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Review

CLASS IC ANTIARRHYTHMIC DRUGS: INFORMED CHOICE

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The article presents data on the most commonly used antiarrhythmic drugs of subclass IC: propafenone, flecainide, and a drug manufactured in Latvia — ethacizine. The features and priority areas of each drug use were identified. The author conducted a critical analysis of the results of Cardiac Arrhythmia Suppression Trials (CAST)-I and CAST-II and suggested ways to further study of subclass IC antiarrhythmic drugs in the context of current treatment strategies. The results of CAST-I and CAST-II should be interpreted in view of the heterogeneity of the subclass IC antiarrhythmic drugs and the fact that among the drugs of this subclass that are currently registered and approved for use in Ukraine, only flecainide was studied in CAST-I, and none of these drugs — in CAST-II. Ethacizine has a special position as a promising drug, especially effective in the treatment of vagus-induced heart rhythm disorders, with a small number of contraindications and drug interactions compared with propafenone and flecainide. Despite many years of use in several countries, this drug remains "invisible" to researchers around the world due to a limited number of international studies. The author draws attention to the need to re-evaluate antiarrhythmic drugs with an outdated evidence, in some cases quite limited, and to plan new experimental studies to clarify the possibility of subclass IC drugs to influence new pharmacological targets in arrhythmology, as well as large-scale well-planned studies of the safety and efficacy of subclass IC antiarrhythmic drugs in real present-day clinical practice.

Keywords: *antiarrhythmic therapy, ethacizine, flecainide, propafenone, arrhythmias.*

INTRODUCTION

Cardiac arrhythmias and their treatment are always a reason for special caution, not only for general practitioners, but also cardiologists, due to possible side effects of antiarrhythmic drugs (AADs) in particular class I. The purpose of this article is to highlight the current state of the issue of subclass IC AADs used in Ukraine, to identify gaps in understanding their effectiveness and safety from the positions of new treatment strategies in cardiology and pharmacological targets in arrhythmology, as well as to search for promising directions for their further study to provide a current evidence base for their use, which may influence the formation of guideline recommendations in the future.

CAST-I AND CAST-II STUDIES: ARE THEIR RESULTS REALLY CONCLUSIVE?

The results of Cardiac Arrhythmia Suppression Trials (CAST)-I and CAST-II played not the last role in a wary attitude of physicians to subclass IC AADs, and even the "pre-CAST era" and "post-CAST era" were distinguished (Moroz and Lipnitskiy, 2006). However, it should be emphasised that the results of these studies, published more than 30 years ago, require some critical consideration, given the fact that the current guidelines of drugs involved in these studies, with the exception of flecainide, are not used in clinical practice (at least in Ukraine), in contrast to the AADs that were not investigated in these studies, but they were forced to assume the burden and limitations of these results. Therefore, to restore justice, the results of CAST-I and CAST-II should be considered in detail.

The aim of CAST-I was to evaluate the safety of subclass IC AADs encainide, flecainide and moracizine in patients after myocardial infarction (MI) with asymptomatic or moderately symptomatic ventricular arrhythmias (The CAST Investigators, 1989).

The inclusion criteria in this multicenter randomised placebo-controlled study were:

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- term from 6 days to 2 years after the MI;
- availability of Holter electrocardiogram (ECG) monitoring data for at least 18 hours;
- the presence of an average of 6 premature ventricular depolarisations per hour;
- left ventricular ejection fraction (LV EF) less than 55% for patients who had MI within 90 days before enrollment, or less than 40% for those who experienced MI 90 days to 2 years ago.

Exclusion criteria were the presence of severe symptomatic ventricular arrhythmias (with symptoms leading to disability, syncope or presyncope) or ≥ 15 consecutive premature ventricular depolarisations at a rate of 120 per 1 min.

In the first phase of the study, AADs were prescribed to identify individuals in whom ventricular ectopic contractions were effectively suppressed and who were subsequently assigned to receive AADs or appropriate placebo (open titration phase). The main endpoint was arrhythmic death or cardiac arrest.

