Perspective Görüş

New Oral AntiCoagulants Use in REnal Disease and AF (NOACURE-AF) - Where do we stand?: An expert consensus view using the Delphi method

Böbrek Hastalığı olan AF Olgularında non-vitamin K antagonisti oral antikoagülanların kullanımı (NOACURE-AF) - Neredeyiz?: Delphi yöntemi kullanan bir uzman uzlaşı raporu

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The risk of atrial fibrillation (AF) is increased in patients with chronic kidney disease (CKD) and end stage renal disease (ESRD) requiring dialysis. The prevalence of AF is 8%-18% in CKD population, 7%-27% in patients treated with hemodialysis (HD), and 0.4%-1.0% in non-CKD general population.[1] The most common risk stratification scheme validated and suggested by current guidelines for predicting stroke in patients with AF is the CHA_2DS_2-VASc score, and the HAS-BLED risk score has been developed to determine the risk of bleeding.[2] However, these scoring systems were developed and validated exclusively in patients not receiving dialysis; significant components of the scores, such as hypertension, diabetes, vascular disease, and congestive heart failure in CHA_2DS_2-VASc, may not reliably predict stroke risk in patients on dialysis.[3] Previous data indicated that the majority of patients on renal replacement therapy (RRT) have higher stroke risk according to the CHA_2DS_2-VASc score. In a study of 12,284 patients on dialysis in the United States, less than 10% of patients had a CHA_2DS_2-VASc score lower than 2 indicating a low risk of ischemic stroke.[4] Furthermore, recent studies have demonstrated that $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores can predict ischemic strokes but not bleeding events in patients on dialysis.[5,6]

There is no randomized clinical trial (RCT) data on the use of warfarin to prevent ischemic-embolic stroke in patients on HD with AF. Numerous observational studies showed conflicting results for vitamin K antagonists (VKA) therapy regarding efficacy in patients on dialysis.[1,3] Most studies suggested a lower incidence of stroke and embolism when warfarin was used, but also a markedly increased bleeding risk.[7,8] Studies have demonstrated that the risk of stroke is reduced when the time

Abbreviations:

ACC	*American College of Cardiology*
AF	*Atrial fibrillation*
AHA	*American Heart Association*
CKD	*Chronic kidney disease*
EHRA	*European Heart Rhythm Association*
ESC	*European Society of Cardiology*
ESRD	*End stage renal disease*
HD	*Hemodialysis*
HRS	*Heart Rhythm Society*
IC	*Intracranial*
KDIGO	*Kidney Disease Improving Global Outcomes*
LAA	*Left atrial appendage*
NOACs	*Non-vitamin K oral anticoagulants*
OAC	*Oral anticoagulant*
PD	*Peritoneal dialysis*
RCT	*Randomized clinical trial*
RRT	*Renal replacement therapy*
TTR	*Time in therapeutic range*
VKA	*Vitamin K antagonists*

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Table 1. Round one open-ended questions

Question 1	What is the efficacy/safety evaluation of oral anticoagulant therapy use in preventing stroke in patients with atrial fibrillation and end-stage renal disease (whether under renal replacement therapy or not)?
Question 2	If the use of the non-vitamin K antagonist oral anticoagulant (NOAC) is default for the relevant patient population, is a particular agent more prominent?

in therapeutic range (TTR) is >70%, but patients on dialysis receiving daily warfarin often have TTR of <50%.[9] Of note, the use of warfarin in patients on dialysis may result in calciphylaxis, a painful and often life-threatening condition caused by calcification and occlusion of cutaneous arteries and arterioles.[10]

The efficacy and safety of non-vitamin K oral anticoagulants (NOACs) in patients with ESRD, including those on dialysis are unclear and is an important subject in ongoing studies. The major problem assessing the effectiveness of anticoagulants in patients with CKD is that those with advanced stages of CKD have been excluded from phase 3 pivotal trials.

