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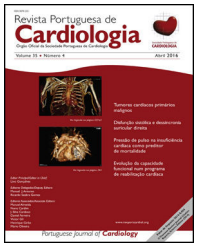

EDITORIAL COMMENT

Atrial fibrillation management: Time for new goals

Tratamento da fibrilhação auricular, tempo para novos horizontes

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Atrial fibrillation (AF) relevancy is deeply justified by its high prevalence and significant clinical outcomes. Estimated to be present in about 2.5% of Portuguese individuals aged over 40 years,[1] AF has been independently related to higher cardiovascular morbidity and mortality, mainly due to sudden death, heart failure and stroke.[2] The aging of the population and the increasing survival of patients with comorbidities that predispose to AF are likely to increase its prevalence and the associated medical and social costs in coming years.

The Framingham study estimated a fivefold increase in risk of stroke for AF patients without rheumatic heart disease[3] and a recent registry of patients admitted for acute stroke reported a high proportion of embolic etiology, with AF being responsible for 36% of all ischemic strokes.[4] The nature of embolic stroke in AF, with thrombus arising from the left atrial appendage, is distinct from stroke related to atherosclerosis. In the former case, antiplatelet therapy does not provide adequate protection and oral anticoagulation is warranted.

In this context, vitamin K antagonists (VKAs) are among the most effective drugs in cardiovascular medicine, with relative risk reductions of 26% in mortality and 64% in stroke.[5] Despite this, oral anticoagulation is reported to be dramatically underused, with a meta-analysis of Portuguese registries estimating that only 40% of high-risk AF patients are treated.[6] Underuse of VKAs is closely related to fear of bleeding complications and to the complexity of therapeutic regimens, with need for frequent blood testing and adjustments. Even in phase III clinical trials, with optimized follow-up protocols, the time in therapeutic range of VKAs was between 55.2% to 64.9%,[7] meaning that for nearly 45% of the time, patients are either under- or over-treated and consequently exposed to a higher thrombotic or bleeding risk, respectively. In real life, up to 85% of patients with AF admitted for ischemic stroke are inadequately anticoagulated.[4]

The novel oral anticoagulants (NOACs), both factor Xa and direct thrombin inhibitors, have led to a significant simplification of treatment strategies, with fixed-dose regimens and more predictable dose effects. These new drugs show a better safety-efficacy profile, with half the relative risk of intracranial hemorrhage and, most notably, a 10% relative risk reduction in all-cause mortality compared to VKAs.[8] Over the years, prescription of NOACs has increased, as has the proportion of AF patients treated, with a likely improvement in stroke prevention strategies.[9]

Nevertheless, some questions remain, such as the outcomes of NOAC usage in the very elderly and those with low body weight, and off-label reduced dosage in other clinical scenarios that are less well represented in phase III clinical trials. Registries like Edoxaban Treatment in routiNe clinical prActice in patients with non-valvular Atrial Fibrillation (ETNA-AF) are likely to provide further knowledge and lead to more accurate usage of NOACs in clinical practice.

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The well-written article by Pedro Monteiro published in this issue of the *Journal*[10] focuses on baseline Iberian data from the ETNA-AF registry. The design of this registry, since it includes only patients selected for oral anticoagulation with edoxaban, does not allow estimation of AF prevalence. Nevertheless, it provides valuable baseline data from a contemporary cohort of patients eligible for oral anticoagulation.

Overall, half of the included population were over 74 years old, the age-group in which AF and comorbidities are most prevalent. One of the most interesting findings in this population is the relatively high proportion of patients prescribed lower-dose edoxaban: 45% of patients over 74 years old and 58.2% of all females, representing in total 24.7% of the overall population. It is worth noting that the low-dose cohort has a higher proportion of patients with CHA_2DS_2-VASc score $\geq$4 (55.9% vs. 37.9%). According to the data presented, 59% of patients received a lower edoxaban dose due to renal criteria (creatinine clearance <50 ml/min) and 32.5% due to body weight <60 kg but, most importantly, 28.6% of patients treated with the low dose had no dose reduction criteria at all, leading to 7.1% of underdosing in the overall population. On the other hand, 8.6% of patients in the 60 mg edoxaban group had at least one dose reduction criterion, leading to 6.5% overdosing overall. Also, 1.8% of patients receiving edoxaban 60 mg had CHA_2DS_2-VASc 0, probably prescribed the high dose as part of pericardioversion or periablation management and thus not requiring chronic oral anticoagulation. These findings clearly indicate the need for ongoing management to optimize NOAC use in clinical practice.[11] In line with this, data from follow-up will be crucial to estimate the consequences of both under- and over-dosing.

Overall, NOACs have brought great improvements in AF-related stroke prevention and contemporary registries like ETNA-AF may further help to fine-tune their usage. Nevertheless, current AF management does not rely solely on risk stratification and stroke prevention, and in our opinion also other key pillars of AF management need to receive more attention.

Roughly half of AF patients in this registry appeared to be asymptomatic. The fact that such a high proportion of AF patients may have no or minimal symptoms is important, as they are less likely to seek medical advice or attention, risking a delay in diagnosis and timely treatment. This also highlights the need for adequate screening for silent AF in high-risk groups.[12] Current guidelines recommend opportunistic screening for AF in all clinical assessments by pulse palpation or ECG rhythm strip in patients over 65 years old and by prolonged ECG monitoring in cases of prior transient ischemic attack or ischemic stroke and systematic screening in patients over 75 years old or at high stroke risk. In the future, wearable technology should be able to significantly improve AF screening, ideally providing cost-effective solutions with widespread availability to reduce the burden of high-risk AF patients without adequate protection.

Finally, comorbidities like hypertension (76.7%), hyperlipidemia (50.9%), diabetes (26.8%) and coronary heart disease (11.1%) were frequent in the study population and should be treated appropriately. This is consistent with data from other large databases,[13] and in fact, a patient with AF over 65 years old very rarely has lone AF. Congestive heart failure, sudden cardiac death and other non-stroke-related complications are leading causes of death in AF patients.[14] Thus, appropriate management, including integrated AF care with multidisciplinary teams addressing lifestyle changes, underlying cardiovascular comorbidities, and rate/rhythm control, should be the gold standard aiming to reduce cardiovascular hospitalization and death, especially in the elderly who are predominantly treated in primary care.[15]

While there is still room to improve stroke prevention in the era of NOACs, it is now time to take the next step, aiming for integrated care. This should be the next goal in AF management.

Conflicts of interest

The authors have no conflicts of interest to declare.

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