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EDITORIAL COMMENT

Anticoagulation in Elderly Patients With Atrial Fibrillation and Renal Dysfunction*

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In this issue of the *JACC: Asia*, Shimizu et al[1] present data from the ANAFIE (All Nippon AF in the Elderly) registry, a multicenter prospective registry of >30,000 elderly patients (75 years or older) with nonvalvular atrial fibrillation (AF). Participants were enrolled across 1,273 medical sites across Japan and were followed over a median of 2.0 years. The investigators reported the cumulative incidences of stroke, systemic embolic events, major bleeding, clinically relevant nonmajor bleeding, cardiovascular death, all-cause death, and net clinical outcomes and stratified them by renal function (creatinine clearance [CrCl]). The results are an important contribution to the literature and our understanding of direct-acting oral anticoagulant (DOAC) use among elderly patients with renal dysfunction, and the investigators are to be commended on this important study.

In their analyses, Shimizu et al[1] showed that reduced CrCl was associated with an increased incidence of clinical events when compared to those with a CrCl ≥50 mL/min. Furthermore, the investigators demonstrated similar or improved effectiveness of DOACs over warfarin down to CrCl 15-30 mL/min. Compared to warfarin, DOAC use was associated with fewer thromboembolic and death events and less or similar bleeding. Based on these findings, the investigators concluded that DOACs are safe and effective in patients with renal dysfunction (CrCl 15-50 mL/min).

LIMITATIONS OF THE ARTICLE

Although the results presented are convincing, there are several important considerations when interpreting these data. First, the ANAFIE registry is a nonrandomized study in Japanese patients, which may limit the generalizability of these findings. Observational findings are potentially subject to confounding, as patients prescribed DOACs over warfarin may have different baseline risk profiles caused by underlying biases in DOAC prescription. It is conceivable that patients at lesser risk for adverse outcomes are preferentially prescribed DOACs over warfarin. Furthermore, a substantial proportion of the cohort were not taking oral anticoagulants at all: whereas the "no-OAC" subgroup had a higher risk of stroke and systemic embolism, those with "no-OAC" and a CrCl between 30 and 50 mL/min had a significantly lower rate of cardiac events, suggesting that these patients may have a generally lower profile than the anticoagulated groups. Almost 20% of the ANAFIE cohort also had missing baseline CrCl values.

Another important consideration when evaluating outcomes in patients with renal dysfunction is the competing risk for noncardiovascular events and death. It was well known that patients with renal dysfunction suffer from higher rates on noncardiovascular adverse events, which in turn may shroud the ascertainment of stroke and systemic embolism. Whereas Shimizu et al[1] suggest that their findings remain consistent in their Fine-Gray hazard models, accounting for all-cause death as a competing risk, it is likely that additional competing risks to stroke and systemic embolism exist apart from all-cause death alone.

Finally, Shimizu et al[1] did not perform analyses on the impact of DOACs versus warfarin in patients with the lowest CrCl below 15 mL/min, because of their small sample size (n = 404) and the contraindication

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of DOACs in this population. This population remains a critical evidence gap in our literature, because large cohorts demonstrating efficacy or safety of anticoagulants in patients with these markedly reduced renal function are needed. The small sample size in the lower CrCl subgroups also meant that their multivariable analyses are likely to be overfit, because there are few outcomes occurring within each subgroup.

WHAT DO OUR GUIDELINES SAY FOR AF AND DOACs IN RENAL DYSFUNCTION?

Clinical guidelines typically recommend the use of DOACs in patients with a normal or mild-to-moderately reduced renal function (CrCl ≥30 mL/min), which is supported by data from randomized controlled trials and observational analyses[2-4] such as the present study. In patients with more severe renal function, guideline recommendations are mixed in the absence of large-scale, randomized data. In those with CrCl 15-30 mL/min, the 2019 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) AF guideline update suggests that reduced doses of apixaban, dabigatran, rivaroxaban, or edoxaban could be considered.[4] The 2020 European Society of Cardiology AF guidelines suggest that reduced doses of apixaban, rivaroxaban, and edoxaban, but not dabigatran, may be considered with caution.[3] In the 2020 Canadian Cardiovascular Society AF guidelines, it is stated that a DOAC is preferred in patients with AF and chronic kidney disease stages 1-4 who are prescribed anticoagulation, although only apixaban and rivaroxaban are approved in the CrCl 15-30 mL/min subgroup.[2] A 2021 Kidney Disease Improving Global Outcomes consensus statement suggests that anticoagulation is generally recommended but the choice of agent should depend on the trajectory of their renal function and should be discussed with the nephrologist.[5] In the setting of end-stage renal disease and dialysis (CrCl <15 mL/min), controversy persists as to whether any net benefit for anticoagulation exists.[6] Whereas the 2019 AHA/ACC/HRS guidelines suggests that apixaban (or warfarin) may be reasonable,[4] others recommend individualized decision making (Kidney Disease Improving Global Outcomes 2021[5]) or note that DOACs are not approved and should generally not be used in this group (European Society of Cardiology 2020[3] and Canadian Cardiovascular Society 2020[2]).

HOW DOES THIS ARTICLE FIT INTO THE CURRENT LANDSCAPE?

