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Results of a Survey "Ethacizine evaluation for acute and chronic treatment of atrial fibrillation in real practice: Ukrainian national survey (ETERNITY)"

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The aim of the study: based on a survey of physicians, the study aims to identify the real clinical practices regarding the use of class IC antiarrhythmic drugs in Ukraine, particularly ethacizine, for restoring sinus rhythm in paroxysmal and persistent forms of atrial fibrillation, employing a methodology similar to the "pill-in-the-pocket" approach.

Materials and methods. Data were analysed from 100 anonymous voluntary questionnaires. We used snowball sampling to collect the responses. Participants had the option to skip questions, and calculations were based on the number of respondents who answered each question.

Results. More than half of the respondents actively prescribe class IC antiarrhythmic drugs (AADs), with ethacizine being the most commonly prescribed (56.8 % of respondents). Notably, 61.4 % of respondents had never prescribed flecainide, 34.3 % had never prescribed propafenone, and 18.6 % had never prescribed ethacizine. The primary indication for prescribing class IC AADs was atrial fibrillation (AF) (43.3 %), followed by the combination of ventricular and supraventricular rhythm disturbances (34.4 %). Only 13.8 % of respondents initiate therapy with class IC AADs exclusively in inpatient settings, while 31.9 % primarily did so in outpatient settings with ECG monitoring. More than half of the respondents reported experience restoring sinus rhythm (SR) in AF with ethacizine using a regimen similar to "pill-in-the-pocket"; over a quarter of these cases were decisions made by patients already on ethacizine for SR maintenance. More than a quarter of respondents had experience using ethacizine for the "acute treatment" of AF in single doses higher than the standard 100 mg (125 mg – 6.8 %; 150 mg – 20.3 %). At the same time, 31.9 % of respondents prescribed ethacizine for SR restoration in AF as discrete regimens, prescribing low doses at shorter intervals (1–3 hours).

Conclusions. The survey results indicate that class IC AADs, especially ethacizine, are actively prescribed in real clinical practice not only for arrhythmia prevention, including AF, but also for SR restoration. This underscores the need for high-quality clinical studies to assess the efficacy and safety of such treatment strategies for ethacizine, which remains less studied within class IC AADs.

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Результати опитування «Оцінювання етацизину для гострого та хронічного лікування фібриляції передсердь у реальній практиці: українське національне опитування (ETERNITY)»

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Мета роботи – на підставі опитування лікарів виявити умови реальної клінічної практики використання в Україні антиаритмічних препаратів (ААП) IC класу, а також окремо етацизину для відновлення синусового ритму (СР) у форматі, схожому на стратегію «таблетка в кишені», при пароксизмальній та персистуючій формах фібриляції передсердь (ФП).

Матеріали і методи. Проаналізовано дані 100 анкет анонімного добровільного опитування лікарів; для збору анкет застосовано метод snow-ball. У респондента була можливість пропускати запитання, розрахунки проводили за кількістю тих, хто відповів на кожне запитання.

Результати. Більше ніж половина опитаних активно використовує ААП IC класу, найчастіше етацизин (56,8 % опитаних). Ніколи не призначали флекаїнід 61,4 % опитаних, пропафенон – 34,3 %, етацизин – 18,6 %. Найбільш частим показанням до призначення ААП IC класу були ФП (43,3 %) та поєднання шлуночкових та суправентрикулярних порушень серцевого ритму (34,4 %). Тільки 13,8 % респондентів завжди розпочинають терапію ААП IC класу виключно в стаціонарі, 31,9 % – переважно в амбулаторних умовах з оцінкою електрокардіограми. Більше половини опитаних мали досвід відновлення СР при ФП етацизином в режимі, схожому на «таблетку в кишені», більше чверті таких випадків є рішенням пацієнта, який вже отримував етацизин для підтримання СР. Більше чверті респондентів мають досвід застосування

етацизину «в гострому лікуванні» ФП у разових дозах, вищих за загальноприйняті 100 мг (125 мг – 6,8 %, 150 мг – 20,3 %), при цьому 31,9 % опитаних застосовували етацизин для відновлення СР при ФП у дискретному режимі, призначивши невисокі дозі з коротшими інтервалами (1-3 годин).