Based on data as of 30 March 1989, 2309 patients entered the phase of open titration in CAST-I, and effective suppression of ventricular arrhythmia was achieved in 1727 patients, who were subsequently randomised to receive blinded therapy:

- 1455 people received encainide 35–50 mg three times daily or flecainide 100–150 mg twice daily (n = 730) or a placebo (n = 725). The results are presented for both drugs together because "the study was not designed to detect individual differences between these two drugs" (The CAST Investigators, 1989);
- 272 people received moracizine or placebo. The results of this part of the study were not published due to the decision of the CAST Data and Monitoring Board to continue monitoring this drug.

The analysis of the basic characteristics of patients included in CAST-I draws attention to the relatively long-time interval after MI, which, in our opinion, could have affected the results, and the significant number of drugs (other than AADs) prescribed to study participants. Most often (36.0–40.0%) patients received more than five drugs, including those that interact with subclass IC AADs or could have their own proarrhythmogenic potential. For example, digoxin was given to 21.2% of patients additionally to encainide/flecainide.

A preliminary CAST-I report showed that, over an average 10-month follow-up period, both total mortality and non-arrhythmic death or cardiac arrest were significantly less frequent in the placebo group compared with that in the group of patients receiving encainide or flecainide (The CAST Investigators, 1989). The overall mortality in patients treated with encainide or flecainide was 7.7%, and 3.0% in the placebo group (relative risk (RR): 2.5; 95% confidence interval (CI), 1.6–4.5), mortality from arrhythmia and non-fatal cardiac arrest: 4.5 and 1.2%, respectively (RR: 3.6; 95% CI, 1.7–8.5). However, considering the study design and the prerequisites for inclusion of patients in the study, these drugs demonstrated their antiarrhythmic effect, and their use significantly reduced the total number of premature ventricular depolarisations.

The overall conclusion of the CAST-I was as follows: "Neither encainide nor flecainide should be used in the treatment of patients with asymptomatic or minimally symptomatic ventricular arrhythmia after MI, even though these drugs may be effective initially in suppressing ventricular arrhythmia. Whether these results apply to other patients who might be candidates for antiarrhythmic therapy is unknown" (The CAST Investigators, 1989).

In April 1989, the CAST Data and Monitoring Board recommended to discontinue further studies on encainide and flecainide due to significantly higher mortality in the group of patients receiving such drugs. During this period, the CAST-I study already surveyed 320 patients in the arm "moracizine vs. placebo" and found a positive trend in reducing mortality in the active treatment group, which led to the extension of the moracizine study in CAST-II.

The design of CAST-II was focused on patients in whom antiarrhythmic therapy with subclass IC AADs could be more effective. For this reason, the design of the CAST-I was changed — the period of patient inclusion after MI was reduced to 90 days, LV EF was limited by range ≤ 40%, patients with ventricular tachycardia lasting ≥ 30 sec were excluded, and it was allowed to increase the dose of moracizine up to 900 mg/day, if necessary, for adequate arrhythmia suppression achieving (reduction of premature ventricular depolarisations by at least 80% or at least 90% of unstable ventricular tachycardia cases) (The CAST II Investigators, 1992).

The authors of the study planned to conduct it in two stages: short-term (n = 2200) until 1 January 1992, and long-term (n = 2100) until 1 April 1994.

In July 1991, the CAST Data and Monitoring Board recommended the early CAST-II closure at the short-term stage for two reasons (The CAST II Investigators, 1992):

- data from a two-week study of low doses of moracizine (200 mg three times daily) showed higher mortality in the active treatment group compared with the placebo (17 cases compared with three cases, unadjusted $p < 0.001$, adjusted $p < 0.02$, RR: 5.6; 95% CI, 1.7 to 19.1);
- the probability of positive results of the long-term phase of the study was low.

It is important to underline that 14 out of 17 deaths in the moracizine group in this short-term arm of CAST-II were related to arrhythmias. Nevertheless, for the long-term part of the study, placebo and moracizine groups did not differ significantly in number of death or cardiac arrest cases due

to arrhythmias (42 vs. 49 cases, respectively, $p = 0.40$), but nonfatal adverse effects were more frequent in the moracizine group compared with the placebo group (two-tailed $p = 0.03$). The conclusion of CAST-II, as in the case of AAD, which were studied in CAST-I (flecainide and encainide), suggests that the use of moracizine to suppress asymptomatic or moderately symptomatic premature ventricular depolarisations with the aim to reduce mortality in patients with MI seems to be not only ineffective but even harmful (The CAST II Investigators, 1992).

