

The many NOs to the use of Class IC antiarrhythmics: weren't the guidelines too strict?

Dario Turturiello and Riccardo Cappato*

IRCCS MultiMedica, via Milanese 300, Sesto San Giovanni, Milan

KEYWORDS

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Class IC antiarrhythmic drugs (AADs) currently represent a cornerstone in the therapy of atrial fibrillation, both for the restoration of sinus rhythm and for the prophylaxis of long-term relapses. They also play an important role in the treatment of idiopathic ventricular arrhythmias. Following the results of the Cardiac Arrhythmia Suppression Trial study, flecainide and by extension the other Class IC AADs were contraindicated in patients with ischaemic and structural heart disease, due to their pro-arrhythmic effect and the consequent increase in mortality observed in the study. Recent studies carried out on patients with chronic coronary heart disease without previous heart attacks and/or residual ischaemia have shown a good safety profile for this class of drugs. In addition, other studies have shown excellent efficacy in the absence of pro-arrhythmic effects of Class IC AADs in patients with structural heart disease such as arrhythmogenic right ventricular cardiomyopathy (ARVC) and tachy-cardiomyopathy. The purpose of this review is to evaluate the appropriate use of Class IC AADs in the different patient subgroups, in the light of the evidence and new diagnostic and therapeutic tools available.

Introduction

Class IC antiarrhythmic drugs (AADs) perform their antiarrhythmic action mainly by blocking rapid sodium channels, thereby slowing down the Phase 0 of the monophasic action potential and consequently the impulse conduction, mainly in the common myocardial cells.^{1,2}

This class of drugs, initially approved for the treatment of symptomatic ventricular tachycardia (VT), currently has a wide variety of clinical indications.³ In particular, flecainide and propafenone have become a cornerstone in the rhythm control strategy in patients with atrial fibrillation (AF). These drugs have also carved out an important role in the prophylaxis and therapy of ventricular arrhythmias in patients without structural heart disease, Wolff-Parkinson-White (WPW) syndrome, supraventricular ectopic tachycardia, and catecholaminergic polymorphic VT.^{1,4}

An important limitation to the use of Class IC AADs has arisen following the publication of the CAST (Cardiac Arrhythmia Suppression Trial) and CASH (Cardiac Arrest Study Hamburg) studies. These studies showed an increase in mortality in patients receiving flecainide and propafenone, respectively, compared with control groups. It is important to underline that in the CAST study, the enrolled patients had post-infarct ischaemic heart disease, reduced ejection fraction, and frequent ventricular ectopic beats, while in the CASH study the population under examination had secondary VT cardiac arrest and/or ventricular fibrillation.^{5,6} Based on these results, the administration of Class IC antiarrhythmics is currently contraindicated in patients with chronic post-infarct ischaemic heart disease with or without depressed ejection fraction. In addition, current guidelines have extended the results of the CAST study to patients with non-ischaemic structural heart disease despite no consistent evidence in this population.⁴⁻⁸

At present, there is a large grey area, consisting of patients with critical or subcritical coronary heart disease

*Corresponding author. Email: riccardo.cappato@multimedica.it

without previous myocardial infarction and/or inducible ischaemia and with the preserved systolic function of the left ventricle, in addition to patients with non-ischaemic structural heart disease. These patients, despite having a lower pro-arrhythmic risk profile than those represented in the CAST and CASH studies, still see the option of using Class IC AADs in case of need, precluded.

The purpose of this review is to critically evaluate the available evidence, asking whether it is still right to exclude all patients with structural heart disease from treatment with Class IC AADs.

Electrophysiological properties of Class IC antiarrhythmic drugs

Class IC AADs block rapid sodium channels in a voltage- and frequency-dependent manner, thus causing a reduction in the slope of Phase 0 of the monophasic action potential of myocardial cells. This action results in a slowing of impulse conduction through the His-Purkinje system and the cells of the common myocardium.^{1,2,7} (Figure 1).