Висновки. Згідно з опитуванням, ААП IC класу, зокрема етацизин, в реальній практиці активно застосовуються не тільки при профілактиці аритмій, зокрема ФП, але й для відновлення СР, що потребує планування якісних клінічних досліджень ефективності та безпеки такої стратегії для етацизину, як менш вивченого з групи IC класу ААП.

Сучасні медичні технології. 2025. Т. 17, № 4(67). С. 266-278

The "pill-in-the-pocket" approach was proposed by the European Society of Cardiology Guidelines for managing atrial fibrillation (AF) as a convenient, though less effective, method for restoring sinus rhythm (SR) in patients with paroxysmal and persistent AF. This approach is also supported by national Ukrainian guidelines and protocols [1,2,3]. In this method, developed to reduce the burden for healthcare systems, patients self-administer a single oral dose of propafenone (450–600 mg) or flecainide (200–300 mg) during an AF paroxysm [4,5,6].

The "pill-in-the-pocket" strategy, which is exclusive to class IC antiarrhythmic drugs (AADs), is recommended only for selected patients, particularly those with infrequent episodes (ranging from once a month to once a year) of AF accompanied by severe symptoms. However, its efficacy and safety must be established before initiation in inpatient settings, where contraindications and the presence of severe structural heart diseases should be ruled out for eligible patients [1,2].

The national Ukrainian regulatory documents on AF management, including a guideline and unified clinical protocol approved by Order of the Ministry of Health of Ukraine No. 597 dated 15/06/2016 [7,8], as well as the Duodecim guideline of 2018 [9], are largely outdated. The European regulatory framework has been updated twice since then. Currently, Ukrainian cardiologists adhere to standards set by the Ukrainian Association of Cardiology, which, unlike the documents of the Ministry of Health of Ukraine, are updated almost annually. It is important to note that in guidelines designed for primary care (Duodecim), propafenone is not mentioned for SR restoration in AF, despite its internationally recognized role in such situations. Only flecainide [9] is mentioned, which has been available in Ukraine since 2020.

The national Ukrainian standards for the diagnosis and treatment of AF, apart from propafenone and flecainide – whose roles in the "pill-in-the-pocket" approach for restoring and maintaining SR in AF patients are internationally recognized – the class IC AAD ethacizine also mentioned, previously for treating vagally-induced AF [3,10]. Recently, the stance of the Ukrainian Association of Cardiology towards ethacizine as a drug, along with propafenone and flecainide, also capable of restoring SR in AF paroxysm, has evolved. The 2024 resolution from the Ukrainian Association of Cardiology and the Ukrainian Association of Arrhythmologists officially recommended ethacizine for restoring SR based on a local retrospective study results, which led to the new recommendations in recent national Ukrainian AF treatment standards 2025 for restoring and maintenance SR in patients with paroxysmal/persistent AF with ethacizine regardless their autonomic nervous system state [11,12,13]. This study showed that ethacizine, when self-administered by patients with paroxysmal and persistent AF and arterial hypertension, was effective in a regimen similar to the "pill-in-the-pocket" approach [14].

Notably, the first studies assessing the efficacy of oral ethacizine for restoring SR in AF were conducted back in 1989, establishing the recommended safe dose of 100 mg for single oral administration [15]. The efficacy of the drug at that time ranged from 50 % to 77.7 %. At that time, researchers also explored regimens with discrete use of lower doses of ethacizine for rhythm restoration, seeking effective intervals for administration [15]. However, the small sample size, single-centre design, and other limitations of the studies, along with the superficial nature of the published results, hindered their recognition.

According to the previously mentioned study conducted in Ukraine involving more than 500 patients [14], the efficacy of ethacizine for restoring SR in AF when used as "pill-in-the-pocket" was approximately 61–63 % [14]. This is comparable to the efficacy of the "pill-in-the-pocket" approach with propafenone (50–60 %, up to 85 %) and flecainide (45–55 %, up to 78 %) [2]. An interesting finding from the study conducted by O. S. Sychov et al. [14] indicated that depending on the concurrent use of ethacizine, the effective "pill-in-the-pocket" dose could be lower for patients taking the drug continuously while potentially being higher (including exceeding the recommended 100 mg) for those not receiving AADs for prophylactic purposes.

