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Editorial

The management of anticoagulant treatment in non-valvular atrial fibrillation real-world patients

The interest on the primary and secondary prevention of stroke in patients with non-valvular atrial fibrillation (NVAF) has greatly increased after the introduction of the direct oral anticoagulants (DOAC). Following the results of pivotal phase III randomized clinical trials (RCT), current international guidelines, such as those published by the European Society of Cardiology, recommend the use of DOACs over vitamin K antagonists (VKAs) for stroke prevention in patients with NVAF as they offer a favorable balance between efficacy and safety [1].

Over the last years, clinical research in this field has largely moved towards observational studies aiming to collect evidence to confirm the safety and effectiveness of these drugs in the so called "real-world". Observational studies allow the inclusion of a larger range of patient types, can inform about less well represented patient groups, and can document routine clinical management at a regional, national, or global level. Strengths of evidence produced by these studies vary according to their designs, which include retrospective cohort studies, claims database analyses, prospective registries, and phase IV non-interventional studies. Due to the lack of head-to-head comparisons among DOACs, to the difficult interpretation of indirect evaluations and to the partial selection of RCT populations, real-world data are also expected to add relevant information about the safety and effectiveness of each individual anticoagulant strategy.

In this issue of the European Journal of Internal Medicine, Marietta and colleagues report the results of an observational study on a cohort of 4191 NVAF patients requiring DOAC or VKA therapy that was prospectively enrolled by seven anticoagulation clinics of the Emilia Romagna region in Italy [2]. Although the authors define the selection of specialized centers as a potential limitation of the study, the reported high mean therapeutic adherence highlights an ideal real-world setting for the management of anticoagulated patients (mean Time in Therapeutic Range of 74.0% and mean estimated DOAC assumption of 94.0%). Such high quality of treatment and adherence, usually observed in RCTs only, often represents a difficult goal to be achieved in the real-world. Therefore, this study first of all shows how much the role of specialized anticoagulation clinics can overcome many of the issues related to the safety of anticoagulant drugs. High treatment quality results in reduced outcome rates and in a substantial advantage in terms of costs. This suggests that each region should count on a sufficient number of specialized centers in which trained clinicians are tightly connected with a skilled nursing team for the management of anticoagulated patients.

The appropriateness of prescription is another important issue. Recent real-word data highlighted a number of problems, in particular related to the indication to anticoagulation and to the use of correct dosages [3,4]. NVAF is generally associated with other cardiovascular diseases, multiple underlying comorbidities, and polypharmacotherapy. Correct stroke prevention strategies require a thorough individual assessment of stroke-bleeding risk ratio, patient fragility status, dynamic renal function alterations and possible drug-to-drug interactions. After balancing these factors, clinicians need to identify the most appropriate anticoagulation strategy and to periodically reassess it. The population enrolled in this study included many elderly patients (about 40% of them was $\geq$80 years old), most with comorbidities and a high cardiovascular risk profile (mean CHA_2DS_2-VASc score of 3.51). Thus, this population was somewhat different from most of the populations enrolled in RCTs. In their analysis, the authors performed two comparisons: the first between all DOACs and VKAs (Scenario 1, crude and propensity-score adjusted hazard ratio), the second between individual DOACs and VKAs (Scenario 2, crude hazard ratio). In the first comparison, primary effectiveness and safety outcomes did not differ between DOACs and VKAs. This likely reflects the optimal management of VKA therapy (high mean TTR) and the higher than expected incidence rate of major bleeding in the DOAC group (in particular with regard to intracranial hemorrhage), possibly related to the older age and greater complexity of the study population. As a caveat in the interpretation of the figures, major bleeding definition was slightly different from the one proposed by the International Society on Thrombosis and Haemostasis and used in most RCTs, as data on the decrease in hemoglobin levels and on the need for blood transfusion was not available [5]. This information was replaced by "bleeding resulting to hospital admission". This is attributable, at least in part, to the use of administrative databases to collect information on clinical outcomes during follow-up.

In the second comparison, the incidence of the primary safety outcome (in particular with regard to intracranial hemorrhage) was higher in patients receiving apixaban than in patients treated with dabigatran and rivaroxaban and some differences in the incidence of outcome events were observed among the three DOACs when compared with VKAs. The interpretation of these findings requires some caution. In particular, due to the lack of randomization, the baseline patient characteristics of all study groups presented some relevant differences. For example, a greater proportion of patients on apixaban were $\geq$80 years old and presented a history of major bleeding and cerebrovascular disease. This could reflect a preference for apixaban administration in fragile patients, based on both the results of the individual RCTs and of previous indirect comparisons in real-world data suggesting its safer profile as compared to dabigatran and rivaroxaban [6–8]. Another limitation acknowledged by the authors is the limited sample size for some subgroup analyses, which weakened the precision

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of these comparisons.

In conclusion, the study by Marietta and colleagues confirms that the management of NVAF patients on anticoagulant treatment by specialized anticoagulation clinics results in a high quality of therapy for both VKAs and DOACs and in a low incidence of primary outcome events. This clearly confirms the importance of these clinics which need to be implemented in most hospitals. Comparisons between DOACs and VKAs failed to show meaningful differences (with a few exceptions), but readers must be aware that observational studies are intrinsically subject to a number of limitations, including the collection of non-randomized data and incomplete data collection and by no means can replace RCTs for the comparison of different agents.

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