Two RCTs comparing NOACs with VKAs in patients with ESRD are ongoing (NCT02933697, NCT03987711). However, the RENAL-AF trial, which compared apixaban with warfarin for stroke prevention in patients with AF on hemodialysis, was stopped early owing to lack of funding after 155 of a planned 760 patients were enrolled and produced inconclusive results on relative stroke and bleeding rates.[11]

In the United States (but not in Europe), apixaban 5 mg BID and rivaroxaban 15 mg OD are currently approved in chronic, stable dialysis-dependent patients with dosing recommendations per the pharmacokinetic and pharmacodynamic data.[12] However, plasma levels with apixaban 5 mg BID were recently shown to be supra-therapeutic.[13] Some pharmacokinetic studies claimed that appropriate NOAC doses in patients with ESRD or on dialysis are 2.5 mg BID for apixaban, 15 mg od for edoxaban, and 15 mg or 10 mg od for rivaroxaban.[14,15]

A retrospective cohort study of Medicare beneficiaries sought to determine patterns of apixaban use and its associated outcomes in patients with AF on dialysis. The study showed that a standard 5 mg twice daily dose of apixaban was associated with a lower risk of major bleeding and a reduction in thromboembolism and mortality compared with warfarin.[16]

Current guidelines do not provide definitive recommendations regarding the use of NOACs in patients with AF on dialysis. To provide perspective on the use of these agents, an expert panel was convened to develop consensus statements for the initiation of NOACs in patients with ESRD and on dialysis.

METHODS

Delphi method

The Delphi method is an interactive forecasting method which is commonly used in scientific and medical settings to reach an agreement within a group of experts, when scientific evidence is absent or conflicting.[17] In this paper, a three-round Delphi method was used to assess the consensus on clinical management of NOACs in patients with AF and ESRD.

An information letter was sent to the experts describing the aims and the study procedure. Two open-ended questions were prepared and sent to the panel experts by e-mail in the first round (Table 1). The expert comments were summarized, and 14 additional questions were derived according to responses from the first round (Table 2). In the second round, the experts were asked to rate their level of agreement with each questionnaire item on a 5-point Likert scale from 1 (completely agree) to 5 (completely disagree). Consensus was reached when the sum of items 1, 2, and 3 (agree) or 4 and 5 (disagree) reached 60%. To limit the possibility of bias or impact by the other specialists' opinions, the answers were anonymous. Round three comprised a teleconference meeting among the experts to assess those issues that did not reach consensus in round two. The panel members discussed the non-consensus items until agreement was reached.

Delphi participants

The basic criteria for panelist selection were being in the relevant clinical discipline, engagement in scientific and academic activities in the relevant clinical field, and actively taking part in the management of

Table 2. 5-point Likert questionnaire

Question	Absolutely agree	Agree	Undecided	Absolutely disagree	Disagree
The CHA_2DS_2-VASc score is useful in determining the risk of ischemic stroke in patients with ESRD + AF					
In patients with ESRD + AF, if the CHA_2DS_2-VASc score is >2, I definitely initiate OAC treatment.					
In patients with ESRD + AF, if the CHA_2DS_2-VASc score is >2, the risk of bleeding is determinant when deciding on OAC treatment.					
In patients with ESRD + AF, OAC should be initiated in secondary prevention of ischemic stroke regardless of the risk of bleeding.					
If I decide to start OAC in patients with ESRD + AF, the first choice would be VKA.					
If I decide to start OAC in patients with ESRD + AF, first choice would be NOAC.					
If I decide to start NOAC in patients with ESRD + AF, first choice would be apixaban					
In the 2019 AHA/ACC guideline, the class IIb recommendation level of apixaban treatment in patients with ESRD + AF should be updated in future versions.					
If I decide to start OAC in patients with AF and stage 4 CKD, the first choice would be VKA.					
If I decide to start OAC in patients with AF and stage 4 CKD, the first choice would be NOAC.					
If I decide to start NOAC in patients with AF and stage 4 CKD, the first choice would be rivaroxaban.					
If patients with ESRD + AF are under PD program instead of HD, my approach in terms of OAC treatment would be different.					
LAA closure should be considered regardless of the history of major bleeding in patients with ESRD + AF.					
A placebo arm should definitely be included in prospective trials of stroke prevention strategies in the ESRD + AF population.					

AF: atrial fibrillation; CKD: chronic kidney disease; ESRD: end-stage renal disease; HD: hemodialysis; LAA: left atrial appendage; NOAC: non-vitamin K antagonist oral anticoagulant; PD: peritoneal dialysis; VKA: vitamin K antagonist.

patients with discussed clinical condition. According to these criteria, three cardiologists and three nephrologists from different healthcare providers (university hospital, state hospital, and private practice) were invited to participate in the panel. No demographic, clinical, or laboratory data of any volunteer or patient was used at any stage of the panel workflow. For this reason, an ethics approval for the described processes was not required. All participants of the Delphi procedure approved the final version of the article.