Thus, both CAST-I and CAST-II were dedicated to study the impact on survival of patients with MI of only three subclass IC AADs — encainide and flecainide in the combined group (both benzamide derivatives), and moracizine (phenothiazine derivative). The causes and mechanisms of increased mortality due to arrhythmias and overall mortality in patients with a history of MI receiving indexed subclass IC AADs have not been established to date (probably due to proarrhythmogenic effect), although these drugs did cope with their main task — to reduce the number of premature ventricular depolarisations.

Both CAST-I and CAST-II did not assess the currently widely used subclass IC AADs propafenone and ethacizine, and restrictions on their use were the result of extrapolation of the results obtained for flecainide, encainide, and moracizine. Interestingly, the latter, like ethacizine, was developed in the USSR, and the license for moracizine manufacturing was sold to Du Pont in the late 1970s (Chazov and Golicin, 2010). Moracizine began to be studied and used in the United States and received a name in the International Nomenclature of Non-proprietary Names of Medicinal Products (https://extranet.who.int/tools/inn_global_data_hub/INN_Hub.php?code=aSJINNINNINNnLZGWZTN6U9m/mIGQmjgcr4bGOmyIopoeAkH6Vlspz0qA65JTwZ4OF4qrGxc). History cannot be changed, but it would be interesting to look at the results of randomised controlled trials if they included current subclass IC AADs (e.g., propafenone and ethacizine).

It should be noted that CAST-I and CAST-II were conducted at a time when other strategies (surgical revascularisation) and drugs that are currently used in patients with coronary heart disease had just begun and had limited availability, and knowledge about pathophysiology of myocardial infarction was incomplete. Moreover, some of up-to-date treatment approaches have direct and indirect antiarrhythmic effects and contribute to better survival of such patients: beta-blockers, blockers of the renin-angiotensin system, statins, antiplatelet/anticoagulant therapy, etc. (Lei *et al.*, 2018; Sydorova, 2021). Thus, their interaction with subclass IC AADs may be both important and beneficial, and requires new investigation.

Thus, the CAST-I and CAST-II (conducted more than 30 years ago) do not fully correspond to current clinical practice, their results are based on the study of drugs that, with the exception of flecainide, are not currently used in most countries, while restrictions imposed due to these results apply to the entire subclass IC. It should also be considered that the present-day practice of managing patients in both the acute period of MI and the post-infarction period is significantly different compared to the period of the 1980s, and most of the new approaches to managing patients have a beneficial effect in the prevention of arrhythmias and the prognosis of such patients. The above conclusions justify the beginning of the discussion of the need for a new stage in the study of subclass IC AADs, both in terms of the general characteristics of the class of currently used drugs, and the clarification of their individual characteristics.

