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Choosing a class IC antiarrhythmic drug for the treatment of patients without structural heart disease: clinical advantages of the most common agents (literature review)

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

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Ключові слова: антиаритмічні препарати, IC клас, етацизин, пропафенон, порівняльна характеристика, особливості.

Aim: to analyze the pharmacological features and updated evidence-based medicine data of Class IC antiarrhythmic drug (AAD) ethacizine compared to propafenone to optimize the choice of treatment for cardiac arrhythmias in patients without structural heart disease.

Materials and methods. According to the purpose, a search was conducted for available scientific literature with an emphasis on publications of the last 5 years. We also analyzed scientific information on scientific platforms of the European Society of Cardiology (ESC 365) and the Association of Cardiologists of Ukraine.

Results. At first glance, Class IC AADs seem to be identical in the mechanism of action, which creates certain difficulties for practicing physicians when choosing AAD of this class for the treatment of arrhythmias in each specific case. Ethacizine and propafenone were chosen for comparison as the most frequently used Class IC AADs in our country. We presented data from studies comparing the efficacy and safety of the selected AADs with an emphasis on recent studies of ethacizine, as a less well-known AAD in Europe and globally. In addition, this article includes the main design features of new studies on real-world clinical use of Class IC AADs, including use as a "pill-in-the-pocket" for restoring sinus rhythm in patients with atrial fibrillation (ETERNITY study) and comparing the efficacy of propafenone and ethacizine in maintaining sinus rhythm in patients with paroxysmal and persistent forms of atrial fibrillation.

Conclusions. Propafenone and ethacizine have significant differences in pharmacological properties, specific contraindications, drug interactions, and evidence base, which can be considered to determine the optimal agent for a particular patient. The choice of the optimal Class IC AAD will depend on the presence and type of dysautonomia of the patient.

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Вибір антиаритмічного препарату IC класу для лікування пацієнтів без структурних змін серця: клінічні переваги найпопулярніших засобів (огляд літератури)

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Мета роботи – проаналізувати фармакологічні особливості й оновлені дані доказової медицини щодо антиаритмічного препарату (ААП) IC класу етацизину порівняно з пропафеноном для оптимізації лікування порушень серцевого ритму у пацієнтів без структурного ураження серця.

Матеріали і методи. Здійснили пошук наукової літератури з відкритим доступом, передусім до аналізу залучали публікації за останні 5 років. Крім того, вивчено матеріали, що представлені на наукових платформах Європейського товариства кардіологів (ESC 365) та Всеукраїнської асоціації кардіологів України.

Результати. Препарати IC класу, на перший погляд, є однаковими за механізмом дії, що створює певні труднощі для лікарів-практиків під час призначення ААП цього класу для лікування аритмій у кожному конкретному випадку. Для порівняння обрано етацизин і пропафенон як ААП IC класу, що найчастіше застосовують в Україні. Наведено результати досліджень щодо порівняння ефективності та безпеки обраних ААП з акцентом на останніх розвідках з вивчення етацизину як менш відомого в Європі та світі ААП. Наведено основні позиції дизайну нових досліджень, що присвячені вивченню реальної клінічної практики застосування ААП IC класу, зокрема як «таблетки в кишені» для відновлення синусового ритму при фібриляції передсердь

Conflicts of interest: Sydorova N. M. has participated as a guest speaker at educational events financially supported by Olainfarm (Latvia) and Acino (Switzerland). Kolesnyk M. Yu. has participated as a guest speaker at educational events financially supported by Olainfarm (Latvia).

Конфлікт інтересів: Сидорова Н. М. брала участь як запрошений доповідач в освітніх заходах, які фінансово підтримували Olainfarm (Латвія) та Acino (Switzerland). Колесник М. Ю. брав участь як запрошений доповідач в освітніх заходах, які фінансово підтримувала Olainfarm (Латвія).

(дослідження ETERNITY), та порівняння ефективності пропафенону та етацизину у підтриманні синусового ритму у пацієнтів із пароксизмальною та персистентною формами фібриляції передсердь.

Висновки. Пропафенон та етацизин мають особливості фармакологічних властивостей, специфічних протипоказань, лікарських взаємодій і доказової бази. Врахування цих даних сприяє визначенню оптимального засобу для конкретного пацієнта. Вибір оптимального ААП IC класу насамперед залежатиме від наявності та типу дисавтономії пацієнта.