RESULTS

The panel members considered that the CHA_2DS_2-VASc score to be useful in determining the risk of ischemic stroke in patients with AF (66% positive consensus), but also emphasized the limitations of the score in low-risk patients according to the score (i.e., CHA_2DS_2-VASc of 0). The panel recommended modification or expansion of the score in the ESRD population, which may be useful in identifying true low-risk cases.

The panel considered that oral anticoagulant (OAC) therapy should be definitely initiated in patients with ESRD if the CHA_2DS_2-VASc score was above 2 (83% positive consensus). All the panelists agreed that the risk of bleeding is determinative when deciding OAC treatment, particularly in patients with a history of major/intracranial (IC) bleeding. Panelists recommended the use of OACs in patients with AF and ESRD for secondary prevention of ischemic stroke regardless of the risk of bleeding (83% positive consensus).

The majority of the panel (83%) agreed with the use of NOACs, instead of warfarin, as the initial anticoagulant treatment when OAC is indicated. The panel did not confer any specific NOAC agent. Despite the level 2b recommendation of apixaban use in patients with AF and ESRD by current focused update of the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guideline, the panelists emphasized weakness of the evidence, lack of RCTs, and shortcomings of the RENAL AF trial.[11,18]

In patients with stage 4 CKD, however, the panel agreed with the use of NOACs, instead of warfarin, as the initial anticoagulant treatment.

The panel members pointed to importance of possible reno-protective effects of rivaroxaban in patients with stage 4 CKD, but also emphasized the need for more data in terms of mechanistic and clinical data collected prospectively.

The majority of the panel (83%) did not recommend left atrial appendage (LAA) closure in patients with ESRD and AF on dialysis for stroke prevention owing to lack of any evidence.

Finally, the panel concluded a lack of high level of evidence in terms of net clinical benefit of OAC therapy in AF population with ESRD. They remarked on the need for inclusion of a placebo arm to OAC trials focusing on this patient population.

DISCUSSION

AF and CKD share many common risk factors. Although CKD is an obvious risk factor for incidental AF, AF also accelerates the progression of CKD. It is not surprising that the coexistence of AF and CKD is quite common. Almost half of the AF population has CKD, whereas one-fifth of patients with CKD have concurrent AF.[2] CKD is both a prothrombotic and pro-hemorrhagic condition. The risk of ischemic events increases exponentially in the presence of AF, and concomitant anticoagulant therapy also increases the risk of bleeding.[12] In this context, the management of cases with CKD and AF coexistence has some difficulties. Furthermore, the evidence for ESRD population is limited. Epidemiological data reveal that the prevalence of AF in the ESRD population is undeniably high.[1]

The validity of the $CHADS_2VA_2Sc$ score in the ESRD population is questioned from several aspects. Primarily, almost 80% of the ESRD population has a $CHAD_2S_2$-VASc score of 2 or above.8 However, the more important point is the discriminative value of the $CHAD_2S_2$-VASc score in identifying low-risk cases ($CHAD_2DS_2$-VASc=0) in the ESRD population. In this regard, it is suggested that CKD should be added to the $CHAD_2S_2$-VASc score as an extra risk factor.[18-21] However, there is no up-to-date alternative risk scoring systems validated by large-scale studies. In this Delphi panel, the panelists highlighted their doubts about the role of the $CHAD_2S_2$-VASc score in identifying cases with "truly low stroke/systemic embolism risk" in the ESRD population, but also pointed out that the widespread use, ease of use, and familiarity of this score should not be overlooked. The panelists also stated that many patients with ESRD were at high risk according to the relevant score, emphasizing that low-risk patients represented only a minority. They pointed out the need for alternative risk scores for this population, which "focuses on identifying truly low-risk cases."

Current AF guidelines recommend OAC treatment for stroke prevention in patients with AF with CHA_2DS_2-VASc score ≥2 in men or ≥3 in women, regardless of the risk of bleeding and AF pattern.