The main drugs belonging to this class are flecainide and propafenone, as well as drugs such as encainide and moricizine, currently in disuse mainly due to their weak efficacy associated with the poor safety profile highlighted in the CAST and CAST II studies.^{5,6,9} Furthermore, this class of drugs carries out its antiarrhythmic action through other mechanisms of action which include: (i) inhibition of the opening of potassium channels (in particular, the rapid component of the IKr rectifying current of the atrial and ventricular myocardial cells), thus resulting in an increase in the duration of the monophasic action potential (flecainide and propafenone), (ii) blocking the opening of the ryanodine receptor, thus reducing the spontaneous release of

intracellular calcium from the sarcoplasmic reticulum (flecainide); this mechanism justifies the use of this drug for the prophylaxis of patients with polymorphic catecholaminergic VT (hereditary disease secondary to mutations in the gene encoding ryanodine or the gene for calsequestrin), and (iii) beta-blocking action (propafenone), thanks to the biochemical characteristics of its molecule which are common to some drugs of the beta-blocking class.^{1,2,7}

Class IC AADs also exert a negative inotropic effect secondary to the reduction of Na⁺ entry and the consequent reduction of Ca²⁺ entry through sodium-calcium transport into myocardial cells.^{2,7}

Finally, these drugs exert an important impact on the electrophysiological characteristics of the atrioventricular conduction intervals: the AH interval can increase by 15-22%, the HV interval by 25-50%; the QT interval can also have an increase of about 8%, but it is mainly due to the increase in the duration of the QRS determined by the drug.^{1,7}

Therapeutic indications

Pharmacological therapy of atrial fibrillation

Currently Class IC AADs are mainly used for the pharmacological cardioversion of persistent or paroxysmal AF. The restoration of sinus rhythm is mediated by the ability of the Class IC antiarrhythmics (AA ICs) to slow intra-atrial conduction and increase the refractoriness of myocardial cells, thus causing the interruption of the multiple circuits that form in the fibrillating atrium.^{1,7}

Martinez-Marcos *et al.* have shown that the intravenous administration of flecainide is more effective than propafenone and amiodarone in restoring sinus rhythm after 12 h of observation from the start of therapy.

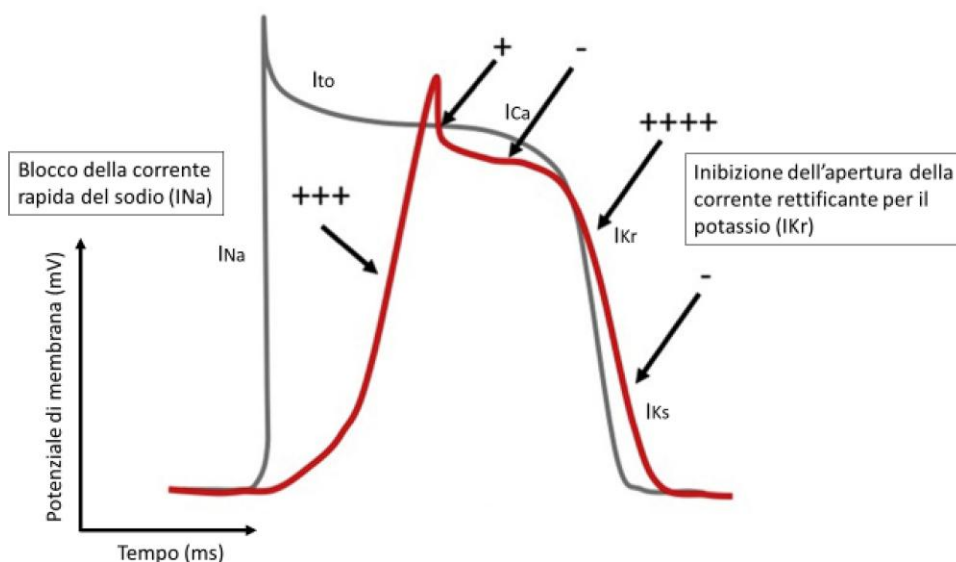


Figure 1 Effects of AA IC on the action potential of myocardial cells. The main effect is the reduction of the slope of Phase 0 with a minimum increase in the duration of the action potential.