The use and safety of DOACs in patients with severe renal insufficiency remains underinvestigated, as demonstrated by a lack of guideline consensus. Randomized data remain limited in the setting of end-stage renal disease. The RENAL-AF (Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation) trial randomized patients with AF who are on hemodialysis to apixaban or warfarin.[7] Unfortunately, the trial was terminated early because of enrollment challenges, with 154 patients randomized. The primary outcome of major or clinically relevant nonmajor bleeding was high in both groups (26%-32% at 1 year), and 10-fold higher than the rates of stroke or systemic embolism (3.0%-3.3% at 1 year, respectively). Similarly, the AXADIA-AFNET 8 (Compare Apixaban and Vitamin K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease) study randomized 97 patients with AF who are on hemodialysis to either apixaban or warfarin.[8] After 1 year of follow-up, the composite efficacy (45.8% vs 51.0%) and safety endpoints (20.8% vs 30.6%) were not significantly different between the 2 groups. Other trials remain ongoing, including the AVKDIAL (Oral Anticoagulation in Haemodialysis Patients; NCT02886962), SAFE-D (Strategies for the Management of Atrial Fibrillation in Patients Receiving Dialysis; NCT03987711), and the SACK (Swedish Stroke Prophylaxis with Apixaban in CKD5 Patients with Atrial Fibrillation) trials.

In the absence of adequate randomized data, observational analyses provide important insights. Notably, a small proportion (1.3%) of patients had a CrCl <15 mL/min in the ANAFIE registry, and these individuals had significantly worse outcomes compared to those with less severe renal dysfunction. However, this subgroup was not included in safety and efficacy analyses because of the lack of DOAC indication in this subgroup in Japan. Other observational data suggest that DOACs may be an option in these individuals. For example, among 23,523 U.S. Medicare beneficiaries with AF who are on dialysis, apixaban use appeared to be associated with lower bleeding and, at a standard 5 mg twice daily dose, potentially reducing thromboembolism and mortality.[9] It is clear that more data would be welcome while randomized trials are ongoing.

Compared to those with end-stage renal dysfunction, patients with mild or moderate renal dysfunction have a lesser bleeding risk and thus potentially receive greater benefits from oral anticoagulation. Secondary analyses of the ROCKET-AF (An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation) trial demonstrated a lower incidence of stroke or systemic embolism with

rivaroxaban use compared to warfarin, irrespective of baseline CrCl.[10] Similarly, subgroup analyses of the ENGAGE AF-TIMI 48 (Global Study to Assess the Safety and Effectiveness of Edoxaban [DU-176b] Versus Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation) trial demonstrated similar efficacy outcomes with edoxaban compared to warfarin in patients with CrCl ≤50 mL/min.[11] The results of the ANAFIE registry provide real-world evidence supporting these findings reported in large randomized trials and potentially extrapolate DOAC efficacy and safety to patients with CrCl between 15-30 mL/min. Lastly, data from the ANAFIE registry also highlight the ongoing work needed to ensure appropriate DOAC use. According to Shimizu et al,[1] 31.4% of patients with CrCl ≥50 mL/min received an underdosing of DOAC. Although they did not report the incidence of underdosing in patients with CrCl <50 mL/min, these findings highlight a recurring finding in real-world studies: that DOAC regimens are frequently underdosed. It would be particularly interesting if the investigators have data as to whether underdosed patients are at higher risk for adverse events, as was previously reported in literature.

CONCLUSIONS/FUTURE AREAS OF DEVELOPMENT

The findings of the ANAFIE registry provide important real-world evidence into the outcomes of patients with renal dysfunction and support the safety and effectiveness of DOACs over warfarin in this important population. Shimizu et al[1] definitively show a higher rate of adverse clinical events in patients with lower CrCl and a consistent reduction in stroke and systemic embolism outcomes with DOAC use compared to warfarin. These findings reinforce our understanding of DOAC use in patients with renal dysfunction and perhaps also extend the safety of DOACs to those with CrCl 15-30 mL/min.

There remains an important need to understand the safety and effectiveness of DOACs in patients with the greatest renal dysfunction (CrCl <15 mL/min) and those on hemodialysis, with recent trials terminated prematurely because of recruitment failures. The ANAFIE registry results also highlight the ongoing challenges and need to optimize DOAC dosing, with a substantial portion of participants underdosed in their DOAC regimen. Taken together, these findings provide important insight into a challenging population and highlights the ongoing need for research in this space.

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REFERENCES

1. Shimizu W, Yamashita T, Akao M, et al. Renal function and clinical outcomes among elderly patients with nonvalvular atrial fibrillation from ANAFIE. *JACC: Asia*. 2023;3(3):475–487.

2. Andrade JG, Aguilar M, Atzema C, et al, Members of the Secondary Panel. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society comprehensive guidelines for the management of atrial fibrillation. *Can J Cardiol*. 2020;36(12):1847–1948.

3. Hindricks G, Potpara T, Dagres N, et al, ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373–498.

4. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2019;74(1):104–132.

5. Kelly DM, Ademi Z, Doehner W, et al. Chronic Kidney Disease and Cerebrovascular Disease: Consensus and Guidance From a KDIGO Controversies Conference. *Stroke*. 2021;52(7):e328–e346.

6. Wong CX, Odutayo A, Emdin CA, Kinnear NJ, Sun MT. Meta-analysis of anticoagulation use, stroke, thromboembolism, bleeding, and mortality in patients with atrial fibrillation on dialysis. *Am J Cardiol*. 2016;117(12):1934–1941.

7. Pokorney SD, Chertow GM, Al-Khalidi HR, et al, RENAL-AF Investigators. Apixaban for patients with atrial fibrillation on hemodialysis: a multicenter randomized controlled trial. *Circulation*. 2022;146(23):1735–1745.

8. Reinecke H, Engelbertz C, Bauersachs R, et al. A randomized controlled trial comparing apixaban with the vitamin K antagonist phenprocoumon in patients on chronic hemodialysis: the AXADIA-AFNET 8 study. *Circulation*. 2023;147(4):296–309.

9. Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. *Circulation*. 2018;138(15):1519–1529.

10. Fox KA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J*. 2011;32(19):2387–2394.

11. Bohula EA, Giugliano RP, Ruff CT, et al. impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 trial. *Circulation*. 2016;134(1):24–36.

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