European Heart Journal Supplements (2023) **25** (Supplement C), C12–C14
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad033

ESC
European Society
of Cardiology

Anti-arrhythmic drugs in atrial fibrillation: tailor-made treatments

Alessandro Capucci[1,2]*, Giulia Stronati[1,2], and Federico Guerra[1,2]

[1]Cardiology and Arrhythmology Clinic, Marche University Hospital, via Conca 71, Ancona 60126, Italy; and [2]Department of Biomedical Sciences and Public Health, Marche Polytechnic University, via Conca 71, Ancona 60126, Italy

KEYWORDS
Anti-arrhythmic drugs;
Atrial fibrillation;
Pharmacological therapy;
Rate-control;
Rhythm control

During the last decades, many improvements have been made regarding the treatment of atrial fibrillation in terms of risk prevention, anti-coagulation strategies, and gain in quality of life. Among those, anti-arrhythmic drugs (AADs) have progressively fallen behind and overtaken by technological aspects as devices as procedures are now the standards of care for many patients. But is this it? Are AADs doomed to be relegated to an obscure and rarely read paragraph of the European recommendations? Or could they be still employed safely and effectively? In the present paper, we will discuss contemporary evidence in order to define where AADs still play a pivotal role, how should AADs be used, and whether a tailored approach can be the way to propose the right treatment to the right patient.

Introduction: a historical perspective

Nearly 100 years have passed since the first descriptions of the effects of quinine by Wenckebach in his landmark paper.[1] At the time, the use of quinidine for the treatment of cardiac arrhythmias was a breakthrough, with the drug used mainly to relieve gastric symptoms of digitalis, seen by Wenckebach himself as 'the most powerful and most brilliant of all heart drugs'. Nowadays, much of the hype has long passed, and anti-arrhythmic drugs (AADs) have progressively fallen off the toolkit of the clinical cardiologist.

There are many different explanations for the decline of AADs in everyday clinical practice. First of all, AADs are cheap, their patent long expired, and easy to produce. Hence, the pharmacological industry is not interested in supporting clinical and research activity related to old molecules.[2] The physicians themselves often neglect this kind of drug, while focusing on the latest and most technologically advanced catheter to perform radiofrequency ablation. It could also be said that, in this setting, AADs make it more difficult for the 'aggressive' electrophysiologist to propose even recurrent ablations to a vast majority of patients. Finally, scientific societies follow the wave of enthusiasm regarding the latest anti-coagulant, implantable device, or surgical technique and devote less and less time to spreading scientific evidence on anti-arrhythmic therapy.

Therefore, it is not surprising that the average cardiologist is not able to use such pharmacological armamentarium to its full potential.[3] Nonetheless, AADs remain 'a cornerstone of rhythm-control therapy'.[4] In the present review, we aim to briefly discuss some contemporary topics related to AADs in terms of clinical use, patient-tailored approach, and future perspectives.

Risk vs. perception of risk in anti-arrhythmic drugs

Historically, and regardless of European and American recommendations, class IC drugs are still underused for rhythm control of AF, while amiodarone is the preferred drug in a variety of clinical settings. A retrospective study found that amiodarone was vastly preferred to IC AADs, with the latter preferred in females, atrial flutter, and patients already treated with verapamil or diltiazem.[5] On the other hand, flecainide and propafenone were mostly avoided in elderly or comorbid patients or patients with diabetes. This finding has various potential explanations,

*Corresponding author. Tel: +39 0715966593, Email: profacapucci@gmail.com

© The Author(s) 2023. 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 journals.permissions@oup.com

with the most plausible related to the very high perceived risk of serious adverse events during treatment with IC class.

Surprisingly by contemporary standards, flecainide was first approved not for AF but for the suppression of malignant ventricular arrhythmias, mainly based on a pioneer study demonstrating complete suppression of complex ventricular arrhythmias in eight patients and markedly suppressed in the other three.[6] After seven years, The CAST trial (whose aim was to prove the benefit of flecainide, encainide, and moricizine in terms of arrhythmic death in patients with ischaemic heart disease) was stopped *in itinere* due to the higher mortality in the experimental group.[7] Findings from the CAST planted the first seed for what is now a common perception of a 'harmful' drug and delivered the final evidence for an absolute contraindication of IC AADs in patients with myocardial ischaemia.

Moreover, more should be said regarding the use of AADs outside what is commonly recommended by clinical guidelines, a widespread practice but prone to increase side effects and hamper safety. In the EORP-AF pilot registry, 36% of patients with paroxysmal AF received digoxin and 29% of patients with permanent AF received class II AADs.[8] In the ORBIT-AF, it was estimated that at least one patient out of three received at least one drug that was not in agreement with the European recommendations.[9]

A tailored approach

A 'one-size-fits-all' approach is doomed to failure. Different comorbidities mean a different substrate and, thus, a different therapeutic strategy. This concept is also underlined by the recent European guidelines, suggesting that risk factor management and trigger avoidance should be pursued to facilitate rhythm control and slow AF progression (class of recommendation IIa, level of evidence B).[10] Of course, this aspect could be considered redundant, but there are still many settings that are considered grey areas in terms of effective pharmacological treatment, such as post-operative AF[11] or tachycardiomiopathy,[12] and in whose, the guidelines still do not offer strong levels of evidence.

