Stroke and Anticoagulation in Heart Failure Without Atrial Fibrillation:

From Risk to Opportunity

Running title: Homma et al.; Stroke and Anticoagulation in HF Patients in SR

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The association between heart failure and stroke risk has been described for more than three decades.\textsuperscript{1} Hypercoagulability and left ventricular blood stasis are thought to contribute to stroke risk in patients with heart failure,\textsuperscript{2} in addition to common risk factors such as hypertension and atrial fibrillation. Regardless of the mechanism, however, for the majority of patients with heart failure who do not have atrial fibrillation, this elevated stroke risk is appreciated but not managed.

The current 2013 American College of Cardiology Foundation / American Heart Association Guideline on Management of Heart Failure states that “anticoagulation is not recommended in patients with chronic heart failure with reduced ejection fraction without atrial fibrillation, a prior thromboembolic event, or a cardioembolic source.”\textsuperscript{3} The 2012 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure similarly acknowledges the elevated stroke risk, but recommends against treatment with anticoagulation.\textsuperscript{4} The recommendations are based on the results of previous randomized, controlled trials that assessed anticoagulation with warfarin in patients with heart failure but without atrial fibrillation. These include the WASH, HELAS, and WATCH trials, as well as the WARCEF trial that was the largest and was conducted with patients receiving contemporary heart failure therapy.\textsuperscript{5-8} Consistently, these trials failed to show the benefit of warfarin for primary outcomes that included death and stroke. In addition, warfarin therapy in these trials was associated with increased bleeding, though the risk for the most devastating bleeding outcome, intracranial hemorrhage, remained very low and was not significantly different compared with aspirin.

It is important to note, however, that when the stroke outcome is considered by itself, both WARCEF and subsequent meta-analyses including all four trials show that warfarin can effectively prevent stroke in patients with heart failure in sinus rhythm.\textsuperscript{8-10} In the WARCEF trial,
the risk of stroke was only 0.72% per year in the warfarin arm, compared to 1.36% per year in the aspirin arm. Nonetheless, these numbers are a fraction of other adverse events such as death and heart failure hospitalizations. It is thus likely that the stroke prevention benefit of warfarin is hidden by competing risks from other clinical events.

In this issue of Circulation, Abdul-Rahim et al. shed further light on the frequency of stroke in patients with heart failure without atrial fibrillation, while highlighting the potential for using predicted stroke risk to refine patient selection. In a rigorously performed analysis, the authors pooled 9,585 patients from the CORONA and GISSI-HF heart failure trials. In the subset of 6,054 patients without atrial fibrillation, a stroke rate of 1.11% per year was observed. A risk model for stroke prediction was derived from five clinical predictors, including age, New York Heart Association Class, diabetes treated with insulin, body mass index, and a history of previous stroke. The model was validated using an independent cohort from the CHARM HF-REF trials. For patients classified in the highest tertile of stroke risk by the model, stroke rate was 1.98% per year in the derivation cohort and 1.79% per year in the validation cohort. In patients in whom NT-proBNP was measured, NT-proBNP further simplified and improved stroke risk prediction when added to the model.

However, in interpreting these results, some caution must be taken given this is a retrospective analysis that combined two different clinical trials. Another concern is that only 16% of the 6,054 patients without atrial fibrillation received anticoagulant therapy at baseline, compared to 62% of patients with atrial fibrillation. The stroke rate in non-anticoagulated patients with atrial fibrillation was 2.17% per year, but since anticoagulation was not randomized, this risk may be over or underestimated. These factors may limit comparison between this group and the subgroup of patients without atrial fibrillation in the highest tertile of
predicted risk.

Additionally, bleeding risk was not a part of this analysis, thereby precluding considerations of net clinical benefit that often serve as the basis for decisions regarding anticoagulation. However, the stroke rate for the highest risk tertile was similar to the 1.9% annual rate of stroke seen in atrial fibrillation patients with CHA2DS2-VASc score of 2, for whom anticoagulation is thought to have net clinical benefit and is recommended by current guidelines.\textsuperscript{12, 13} A recent decision analysis by Eckman and colleagues suggests that, for non-warfarin oral anticoagulants, the stroke risk threshold for net clinical benefit could even be as low as 0.9% per year.\textsuperscript{14} Non-warfarin anticoagulants are also thought to have more consistent anticoagulation effect, and further analysis of the WARCEF patients has shown that, for heart failure patients in sinus rhythm, higher quality anticoagulation as reflected by time-in-therapeutic range is associated with better clinical outcomes.\textsuperscript{15} It is thus reasonable to propose, as the authors do, that a randomized, controlled trial should test whether newer oral anticoagulants can prevent stroke in heart failure patients in sinus rhythm.

A substantial number of patients are at risk. Of the estimated 5.7 million Americans with heart failure, 2.6 million will have reduced ejection fraction.\textsuperscript{16} Using conservative assumptions, three quarters of those patients, or roughly 1.9 million, will be in sinus rhythm.\textsuperscript{17} A stroke risk of 1.8% per year for the 630,000 patients in the highest tertile of risk would translate into roughly 11,000 strokes each year.

The question of whether newer oral anticoagulants can prevent stroke in heart failure patients in sinus rhythm can only be answered through an adequately powered randomized, controlled trial. The risk score for stroke prediction proposed by Abdul-Rahim et al., along with other selection approaches,\textsuperscript{8} could guide the identification of potential trial participants.
Alternatively, given the improved risk-benefit profile of newer oral anticoagulants, a more inclusive trial design similar to WARCEF may be appropriate. A better characterization of bleeding risk in this patient population may also improve the risk benefit balance and guide patient selection.18

The choice of endpoints will also need to be carefully considered in such a trial, given the competing risks of death and heart failure hospitalizations observed in the WATCH and WARCEF trials.7,8 Since patients have consistently expressed strong preferences for avoiding severe stroke and often consider these worse than deaths,19 it will be reasonable to emphasize stroke outcomes in trial design. Ultimately, an innovative trial testing the effect of newer oral anticoagulants on stroke in patients with heart failure in sinus rhythm will represent an opportunity to align risk, treatment, and patient-centered outcomes.

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**References:**


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