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Treatment of heart rhythm disorders in young individuals, as well as those without significant cardiovascular disease, remains a relevant challenge in contemporary medicine. In managing such patients, it is essential to balance the safety and efficacy of antiarrhythmic drugs (AADs) or interventions, while also accounting for the potential presence of genetically determined causes of arrhythmia or dysautonomia. In younger patients without structural heart disease, heart rhythm disorders are often associated with conditions that result in dysautonomia. Therefore, treatment includes restoring the balanced functioning of the autonomic nervous system, which explains the frequent use of Class IIA AADs under the new classification (i. e., beta-adrenergic blockers), Class IC AADs, and, to some extent, non-dihydropyridine calcium channel blockers (Class IVA AADs) as antiarrhythmic agents [1,2].

Beta-adrenergic blockers have a broad application profile, with indications encompassing nearly all clinical conditions associated with cardiovascular disease, including atherosclerotic coronary artery disease, acute coronary syndromes, hypertension, and heart failure [3]. This drug class has demonstrated high efficacy in treating functional cardiac rhythm disorders, particularly in cases of sympathicotonia [2,3,4,5]. However, their use may be limited by their effects on blood pressure and heart rate (a consideration that also applies to calcium channel blockers), which can prevent the administration of doses sufficient to achieve a full antiarrhythmic effect.

There are also restrictions on the use of beta-adrenergic blockers and non-dihydropyridine calcium channel blockers in patients with accessory pathways [6,7]. Furthermore, the issue of membrane-stabilizing properties arises, as the absence of this effect in certain beta-blockers results in a lack of labeling for arrhythmia treatment in some members of this class [2,3,4,5].

Consequently, the use of beta-adrenergic blockers as monotherapy for rhythm disorders may not always be effective or adequate to ensure a complete antiarrhythmic response. Drugs with membrane-stabilizing properties are typically classified as Class I AADs, while beta-blockers are generally recommended as adjunctive therapy in patients with atrial fibrillation (AF) receiving propafenone or flecainide, to prevent the conversion of AF into atrial flutter with 1 : 1 atrioventricular conduction [3,8]. Thus, in clinical practice, when Class IC AAD therapy is considered for the treatment of AF, dual therapy with a Class IC AAD and a beta-blocker is frequently employed.

Accordingly, *Table 1* presents the main differences among Class IC, IIA, and IVA AADs, as defined by the new classification [1], which are commonly used in patients without significant structural heart disease.

In Ukraine, the most commonly used Class IC AADs are ethacizine and propafenone [9,10]. Flecainide is associated with physician concern due to findings from the Cardiac Arrhythmia Suppression Trial (CAST), in which flecainide, along with encainide, was shown to negatively affect the prognosis of patients with a history of myocardial infarction [11,12,13]. Furthermore, flecainide has notable limitations in the treatment of ventricular arrhythmias, being recommended only for severe cases and not for mild, asymptomatic, or non-life-threatening rhythm disorders. Its use is also complicated by numerous drug interactions, which require close monitoring of the patient's overall pharmacotherapy regimen [9,10]. Consequently, when a Class IC AAD is indicated, clinicians most often choose between propafenone and ethacizine. In such cases, it is critically important to consider the specific pharmacological and clinical characteristics of each agent to optimize treatment outcomes.

Aim

The objective of this review is to analyze the pharmacological features and updated evidence-based medicine data of Class IC antiarrhythmic drug ethacizine compared to propafenone to optimize the choice of treatment for cardiac arrhythmias in patients without structural heart disease.

Materials and methods

To achieve the stated objective, we conducted an analysis of sources in the PubMed, EMBASE, and Google Scholar databases using keyword searches in various combinations: "antiarrhythmic drugs", "Class IC", "ethacizine", "propafenone", "comparative characteristics", "features of antiarrhythmic drugs", "arrhythmias without structural heart disease", "dysautonomia", "atrial fibrillation", "ventricular rhythm disorders".

Additionally, we performed a review of the latest European guidelines on the management of heart rhythm disorders, along with an analysis of presentations at European congresses of arrhythmologists and cardiologists organized by the ESC (scientific platform ESC 365), and at National Congresses of Cardiologists of Ukraine (scientific platform of the All-Ukrainian Association of Cardiologists of Ukraine), published since 2019.

