Editorial

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Oral Anticoagulation in End-Stage Renal Disease: Is It Time to Absolve Warfarin?

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Despite the known high prevalence and incidence of atrial fibrillation (AF) in patients with end stage renal disease (ESRD) on hemodialysis (HD), up to a few years ago, there were only very few studies addressing this topic. Recently, there have been some studies showing that not only are ESRD patients presenting this arrhythmia frequent but also AF in HD patients being associated with an increased mortality with regard to the general population as well. In heart disease patients with AF and preserved renal function, the main factor associated with reduced survival is the increased risk in thromboembolic stroke. For this reason, the cardiology guidelines consider oral anticoagulant therapy (OAT, i.e., vitamin K inhibitors, warfarin or direct oral anticoagulants) of fundamental importance in the prevention of stroke in AF patients. However, the data on the efficacy of OAT on thromboembolic risk in ESRD patients are extremely conflicting and there is no clear evidence of the fact that warfarin is associated with a reduced incidence of cerebrovascular events in HD patients. On the contrary, there seem to be a clear association between vitamin K inhibitors and the risk of bleeding [1, 2].

The relationship between OAT and mortality in ESRD patients has been studied even less. In 2009, in an important and provocative article, Chan et al. [3] affirmed that the use of warfarin in HD patients was linked to an increase in mortality. This information was confirmed by what could be deduced from the DOPPS study [4]. These findings raised many doubts among nephrologists who were supposed to set up a thromboembolism prophylaxis program in their HD patients with AF. More recently studies with opposite results appeared, which suggested that in HD patients OAT, besides reducing thromboembolic risk, could be associated with a reduction in mortality [2, 5].

There are several methodological issues related to the studies on warfarin, HD and AF. First, the involved studies are almost exclusively retrospective. Second, there is a problem of under-treatment: the proportion of patients who are actually taking warfarin, compared to those who according to the cardiology guidelines should take the therapy is very small. Furthermore, many patients taking warfarin suspend their therapy because of supervening complications, mostly represented by hemorrhagic events. Even if the necessity of a randomized study on the treatment with OAT in ESRD patients has been frequently emphasized, such a study is unlikely to ever be performed, as randomization of this kind of patients is ex-

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tremely difficult. ESRD patients at elevated hemorrhagic risk are many, and even if they were included in a randomized study (entailing possible ethical problems), they would likely to drop out early due to incident major bleeding.

The study by Brancaccio et al. [6], published in this issue of the American Journal of Nephrology, describes a better survival in subjects taking warfarin compared to those not taking the drug in a population of ESRD patients with AF. This study was performed with the help of a one-to-one matching analysis after balancing the 2 patient cohorts (warfarin users versus non-users). The used statistical approach reduces the bias related to the decision to start the treatment and allows the simulation of a randomized trial. The conclusion drawn by the authors is similar to what was observed by Shen et al. [5] in a population of ESRD patients with new onset AF. In the latter study, the authors showed a lower incidence of death in subjects treated with warfarin by performing an as-treated analysis after balancing the 2 patient cohorts that did or did not take warfarin by a propensity score analysis.

It is interesting to note that in both studies, and also in other studies with similar outcome [2], the result of improved survival in the cohort of patients on OAT was achieved without observing any reduction in stroke incidence. ESRD patients on HD therapy usually take heparin 3 times a week, on the occasion of the dialysis session. Moreover, it is known that these patients suffer from a malfunctioning coagulation system characterized, amongst others, by platelet dysfunction. These 2 factors could concurrently not only increase the hemorrhagic risk but also reduce the risk of thromboembolism.

We are aware that HD patients represent a quite particular population with special characteristics, in which clinical assumptions that are generally accepted in other categories of patients do not always apply. By means of a competing risk analysis, a recent study showed an excess mortality in HD patients with AF that was not associated with an increased number of cerebrovascular events [7]. Adding the results of the study by Brancaccio et al. [6] to those already available in literature, we may try to look at the problem of OAT and mortality risk in ESRD subjects with AF from a new point of view and speculate that in ESRD patients, OAT may provide a benefit that is not due to its protection from thromboembolic risk. As already reported in heart disease patients with and without AF, vitamin K inhibitors may exert a protective effect on cardiovascular events and mortality that goes beyond their ability to reduce thromboembolic events. Patients on HD often suffer from coronary ischemic and cerebrovascular diseases that could benefit from the protective effect of warfarin.

The hypothesis that a mortality reduction in HD patients with AF may be associated with the use of vitamin K inhibitors is fascinating, but should be examined very carefully. The study by Brancaccio et al. [6] has several weak points: it is a retrospective study, in which the identification of patients with AF was achieved a posteriori by the ICD-10-CN code of the arrhythmia. Furthermore, in spite of all the statistical adjustments that were applied, it remains possible that those ESRD patients who succeeded in continuing to take the therapy were the ones who were less frail and had a better compliance. Consequently, it could have been easier for the nephrologists in charge to maintain the international normalized ratio (INR) within an adequate therapeutic range in those patients. Unfortunately the authors do not provide any information concerning the possible discontinuation of the drug or INR monitoring in their patients. Moreover, there are no imaging documents revealing the nature (ischemic or hemorrhagic) of the recorded cerebrovascular events. A slight benefit in terms of stroke risk and a more sizeable reduction in acute myocardial infarction risk for patients on warfarin was observed, however, even if none of such association estimates were statistically significant.

In view of the objective difficulties in conducting studies in this particular category of patients without the risk of methodological biases, I believe that we still do not have enough information to strongly affirm which instructions should be given regarding the use of oral anticoagulants in this population. Nevertheless, new data emerging from the literature, also including the last described study, suggest that the use of vitamin K inhibitors in ESRD patients with AF might have been excessively demonized and that part of these patients, if adequately monitored, could benefit from OAT. Considering the current lack of randomized studies that can hardly be carried out in this setting, I believe that prospective studies using a statistical approach, in order to simulate estimation of a randomized controlled trial, may contribute in giving us information about a correct therapeutic approach when treating these complex patients.

Disclosure Statement

None declared.

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