Letter to the Editor — Editöre Mektup

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

Dear Editor,

I read the perspective paper titled, "New Oral AntiCoagulants Use in Renal Disease and AF (NOACURE-AF) - Where do we stand?: An expert consensus view using the Delphi method" by Arıcı et al.[1] with great interest. Oral anticoagulation (OAC) in patients with end-stage renal disease (ESRD) and/or on dialysis is a challenging issue for clinicians. Observational studies and retrospective data from insurance claims have reported conflicting results on the use of OACs (vitamin K antagonists [VKA] and novel OACs [NOACs]) in this patient population in terms of effectiveness and bleeding without a clear indication of benefit.[2] As the panelists state in their paper, randomized controlled trial data that focused on OAC use in this patient population are scarce and had inconclusive results. Panelists of the NOACURE-AF had a positive consensus about the initiation of OACs in the ESRD with atrial fibrillation (AF) in conditions of either high thromboembolic risk (CHADS-VASc score > 2) and low bleeding risk, or if the patient had a history of ischemic stroke regardless of the bleeding risk.

The panelists also had consensus on NOAC preference rather than VKA when the decision of OAC therapy had been made. However, the members focused on apixaban and rivaroxaban and not edoxaban in their paper. Indeed, many observational studies include data about these agents owing to marketing timelines. However, Koretsune et al.[3] demonstrated similar bleeding rates, plasma concentrations, and biomarkers of blood coagulation/fibrinolysis between the patients with severe renal impairment and normal renal functions with different edoxaban regimens (edoxaban 15 mg once daily and edoxaban 60 mg once daily). In addition, in the subgroup analysis of the ENGAGE AF-TIMI 48 trial, different levels of renal impairment did not show any significance in clinical outcomes with adjusted edoxaban doses.[4]

In terms of the pharmacokinetic profile, we believe that edoxaban had no major difference in terms of bioavailability than apixaban and rivaroxaban in patients with ESRD and/or on dialysis. We also believe that marketing access timelines had a major role on observational data and may explain scarce real-life data on edoxaban therapy in this patient population.

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Author's reply

Dear Editor,

We would like to thank the reader for interest in our article titled, "New Oral AntiCoagulants Use in Renal Disease and AF (NOACURE-AF) - Where do we stand?: An expert consensus view using the Delphi method." Evidence-based medicine approach forms the basis of clinical decision making process. Randomized controlled clinical trials (RCTs) form an essential part of the evidence. However, conducting of RCTs is difficult for obvious reasons, such as being a time-consuming process and often has high costs. In

clinical situations where RCTs results are not available, clinical studies other than RCTs may guide the decision making of physicians beyond relevant guidelines. Retrospective social security database analyses and observational drug (pharmacovigilance) studies, which are evaluated as real-life studies, have been gaining popularity recently, especially in the field of cardiology. However, the basic condition for carrying out these studies is that the relevant drug has completed the market access process.

The use of oral anticoagulants (OACs) for the prevention of stroke in patients with atrial fibrillation and end-stage renal disease (ESRD) and on hemodialysis (HD) is an area where there is no adequate RCT evidence.[1] However, after the off-label use of the related drugs in real-life conditions, a significant amount of real-life data could be obtained in the relevant field.[1,2]

The NOACURE Delphi panel was conducted on the basis of the relevant literature on real-life data and international guidelines focused on the subject. The delayed conduction of the preclinical, early clinical, and key trials for edoxaban compared with other NOACs resulted in delay in marketing access than other NOACs, as expected. This delay is the main reason why edoxaban therapy is not included in the literature focused on by the panel. Supportively, it will appear that a significant portion of the 2019 American College of Cardiology/American Heart Association/Heart Rhythm Society focused update on the topic is geared toward edoxaban therapy.[3]

Although there were some concerns over a decrease of edoxaban in relative efficacy in the upper range of creatinine clearance > 95 mg/mL,[4] a nationwide cohort study using insurance claims data did not confirm this concern.[5] However, both pharmacokinetic data and early phase studies have demonstrated no sign that edoxaban may differ from other anti-Xa agents in terms of efficacy/safety profile in patients with ESRD/HD. It is obvious that real-life data on the use of edoxaban in the relevant population are also limited. It is expected that real-life data on edoxaban treatment, which is widely used in relevant indications as other NOACs, will be added to the literature soon.

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