[2,22] High thromboembolic and bleeding risks in the ESRD population make OAC treatment more challenging. The second question put to the panelists on the Delphi panel was whether to start OAC treatment in patients with a $CHAD_2S_2$-VASc score >2 in the ESRD population, regardless of presence or absence of other factors. The panelists emphasized that the high risk of stroke and bleeding in the ESRD population mentioned above should be evaluated together, and the current ACC/AHA guideline recommendation should not be ignored, albeit with a low level of recommendation. Panelists noted that ischemic stroke is a severe devastating clinical entity as a major bleeding event from patient, healthcare provider, and general healthcare system perspectives. The third question asked to the panelists was whether the risk of bleeding was a determinant when starting OAC treatment in patients with ESRD with a $CHAD_2S_2$VASc score > 2, and the panelists agreed that the risk of bleeding should not be ignored.

The panelists reached a consensus that OAC treatment should be initiated in secondary prevention of ischemic stroke in ESRD population with AF, emphasizing that from a patient perspective, stroke is more important than a bleeding event. The panelists also emphasized the results of a study that showed the fear of stroke is much more dominant than the fear of bleeding from a patient perspective, and secondary prevention patients have higher rates of OAC compliance and persistence.[23]

Data on the efficacy and safety of warfarin treatment for preventing stroke in AF in the ESRD population was obtained from observational studies and offer conflicting results.[8,24-27] These inconsistent results may be attributed to differences in the study population, treatment management (TTR), or outcome descriptions. However, many studies indicated an increased risk of major bleeding and concluded drawbacks with warfarin therapy in perspective of net clinical benefit.[28-31]

These contradictory results have led to conflicting recommendations between the relevant guidelines. The Kidney Disease Improving Global Outcomes (KDIGO) 2011 guideline has not recommended routine anticoagulation with warfarin for primary prevention of ischemic stroke in patients with ESRD, ACC/AHA/HRS 2014 guidelines recommended warfarin treatment with Class IIa recommendation level.[32] However, in the focused update of the ACC/AHA/HRS 2019 guidelines, the relevant recommendation level has been downgraded to a Class IIb recommendation.[22] It is noteworthy that the current European guidelines do not make any recommendations on this subject.[2]

Concerns about warfarin therapy in the ESRD population are not only limited to an increased risk of bleeding. Warfarin-induced vascular calcification, calciphylaxis owing to cutaneous arteriolar calcification,[10] and progressive deterioration in renal functions thought to be because of glomerular micro-hemorrhages[33,34] are other concerns regarding warfarin therapy. Moreover, the lower TTR in the ESRD population compared with the normal population,[35] polypharmacy owing to increased comorbidity, and the need of additional heparin during HD sessions make the management of warfarin therapy more challenging.[16] In the ESRD population, the rate of warfarin use for prevention of stroke in AF varies considerably between countries. Canadian data showed that 37% of ESRD+AF cases were under warfarin treatment, whereas this rate was only 2% in Germany.[36] Recent data from North America showed that almost one-fourth patients were under warfarin treatment.[12] The demographic data about this population in Turkey was derived only from a single center cross-sectional study, which indicated an AF prevalence of 14.5%, mean $CHAD_2S_2$-VASc score of 2.87±1.5, and warfarin usage rate of 9.8%.[37]

Although the absence of any RCT evidence in terms of safety and efficacy, NOACs have begun to be prescribed "off-label" in the relevant patient population in daily practice.[14] Retrospective social security records provide detailed efficacy and safety data on the use of NOACs in the ESRD population in real life.[38] In these retrospective analyses, NOACs other than edoxaban were evaluated. Some of them concluded that apixaban[16] and rivaroxaban[38] treatments were safer than warfarin in terms of major bleeding, but there is no significant difference in terms of efficacy. It should be kept in mind that these studies were retrospective, and residual confounding factors cannot be completely excluded as there was no real randomization. Based on the aforementioned retrospective data,[16] the AHA/ACC/HRS guideline focused update recommended apixaban or warfarin in patients with AF with a $CHAD_2S_2$VASc score ≥ 2 in the ESRD population as a Class IIb recommendation level. The recommendation level for other NO-

ACs in the relevant population is Class III. European Society of Cardiology (ESC) 2020 guidelines for the diagnosis and management of AF do not provide any specific recommendations for OAC treatment in the ESRD+AF population.[2]

Within the framework of the Delphi panel, the panelists were asked whether their first choice would be warfarin or NOAC when they decided to start OAC in patients with ESRD+AF. The panelists reached a consensus that their choice of OAC would be a NOAC. The limitations mentioned above regarding warfarin treatment, doubts about its effectiveness, and the significant increase in bleeding risk were the main reasons for NOAC preference.