Furthermore, both AA ICs showed a shorter time in determining the restoration of sinus rhythm than amiodarone.¹⁰ In accordance with these evidences, the guidelines of the European Society of Cardiology recommend flecainide, propafenone, and vernakalant as first-choice drugs in the attempt of pharmacological cardioversion of AF (class of recommendation I, level of evidence A).⁴

Class IC AADs are also widely used in the rhythm control strategy in patients with paroxysmal and/or persistent symptomatic AF, without structural heart disease, as recommended in the latest guidelines of the European Society of Cardiology (Class I, level of evidence A).⁴ This action cannot be explained by the state-dependent inhibition of sodium channels by these drugs. The maintenance of the sinus rhythm could, on the other hand, be determined by the inhibition of potassium currents and, indirectly, by the reduction of calcium entry into the myocardial cells.⁷

Many studies to date have evaluated the effects of AADs in the prophylaxis of AF relapses. However, many of them have been developed on small samples, different therapeutic schemes have been tested and are, therefore, difficult to compare with each other.⁴ Nevertheless, the 2015 Cochrane Database meta-analysis shows that flecainide in chronic therapy is more effective than placebo in maintaining sinus rhythm, and this efficacy is secondary only to amiodarone therapy (odds ratio amiodarone 0.31 vs. flecainide 0.19).¹¹

The 2014 Pythagorean study is a prospective, randomized, single-blind, multicenter study comparing amiodarone and AA ICs in maintaining sinus rhythm. Only flecainide has been shown not to be inferior to amiodarone in preventing arrhythmic relapses.¹²

Ventricular arrhythmias therapy

Except for beta-blockers, there are no randomized controlled trials documenting the ability of antiarrhythmics to improve prognosis when used in primary or secondary prevention of sudden cardiac death.^{8, 13} However, antiarrhythmics play a fundamental role in the therapy of idiopathic VTs for the control of symptoms and/or for the reduction of the arrhythmic burden.¹⁴

Treatment of VT and ventricular ectopic beats represented the first historical clinical indication for flecainide.³ Following the publication of the results of the CAST study, the use of flecainide and by extension of the other Class IC AADs underwent an important downsizing. Currently, Class IC AADs can be used in the therapy of symptomatic VT and/or ventricular ectopic beats only in patients without structural heart disease.^{5, 8, 13}

Other indications

Class IC antiarrhythmics find further indications in the following conditions:

- (1) Ventricular pre-excitation syndrome (WPW) leads to a prolongation of the refractoriness of the accessory pathway up to conduction block (antegrade in 40%, retrograde in 50% of cases). They can be used for the acute interruption of atrioventricular re-entry

Table 1 Modified from Hindricks G. "et al". 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation⁴

Current contraindications and precautions for use of Class IC antiarrhythmics according to the guidelines of the European Society of Cardiology for the management of atrial fibrillation (2020)

DRUG
Flecainide
Propafenone

- tachycardia and in the long-term prophylaxis of the same with success rates of 72 and 70%, respectively.
- (2) Acute treatment and prophylaxis of atrioventricular nodal re-entry tachycardia (efficacy rate of 83 and 78%, respectively).
 - (3) Focal atrial tachycardia with an efficacy of 86% in acute and 95% in the long-term.
 - (4) Catecholaminergic polymorphic VT, where flecainide plays an important role in association with beta-blockers in reducing relapses of exercise-induced ventricular arrhythmias and defibrillator interventions.
 - (5) LQTS 3 where flecainide, similarly to mexiletine, inhibits both the fast and the slow component of the sodium channel.
 - (6) Andersen-Tawil syndrome is a rare disease characterized by a triad composed of arrhythmias, including bidirectional and polymorphic VT, dysmorphism, and periodic paralysis. Preliminary studies have shown the good efficacy of flecainide in antiarrhythmic prophylaxis in these patients.¹

