

Antiarrhythmic drugs in the era of atrial fibrillation ablation

Giuseppe Boriani ^{1*}, Davide Antonio Mei ^{1,2},
and Jacopo Francesco Imberti ^{1,2}

¹Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, Italy University of Modena and Reggio Emilia, Policlinico di Modena, Via del Pozzo 71, 41121 Modena, Italy; and ²Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Italy

Online publish-ahead-of-print 3 May 2024

Keywords

Ablation • Antiarrhythmic drugs • Atrial fibrillation • Heart failure • Stroke

This editorial refers to ‘Safety and efficacy of long-term sodium channel blocker therapy for early rhythm control: the EAST-AFNET 4 trial’, by A. Rillig et al., <https://doi.org/10.1093/europace/euae121>.

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

The opinions expressed in this article are not necessarily those of the Editors of *Europace* or of the European Society of Cardiology.

* Corresponding author. Tel: +39 0594222241. E-mail address: giuseppe.boriani@unimore.it

© The Author(s) 2024. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

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	<ul style="list-style-type: none"> • Ischaemic heart disease • Significant SHD • Reduced LVEF • CrCl <35 mL/min/1.73 m² • Significant liver disease 	<ul style="list-style-type: none"> • Prior MI • Significant SHD • CrCl <35 mL/min/1.73 m² • Brugada syndrome • Severe sinus node dysfunction • Severe AV or IV conduction disturbances • LQTS (other than LQTS 3) 	<ul style="list-style-type: none"> • Previous MI • Significant SHD • HFrEF (LVEF ≤40%) • Ventricular scar or fibrosis
Propafenone	<ul style="list-style-type: none"> • Ischaemic heart disease • Reduced LVEF • Significant renal disease • Significant liver disease • Asthma 	<ul style="list-style-type: none"> • Prior MI • Significant SHD • Significant renal disease • Significant liver disease • Brugada syndrome • Severe sinus node dysfunction • Severe AV or IV conduction disturbances • LQTS 	<ul style="list-style-type: none"> • 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 organization²⁴ 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.

Funding

No funding was received for the present article.

Conflict of interest: G.B. reported speaker fees of small amount from Bayer, Boston, Boehringer, Daiichi-Sankyo, Janssen, Sanofi, outside the submitted work. The other authors reported no conflict.

Data availability

No new data were generated or analysed in support of this research.

