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Predictors of Inappropriate Dosing of Direct Oral Anticoagulants in Nonagenarian Patients With Atrial Fibrillation

Direct oral anticoagulants (DOACs) are presented as a good option for older patients owing to their safety profile. However, the dosing of these drugs can become challenging. This is due to the fluctuation of renal function in this population, together with the presence of comorbidities and the concomitant use of other drugs, among other reasons. Prior studies reported high rates of nonstandard dosing in elderly patients,[1] increasing the risk of adverse events.[2]

The authors analyzed the use of DOACs in a retrospective multicenter registry of patients aged ≥90 years with a diagnosis of AF from 3 health areas in Spain. We studied the dosing, differentiating between appropriate dose, underdosing, and overdosing. Optimal dose was based on European Medicines Agency recommendations. To evaluate the potential variables related to inappropriate dosing, we used the command *allsets* of Stata 15 (StataCorp, College Station, TX) with the Akaike information criterion for the selection of the best predictive model. All relevant variables with theoretical justification were included.

A total of 716 nonagenarian patients anticoagulated with DOACs were evaluated. Mean age was 93.0±5.2 years, and 60% were female. More information about the registry and baseline characteristics are available in prior publications.[3]

Among patients with DOAC, 339 patients received rivaroxaban (47.3%), 237 apixaban (33.1%), 105 dabigatran (14.7%), and 35 edoxaban (4.9%). We observed a significant proportion of DOAC patients received a suboptimal dose (41.5%, n = 297): 35.3% were underdosed and 6.1% overdosed. The rate of suboptimal dosing was higher for apixaban and lower for dabigatran (Figure 1A).

In our registry, we found the following predictors of inappropriate dosing: kidney function (according to Chronic Kidney Disease Epidemiology Collaboration) odds ratio (OR) 1.04 [95% confidence interval (CI) 1.03-1.05, $P < .001$]; weight measured in kilograms, OR (per 1 kg of weight) 1.04 (95% CI 1.01-1.07, $P = .012$); and high blood pressure (HBP), OR 1.61 (95% CI 1.02-2.53, $P = .041$) (Figure 1B). Other clinically relevant variables such as HAS-BLED [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly [≥65 years], Drugs/alcohol, concomitantly], CHA2DS2-VASc Score [Congestive Heart Failure, Hypertension, Age ≥75 (Doubled), Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack (Doubled), Vascular Disease, Age 65-74, Female], anemia, prior bleeding, or concomitant use of antiplatelet therapy, were not significantly related to the prescription of an inappropriate dose.

These results suggest that the percentage of older patients receiving an inappropriate dose of DOAC is high, reaching almost half of the patients in our registry. These findings are consistent with data obtained in other real-life studies.[4] Specifically, the most frequently underdosed drug was apixaban, in the same way as in a retrospective cohort registry carried out by Whitworth et al,[5] in this case following the recommendations of the US Food and Drug Administration (FDA). Apixaban is the DOAC with more dose reduction criteria, whereas dabigatran dosing is simpler. This reason may explain the results in our sample.

One of the challenging factors in choosing the appropriate dose is kidney function. Because of the fluctuating kinetics of glomerular filtration in older patients, close monitoring of renal function is required to modify dose when necessary. Otherwise, we would run the risk of overdosing, or more frequently, underdosing our patient with the consequent increase in embolic risk.[2]

Weight is another factor involved in the choice of doses of apixaban and edoxaban. However, it should not influence the choice of dose with dabigatran or rivaroxaban. In clinical practice, it is common to estimate the patient's weight visually. This can be a source of error, especially in older patients, where sarcopenia is frequent.

HBP is a variable included on the thrombotic and hemorrhagic risk scales. HBP is not a variable contemplated in the European Medicines Agency or US Food and Drug Administration dose adjustment indications, so it should not be a determining factor when choosing the dose. It is worth mentioning that in a previous publication analyzing this same population, HBP was not a predictor of bleeding risk.[6]

The finding of renal function as a predictor of inappropriate dosing is plausible because it is a factor present in the choice of dose of all DOACs. Because apixaban is the most frequently misdosed drug in this registry, it is consistent with the fact that both weight and kidney function are 2 of the 3 apixaban dose reduction criteria.

We want to highlight that the use of an inappropriate dose of DOAC in older patients is common; in our study with nonagenarians, it was found in approximately 40% of cases. Apixaban was the most frequently underdosed DOAC. High blood pressure, weight, and kidney function were associated with an inappropriate dosing prescription. Therefore, it is important to carefully evaluate the characteristics of the patient to prescribe the appropriate dose that guarantees a correct action.

The authors declare no conflicts of interest.

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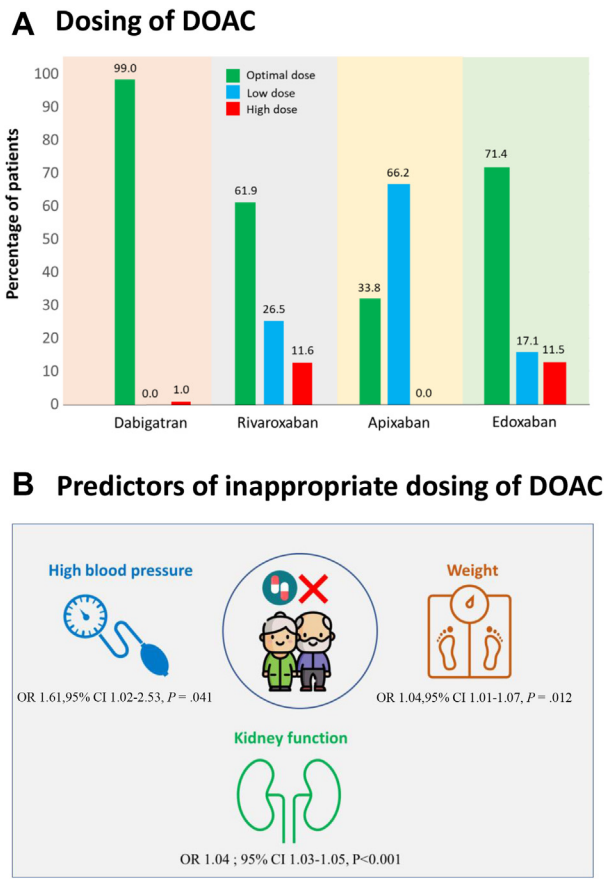

Fig. 1. (A) Dosing of DOAC: optimal dose or inappropriate dose (separating in low dose or high dose). (B) Variables associated with inappropriate dose of DOAC.

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