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EDITORIAL

Antiarrhythmic drugs in the era of atrial fibrillation ablation

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The interest on antiarrhythmic drugs (AADs) for the prevention of atrial fibrillation (AF) recurrences declined in recent years in parallel with the increasing adoption of AF ablation, even as a first-line treatment.[1,2] An important stimulus to the validation of AF ablation as a safe approach for appropriately selected patients with AF was originated by the AFFIRM trial, published more than 20 years ago and designed to compare a strategy of rate control vs. rhythm control[3] The AFFIRM trial raised concern on the actual safety of AADs for rhythm control, but the results were mostly related to specific AADs, namely amiodarone, quinidine, and sotalol (used for initial therapy in 73.4% of patients at baseline in the rhythm-control arm), while Class IC agents, specifically propafenone and flecainide, were used at baseline in only 9.3% and 4.5% of patients, respectively.[3] Indeed, the AFFIRM trial prompted a general concern on the risk of proarrhythmia associated with AADs, even if the findings had to be considered strictly dependent on patient profile, type of AAD, underlying cardiac substrate, left ventricular (LV) systolic function, and susceptibility to ventricular tachyarrhythmias.

For Class IC AADs, a concern on the risk of adverse outcomes and proarrhythmia emerged after the publication of the CAST trial, a controlled trial performed in patients with frequent nonsustained ventricular tachyarrhythmias and LV systolic dysfunction after a myocardial infarction (MI).[4] The trial tested the hypothesis that suppressing ventricular ectopies could be beneficial. As known, an excess in all-cause mortality was found for patients treated with flecainide or encainide, and this led to specific contraindications for the use of flecainide in patients with LV systolic dysfunction and with ischaemic heart disease.[4,5]

The combination of the lack of evidence for a superiority of rhythm control over rate control and the concerns on the safety of AADs have induced to consider for two decades that these two strategies were clinically equivalent, but this view dramatically changed with the EAST-AFNET 4 trial, published in 2020.[6] The EAST-AFNET 4 trial enrolled patients between 2011 and 2016 and proved that in patients with early AF (diagnosed ≤1 year before enrolment), presenting cardiovascular risk factors and age > 65 years, rhythm control is a strategy associated with better hard outcomes (including all-cause death and stroke) as compared to a strategy based on rate control with subsequent switch to rhythm control in case of severe symptoms.[6] The EAST-AFNET 4 trial was halted by the data monitoring committee after inclusion of 2800 patients for clear superiority of the early rhythm-control arm. The primary endpoint (composite of cardiovascular death, stroke or transient ischaemic attack, and heart failure (HF) or acute coronary syndrome hospitalization) was reduced by 21% (hazard ratio 0.79, 95% confidence interval 0.66–0.94, $P = 0.004$). Compared with usual care, early rhythm control was associated with significantly lower rates of cardiovascular death and stroke (35% and 28% relative risk reduction, respectively).[6] Additionally, the clinical benefits of early rhythm control found in EAST-AFNET 4 trial were also associated with a favourable cost-effectiveness profile in a healthcare payer's perspective.[7]

The positive results of the EAST-AFNET 4 trial actually induced a change in the paradigm of AF management, with the recommendation of adopting rhythm control as the preferable strategy, to be applied for outcome improvement in the large majority of patients with history of AF lasting less than 1 year, after an appropriate selection, together with anticoagulation in patients at risk of stroke, as per guideline

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Table 1 Contraindications to flecainide and propafenone use according to recent consensus guidelines

	Contraindications		
	ESC 2020 AF guidelines[5]	**ESC 2022 VA/SCD guidelines[14]**	**ACC/AHA 2023 AF guidelines[15]**
Flecainide	• Ischaemic heart disease • Significant SHD • Reduced LVEF • CrCl <35 mL/min/1.73 m^2 • Significant liver disease	• Prior MI • Significant SHD • CrCl <35 mL/min/1.73 m^2 • Brugada syndrome • Severe sinus node dysfunction • Severe AV or IV conduction disturbances • LQTS (other than LQTS 3)	• Previous MI • Significant SHD • HFrEF (LVEF ≤40%) • Ventricular scar or fibrosis
Propafenone	• Ischaemic heart disease • Reduced LVEF • Significant renal disease • Significant liver disease • Asthma	• Prior MI • Significant SHD • Significant renal disease • Significant liver disease • Brugada syndrome • Severe sinus node dysfunction • Severe AV or IV conduction disturbances • LQTS	• Previous MI • Significant SHD • HFrEF (LVEF ≤40%) • Ventricular scar or fibrosis

ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; AV, atrioventricular; CrCl, creatinine clearance; ESC, European Society of Cardiology; HFrEF, heart failure with reduced ejection fraction; IV, intraventricular; LVEF, left ventricular ejection fraction; LQTS, long QT syndrome; MI, myocardial infarction; SCD, sudden cardiac death; SHD, structural heart disease; VA, ventricular arrhythmias.

recommendations.[8–12] It is noteworthy that the EAST-AFNET 4 trial was mainly based on rhythm control using AADs, since only 8% of patients at baseline and 19.4% at 2 years underwent AF ablation in the rhythm-control arm.[6]

In the current issue of *Europace*, Rillig *et al.*[13] report on a post-hoc analysis of the EAST-AFNET 4 trial, focusing on the primary safety outcome (death, stroke, or serious adverse events related to rhythm-control therapy) and on the primary efficacy outcome (cardiovascular death, stroke, and hospitalization for worsening of HF or acute coronary syndrome) in the subgroup of 1395 patients treated with flecainide or propafenone for early rhythm control. The results show that the 689 patients treated with flecainide or propafenone at baseline had a high probability of being in sinus rhythm at 2 years, with no statistical differences vs. patients not assuming sodium channel blockers, and were less often treated with catheter ablation.