One of the specific approaches proposed in the last decade is the one called 'pill-in-the-pocket'.[13] Health technology assessments highlighted that a 'pill-in-the-pocket' approach might be slightly less cost-effective than daily anti-arrhythmic therapy, mainly due to reduced prevention of recurrences. However, the benefits in terms of quality-adjusted life years (QALYs) were very similar, and the results confirmed that the 'pill-in-the-pocket' strategy was associated with a consistent decrease in medical contacts.[14] Also, a history of previously tolerated therapy with intravenous flecainide does not predict adverse events during self-termination of AF episodes with a 'pill-in-the-pocket' strategy.[15] If administered early (< 10 min after the symptoms started), 94% of patients reported the resolution of symptoms within 4 h, thus avoiding the need for medical consultation, and only 7% described (mostly mild) adverse events.[13] A 'pill in the pocket' approach could be also recommended to those patients with sporadic, albeit highly symptomatic, recurrences to reduce the number of medical contacts and postpone the start of more traditional rhythm control.

Another tailored approach is the use of a multipharmacological strategy for rhythm control. This approach, albeit not explicitly indicated in the current guidelines due to the lack of evidence (especially randomized controlled trials), is common in clinical practice.

A few years ago, we led the first experimental experience on the combination of flecainide and metoprolol tartrate in preventing symptomatic recurrences.[16] The study open-blindly randomized 173 patients with persistent or paroxysmal AF into flecainide + metoprolol, flecainide only, or metoprolol only. Efficacy, defined as the one-year incidence of symptomatic recurrence, safety, and tolerability were tested. We demonstrated that the combination therapy reduced recurrences when compared with flecainide alone and metoprolol alone (33.3 vs. 53.2% vs. 100%; $P = 0.001$).[16] Also, patients treated with flecainide + metoprolol experienced an increased quality of life, while adverse events were few, well-tolerated, and not associated with long-term effects. This was probably due to the synergistic effect of these two drugs, as the addition of metoprolol contributed to reducing the dose of flecainide and, with that, the dose-related adverse events. This was also supported by the lack of cases of atrial flutter with 1:1 conduction. Another prospective study investigated the combination of flecainide and amiodarone for rhythm control in AF patients after at least one failed ablation or pharmacological attempt.[17] Despite the lack of a control group, three patients out of four reported an improvement in AF-related symptoms, while no arrhythmic deaths or syncope were noted. On a negative note, efficacy decreased to 60% at the end of the second year, as 37% of all the patients had to withdraw from the combination therapy due to side effects.

The third way of action is to modify the medium used to bring the desired drug to the right plasma concentration. A couple of examples are the ones that follow. For flecainide, a modified-release formulation was developed to cut the 'twice-a-day' regimen and reduce the total number of medications which represents a large problem, especially for older patients with many comorbidities. This modified-release formulation was associated with a similar efficacy when compared with the immediate-release and the controlled-release formulations.[18] A prospective, randomized study concluded that the two formulations had similar pharmacodynamics and suggested that the QRS length (used as a proxy for potential pro-arrhythmic effects) varied during the day only in those patients treated with the immediate-release formulation.[19] Therefore, the authors speculated that avoiding the fluctuations in QRS length could increase the incidence of side effects while lowering the bathmotropic effect and thus the anti-arrhythmic effect of the drug itself. Unfortunately, despite this formulation being commercially available for many years, still, very little evidence exists, and simply mediating all the indications and precautions from the immediate-release formulation could not be completely correct both from a pharmacodynamical and a clinical perspective.

A revolutionary approach steers clear of the traditional *per os* delivery method, burdened by a relatively long latency and prone to potential tolerance issues, to focus on pulmonary delivery. The idea is to use a hand-held device to nebulize a more concentrated and soluble formulation of flecainide directly into the patient's airways to

produce a rapid spike of plasma concentration for a limited time.[20] In an animal model, pulmonary administration of flecainide caused a rapid and constant increase in plasma concentrations, along with a good rate of conversion from AF to normal sinus rhythm. Preliminary data suggest that in healthy human subjects, flecainide inhalation by the means of a breath-activated nebulizer can quickly produce the 'hallmark' QRS prolongation, a classic sign of class IC efficacy.[20] Albeit promising, the present approach is still in the early stages of development and not currently recommended or commercially available.

Conclusions

Pharmacotherapy with anti-arrhythmic drugs is still a very useful approach to hyperkinetic arrhythmias. Although the more and more sophisticated ablative approach became of primary importance in the last decade, the possibility to have a hybrid approach for rhythm control and/or to acutely interrupt AF with short-acting drugs has still a relevant role also for the quality of life. New AADs formulations and new AADs, along with the proper knowledge on how to use the 'old' Ic AADs at the right dosage for the right patient may constitute a staple for everyday clinical practice.

