EDITORIAL COMMENTARY

Residual stroke risk in atrial fibrillation: Our patients must be our partners

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In this issue of *Heart Rhythm O*^{2}, Carlisle et al[1] performed a retrospective analysis of the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation I and II (ORBIT-AF I and II) trials to define the magnitude of residual risk of stroke and systemic embolism (SSE) and transient ischemic attack (TIA) in patients with atrial fibrillation (AF) treated with oral anticoagulation (OAC). ORBIT-AF I gathered data on real-world treatment of AF, including rate and rhythm control, stroke prevention, and clinical outcomes, from patients with AF in community practice settings.[2] ORBIT-AF II focused on safety and effectiveness of novel oral anticoagulants (NOACs) used for AF in community practice settings.[3] A total of 18,955 patients were analyzed using multivariable Cox proportional hazards modeling. The mean age was 72 years, and 42% were women. There were 451 SSE events.

The main finding was that despite being prescribed OAC by their primary physicians, patients with AF have a high residual risk of SSE/TIA, ranging from 0.56 to 4.98 per 100 patient-years, and this residual risk rises as CHA_2DS_2-VASc scores increase from 0 to >7 despite OAC. What is novel and disappointing is that initiation of anticoagulation, according to guidelines, does *not* adequately protect patients from stroke and, more worrisome, does not protect those at highest risk.

The fact that CHA_2DS_2-VASc scores stratify patients for poor outcomes is not at all surprising since each component of the CHA_2DS_2-VASc score is a marker of poor health. The authors state that the increased residual stroke risk with increasing CHA_2DS_2-VASc scores could be due to factors unrelated to AF, such as nonembolic stroke risk, underlying atherosclerotic disease, or comorbidities independent of AF. I believe that the increased stroke risk has to be combination of all 3 mechanisms, which would be expected to be incrementally higher as CHA_2DS_2-VASc scores increase. This is the simplest and quite plausible explanation for residual stroke risk not eliminated by OAC.

Another possible explanation for residual stroke risk is that patients were *not* properly taking their anticoagulant medication or were not taking the proper dose. In order to address that hypothesis, the authors tell us that analysis of the ORBIT-AF registry reported therapeutic international normalized ratio values in only 59% of those measured. NOAC efficacy/adherence is probably somewhat higher than that, being that simply taking the medication puts one in therapeutic range, and some of the 41% not in the therapeutic range on warfarin were likely taking their medication, just not properly. Even if we are extremely generous, it is safe to say at least 20%–25% of patients are not anticoagulated because of either improper dosing or inadequate compliance. Unfortunately, we have no way of knowing which patients were compliant or which patients had subtherapeutic dosing, because data were not collected on medication compliance. As the authors pointed out, programs such as Get With The Guidelines AFib are essential to improving OAC adherence and have been shown to increase prescription rates. Other programs that educate patients and help them understand their illness and take ownership of their care will continue to be critical for medication compliance and stroke prevention.

The highest risk markers for recurrent stroke noted in the study were *prior SSE/TIA*, *female sex*, *hypertension (HTN)*, and *permanent AF*. In our efforts at treatment, we cannot change the fact that a patient had a prior stroke, and we cannot change their biological sex. Therefore, the critical remaining risk factors that we as clinicians can modify are HTN and permanent AF.

HTN has been repeatedly shown to be the most important modifiable risk factor for AF. The Danish loop study screened low to moderate risk patients for AF with an implantable loop recorder. The initial data from that study reported on the natural history of newly detected AF; the frequency of AF detection, and patterns of progression and regression of AF.[4] The results showed that both HTN and previous stroke were associated with progression of AF, and those same risk factors were also associated with decreased odds of AF remission. HTN and previous stroke were the only common risk factors for progression and absence of regression of AF in that study, similar to the

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significant risk factors identified in the present study. A multivariable regression analysis of 5390 patients from the Randomized, Double-Blind Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the NOAC Dabigatran Versus Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source trial showed that the significant clinical predicators of developing AF were HTN, age, and body mass index.[5] Without question, I firmly believe that HTN is the most important clinical factor that can and should be modified when any type of AF is detected.

Permanent AF is the other marker for increased residual stroke risk that could theoretically be modified. We have recently learned that there are significant benefits to early treatment of AF. The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) showed that early rhythm control was associated with a lower risk of adverse cardiovascular outcomes compared with usual care for patients with early AF and cardiovascular conditions.[6] Perhaps, as we continue to treat AF early, thereby slowing AF progression, we could significantly decrease the number of patients who have permanent AF in the population and thereby decrease residual stroke risk.

There were some differences in predictors of residual stroke risk between patients taking NOACs and those taking warfarin. Peripheral vascular disease and chronic obstructive pulmonary disease were independent risk factors in the warfarin group. Prior myocardial infarction and decreased glomerular filtration rate were independent factors in the NOAC group. Decreased glomerular filtration rate emerging in the NOAC-only group could be explained by possible lower dosing of NOAC in that setting. There were some differences in predictors when stroke only was analyzed vs TIAs. Highest risk factors for *stroke only* were prior SSE and current smoking; permanent AF was no longer significant. Peripheral vascular disease and severe left atrial enlargement emerged as risk factors for *stroke only* in the *NOAC-only* subgroup. There were some differences when the highest risk group (CHA_2DS_2-VASc score ≥ 4) was compared with the lower risk group (CHA_2DS_2-VASc score <4); in the highest risk patients prior SSE and current smoking were the highest risk factors. Overall, the variation in risk factors by subgroup is noted, but clinically, all the risk factors that contribute to increased stroke risk are important and should be modified regardless of CHA_2DS_2-VASc score, anticoagulant used, or medical history.

There was a counterintuitive association of increased stroke risk with concomitant antiplatelet use, which was present in the entire cohort and in the higher risk patients (CHA_2DS_2-VASc score ≥ 4). The authors comment that perhaps the addition of antiplatelet to OAC could have a detrimental effect; I think that is unlikely. I imagine that the increased stroke risk in patients on both antiplatelets and OACs is more likely due to the alternative explanation that the authors provide: that concomitant antiplatelet use is a confounding factor that represents patients with more comorbid disease (eg, more advanced atherosclerotic disease). It is possible that those patients on dual anticoagulants would have had an even higher residual stroke risk were they not on the concomitant antiplatelet medication.

What should we do with the results of the study?

I agree with the authors that in the future, residual stroke risk could be reduced by emerging novel anticoagulants, combination anticoagulant regimens (I would not be afraid to try despite the apparent increased risk identified in this study), newer LAA occlusion devices, and increased and mandatory measures for lifestyle modification (smoking cessation, blood pressure management, and weight loss).

Another way to reduce residual stroke risk, is to ask our patients to partner with us in their care. Prior studies have shown that patients who refuse to participate in clinical trials have worse outcomes than do those who agree to participate.[7] Although the explanation for this is multifactorial, a plausible factor is that those who refuse to participate invest less in caring for themselves and likely have a higher incidence of other unhealthy behaviors: smoking, obesity, and medication noncompliance. The same applies when caring for AF; those with the most unhealthy lifestyles are the ones with the highest risk. We cannot successfully care for our patients, unless they partner with us, and take responsibility for their part in improving their health.

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