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EDITORIAL COMMENT

Left Atrial Appendage Occlusion in Patients Receiving Hemodialysis

A Viable Approach to Stroke Prevention?

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There is much debate about appropriate strategies for stroke prevention in patients with atrial fibrillation (AF) and advanced chronic kidney disease, especially in patients requiring maintenance dialysis. Oral anticoagulant (OAC) use is particularly challenging in this cohort, with—on one hand—higher thromboembolic rates *despite anticoagulation*, and—on the other—a higher incidence of major bleeding events *because of anticoagulation*.[1] The role of alternative stroke mitigation strategies in hemodialysis-treated patients with AF, including the strategy of left atrial appendage occlusion (LAAO), are poorly characterized. In the general group of patients with AF, LAAO is recommended as an alternative for stroke risk reduction in high-risk patients with previous major bleeding or contraindication to long-term OAC use, although recent European guidelines give it a Class IIb recommendation with Level of Evidence: C.[2,3] The potential for LAAO to facilitate OAC discontinuation in patients with AF requiring hemodialysis, and thereby to reduce both bleeding and stroke risk, is therefore an enticing proposition.

In this issue of *JACC: Asia*, Tanaka et al[4] report the feasibility of LAAO in patients undergoing hemodialysis from a prospective Japanese registry. Among 1,464 patients undergoing LAAO at 20 centers between 2019 and 2022, 172 patients (11.7%) were undergoing maintenance hemodialysis at the time of their procedure. The hemodialysis cohort had CHA_2DS_2-VASc scores (4.8 ± 1.6 vs 4.9 ± 1.5; $P = 0.50$) and rates of previous ischemic stroke (40% vs 37%; $P = 0.56$) similar to those of the nonhemodialysis cohort, but the cohort was younger (74.2 ± 8.2 years vs 77.5 ± 7.5 years; $P < 0.0001$), with a lower history of previous major bleeding (34% vs 61%; $P < 0.001$) despite a higher HAS-BLED score (3.9 ± 1.1 vs 3.0 ± 1.0; $P < 0.0001$). Cardiovascular comorbidities, namely, diabetes mellitus, uncontrolled hypertension, aortic stenosis, and vascular disease, were more prevalent in the hemodialysis group.

Overall, device implantation success rates were high and similar in both groups (hemodialysis group, 97.1% vs nonhemodialysis group, 97.3%; $P = 0.88$), with no significant differences in periprocedural complication rates (pericardial effusion, 0.6% vs 0.5%; $P = 0.98$; access site complications, 0.6% vs 0.6%; $P = 0.95$; bleeding during hospitalization, 0.6% vs 0.9%; $P = 0.70$; no strokes or deaths in either group). Over a median 12-month follow-up, the ischemic stroke rate following LAAO was 1.1% per 100 patient-years in the hemodialysis group (95% CI: 0.3%-1.9%), compared with 2.6% (95% CI: 2.1%-3.0%) per 100 patient-years in the nonhemodialysis group. Notably, all-cause mortality at 1 year was higher in the hemodialysis group (8.8% vs 4.6%; $P = 0.001$), driven by higher cardiovascular mortality.[4] Imaging follow-up revealed similar rates of peridevice leakage and device-related thrombus in both groups. On the basis of these data, Tanaka et al[4] conclude that LAAO is feasible in patients undergoing hemodialysis, with results comparable to those observed in the nonhemodialysis cohort.

In this editorial, we consider 2 important questions in the context of this study (**Figure 1**). First, how can clinicians best assess stroke risk in hemodialysis-treated patients with AF? Second, what is the optimal approach to stroke prevention in this cohort?

