treatment decisions. Future research is crucial to unlock their full potential, paving the way for personalized and impactful treatment approaches.

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