PLACE OF SUBCLASS IC AADS IN UP-TO-DATE ARRHYTHMOLOGY

The place of subclass IC AADs in up-to-date arrhythmology is regulated by current guidelines. In the treatment of atrial fibrillation (AF), these AADs (propafenone and flecainide) are the options for pharmacological cardioversion of recent-onset AF, excluding patients with recent acute coronary syndrome or severe heart failure (Class I, Level A), for facilitation of electrical cardioversion in patients with AF (Class IIa, Level B), as "pill in the pocket" strategy in selected patients with rare and recent-onset AF without severe structural or coronary artery disease (Class IIa, Level B), and for long-term therapy as rhythm control strategy in patients with AF without LV dysfunction and structural heart disease (significant LV hypertrophy or myocardial ischemia (Class I, Level A) (Hindricks *et al.*, 2021). Propafenone and flecainide are also recommended by European Society of Cardiology (ESC) as an option for therapy of focal atrial tachycardia (Class IIb, Level C for acute therapy, Class IIa, Level C for chronic therapy), and atrioventricular re-entrant tachycardia as a result of manifest or concealed accessory pathways (Class IIa, Level B for acute therapy of antidromic type, Class IIb, Level B for chronic therapy) (Brugada *et al.*, 2020). This subclass of AADs is also recommended for several ventricular arrhythmias, but absence of severe structural heart disease is still obligatory for such prescription: haemodynamically tolerated sustained monomorphic ventricular tachycardia (flecainide, Class IIb, Level C), in symptomatic patients with idiopathic ventricular tachycardia, premature ventricular complexes from the right ventricular outflow tract or the left fascicles (flecainide, if catheter ablation is not available, Class IIa, Level B), in symptomatic patients with idiopathic ventricular tachycardia, premature ventricular complexes with origin other than the latter (flecainide, Class IIa, Level C) (Zeppenfeld *et al.*, 2022). Ukrainian national guidelines in the field of arrhythmology are almost the same, but ethacizine is also recommended for patients with vagus-mediated AF in the absence of severe structural heart disease (Kovalenko *et al.*, 2021).

The current limitations for subclass IC AADs administration are developed on the basis of CAST-I and CAST-II results. The 2020 ESC Guidelines for the diagnosis and management of AF developed in collaboration with the European Association for Cardio-Thoracic Surgery mentioned several contraindications for two subclass 1C AADs

(flecainide and propafenone): significant liver disease, significant kidney disease (creatinine clearance < 35 ml/min/1.72 m^2); coronary heart disease, decreased LV EF, disturbances of cardiac conduction, and significant LV hypertrophy (Hindricks *et al.*, 2021), which corresponds to other ESC Guidelines (Brugada *et al*., 2020; Zeppenfeld *et al*., 2022).

It should be noted that some studies underline positive effects of subclass IC AADs in the course of AF. For example, De Vos *et al*. (2012) investigated the effects of different confounders, including AADs, on progression of AF (change from paroxysmal to persistent/permanent AF) and found that the use of subclass IC AADs is associated with less AF progression during the first year ($p < 0.0013$). It is important to underline that other AADs (subclass IA, beta-blockers except sotalol, sotalol, class III, calcium-channel blockers) did not show so impressive improvement in the natural course of this clinical condition during the index period, and cardiac glycosides even were associated with significantly more often AF progression, so researchers found subclass IC AADs quite helpful and a promising option for AF treatment (Shukla and Curtis, 2014). Such results can be explained by more severe clinical conditions of those patients who received cardiac glycosides, and milder — in cases treated with subclass IC AADs, but this is a reason to study subclass IC current agents in present-day clinical practice.

Moreover, the list of subclass IC ADDs available in practice has changed since the end of the twentieth century, and their comparative studies are almost non-existent, although subclass IC AADs differ not only in their evidence base. In addition, approaches to the AADs classification are being reviewed today. For example, there is a modernised classification (Lei *et al.*, 2018), which, for convenience, could be called the Modified "Oxford" (by first author affiliation) Classification and could potentially replace the classification of V. Williams 1970 (Williams, 1970), to which a class of slow calcium channel blockers was later added (Singh, 1972), and class I was divided into three subclasses (Harrison, 1985).

The Modified "Oxford" Classification, which is also based on classes/subclasses principles, has a significant perspective potential (Lei *et al.*, 2018). It identifies specific targets for antiarrhythmic therapy, including those previously not considered, as well as AADs that may affect these targets. This approach opens opportunities for the development of new drugs as well as reassessment of "new" effects of "old" AADs, which are already actively used in real clinical practice (Sydorova, 2021).

According to the Modified "Oxford" Classification, class I AADs still include blockers of cardiac Na^+-channels Nav1.5, but the understanding of this process has changed (Lei *et al.*, 2018). In this classification, not only do class I AADs significantly differ in their properties, but also subclass IC AADs (Table 1).