A very interesting aspect of this analysis is that 26% of the patients treated with Class IC AADs had stable HF, corresponding in 77% of the cases to HF with preserved ejection fraction (HFpEF). Additionally, 6% of the patients treated with Class IC AAD had severe coronary artery disease (defined as previous MI, coronary artery bypass graft, or percutaneous intervention) and around 4% had left ventricular hypertrophy (LVH) (defined as LV wall thickness > 15 mm at echocardiography). Even if left ventricular ejection fraction (LVEF) was abnormal in only around 6% of the patients treated with Class IC AADs, it is clear that the analysis offers the opportunity to assess the efficacy and safety of sodium channel blockers in categories of patients not included in the recommendations of consensus guidelines with regard to use of Class IC AADs in AF,[5,14,15] and in some cases corresponding to specific contraindications, as highlighted in Table 1. Of note, some differences can be found when comparing the contraindications to Class IC AADs reported in recent guidelines since, for instance, the category of 'ischaemic heart disease' implies a larger group of patients as compared to 'prior myocardial infarction', a category more strictly linked to the population enrolled in the CAST trial.

The data collected during the follow-up of the EAST-AFNET 4 trial appear reassuring about the safety of treatment with Class IC agents even in these categories of patients, since no important changes in LVEF and no differences in worsening of NYHA functional class were observed in patients treated with sodium channel blockers vs. patients not treated with this type of AADs. Furthermore, the analysis of the primary efficacy and safety endpoints confirmed, both in terms of favourable outcome and safety, that treatment with Class IC AADs was clinically reliable and safe in patients selected by the trial investigators as appropriate for using these agents, including patients with stable HF and HFpEF, or with LVH at the echocardiographic assessment or with revascularized or, anyway, stable coronary artery disease. Obviously, these findings should be interpreted considering the specific setting of cardiology centres with known expertise in the field and with appropriate clinical and electrocardiographic checks (conduction intervals, QRS duration) after institution of AAD treatment, also including weekly short-term electrocardiographic recordings, as per study protocol.[6,13] Additionally, it should be stressed that the median age of patients treated with Class IC agents was 69 years and only 25% of the patients had an age >75, thus limiting the generalizability of study findings to the large amount of very old patients presenting AF in the real world, often affected by many co-morbidities and frailty.[16,17]

In the real world, use of Class IC AADs in settings such as hypertension with LVH, or in selected patients with stable HFpEF, or in selected patients with stable coronary artery disease, also named chronic coronary syndromes, is not uncommon, as highlighted by observational studies.[18–20] and surveys,[21,22] suggesting that non-adherence to guidelines recommendation occurs quite frequently both in Europe and the USA. In our view, these data should prompt to consider at one hand the need for improving knowledge on AADs, but on the other hand, we have to recognize that some deviation may be reasonable in selected patients, if based on careful assessment of the risk–benefit ratio and careful patient monitoring.

In consideration of the obvious limitation of extrapolating to patients currently affected by chronic coronary syndromes the results of the

CAST trial, performed in patients with prior infarction, not treated with acute percutaneous revascularization, and with LV dysfunction and frequent ventricular ectopies, some observational studies were targeted to reassess the actual safety of Class IC AADs, when used after careful assessment of the risk–benefit ratio and under appropriate clinical monitoring.[18–20] With all the limitations of the observational nature of these studies and of the risk of unmeasured confounding, there is a general concordance that flecainide and propafenone are not associated with an increased risk of proarrhythmia (bradycardia, torsade de pointes, sustained ventricular tachyarrhythmias, or sudden cardiac death) or with an increased risk of acute HF events in patients with stable or revascularized coronary artery disease or in patients with structural heart disease and LVH when compared to treatment with other AADs and specifically when compared with Class III AADs.[23]

The authors of EAST-AFNET 4 have to be commended for proposing an interesting *post-hoc* analysis that suggests the need to reconsider the possibility of using Class IC AADs also in populations in whom consensus guidelines do not recommend or even contraindicate its clinical use (*Table 1*). These findings should prompt prospective cohort studies for additional validation. Anyway, the proper interpretation of these findings has to consider that clinical assessment of patient's clinical conditions, in terms of stability of underlying cardiac substrate (revascularized ischaemia, LVEF, etc.) and co-morbidities (renal function, electrolytes, etc.) are crucial components of AF management, including the decision making to prescribe a Class IC AAD in these conditions and the definition of the appropriate drug dosing, as well as planning of periodic checks (clinical and ECG, also using wearables). Rhythm control is nowadays the reference strategy to be considered for AF management and appropriate use of AADs should be considered even in the era of widened indications to AF ablation. Planning of AF ablation procedures requires an optimized organization[24] and well trained operators, and therefore there is still need for AADs, to be used in the real world in the waiting period before ablation, or after the procedure to maximize its efficacy (i.e.: in the blanking period) or to be used for rhythm control after few episodes of AF, even in the form of 'pill in the pocket' treatment for controlling AF-related symptoms. The process of validation of AADs is very complex, and few new AADs are at the horizon.[25] Therefore, we need to implement in the best ways the agents that became available in the last decades. In any clinical setting, appropriate knowledge of AADs characteristics, in terms of dosing, effects and interactions, and an adequate planning of cardiological checks are key component of the rhythm-control strategy, to be applied in combination with the ABC pathway, as guarantee of safety and effectiveness.

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Data availability

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