**EDITORIAL**

**Stroke risk stratification in patients with heart failure and sinus rhythm.**

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Although more than 160 years have passed since the original publication of Virchow’s triad on the key factors that lead to thrombogenesis, the principles that vessel wall abnormalities, abnormal blood flow, and abnormal blood constituents promote venous and arterial thromboembolism continue to be applied to various cardiovascular diseases. Atrial fibrillation (AF), which remains one of the major causes of stroke, represents a fine example of Virchow’s triad outside the vascular bed, where atrial remodeling, blood stasis especially in the left atrium appendage, and hypercoagulopathy increase the risk of thrombus formation, while anticoagulation effectively reduces the risk of ischemic stroke and systemic embolism1.

Based on the same pathophysiological background, heart failure with reduced ejection fraction (HFrEF), characterized by low cardiac output, poor contractility and “abnormal blood flow”, coupled with ventricular remodeling and chronic hypercoagulopathy, increases the risk of thrombogenesis and causing a prothrombotic or hypercoagulable state2, promoting a greater risk of ischemic stroke and thromboembolism3. Thus, from a pathophysiological perspective, oral anticoagulation (OAC) in these patients may plausibly be effective in reducing the risk of stroke or systemic embolism. Indeed, a meta-analysis of randomized controlled trials comparing warfarin or rivaroxaban to aspirin showed that although OAC reduced the risk of stroke in the unselected population of HFrEF patients with sinus rhythm, this benefit was outweighed by an increase in major hemorrhages3. Indeed, a Cochrane review of OAC versus placebo also concluded that there was no impact of OAC on mortality in people with HFrEF in sinus rhythm, but rivaroxaban probably reduced the risk of stroke, with an increased risk of major bleedings4. When compared to antiplatelet therapy, treatment with warfarin was associated with a 20% reduction in non-fatal cardiovascular events but a two-fold higher risk of major bleeding5. Overall, the available evidence does not support the routine use of anticoagulation in people with HFrEF who remain in sinus rhythm.

Hence, although anticoagulation has the potential to reduce the risk of embolic events in HFrEF patients with sinus rhythm, a ‘one-size-fits-all’ antithrombotic treatment approach does not work. Risk stratification strategies need to be considered to identify those at the highest thromboembolic risk who could be considered for thromboprophylaxis with OAC6.

In the current issue of the *European Heart Journal*, Kondo et al. show that a simplified version of a previously published risk stratification tool7 effectively identified HFrEF patients with sinus rhythm who were at high risk of ischemic stroke8. Using individual patient data from three contemporary randomized control trials of patients with HFrEF, they derived a risk stratification model based on the presence of previous stroke, diabetes mellitus treated with insulin and the value of N-terminal proB-type natriuretic peptide (NT-proBNP), leading to the proposed S2I2N0-3 score8. Interestingly, the HFrEF patients (in sinus rhythm) in the highest quintile of the S2I2N0-3 score had similar ischemic stroke rates to patients with HFrEF and AF who were not treated with OAC. Patients with the highest S2I2N0-3 score had an 11-fold increase in the risk of ischemic stroke compared to those with the lowest, while the S2I2N0-3 score showed a good discrimination capacity [C-index: 0.84 (95%CI: 0.76-0.92)] (**Visual Abstract)**.

Several risk stratification tools have been proposed for the prediction of stroke in patients with HFrEF and sinus rhythm, but only with modest prediction accuracy9. Among them, one risk assessment tool incorporating age, New York Heart Association class, diabetes mellitus treated with insulin, body mass index, previous stroke and NT-proBNP, provided good discrimination [C-index: 0.80 (95% CI, 0.61–0.94)], but on external validation its discrimination capacity was lower [C-index: 0.71 (95% CI, 0.52–0.87)]7. The simplified version of this model, which was tested by Kondo et al. provided better results in patients with HFrEF and sinus rhythm8.

Nevertheless, the clinical dilemma related to whether the risk of ischemic stroke in HFrEF patients with sinus rhythm outweighs the bleeding risk to justify the use of oral anticoagulation remains unanswered. Due to the accumulation of several cardiovascular comorbidities, AF patients who are at higher risk of thromboembolism also have an increased risk of bleeding, yet the net benefit-to-risk ratio is in favour of anticoagulation10. An excessive risk of bleeding could be partially attributed to the use of warfarin with a suboptimal time in therapeutic range, but the non-vitamin K antagonists (NOACs), due to their favourable safety profile in AF, may be associated with fewer bleeding events in HFrEF and sinus rhythm; however, this needs to be investigated in further prospective clinical trials. In the COMMANDER HF trial, rivaroxaban 2.5 mg twice daily did not reduce the composite of the first occurrence of death, stroke, or myocardial infarction compared with placebo in patients with HFrEF, coronary artery disease and sinus rhythm11.

Also, various risk stratification scores of varying complexity have been proposed for different conditions. Most simple clinical risk scores only have rather modest predictive value (with c-indexes of approximately 0.6), with can be improved (at least statistically) by more complicated weighted risk scores based on formulae derived from multivariate analysis, machine learning or artificial intelligence, or by the addition of various biomarkers. For example, NT-proBNP level values (a biomarker commonly used to evaluate HFrEF) can change with ageing and incident comorbidities or alterations in drug therapy, and the analysis by Kondo et al. did not factor in such biomarker fluctuations nor how dynamic changes in risk may affect clinical risk stratification assessment8. Many biomarkers are also non-specific, and are predictive of events beyond the outcomes they are proposed for12. Machine learning approaches have offered some opportunity to account for dynamic changes in risk factors, and may offer improved prediction and stroke risk stratification13. In any care, risk stratification in real world clinical practice would really need to balance simplicity, practicality and (especially with multiple biomarkers) costs, against marginally improved (but statistically significant) risk prediction.

Nevertheless, the simple, practical and accurate identification of HFrEF patients in sinus rhythm at high thromboembolic risk, promotes a more patient-specific therapeutic strategy, especially in the frail and multimorbid HF population. Of note, many patients with HFrEF may develop ‘silent’ episodes of AF, which confers a poor outcome14. Finally, we should also not forget the impact of a holistic or integrated care approach (that encompasses careful attention to comorbidities and lifestyle factors) in reducing adverse outcomes, including cardiovascular mortality, stroke, and bleeding15. Future randomized control trials, in selected HFrEF patients with sinus rhythm at high thromboembolic risk (selected with refined, simple risk stratification tools that account for dynamic changes in risk profile), may provide more evidence before embracing any ‘one size fits all’ anticoagulation strategy, as well as important insights into personalized stroke risk assessments.

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