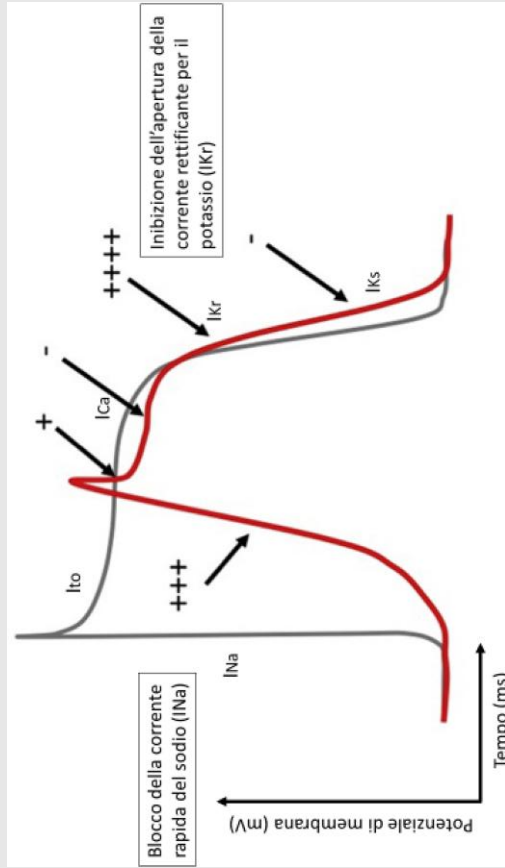
Current contraindications to the use of Class IC antiarrhythmic drugs: evidence and future prospects

Chronic ischaemic heart disease

The initial enthusiasm created following the good results of the first studies conducted with Class IC AADs in the therapy of VTs led to the need to want to test this class of drugs in the therapy of VTs in the post-infarct period.

In 1989, preliminary data from the CAST study were published. In this study, 1498 patients with a history of myocardial infarction 6 days to 2 years prior to enrolment and left ventricular ejection fraction (LVEF) \leq 0.55, at least 6 VEBs per hour, and no VT episode \geq 15 beats or with a rate above 120 b.p.m. were randomized to treatment with Class I antiarrhythmics (including flecainide) or placebo. The study was terminated early due to high mortality in patients treated with Class IC AADs.⁵ In the CAST study, the increased mortality in patients receiving Class IC AADs was primarily attributed to the higher number of deaths secondary to ventricular arrhythmias.⁵ Based on these findings, the use of flecainide and by extension of the other Class IC AADs was strongly discouraged in patients suffering from ischaemic heart disease with or without left ventricular

Table 2 Renewed interest in the use of Class IC AADs in patients with stable coronary heart disease, in the absence of scar and/or myocardial ischaemia



Study	Type of study	Study design	Exclusion criteria	Endpoints	Results	Limitations
Pantlin <i>et al</i> (2020) ¹⁷	Cohort, observational, retrospective study	AF patients with occult coronary artery disease evidenced by myocardial PET, matched by age in two groups: therapy with AA IC (78 patients) Not on AA IC therapy (78 patients) Mean follow-up of 719 ± 572 days	Clinical coronary artery disease and ejection fraction <50%. Clinical coronary artery disease is defined as: previous acute coronary syndrome, previous myocardial revascularization, evidence of significant coronary stenosis on coronary angiography, or reduced myocardial perfusion on PET images Myocardial infarction, unstable angina or hospitalization for ACS in the last year	Composite of all-cause mortality, SCD, and non-SCD cardiac death	No significant difference in mortality between the two groups. (HR 0.63, P: 0.44)	Observational, retrospective study. Reduced sample size
Burnham <i>et al</i> (2022) ¹⁸	Observational, propensity-matched analysis cohort study	Two study populations Patients with AF and non-critical coronary artery disease, treated with: AA IC (flecainide): 1114 pts		Composite of death, hospitalization for ACS and ventricular tachycardia	In patients with non-critical coronary artery disease: significant reduction in death, hospitalization for ACS in patients treated with AA IC.	Observational, retrospective study. Diagnosis of coronary artery disease, VT, ACS are