References

- Imberti JF, Ding WY, Kotalczyk A, Zhang J, Boriani G, Lip G, et al. Catheter ablation as first-line treatment for paroxysmal atrial fibrillation: a systematic review and meta-analysis. *Heart* 2021;**107**:1630–6. doi:10.1136/heartjnl-2021-319496
- Boersma L, Andrade JG, Betts T, Duytschaever M, Pürerfellner H, Santoro F, et al. Progress in atrial fibrillation ablation during 25 years of Europace journal. *Europace* 2023;**25**:eoad244. doi:10.1093/europace/euad244
- Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;**347**:1825–33. doi:10.1056/NEJMoa021328
- Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;**324**:781–8. doi:10.1056/NEJM199103213241201
- Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498. doi:10.1093/eurheartj/ehaa612
- Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;**383**:1305–16. doi:10.1056/NEJMoa2019422
- Gottschalk S, Kany S, König HH, Crijns HJ, Vardas P, Camm AJ, et al. Cost-effectiveness of early rhythm control vs. usual care in atrial fibrillation care: an analysis based on data from the EAST-AFNET 4 trial. *Europace* 2023;**25**:eoad051. doi:10.1093/europace/euad051
- Schnabel RB, Marinelli EA, Arbelo E, Boriani G, Boveda S, Buckley CM, et al. Early diagnosis and better rhythm management to improve outcomes in patients with atrial fibrillation: the 8th AFNET/EHRA consensus conference. *Europace* 2023;**25**:6–27. doi:10.1093/europace/euac062
- Metzner A, Suling A, Brandes A, Breithardt G, Camm AJ, Crijns HJGM, et al. Anticoagulation, therapy of concomitant conditions, and early rhythm control therapy: a detailed analysis of treatment patterns in the EAST—AFNET 4 trial. *Europace* 2022;**24**:552–64. doi:10.1093/europace/euab200
- Imberti JF, Mei DA, Vitolo M, Bonini N, Proietti M, Potpara T, et al. Comparing atrial fibrillation guidelines: focus on stroke prevention, bleeding risk assessment and oral anticoagulant recommendations. *Eur J Intern Med* 2022;**101**:1–7. doi:10.1016/j.ejim.2022.04.023
- Lip GYH, Proietti M, Potpara T, Mansour M, Savelieva I, Tse HF, et al. Atrial fibrillation and stroke prevention: 25 years of research at EP Europace journal. *Europace* 2023;**25**:eoad226. doi:10.1093/europace/euad226
- Boriani G, Bonini N, Imberti JF, Vitolo M, Gerra L, Mantovani M, et al. Clinical decisions for appropriate management of patients with atrial fibrillation. *Panminerva Med* 2024; Epub ahead of print. doi:10.23736/S0031-0808.24.05114-0
- Rillig A, Eckardt L, Borof K, Camm AJ, Crijns HJGM, Goette A, et al. Safety and efficacy of long-term sodium channel blocker therapy for early rhythm control: the EAST-AFNET 4 trial. *Europace* 2024;euae121. doi:10.1093/europace/euae121
- Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;**43**:3997–4126. doi:10.1093/eurheartj/ehac262
- Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2024;**149**:e1–156. doi:10.1161/CIR.0000000000001193
- Savelieva I, Fumagalli S, Kenny RA, Anker S, Benetos A, Boriani G, et al. EHRA expert consensus document on the management of arrhythmias in frailty syndrome, endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). *Europace* 2023;**25**:1249–76. doi:10.1093/europace/euac123
- Wu VC, Wang CL, Huang YC, Tu HT, Huang YT, Huang CH, et al. Cardiovascular outcomes in patients with atrial fibrillation concomitantly treated with antiarrhythmic drugs and non-vitamin k antagonist oral anticoagulants. *Europace* 2023;**25**:eoad083. doi:10.1093/europace/euad083
- Ashraf H, Ko NK, Ladia V, Agasthi P, Prendiville T, O'Herlihy F, et al. Use of flecainide in stable coronary artery disease: an analysis of its safety in both nonobstructive and obstructive coronary artery disease. *Am J Cardiovasc Drugs* 2021;**21**:563–72. doi:10.1007/s40256-021-00483-9
- Burnham TS, May HT, Bair TL, Anderson JA, Crandall BG, Cutler MJ, et al. Long-term outcomes in patients treated with flecainide for atrial fibrillation with stable coronary artery disease. *Am Heart J* 2022;**243**:127–39. doi:10.1016/j.ahj.2021.08.013
- Kiani S, Sayegh MN, Ibrahim R, Bhatia NK, Merchant FM, Shah AD, et al. The feasibility and safety of flecainide use among patients with varying degrees of coronary disease. *JACC Clin Electrophysiol* 2023;**9**:1172–80. doi:10.1016/j.jacep.2022.12.021
- Camm AJ, Blomström-Lundqvist C, Boriani G, Goette A, Kowey PR, Merino JL, et al. AIM-AF: a Physician Survey in the United States and Europe. *J Am Heart Assoc* 2022;**11**:e023838. doi:10.1161/JAHA.121.023838
- Reiffel JA, Blomström-Lundqvist C, Boriani G, Goette A, Kowey PR, Merino JL, et al. Real-world utilization of the pill-in-the-pocket method for terminating episodes of atrial fibrillation: data from the multinational Antiarrhythmic Interventions for Managing Atrial

- Fibrillation (AIM-AF) survey. *Europace* 2023;**25**:eoad162. doi:[10.1093/europace/eoad162](https://doi.org/10.1093/europace/eoad162)
23. Chung SC, Lai A, Lip GYH, Lambiase PD, Providencia R. Impact of anti-arrhythmic drugs and catheter ablation on the survival of patients with atrial fibrillation: a population study based on 199 433 new-onset atrial fibrillation patients in the UK. *Europace* 2023;**25**: 351–9. doi:[10.1093/europace/euac155](https://doi.org/10.1093/europace/euac155)
24. Boriani G, Imberti JF, Leyva F, Casado-Arroyo R, Chun J, Braunschweig F, et al. Length of hospital stay for elective electrophysiological procedures: a survey from the European Heart Rhythm Association. *Europace* 2023;**25**:eoad297. doi:[10.1093/europace/eoad297](https://doi.org/10.1093/europace/eoad297)
25. Remme CA, Heijman J, Gomez AM, Zaza A, Odening KE. 25 years of basic and translational science in EP Europace: novel insights into arrhythmia mechanisms and therapeutic strategies. *Europace* 2023;**25**:eoad210. doi:[10.1093/europace/eoad210](https://doi.org/10.1093/europace/eoad210)