Features of electrophysiological action and additional effects provided drugs of this subclass with a slightly different spectrum of action (Table 2). Analysis of the data on the main characteristics of subclass IC AADs (Table 2) shows

Table 1. Features of electrophysiological properties of subclass IC AADs

Subclass IC AADs	Blockage of Na+-channels	Main electrophysiological effect	Additional effects	Class by MOC
Ethacizine	Prolonged blockade of Na^+-channels on the inner and outer sides of the myocardial cell membrane	Reducing the rate of AP increase: reducing the amplitude and slowing down the processes of inactivation and reactivation of fast Na^+ flow without affecting the resting potential. Prolongation of the duration of refractory periods of the atria and AVN. Slowing down the rate of AP increase in atrial and ventricular Purkinje fibers and additional pathways of excitation by AVN and bundle of Kent	Affects slow Ca^{2+} -channels of membranes. For this drug a moderate vagolytic effect is described	*Ic, IIc(?), IVa(?)*
Flecainide	Pronounced suppression of fast Na^+-channels of the heart (slow binding with and dissociation from the channels)	Differentiated effect on the duration of changes in the bioelectric potential of the ventricular muscles (almost no effect) and Purkinje fibers (reduces the duration)	Weakly suppresses slow Ca^{2+}-channels of the myocardium (in high concentrations)	*Ic, IVb*
Propafenone	Reduction of fast input current with decreasing depolarisation rate	Prolongation of the impulse conduction through the atria, AVN, mainly through the conduction His-Purkinje system. Suppression of impulse conduction through additional pathways (WPW syndrome) due to prolongation of the refractory period or blockade of the conduction pathway in both the antegrade and retrograde directions. Decreased spontaneous excitability due to increased myocardial sensitivity threshold with decreased myocardial electrical excitability as a result of increased ventricular fibrillation threshold	Moderate beta- blocking activity	*Ic, IIa, IVb*

MOC – Modified "Oxford" Classification, AP – action potential, AVN – atrioventricular node

Table 2. Features of clinical use of subclass 1C AADs on the basis of drug label*

Parameter	Ethacizine	Propafenone	Flecainide
Indications	Supraventricular arrhythmias: premature depolarisations, supraventricular and AVN tachycardia (especially in the presence of additional pathways); paroxysmal form of AF		
	Ventricular tachycardia, premature ventricular depolarisation	Ventricular arrhythmia without specification	Ventricular arrhythmias of high severity, life-threatening
Pharmacokinetics / pharmacodynamics			
C_{max}, h	2,5–3	2–3	4
$T_{1/2,}$ h	2,5	2–10 (fast metabolisers) 10–32 (slow metabolisers)	20
Dosage frequency per day	2–3	3	2
Participation in the metabolism of the isoenzyme CYP2D6, the presence of gene polymorphism	Not described	Polymorphism is present	Polymorphism is present
Effect on the duration of ECG intervals			
P	Rarely prolongs	Slightly prolongs	Not described
PR	Rarely prolongs	Slightly prolongs	Can prolong
QRS	Rarely prolongs	Slightly prolongs	Can prolong
QT	At QT > 400 msec – use carefully, > 500 msec – withdraw	Usually does not change	Slightly prolongs
Interaction with other AADs			
Beta-blockers	Concomitant use is recommended to reduce the potential proarrhythmic effect	Very carefully	Caution due to adverse inotropic effects
Amiodarone	Concomitant careful use is possible		
Digoxin	Concomitant careful use is possible (risk of increased digoxin concentrations)		
Warfarin	–	It is recommended to reduce the dose of warfarin	–
Monoamine oxidase (MAO) inhibitors	Contraindicated	–	–
Alcohol	Contraindicated	–	–
CYP2D6, CYP1A2 and CYP 3A4 (ketoconazole, cimetidine, quinidine, erythromycin, grapefruit juice, etc.)	–	Increased serum concentrations of propafenone	–
Rifampicin	–	Increased risk of proarrhythmogenic effect	–
Selective serotonin reuptake inhibitors (fluoxetine, paroxetine)	–	Increase in concentration of propafenone in blood serum	Increase in concentration of flecainide in blood serum
Mizolastine, terfenadine	–	–	Increased risk of proarrhythmogenic effect (ventricular arrhythmia)
Ritonavir, lopinavir, indinavir	–	Contraindicated with ritonavir	Increased risk of proarrhythmogenic effect (ventricular arrhythmia). Increase in concentration of flecainide in blood serum
Phenytoin, phenobarbital, carbamazepine	–	–	Accelerate the excretion of flecainide by 30%
Neuroleptics (clozapine)	–	–	Increased risk of proarrhythmogenic effect
Quinine	–	–	Increase in concentration of flecainide in blood serum
Antifungal drugs (terbinafine)	–	–	Increase in concentration of flecainide in blood serum