Another important aspect is whether apixaban has a favorable safety/efficacy profile than other NOACs in the ESRD+AF population. The 2019 focused update of the AHA/ACC/HRS guideline based on retrospective data recommended apixaban[22] in patients with ESRD+AF with $CHAD_2S_2VASc$ score ≥2 as a Class IIb recommendation. However, neither the European Heart Rhythm Association (EHRA) 2018 NOAC consensus document nor the ESC 2020 AF guideline makes any statement on the use of apixaban in the relevant population. However, it is seen that both the AHA/ACC/HRS guideline and the EHRA 2018 position paper draw attention to the requirement of prospective RCT on this subject.[39]

As a follow-up question to the panelists, it was asked that if they decide to start NOAC in patients with ESRD and AF, whether their first choice would be apixaban. The panelists emphasized that strong clinical implications cannot be made on the basis of available pharmacokinetic data and retrospective data and reached a consensus on the need for prospective RCTs. The panelists stated that the RCTs should be designed with a sample size and follow-up period that will allow the evaluation of effectiveness as well as safety, and beyond that, testing the placebo as a third arm. The panelists also reached a consensus that the relevant recommendation from the ACC/AHA guideline should be updated and changed. As the next question, the panelists were asked about their opinions on OAC treatment and preferences in patients with stage 4 CKD. The panelists emphasized that the stage 4 CKD population is a much larger population than the ESRD population. They stated that although the relevant population was excluded from the phase 3 NOAC studies, there was a significant number of patients progressing to stage 4 CKD in the course of these studies, and subgroup data related to these cases should not be ignored. Even though the relevant subgroup analyses were hypothesis generation in nature, the panel members reached a consensus in choosing NOAC because of the unmet need for the relevant population and the subgroup results similar to the general AF population.

Progressive deterioration of renal functions with warfarin treatment has been shown in previous studies. In this context, NOACs may be a preferable option to preserve residual renal functions in patients with stage 4 CKD. Moreover, a retrospective analysis involving 9,769 patients showed less deterioration in renal function and potential relative reno-protective effects with rivaroxaban and dabigatran therapy when compared with warfarin.[35] This evidence, which is hypothesis-generating in nature, has not been evaluated in translational or prospective clinical studies to shed light on mechanistic reasons. The panelists were asked whether rivaroxaban would be their primary NOAC choice in patients with stage 4 CKD. The panelists emphasized that the relevant retrospective evidence is not sufficient to demonstrate the causality relationship, and the mechanism of possible protective effects should also be revealed.

The panelists were asked whether their approach would be different in terms of OAC treatment in patients with ESRD and AF in the peritoneal dialysis (PD) program instead of HD. In this regard, the panelists stated that the OAC treatment approach should be different because of the differences in the drug dose and the anticoagulant dose during HD.

The panelists were asked whether LAA closure could be offered as a treatment option in the ESRD population currently at high risk of bleeding. In this regard, the panelists reached a consensus that the risk of bleeding is determinative. Although there are several case series related to this issue, a study evaluating the effectiveness and safety of LAA closure in the ESRD population has not been published to this day. The goal of the STOP-HARM study (NCT02885545) is to compare warfarin and watchman device in the relevant population, but clinicaltrials.gov records show that the study was withdrawn owing to failure in recruitment.

The Valkyrie trial randomized patients on HD with AF to a VKA with a target INR of 2-3, 10 mg

rivaroxaban daily, or rivaroxaban and vitamin K2 for 18 months. The trial showed that a reduced dose of rivaroxaban significantly decreased the composite outcome of fatal and nonfatal cardiovascular events and major bleeding complications compared with VKA. [40] This study was not discussed by the panel as it had not been published at that time.

Limitations

The study had some limitations arising from the nature of the Delphi panel. The panel was conducted based on the experiences of participants; therefore, their views may not reflect views of other experts who were not included in the study. The experiences of the panel will clearly have influenced the results of this study. A limited number of panelists is also one of limitations of this study.

Conclusion

Without strong evidence (i.e, phase 3 RCT data), the role of OAC therapy in patients with ESRD and AF remains unclear. This uncertainty and challenging situation have pushed clinicians to manage these patients according to their clinical experience with off-label prescriptions. The Delphi panel study recommendation may help guide clinical decision making for the management of OAC in patients with ESRD and AF.

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