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COMMENTARY

Stroke prevention in atrial fibrillation: not a "one size fits all" endeavor

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Despite recent advances in pharmacology and device technology, thromboembolic cerebrovascular accident (CVA) remains the most dreaded consequence of atrial fibrillation (AF). Prior research demonstrates that AF is associated with a fivefold increase in the risk of CVA, and that the disability secondary to AF-associated CVA is significantly greater than that attributed to non-AF-associated CVA [1]. While direct oral anticoagulants (DOACs) are associated with a significant reduction in CVA among those with AF, this is balanced by an increased risk of major bleed—particularly in high-risk cohorts [2]. For this reason, nearly 50% of patients with AF who are prescribed an OAC do not initiate or maintain use [3].

Left atrial appendage occlusion (LAAO) was approved by the Food and Drug Administration as an alternative mechanism of CVA prevention for AF patients who are candidates for long-term OAC. As pivotal trials demonstrate that LAAO is associated with similar rates of CVA prevention, with lower rates of clinically significant bleeding, than OAC, LAAO has been clinically utilized in patients who are deemed high risk for clinically significant bleed [4]. Oftentimes, the patients we believe most need LAAO represent a clinically frail cohort.

Frailty is a composite measure that is associated with poor outcomes after many percutaneous structural cardiology procedures [5]. In this edition of the *Journal of Interventional Cardiac Electrophysiology*, Darden and colleagues assess the associations between a novel frailty score and clinical outcomes following LAAO in a cohort of 57,728 patients from the National Cardiovascular Data Registry (NCDR) [6]. Authors created a 5-point frailty scale including measures of anemia, renal dysfunction, synthetic function, body mass index, and risk of falls, and categorized LAAO patients into one three cohorts based on their novel frailty score: frail (4–5 points), pre-frail (1–3 points), and not frail (0 points). Results demonstrate that the majority of patients who underwent LAAO were either pre-frail (76.8%) or frail (13.3%). Furthermore, frail, compared to non-frail patients, patients had a higher incidence of in-hospital complications, and 45-day mortality.

While there are numerous validated frailty indices used in clinical practice and prior publications, readers of this manuscript should be aware that the authors created their own frailty index based on variables utilized in prior studies, due to the limited data available in the NCDR. Therefore, the criteria for determining "frail," "pre-frail," and "non-frail" status were arbitrary and may have been better defined had more variables been collected. Validation of this scale is needed for results to be generalizable and understood in context. In addition, by excluding patients without a recorded measure of albumin, > 50% of patients were removed from analysis, potentially limiting the applicability of the results.

Despite these limitations, the authors should be congratulated on this study that adds to our understanding of outcomes after LAAO, and speaks to the fact that embolic CVA prevention in patients with AF is certainty not a "one-size-fits-all" endeavor. These data affirm that a substantial proportion of patients who undergo LAAO are clinically frail. While major complications and death were highest among the frail cohort, the adjusted hazard ratios for increased procedure-related complications in frail patients were modest, and the clinical significance of the large adjusted hazard ratio for death among frail patients is tempered by the low overall number of patients who experienced this outcome. Accordingly, these data, in our mind, should not prevent frail patients from being referred for LAAO, but rather should be

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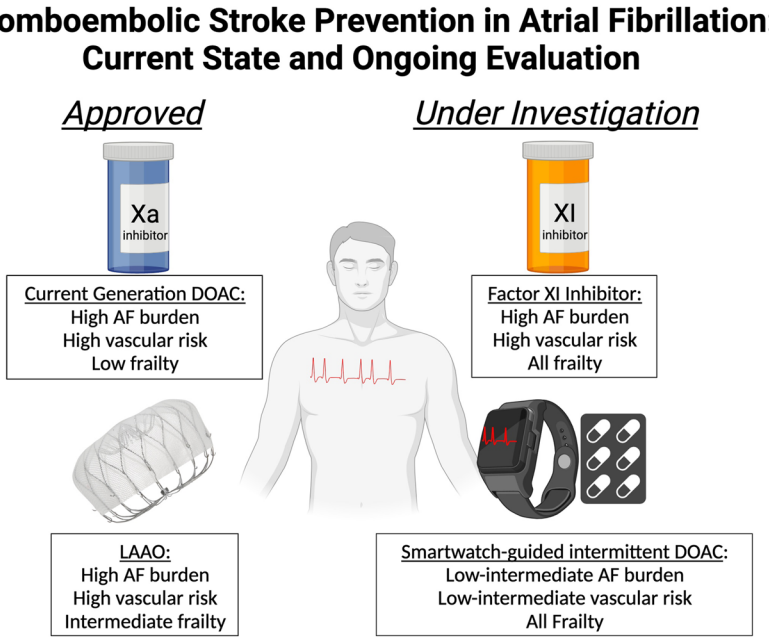

Fig. 1 Thromboembolic stroke prevention in atrial fibrillation: current state and ongoing evaluations. Current generation direct oral anticoagulants (DOAC) and left atrial appendage occlusion (LAAO) are two approved methods of thromboembolic stroke prevention for patients with atrial fibrillation. However, both DOAC and LAAO are associated with elevated risk in frail patients. Future studies will inform the safety and efficacy of factor XI inhibitors, and smartwatch-guided intermittent DOAC use. Figure was created using biorender.com

used to counsel patients when discussing the pros and cons of LAAO.

Importantly, these data do affirm that further work must be done to determine the optimal mechanism of embolic CVA prevention in AF patients with high-risk comorbidities. A particularly interesting drug target currently under investigation is Factor XI. Clinically, patients with Hemophilia C (a congenital deficiency in Factor XI) have a decreased risk of thrombosis without an elevated risk of bleed, and those with elevated levels of Factor XI have demonstrated significantly greater risk of thrombosis [7]. Therefore, novel drugs that inhibit factor XI may prevent clot consolidation (and subsequent thrombosis) without increasing risk of hemorrhage through a differential impact on the clotting cascade than the current generation factor Xa inhibitors. Phase 2 and 3 clinical trials are currently underway to assess the safety and clinical utility of Factor XI inhibitors [7].

Furthermore, the risk of AF-associated CVA is not static. Prior data demonstrate a temporal association between short episodes of AF and CVA, and a duration threshold of AF that is associated with increased risk of CVA [8, 9]. For these reasons, it is reasonable to question why the current status quo is to subject patients with AF to indefinite OAC, when the risk of AF-associated CVA waxes and wanes. The NIH funded Rhythm Evaluation for Anticoagulation Therapy for Atrial Fibrillation (REACT-AF) trial is currently enrolling patients to study the safety and efficacy of targeted, time-delimited OAC guided by an AF-sensing smartwatch [10]. Should these studies produce encouraging results, frail AF patients may have a new array of potential therapies to prevent CVA, while mitigating the potential side effects related to current-generation medications, or procedures.

Balancing ischemic and hemorrhagic risk in patients with AF remains difficult to achieve, particularly in those who are frail. While LAAO may be attractive in frail patients due to the potential to avoid OAC, Darden and colleagues demonstrate a higher risk of in-hospital complications and mortality compared to non-frail counterparts. The results of ongoing clinical trials are eagerly anticipated as we continue to determine the best method of CVA prevention in this high-risk AF cohort (Fig. 1).

Declarations

Conflict of interest Rod S. Passman serves on advisory boards for Medtronic, Abbott, and Janssen, and receives research support from Abbott, American Heart Association, National Institute of Health, and royalties from UpToDate; Northwestern University receives fellowship support from Medtronic.

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