Table 2. (Continued)

Parameter	Ethacizine	Propafenone	Flecainide
Cimetidine	–	–	Increase in concentration of flecainide in blood serum by 30%
Contraindications			
Common to all subclass IC AADs	Hypersensitivity to the components of drugs, severe structural heart disease, severe conduction disorders, severe liver and kidney dysfunction, concomitant use of other class I AADs, severe electrolyte disturbances (hypo- and hyperkalemia, hypomagnesemia)		
Individual	Taking MAO inhibitors, drinking alcohol Caution in angle-closure glaucoma, benign prostatic hyperplasia	Severe obstructive pulmonary disease Brugada syndrome Taking ritonavir Myasthenia gravis	Brugada syndrome. Asymptomatic ventricular arrhythmia or mild symptoms of ventricular arrhythmia
Adverse reactions			
	Dizziness. Disorders of accommodation (at the beginning of treatment). Headache. Slight drowsiness. Imbalance when walking or after sudden movements of the head. Diplopia	Agranulocytosis, which requires control of the white blood cell count in the first 4–6 weeks. Lupus-like syndrome. Decrease in sperm count, follicle-stimulating hormone and testosterone levels. Due to the beta-blocking effect – caution is needed in patients with bronchial asthma and obstructive pulmonary disease	Decrease in the red blood cell count, white blood cell count, and platelet count. Increase in the number of antinuclear antibodies. Increased levels of liver enzymes. Dizziness, hallucinations, depression, confusion, anxiety, amnaesia, insomnia, paresthesia, ataxia, hypoaesthesia, hyperhidrosis, tremor, hot flashes, drowsiness, headache, peripheral neuropathy, convulsions, dyskinesia. Shortness of breath, pneumonitis, pulmonary fibrosis, interstitial lung disease. Allergic dermatitis, including rash, alopecia, urticaria, photosensitivity reaction. Asthenia, fatigue, fever. Oedema

Note: AVN – atrioventricular node

* We used Ukrainian labels for indexed medications represented at the web-site of the Ministry of Health of Ukraine (all last accessed 16 January 2023)

that among the drugs of this group available on the Ukrainian market, ethacizine seems to have the most optimal parameters. This applies to the interaction with drugs of other groups, fewer contraindications additional to the general ones for this group of ADDs (actually only taking MAO inhibitors and alcohol consumption), less in number and severity of the list of side effects. Importantly, the half-life of the drug in the blood is 2.5 hours (propafenone — up to 32 hours, flecainide — 20 hours), which makes this drug more convenient to work in case of proarrhythmogenic effect.

THE PLACE OF ETHACIZINE IN UP-TO-DATE ARRHYTHMOLOGY

In Ukraine, ethacizine, represented by Latvian-made AAD, has remained the most popular and most frequently prescribed subclass IC AAD for decades. Thus, according to current data provided by Proxima Research (https://proximaresearch.com) on our request, 145,756 packages of the drug were sold in Ukraine in 2021, while the total number of packages sold during this time of medicines containing propafenone (various manufacturers) amounted to 111,414 packages, the least popular remains flecainide (all manufacturers) — 43,119 packages sold in 2021 (data are not published). It should be noted that there has been growing popularity of subclass IC AADs as a whole (from 2008 to 2021 increase in the number of packages sold per year more than 3.5 times), and ethacizine (for the same period increased sales of packages by 2.38 times). This indicates a high demand for subclass IC AADs including ethacizine. While propafenone including flecainide are the only subclass IC AADs mentioned in European and world guidelines, ethacizine remains the most frequent choice of subclass IC AADs in Ukraine.