Continued

Table 2 Continued

Study	Type of study	Study design	Exclusion criteria	Endpoints	Results	Limitations
Ashraf <i>et al</i> (2021) ¹⁹	Observational study, retrospective	AA III: 1114 pts Patients with AF and critical coronary artery disease subjected to revascularization, in therapy with AA IC (flecainide): 150 pts AAA III: 1453 pts 3-year follow-up Patients on flecainide therapy for at least 1 year who have had tests for coronary artery disease (coronary angiography or stress-induced MCS): coronarography: non-coronary artery disease (80 pts) Non-obstructive coronary artery disease (82 pts) Obstructive coronary artery disease subjected to revascularization (34 pts) MCS negative (128 pts) positive (24 pts) Mean follow-up of 6.3 years	Patients with structural heart disease, LVEF <50%, presence of moderate to severe valvular disease, previous myocardial infarction, creatinine clearance <35 mL/min.	Primary: all-cause mortality Secondary: sustained and unsustained VT with a daily burden >5%, ventricular arrhythmia that requires defibrillator intervention	In patients with critical coronary artery disease undergoing revascularization: no significant differences between the two groups. No difference in mortality in the three groups of patients undergoing coronary angiography, nor significant increase in arrhythmic burden. Even in patients undergoing MCS there were no significant differences in terms of mortality and increased arrhythmic burden	obtained by ICD-10 codes. Observational, retrospective study. High number of patients with non-obstructive coronary artery disease which could drive the study results
Cay <i>et al</i> (2022) ²⁰	Cohort, observational, retrospective study Propensity-score matched analysis	Patients undergoing AF ablation with coronary artery disease causing stenosis <70% (<50% in the common trunk); in therapy for the prophylaxis of recurrent arrhythmias with: propafenone (212 pcs) Amiodarone (212 pcs) Mean follow-up 11.7 ± 1.7 months	Patients with LVEF <40%, structural heart disease, previous myocardial infarction, reduced coronary reserve after provocative test, previous coronary revascularization.	Primary: non-sustained VT, sustained VT or PV o SCD. Secondary: death from all causes	No patient developed sustained VT, VF, or SCD There were no significant differences in the incidence of unsupported VT in the two groups (propafenone 2.4% vs. amiodarone 1.9%, <i>P</i> : 0.734)	Observational, retrospective study. Short follow-up After 3 months, suspension of therapy study power limited for serious adverse events

AF, atrial fibrillation; PET, positron emission tomography; AA IC, Class IC antiarrhythmics; SCD, sudden cardiac death; AA III, Class III antiarrhythmics; pc, patients; HF, congestive heart failure; VT, ventricular tachycardia; VF, ventricular fibrillation; MCS, myocardial scintigraphy; LVEF, left ventricular ejection fraction; pt, patients.

dysfunction. These results were then prudently extended to all patients with structural heart disease. Therefore, the current guidelines recommend the use of these drugs in the therapy of AF and VT only in patients without ischaemic heart disease and/or reduced LVEF^{4, 8} (Table 1).

It has been hypothesized that the increase in ventricular arrhythmias induced by Class IC AADs in patients with a previous heart attack is determined by the presence of scars within the myocardial muscle that can promote the pro-arrhythmic action of these drugs. In fact, Class IC AADs, by blocking sodium channels and the subsequent slowing of conduction, can lead, in these patients, to heterogeneous impulse conduction and consequently to the formation of re-entry circuits.¹⁵

However, in a sub-analysis of the CAST study, patients with non-Q heart attack and angina showed increased mortality, suggesting that the pro-arrhythmic effect of Class IC AADs is determined by the interaction between drug and ischaemia.^{14, 16}

A further limitation of the CAST study is represented by the population investigated. In fact, the study was developed in the pre-coronary revascularization era. Therefore, the majority of patients did not undergo complete revascularization of the culprit lesion, a procedure that may reduce both post-AMI pro-arrhythmic events and long-term mortality.