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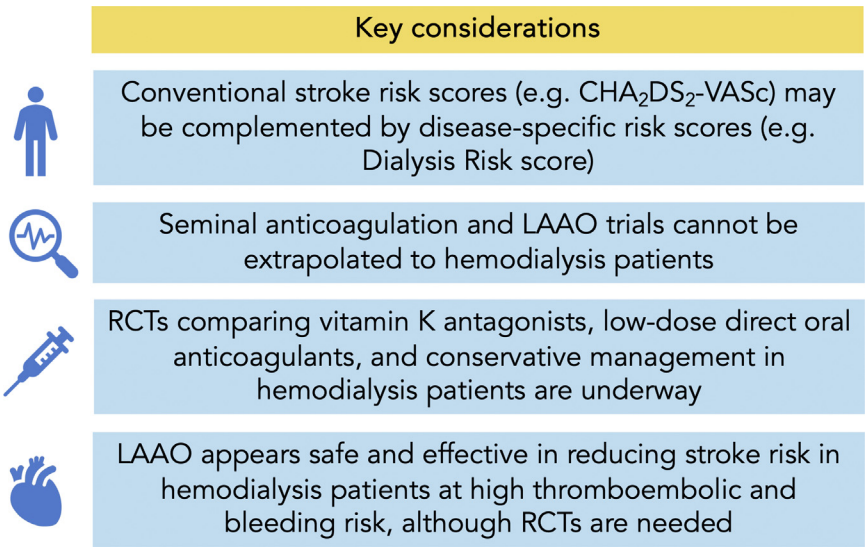
FIGURE 1 Stroke Risk in Patients With Atrial Fibrillation Who Are Undergoing Hemodialysis



Key considerations in assessing and reducing stroke risk in hemodialysis-treated patients with atrial fibrillation. LAAO = left atrial appendage occlusion; RCT = randomized controlled trial.

HOW TO ASSESS STROKE RISK IN PATIENTS UNDERGOING HEMODIALYSIS WHO HAVE AF?

RISK SCORES. Deciding whether to modify stroke risk in a hemodialysis-treated patient with AF depends first on a reliable estimation of thromboembolic risk, balancing this against bleeding risk. In part because of the comorbidities predisposing to chronic kidney disease, patients undergoing hemodialysis are at inherently high risk of cardiovascular disease,[5] thus rendering risk prediction challenging. Indeed, in the general group of patients with AF, the CHA_2DS_2-VASc score is widely used to estimate stroke risk, with guidelines (including those from Asia[6,7]) recommending OAC consideration in patients with a nonsex score (ie, CHA_2DS_2-VA) ≥1.[8] However, in hemodialysis-treated patients with AF, components of the CHA_2DS_2-VASc score are so prevalent that most patients qualify for OAC use according to this indiscriminate approach. This issue is further complicated by the finding that, in patients undergoing hemodialysis, the risk of hemorrhagic stroke approaches that of ischemic stroke, and major bleeding episodes requiring hospitalization are disproportionately high, irrespective of the use of antithrombotic therapy.[1]

Taking into account this altered risk-benefit ratio, and in an attempt to identify those patients most likely to benefit from OAC use, the Dialysis Risk score has been proposed as an alternative to CHA_2DS_2-VASc in patients undergoing hemodialysis.[9,10] By removing comorbidities that were not associated with stroke in the Dialysis Outcomes and Practice Patterns Study (namely, hypertension and heart failure[11]), the Dialysis Risk score comprises previous stroke or transient ischemic attack (3 points), diabetes mellitus (1 point), age >75 years (1 point), and gastrointestinal bleeding in the last year (−1 point), with OAC initiation recommended in those patients with a score of ≥2.[9,10] This approach, although pragmatic, currently lacks widespread validation. Until it does, communicating uncertainty about risk prediction in clinical practice is key when deciding on the need for pharmacologic or interventional management.

ATRIAL FIBRILLATION BURDEN. Beyond risk factors, AF type (paroxysmal, persistent, or permanent), burden (percentage of time spent in AF), and timing (eg, whether AF is related or unrelated to dialysis sessions) *may* play an important role in stroke risk estimation in patients undergoing hemodialysis. Although guidelines do not currently recommend

using AF burden for risk prediction in the general group of patients with AF, there may be a linear association between AF burden and risk of future stroke. Studies suggest that paroxysms of AF are more likely to occur on hemodialysis days, and specifically during dialysis itself (likely a result of fluid and electrolyte shifts).[12] The temporal association between intradialytic AF episodes—when the patient is already heparinized—and stroke risk requires closer study.