Clinical efficacy of ethacizine has been studied mainly in the last two decades of the twentieth century, predominantly in small uncontrolled studies without blinding procedure.

Effectiveness of ethacizine in treatment of recurrent sustained ventricular tachycardia in patients with coronary artery disease was established in a small Estonian study conducted by Kaik *et al* (1992). In their research, only one person of 26 treated with ethacizine had recurrence of ventricular tachycardia during follow-up (mean 16.5, range 3–22 months). It was also found that for the patients with recurrent sustained ventricular tachycardia who were allocated to the quite heterogeneous group with different clinical conditions (from the absence of established cardiac disease to hypertrophic cardiomyopathy but without coronary artery disease) 50% had sustained recurrent ventricular tachycardia episodes, despite treatment with ethacizine. Interesting, the dosage of ethacizine for this study was high and not accepted currently (200–400 mg/day).

Some more recent studies conducted predominantly in non-EU countries have not been large, and their results were

published in journals "invisible" for most famous scientometric bases or PubMed, making this evidence base for ethacizine also "invisible" for researchers around the world. In one of the studies, effectiveness of the drug was demonstrated in elimination of arrhythmias in 71.3% cases in total, ventricular premature depolarisations in 78.9% of cases, AF interruption in 61.7% of cases, and maintenance of sinus rhythm after AF interruption in 58.4% of cases (Hrebenyk and Masliy, 2017). Volkov and Strona (2008) demonstrated reduction of the number of ventricular arrhythmias (by 28–78%) in 82.8% patients with stable angina pectoris treated with ethacizine 150 mg/day with frequency of proarrhythmogenic effects — 9.4%. Another study established that the numbers of premature ventricular and supraventricular depolarisations were reduced by 75 and 68%, respectively, in elderly patients with stable coronary heart disease, in whom such treatment showed no signs of sympatholytic or cardiodepressive effects as well as significant effect on the duration of QT interval on ECG (Lishnevskaja and Papuga, 2007).

One of the largest studies was the evaluation of the efficacy and safety of ethacizine in patients with various arrhythmias conducted by Sychev *et al*. (2016) in Ukraine. This study involved 182 patients without significant structural heart disease — coronary heart disease was diagnosed in 53% of patients, hypertension in 59% cases, and myocardiofibrosis in 47% cases. When evaluating the effect of ethacizine on AF, an increase in the interval between AF episodes was noted from an average of 4.0 ± 1.2 days to 12.0 ± 0.7 days after six months of therapy. The duration of each episode of AF decreased by 58% already in the first month of ethacizine therapy. Moreover, the study reported the ability of ethacizine to reduce the number of premature supraventricular depolarisations (by 96.9% after one month and by 97.4% after six months of therapy) and the number of premature ventricular depolarisations (by 78.5 and 88.2%, respectively) (Sychov *et al*., 2016).

A new wave of interest in ethacizine started in the scope of new pharmacological targets and versatility of the drug in treating both supraventricular and ventricular arrhythmias. The period of ethacizine "invisibility" to the world seems to be coming to an end. In particular, two studies performed at the Rīga Stradiņš University in Latvia (Sokolova *et al.*, 2021a; 2021b) demonstrated at least no less efficacy and safety of ethacizine compared to propafenone. Unfortunately, these results were published as abstracts of the scientific meeting and need more information about study design and features of studied population.

Another promising publication was made in 2021 by Kokina *et al*. In this study, 112 patients with AF successfully underwent electrical cardioversion and received subclass IC or class III AADs for sinus rhythm maintenance. The investigators also assessed efficacy separately for amiodarone and ethacizine, as the most commonly used members of each of the selected AAD classes. It should be noted that patients from the ethacizine group had ischaemic heart disease in 44.8% cases, history of MI in 10.3% cases, history of percutaneous coronary intervention in 10.3% cases, and chronic heart failure in 69.0% cases. There was no statistically significant difference in sinus rhythm maintenance rates between groups of patients treated with amiodarone or ethacizine during the follow-up period of the study (75.0% for amiodarone group vs. 79.3% for ethacizine group after 1 month of therapy, $p = 0.650$; 68.8% vs. 65.5%, respectively, after three months of therapy, $p = 0.757$; 64.1% vs. 58.6%, respectively, after six months of therapy, $p = 0.616$). According to impressive results from this study (also conducted in Latvia), "… if not contraindicated, ethacizine, concomitantly with a beta-blocker, could be used as a similarly effective alternative for amiodarone, which has adverse health effects" in patients with high-risk AF after electrical cardioversion (Kokina *et al.*, 2021).