Publications from Russian and Soviet periodicals were excluded during the literature search. The review includes several historically important early publications on AADs of interest in foreign journals, as well as publications from the CAST trial to provide basic necessary background information.

Results

Ethacizine is an ω-aminoacyl derivative of phenothiazine that was developed in the early 1980s. Initial research on this novel

Table 1. Clinical characteristics of AADs most commonly prescribed for patients without severe structural heart disease or heart failure

Usage feature	Class IC AADs (propafenone, flecainide, ethacizine)	Class IIA AADs (beta-adrenergic blockers)	Class IVA AADs (diltiazem and verapamil)
Sinus rhythm restoration therapy in AF	Yes	No	No
Sinus rhythm maintenance therapy in AF	Yes	Mostly in combination with other AADs	Yes, but better when there are additional indications (e. g., vasospastic angina, hypertension); overall efficacy is not high
Control of ventricular rate in permanent AF	No	Yes, but more often in combination with other drugs	No if AF is associated with heart failure
Possibility of use in clinically manifest heart failure with reduced left ventricular ejection fraction	No	Yes	No
Effect on the sympathetic nervous system	Propafenone – weak beta-blockade	Yes, beta-blockade	Unlike dihydropyridines, do not cause reflex tachycardia
Effect on the parasympathetic nervous system	Ethacizine – anticholinergic effect	No	No
Indicated for ventricular extrasystole	Yes	Yes, but officially not all agents	No
AF or atrial flutter in the presence of accessory pathways	Preferred	Not recommended	Contraindicated

compound was primarily conducted in the former USSR [14,15,16]. In addition to its properties characteristic of Class IC antiarrhythmic drugs (AADs), ethacizine has been shown to block slow calcium channels [17,18] and to exert anticholinergic effects [9,10,19]. Consequently, ethacizine influences multiple components of the physiological substrate involved in arrhythmogenesis, which may account for its high efficacy in both the suppression and prevention of supraventricular and ventricular arrhythmias. *Table 2* summarizes the key clinical differences and shared features of ethacizine and propafenone based on current drug labeling and the references cited above.

In recent years, ethacizine has experienced a research renaissance, with several high-quality clinical trials conducted; however, their geographic scope remains limited to Eastern European countries where the drug is authorized [9,19]. The National Guideline of Latvia officially recommends ethacizine for maintaining sinus rhythm following its restoration in patients with paroxysmal and persistent atrial fibrillation (AF), as well as for pharmacological cardioversion in these settings. In Ukraine, until recently, ethacizine was recommended exclusively for maintaining sinus rhythm in patients with vagally mediated paroxysmal and persistent AF. However, beginning in 2024, a resolution issued by the Ukrainian Association of Arrhythmologists recommends its use for rhythm restoration using the "pill-in-the-pocket" approach [19].

The additional anticholinergic effect of this AAD makes it unique, as currently no other AADs with such properties are authorised in Ukraine. At the same time, vagally-mediated heart rhythm disorders, particularly AF, present a substantial challenge in clinical practice, prompting the development of new agents (e. g. GIRK1 and GIRK4 channel blockers (I_{KACh}) – mediator-dependent potassium channel blockers) and invasive interventions such as cardioneuroablation [22,23,24,25,26]. Unfortunately, although research into new AADs that target vagally mediated arrhythmias is promising, such agents are still in the experimental stage [22,23]. Given the increasing prevalence of obstructive sleep apnoea among patients – which in turn is a risk factor for many cardiovascular events [27], including arrhythmias, especially vagally-mediated ones – the search for pharmacological agents that are effective in such contexts remains a relevant task and may help improve treatment outcomes for many patients.

However, up-to-date research on ethacizine is not limited to establishing its anticholinergic properties. For example, a study by B. Kokina et al. [28], conducted in Latvia, investigated the ability of different AADs to maintain sinus rhythm in patients with paroxysmal AF after electrical cardioversion. Authors evaluated the efficacy both by class and specifically for ethacizine in comparison to amiodarone, with all patients receiving ethacizine also receiving a beta-blocker. In this study, Class IC AADs (nearly three-quarters of patients received ethacizine; the rest – propafenone) were not inferior to Class III AADs (most patients received amiodarone) for maintaining sinus rhythm over 6 months (53.8 % vs. 63.0 %, p = 0.346). Similar results for sinus rhythm maintenance were observed in a direct comparison between amiodarone and ethacizine (64.1 % vs. 58.6 %, p = 0.616) [28]. These rather bold results demonstrating the high efficacy of ethacizine in the management of AF were also confirmed in other small studies [29,30].