HOW TO REDUCE STROKE RISK IN PATIENTS UNDERGOING HEMODIALYSIS WHO HAVE AF?

Altered risk profiles, pathophysiological mechanisms, and pharmacokinetics mean that the results of seminal OAC and LAAO trials cannot be simply extrapolated to patients undergoing hemodialysis. Unfortunately, few randomized controlled trials (RCTs) exist on anticoagulation in this cohort,[13-15], with no LAAO trials. The former are further limited by small sample sizes, with statistical underpowering.[13-15] As a result, recommendations are largely derived from observational studies and expert opinion.

ANTICOAGULATION. When anticoagulation is offered to a hemodialysis-treated patient with AF, vitamin K antagonists (VKAs) are used in most cases because of their well-established therapeutic profile. Evidence of the safety and efficacy of direct OACs (DOACs) in hemodialysis-treated patients is starting to emerge, although it is predominantly limited to pharmacokinetic and observational studies. In a small RCT (n = 132), low-dose rivaroxaban (10 mg daily) resulted in fewer fatal and nonfatal cardiovascular events than VKAs, and rivaroxaban may be used as an alternative in the near future.[15]

However, given the altered risk-benefit ratio in patients undergoing hemodialysis, the more pertinent question is whether *any* form of anticoagulation is beneficial over conservative management. Ongoing studies, namely, the SAFE-D RCT (Strategies for the management of Atrial Fibrillation in patiEnts receiving Dialysis; NCT03987711), aim to answer this question through randomization to VKAs, DOACs, or conservative management in hemodialysis-treated patients with AF.

LEFT ATRIAL APPENDAGE OCCLUSION. The study by Tanaka et al[4] adds weight to earlier observational studies supporting the feasibility and short-term efficacy of LAAO in patients undergoing hemodialysis.[16,17] Ultimately, however, RCTs are required to assess the long-term efficacy and cost-effectiveness of this approach. Over the last decade, 2 such planned RCTs (STOP-HARM [The Strategy to Prevent Hemorrhage Associated With Anticoagulation in Renal Disease Management Trial; NCT02885545] and Watch-AFIB [Left Atrial Appendage Occlusion vs Usual Care in Patients With Atrial Fibrillation and Severe Chronic Kidney Disease; NCT02039167]) were prematurely terminated as a result of slow recruitment, thus illustrating the challenges of studying these patients. The ongoing LAA-KIDNEY trial (Left Atrial Appendage closure in patients with nonvalvular AF and end stage chronic KIDNEY disease; NCT05204212) hopes to be the first RCT to report in this field, with results expected in 2028.

Until the results of such studies are available, we urge cautious patient selection, restricting LAAO to hemodialysis-treated patients with a significant bleeding history in the context of high thromboembolic risk. Shared patient and clinician decision making, carefully discussing uncertainty about long-term efficacy, is paramount. As illustrated in the present study,[4] 1-year all-cause mortality remains high (8.8%) in this cohort, and this must be factored into decision making. Further, given that the benefits of LAAO are likely accrued over a time horizon beyond several years, long-term follow-up studies are crucial.

CONCLUSIONS

Overall, we congratulate Tanaka et al[4] for their study, which provides novel insights into the role of LAAO in patients with AF who are undergoing hemodialysis. Nevertheless, before considering LAAO in this group, careful assessment of thromboembolic and bleeding risk is key, with disease-specific risk scores potentially offering greater nuance over conventional scores. Even in individuals at high risk of stroke, the role of anticoagulation remains uncertain, with comparative studies assessing the role of VKAs, DOACs, and conservative management under way. In individual hemodialysis-treated patients with high thromboembolic risk *and* previous major bleeding, LAAO may be a viable approach, although evidence is currently limited to observational registries only. The impact of LAAO in addition to catheter ablation in selected patients also merits consideration, given the recent OPTION (Comparison of Anticoagulation With Left Atrial Appendage Closure After AF Ablation; NCT03795298) trial, which showed a lower risk of bleeding than with OAC use while being noninferior to OAC use in terms of a composite of death, stroke, or systemic embolism.[18]

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