A somewhat fantastic approach to determining the characteristics and features of "old" drugs, along with determining their impact on modern antiarrhythmic targets, is a new research direction — the study of pharmacokinetics and pharmacodynamics in conditions close to spaceflight. Interestingly, one of the first AADs of the subclass IC to be studied in this sense was ethacizine, which was analysed in the study together with representatives of other classes — verapamil and propranolol (Polyakov *et al.*, 2020).

Undoubtedly, the evidence base of ethacizine today requires large and careful work, including experimental studies to clarify the ability of this drug to influence new pharmacological targets in order to explain its special effects (the vagolytic effect described in a number of small studies). However, this AAD deserves the attention of researchers.

CONCLUSIONS

In view of the above, subclass IC AADs have general indications for use — ventricular arrhythmias and supraventricular arrhythmias (premature depolarisations, supraventricular tachycardia, atrioventricular nodal tachycardia, and paroxysmal form of AF) in patients without severe structural heart disease. However, these drugs are quite different and differ from each other as representatives of the other groups of medicines (beta-blockers, blockers of the renin-angiotensin system, etc.), despite having common class features. In real clinical practice, these differential features should be considered, which will make the prescription of subclass IC AADs both safer and more effective (Table 3).

The study of drug effectiveness is an ongoing process, which not only leads to the removal of undeniably harmful agents, but also allows to discover the potential of the drugs that were deprived of the opportunity to be studied in large-scale trials, including some subclass IC AADs, in new therapeutic conditions, with new resources to choose the best patient-specific treatment strategy. New well-designed studies conducted in present-day clinical practice with the inclusion of currently used subclass IC AADs may provide an opportunity to take a fresh look at their capabilities, clarify and uncover new effects or confirm previous limitations.

Table 3. The choice of subclass IC AADs in real clinical practice

A factor to consider	Ethacizine	Propafenone	Flecainide
Age of the patient, years	18+	18–70 (in older people carefully, in middle-aged men carefully due to the risk of possible adverse effects to reproductive function)	12–70 (in older people carefully)
Pregnancy, lactation	Not recommended	Not contraindicated, but should be prescribed with caution	During pregnancy – only as a last resort, while breastfeeding – stop taking
The state of the patient's autonomic nervous system	Hyperactivation of the parasympathetic nervous system (?)	Hyperactivation of the sympathetic nervous system	Does not matter
Alcohol consumption	Forbidden	Does not matter	Does not matter
Influence of food intake	Does not affect	Does not affect	Significant influence
The beginning of the action	Fast	Fast	Delayed (up to 4 h)
Duration of the action	Relatively short	Long	Long
Drug interaction	Only MAO inhibitors and alcohol	Moderate number	Large number

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IC KLASES ANTIARITMISKIE MEDIKAMENTI: INFORMĒTA IZVĒLE

Raksts ir nozīmīgs literatūras apskats par aktuālu un dažkārt strīdīgu tēmu — IC klases antiaritmisko zāļu praktisko pielietojumu. Kopš 20. gs. 90. gadiem un šajos gados notikušajiem CAST I un CAST II pētījumiem IC klases antiaritmisko līdzekļu pielietojamība tika apšaubīta. Raksta autore precīzi analizē problēmas, kāpēc tas notika, sniedz skaidrojumu par aritmiju ārstēšanas pieeju atšķirībām 20. gadsimta beigās un 21. gadsimtā. Rakstā apskatīti plašāk pieejamie šīs klases medikamenti, tajā skaitā Latvijā ražotie etacizīns, un izskaidroti šīs grupas praktiskā pielietojuma un drošības aspekti.