In the prospective study conducted at the Pauls Stradins Clinical University Hospital (Latvia) 20 patients after electrical cardioversion for persistent form of AF received ethacizine (50 mg daily) and 15 patients – propafenone (300 mg daily) [29]. Their data on the safety and results of bicycle stress test were analyzed pooled and there weren't any deterioration in performed safety tests for the studied group. Initiation of therapy for the studied group had very low rate of proarrhythmogenic events without any such side effects

Table 2. Practical aspects of the use of ethacizine and propafenone for the treatment of heart rhythm disorders in patients without severe structural heart disease

Parameter	Ethacizine	Propafenone
CAST trials	Neither drug was studied in these trials	
Slow calcium channel blockade	Yes	
Beta-blocking effect	No	Weak
Anticholinergic effect	Yes	No
Indications across age groups, pregnancy, and breastfeeding	Similar	
DC index, cited from [19]	Efficacy increases 22-fold when DC >5.9 ms (vagotonia)	More effective when DC <4 ms (sympathicotonia)
Elimination half-life, hours	2.5	Depends on metabolizer type: 2–32 hours
Dosing frequency per day	2–3	3
Notable interactions	Contraindicated with monoamine oxidase inhibitors and alcohol	Warfarin dose should be reduced when co-administered; drugs metabolized via CYP2D6, CYP1A2, and CYP3A4 (e. g. ketoconazole, cimetidine, quinidine, erythromycin, grapefruit juice), rifampicin, as well as selective serotonin reuptake inhibitors increase propafenone concentration; contraindicated with ritonavir
Additional contraindications beyond typical ones of Class IC AADs	With caution in angle-closure glaucoma, benign prostatic hyperplasia	Severe obstructive pulmonary disease, Brugada syndrome, myasthenia gravis
Use as a "pill-in-the-pocket" approach for sinus rhythm restoration in AF	Limited evidence; approved in Latvia and Ukraine	Recognized and approved worldwide
Inclusion in ESC guidelines [8,20,21]	Not included	**Atrial fibrillation** (in the absence of severe structural heart disease or severe coronary artery disease): – option for pharmacological cardioversion of recent-onset AF (Class I, Level A); – for facilitation of electrical cardioversion (Class IIa, Level B); – as "pill in the pocket" strategy in selected patients with rare and recent-onset AF (Class IIa, Level B); – for long-term therapy as rhythm control strategy (Class I, Level A). **Supraventricular arrhythmias:** – option for therapy of focal atrial tachycardia (Class IIb, Level C for acute therapy, Class IIa, Level C for chronic therapy); – 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). **Ventricular arrhythmias:** – option for several ventricular arrhythmias, but absence of severe structural heart disease is still obligatory for such prescription.

DC: deceleration capacity.

during the study. The mean value of bicycle stress test duration positively changed from 5.52 to 6.04 minutes (p = 0.005) [29].

Another study from the same institution [30] included patients after electrical cardioversion for persistent form of AF. In this study, both Class IC AADs ethacizine and propafenone didn't result in negative impact on inotropic function of myocardium, but patients from the ethacizine group had numerically better (lower) AF recurrence rate compared with such in the propafenone group [30].

During the ESC Congress of Cardiologists in 2024, results of a study on the effects of ethacizine on supraventricular and ventricular premature contractions were presented [31]. In this study, ethacizine was administered at a dose of 50 mg twice daily in cases where previous AADs (bisoprolol, metoprolol, sotalol, verapamil, amiodarone, propafenone) were ineffective (i. e. the number of premature contractions remained more than 1000 per 24 hours). The administration of ethacizine resulted in a 9-fold reduction in the mean number of supraventricular premature contractions in the early treatment phase (to 761 per day, p < 0.001), and nearly a 12-fold reduction in the long-term phase (to 574 per day, p < 0.001). As for ventricular premature contractions, the reduction was 5.8-fold in the early phase (to 550 per day, p < 0.001), and 6.5-fold in the long-term phase (to 490 per day, p < 0.001). Adverse effects

of ethacizine therapy were observed in 4 out of 98 examined patients: one case each of Mobitz I atrioventricular block, sustained ventricular tachycardia, asymptomatic nonsustained polymorphic ventricular tachycardia, and asymptomatic transient ST segment elevation detected during 24-hour Holter ECG monitoring [31].

