Editorial

# Heart Failure as a Risk Factor for Stroke: Another Facet of the Heart–Brain Connection

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As the population ages, the prevalence of multi-morbidity increases, an epidemiological observation with profound clinical consequences. Multiple chronic conditions in aging patients generate increasingly complex diagnostic and management challenges. Importantly, certain chronic conditions in aging populations coexist more frequently than expected based on age alone. Such is the case for cardiovascular and neurological diseases and there is robust data indicating that many cardiovascular and neurocognitive conditions share common risk factors and pathophysiology. These observations have led to the formulation of the concept of "heart–brain connection" whereby several pathways have been proposed to delineate how heart disease and neurological diseases interact.[1] Specifically for heart failure (HF), cardiovascular risk factors are shared contributors to both HF and neurological diseases and HF is associated with neurocognitive dysfunction independently of other comorbid conditions.[2] Additional putative causes include hemodynamic factors with low cardiac index,[3] cerebral hypoperfusion, and genetic variants.[1] Because the links between cardiovascular diseases and neurological conditions are complex and multifaceted, studies that shed light on these associations are important for prevention and management. In the present issue of the Journal, Berger et al[4] examined the incremental risk of ischemic stroke among newly diagnosed patients with HF and without atrial fibrillation (AF). Using the Truven Health Analytics MarketScan Databases between 2010 and 2015, the authors report on 52,005 patients with a HF-related claim but without evidence of AF. After adjustment by propensity matching to individuals free of HF, patients with HF/without AF had a nearly twofold increase in the rates of ischemic stroke than patients without HF/without AF during follow-up. The excess risk of ischemic stroke persisted during follow-up, documenting that, even in the absence of AF, HF is associated with an increased risk of ischemic stroke.

The finding of a markedly higher risk of ischemic stroke associated with HF has been previously reported[5–7] while adjusting for AF or restricting some analyses to patients without AF. The present report adds important credence to these reports because it pertains to a large number of patients with HF and without any evidence of AF and documents a large increase in the risk of stroke among these patients compared to patients with neither HF nor AF, observed for ischemic stroke. Several limitations, most of them acknowledged by the authors, must be considered while interpreting these concerning data. First, residual confounding inherent to any observational study, may explain these findings; second, misclassification is particularly problematic with claims data that rely on coding for ascertainment. Importantly, AF could have developed during follow-up and be missed. The variable duration of observation in claims datasets and the inability to assess how the risk of stroke may vary according to the presentation of HF constitute additional limitations. Indeed, cardiac morphology and hemodynamic function are profoundly altered in HF,[8] however, not uniformly. Patients with clinical signs of HF can present without reduction in ejection fraction (EF), underscoring the syndromic and heterogeneous nature of HF. In addition to EF, several other echocardiographic parameters, including ventricular and atrial dimensions, ventricular mass, diastolic filling parameters, and pulmonary pressures, differ across clinical presentations of HF and the risk of stroke likely varies according to the imaging phenotype of HF. Hence, delineating which presentation of the HF syndrome carries the greatest risk of stroke has important management implications that cannot be addressed in the current study.

These limitations notwithstanding, this report and related preceding publications raise important clinical questions, in light of the major public health and clinical burden of HF. The data should prompt us to reexamine our practice with regard to stroke prevention in HF without AF. The Heart

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Manuscript received April 24, 2019; revised manuscript accepted April 24, 2019.

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1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2019.04.014

Failure Association of the European Society of Cardiology (ESC) and the ESC Working Group on Thrombosis provided practice guidance on the use of warfarin. Although oral anticoagulation is clearly recommended in HF with AF, in sinus rhythm, experts concluded that there was no evidence of an overall benefit of warfarin on mortality, with a risk of major bleeding, despite potential reduction in stroke risk. The importance of individualized recommendations based on risk factor profile was underscored.[9] A meta-analysis of the 4 major trials of warfarin in patients with HFrEF in sinus rhythm[10] concludes that there is a benefit of warfarin in stroke prevention at the expense of an increased risk of major hemorrhage. As this conclusion hinges on the safety profile of anticoagulation, the different risk-benefit profile of direct oral anticoagulants warrants evaluating their use for stroke prevention in HF in sinus rhythm. The recently reported COMMANDER HF trial randomized patients with heart failure with reduced ejection fraction, coronary disease, and no AF, to rivaroxaban versus placebo.[11] There was no difference between rivaroxaban and placebo for the composite endpoint of death, myocardial infarction, or stroke. However, there were fewer strokes (a rate difference of 1 percentage point) among patients assigned to rivaroxaban. Although COMMANDER HF was not powered for strokes, this finding can be conceptualized as hypothesis generating. To formally test this hypothesis, a new trial should be conducted that would enroll patients with HF yet not in AF and at higher risk for stroke to observe a sufficient number of endpoints for adequate statistical power. To optimize validity, the design should enable verifying the absence of occult paroxysmal/intermittent AF, which likely would require some form of long-term monitoring, which would likely impact recruitment. Meanwhile, observational data like those reported herein[4] further underscore the importance of careful personalized management, which integrates individual risk profile, characteristics of the HF phenotype including EF and other clinical and imaging parameters as the standard of care.

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