Funding

None declared.

Conflict of interest: None declared.

Data availability

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

References

1. Wenckebach KF. Cinchona derivatives in the treatment of heart disorders. *JAMA* 1923;**81**:472.
2. Paolini E, Stronati G, Guerra F, Capucci A. Flecainide: electrophysiological properties, clinical indications, and practical aspects. *Pharmacol Res* 2019;**148**:104443.
3. Capucci A, Cipolletta L, Guerra F, Giannini I. Emerging pharmacotherapies for the treatment of atrial fibrillation. *Expert Opin Emerg Drugs* 2018;**23**:25–36.
4. Heijman J, Hohnloser SH, John Camm A. Antiarrhythmic drugs for atrial fibrillation: lessons from the past and opportunities for the future. *Europace* 2021;**23**:ii14–ii22.
5. LaPointe NMA, Dai D, Thomas L, Piccini JP, Peterson ED, Al-Khatib SM. Antiarrhythmic drug use in patients <65 years with atrial fibrillation and without structural heart disease. *Am J Cardiol* 2015;**115**:316–322.
6. Hodges M, Haugland JM, Granrud G, Conard GJ, Asinger RW, Mikell FL *et al*. Suppression of ventricular ectopic depolarizations by flecainide acetate, a new antiarrhythmic agent. *Circulation* 1982;**65**:879–885.
7. Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;**321**:406–412.
8. Lip GYH, Laroche C, Ioachim PM, Rasmussen LH, Vitali-Serdoz L, Petrescu L *et al*. Prognosis and treatment of atrial fibrillation patients by European cardiologists: one year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry). *Eur Heart J* 2014;**35**:3365–3376. doi:10.1093/eurheartj/ehu374
9. Barnett AS, Kim S, Fonarow GC, Thomas LE, Reiffel JA, Allen LA *et al*. Treatment of atrial fibrillation and concordance with the American Heart Association/American College of Cardiology/Heart Rhythm Society Guidelines: findings from ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation). *Circ Arrhythm Electrophysiol* 2017;**10**:e005051.
10. 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). *Eur Heart J* 2021;**42**:373–498.
11. Stronati G, Mondelli C, Urbinati A, Ciliberti G, Barbarossa A, Compagnucci P *et al*. Derivation and validation of a clinical score for predicting postoperative atrial fibrillation in noncardiac elective surgery (the HART Score). *Am J Cardiol* 2022;**170**:56–62.
12. Stronati G, Guerra F, Urbinati A, Ciliberti G, Cipolletta L, Capucci A. Tachycardiomyopathy in patients without underlying structural heart disease. *J Clin Med* 2019;**8**:1411.
13. Alboni P, Botto GL, Baldi N, Luzi M, Russo V, Gianfranchi L *et al*. Outpatient treatment of recent-onset atrial fibrillation with the 'pill-in-the-pocket' approach. *N Engl J Med* 2004;**351**:2384–2391.
14. Saborido CM, Hockenhull J, Bagust A, Boland A, Dickson R, Todd D. Systematic review and cost-effectiveness evaluation of 'pill-in-the-pocket' strategy for paroxysmal atrial fibrillation compared to episodic in-hospital treatment or continuous antiarrhythmic drug therapy. *Health Technol Assess* 2010;**14**:1–75.
15. Alboni P, Botto GL, Boriani G, Russo G, Pacchioni F, Iori M *et al*. Intravenous administration of flecainide or propafenone in patients with recent-onset atrial fibrillation does not predict adverse effects during 'pill-in-the-pocket' treatment. *Heart* 2010;**96**:546–549.
16. Capucci A, Piangerelli L, Ricciotti J, Gabrielli D, Guerra F. Flecainide-metoprolol combination reduces atrial fibrillation clinical recurrences and improves tolerability at 1-year follow-up in persistent symptomatic atrial fibrillation. *Europace* 2016;**18**:1698–1704.
17. Kagal DR, Crystal E, Lashevsky I, Tiong I, Lau C, Vitali AC *et al*. Amiodarone plus flecainide combination therapy in patients with amiodarone refractory paroxysmal atrial fibrillation. *Int J Cardiol* 2013;**168**:4262–4263.
18. Aliot E, de Roy L, Capucci A, Hernández J, Denjoy I, Lupoglazoff JM *et al*. Safety of a controlled-release flecainide acetate formulation in the prevention of paroxysmal atrial fibrillation in outpatients. *Ann Cardiol Angeiol* 2003;**52**:34–40.
19. Coumel P, Maison-Blanche P, Tarral E, Périer A, Milliez P, Leenhardt A. Pharmacodynamic equivalence of two flecainide acetate formulations in patients with paroxysmal atrial fibrillation by QRS analysis of ambulatory electrocardiogram. *J Cardiovasc Pharmacol* 2003;**41**:771–779.
20. Verrier RL, Belardinelli L. Pulmonary delivery of antiarrhythmic drugs for rapid conversion of new-onset atrial fibrillation. *J Cardiovasc Pharmacol* 2020;**75**:276–283.