In autumn 2024, at the XXV National Congress of Cardiologists of Ukraine, results of a retrospective study were presented, conducted at the National Scientific Center "M. D. Strazhesko Institute of Cardiology, Clinical and Regenerative Medicine" of the National Academy of Medical Sciences of Ukraine, evaluating the efficacy and safety of ethacizine in patients with AF, including its use for pharmacological cardioversion ("Assessment of the efficacy and safety of ethacizine for relapse-prevention therapy and rhythm restoration in a "pill-in-the-pocket" approach in patients with hypertension and paroxysmal atrial fibrillation" [32]). This study revealed that the sinus rhythm restoration rate with ethacizine use as a "pill-in-the-pocket" in paroxysmal AF was 61.1–63.7 %.

Thus, compared to the efficacy of other Class IC AADs recommended for "pill-in-the-pocket" strategy use [8], ethacizine is generally not inferior to propafenone and flecainide. The questions raised in this study formed the basis for the rationale of a national survey of clinicians (Ethacizine evaluation for acute and chronic treatment of atrial fibrillation in real practice: Ukrainian national survey – ETERNITY) [33], aimed at assessing real clinical practice conditions for the use of ethacizine in maintaining and restoring sinus rhythm in patients with paroxysmal and persistent AF in Ukraine. Preliminary results have already been obtained and are scheduled for presentation at the European Congress of Arrhythmologists [19].

Another direct comparison study of propafenone and ethacizine in the management of patients with AF is planned and is currently in the final stages of planning and approval [19]. This will be an international, multicentre, open-label, randomized clinical trial involving 144 patients with paroxysmal / persistent AF, with a 180-day follow-up period, in which the study drugs will be used to maintain sinus rhythm.

The efficacy and safety of ethacizine in maintaining sinus rhythm in patients with AF was also discussed at the most recent European Congress of Arrhythmologists (EHRA 2025) held in spring 2025 in Vienna [34]. The presentation featured extended results from an open-label, single-centre, prospective study by the Latvian Centre of Cardiology, in which patients with persistent AF received either propafenone (600 mg daily) or ethacizine (100 mg daily) for 6 months following electrical cardioversion and restoration of sinus rhythm. A total of 57 patients completed the study protocol (mean age 62.6 ± 6.8 years, 36.8 % male). The rate of AF recurrence in the ethacizine group showed a near-statistically significant advantage over the propafenone group (55.6 % vs. 72.5 %; p = 0.05). None of the patients in either group experienced serious adverse events, nor were there significant changes in blood test results, biochemical markers, ECG parameters, stress test results, or Holter ECG monitoring findings, including left ventricular ejection fraction. The authors concluded that ethacizine did not affect QT interval duration on ECG or myocardial inotropic function and may potentially be administered immediately after sinus rhythm restoration. They titled their presentation with a rhetorical and timely question for all currently available Class IC AADs: "The many NO's to the use of class I antiarrhythmics: does this also apply to ethacizinum?" [34].

Conclusions

1. Thus, among Class IC AADs available in Ukraine, the main "players" – especially in terms of wide application including benign ventricular arrhythmias – are currently propafenone and ethacizine. These agents are not associated with negative outcomes in the CAST trials, and each has the potential to influence dysautonomia in its own way.

2. The specific contraindications and drug interactions of propafenone and ethacizine allow physicians to choose the safer and more effective option based on the patient's individual characteristics.

3. Ethacizine has in recent years accumulated new evidences from well-designed studies under up-to-date patient management approaches. The results of these studies are now being presented at high-level international scientific events, consistently creating the evidence basis for its broader recognition.

Prospects for further research. The literature and scientific data analysed justify the planning of new studies on Class IC AADs, particularly propafenone and ethacizine, under contemporary conditions of managing patients with heart rhythm disorders, with special attention to dysautonomia as a factor influencing arrhythmogenesis. Such studies are already planned and are at various stages of implementation. Their results are expected to be presented at the European Congress of Arrhythmologists and the National Congress of Cardiologists of Ukraine.

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