Consequently, patients with stable coronary artery disease preserved left ventricular systolic function, no previous myocardial infarction, or evidence of inducible ischaemia represent a grey area in which the absolute paucity of scientific evidence limits the use of Class IC AADs, a measure not convincingly supported by the data.

In recent years, there has been a renewed interest in the use of Class IC AADs in patients with stable coronary heart disease, in the absence of scar and/or myocardial ischaemia (Table 2). In a recent study, Pantlin *et al.*¹⁷ demonstrated the safety of AA ICs in a population of patients with AF and diagnosed occult coronary heart disease by evaluating the capacity of the coronary flow reserve using positron emission tomography.

In a retrospective study on patients with stable coronary heart disease, without previous heart attack and with preserved LVEF, Ashraf *et al.*¹⁹ observed that flecainide therapy is not associated with increased mortality observed in the population under examination. In an observational study performed by propensity-score matched analysis, Burnham *et al.*¹⁸ found that flecainide administered for AF prophylaxis in patients with stable coronary artery disease has a safety profile that is not inferior and in some subgroups even superior to Class IC AADs. Finally, in another retrospective study, propafenone also showed a safety profile similar to amiodarone in patients with mild to moderate coronary artery disease.²⁰

The results of these studies, albeit with numerous limitations determined by their observational and retrospective nature, suggest the possibility of using Class IC AADs in patients suffering from chronic coronary artery disease, but without myocardial disease secondary to previous heart attack or residual ischaemia. These results lay the groundwork for designing future prospective

and randomized studies to evaluate the safety of Class IC AADs in this specific subgroup of patients.

Patients with non-ischaemic structural heart disease

The current guidelines, despite limited scientific evidence, have cautiously extended the results of the CAST study to patients with non-ischaemic structural heart disease.^{4, 8} Furthermore, their negative inotropic action determined both by an indirect reduction of intracellular calcium and by the antagonist action on beta-adrenergic receptors (propafenone), makes the use of Class IC AADs not recommended in patients with reduced ejection fraction.³

Recent studies have shown encouraging results on the use of Class IC AADs in patients with non-ischaemic structural heart disease. Hyman *et al.* conducted a study on patients with tachy-cardiomyopathy induced by frequent ventricular ectopic beats, in which they tested the efficacy and safety of Class IC AADs. The population under examination had a mean ejection fraction of the left ventricle of 37% and a high extra-systole 'burden', even in patients previously subjected to catheter ablation of the arrhythmia. Therapy with AAIC showed, in an average follow-up of 4 years, the ability to suppress the ventricular extra-systole, resulting in the recovery of the ejection fraction. In addition, no serious adverse events occurred during treatment, including death or sustained ventricular arrhythmias, in patients treated with Class IC AADs.²¹

In patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) carrying implantable defibrillators and on antiarrhythmic therapy with beta-blockers, administration of flecainide has been shown to be effective in the management of recurrent ventricular arrhythmias over a mean follow-up of 3 years.²² A double-blind randomized study is currently being conducted with the aim to evaluate the efficacy of flecainide in reducing arrhythmias in patients with ARVC carrying implantable defibrillators.

Finally, the use of flecainide in patients with obstructive hypertrophic cardiomyopathy has shown greater efficacy than disopyramide in reducing both the gradient at the level of the left ventricular outflow tract and the number of episodes of unsustained VT during a follow-up of about 9 years.²³

Conclusions

Class IC AADs represent a cornerstone in AF therapy and a valid tool in VT therapy. Their use is currently limited to selected categories of patients, but recent observations open new perspectives for use in previously ignored patients. Ongoing and future studies will help to clarify the points not yet clarified.

Conflict of interest: None declared.

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