This desire to clarify the current state of class IC AAD usage for managing AF in Ukraine, especially regarding ethacizine – which is unavailable in some other countries – led to the development of the survey study titled "**Et**hacizine **E**valuation for acute and chronic treatment of at**r**ial fibrillatio**n** in real practice: Ukra**I**nian na**T**ional surve**Y** – ETERNITY."

Aim

Based on a survey of physicians, the study aims to identify the real clinical practices regarding the use of class IC AADs in Ukraine, particularly ethacizine, for restoring sinus rhythm in paroxysmal and persistent forms of atrial fibrillation, employing a methodology similar to the "pill-in-the-pocket" approach.

Materials and methods

The detailed rationale and design of the ETERNITY study have been described earlier [15]. This study involved an anonymous voluntary survey conducted among physicians across Ukraine via a questionnaire (targeting internal medicine doctors,

general practitioners, cardiologists, and arrhythmologists) using an online Google Form. A mailing containing the survey link was sent to physicians using available databases and social/professional networks. The snowball sampling was used, which made it possible to form a homogeneous sample: if they wished, invited physicians could forward the survey link to colleagues experienced in prescribing class IC AADs.

The initial target was to collect 100 completed questionnaires. The study commenced on November 15, 2024, and concluded on February 28, 2025.

The survey consisted of four sections: Section I: General minimal information about the physician (4 questions); Section II: General questions regarding class IC AADs (15 questions); Section III: General questions concerning the use of ethacizine (4 questions); Section IV: Use of ethacizine similar to the "pill-in-the-pocket" approach (15 questions). Physicians were encouraged to respond honestly and provide their genuine opinions on the questions. If they were unable or unwilling to answer any specific question, they could skip it – none of the questions, except for those in the first section, were mandatory.

Response censorship procedure. In certain cases, researchers found contradictory responses, such as a physician claiming they had never prescribed AAD while also evaluating it and describing dosing regimens used in practice. In such instances, the researcher analysing the data (N.S.) adhered to the principle of retaining the first response and censored any subsequent answers that contradicted this initial information. If no answers were provided to the key questions, those responses were not considered negative, and subsequent related answers were not censored. The censorship of responses was carried out as follows:

1. The entire questionnaire data were censored if there was a negative answer to the question: "Please confirm that you are a physician and manage patients with rhythm and conduction disorders".

2. For question 3 in Section II, "Which class IC drugs have you never prescribed and have no personal experience with?" if the respondent selected ethacizine, the following answers in Section II were censored: questions 5 and 12 (marked in *Table 2*); all questions in Section III *(Table 4)*; and all questions from 1 to 14 in Section IV (marked in *Table 5*). If propafenone was selected, responses to questions 6 and 13 in Section II were censored. If flecainide was selected, responses to questions 7 and 14 (all marked in *Table 2*) were censored.

3. In case of a negative response to question 1 in Section IV, "Have you ever prescribed/your patients ever used ethacizine as a 'pill-in-the-pocket' approach for AF?", answers to questions 4, 5, 13, and 14 of this section (marked in *Table 5*) were censored. If there was a negative answer to question 2 in Section IV, "Have you ever prescribed/your patients ever used ethacizine in a single high dose (as a 'pill-in-the-pocket' approach) for the treatment of other rhythm disturbances?", the response to question 3 of this section was censored. If negative answers were provided to both questions simultaneously, responses to questions 3 through 9 (inclusive) as well as questions 13 and 14 of Section IV were censored.

4. If a negative answer was given to question 10 in Section IV, "Have you ever prescribed/your patients ever used fractional administration of ethacizine for SR restoration in AF (a prolonged regimen of low doses at short intervals)?", the answers to questions 11 and 12 of this section (marked in *Table 5*) were censored.

When assessing physicians' satisfaction with various class IC AADs, they were asked to give a score from 0 ("completely dissatisfied") to 10 ("completely satisfied"). The mean score for each drug and the frequency of positive/negative ratings were then determined according to the following interpretation: 0–3 points: "Poor," 4–6 points: "Fair," 7–8 points: "Good," and 9–10 points: "Very good." Satisfaction scores for different class IC AADs were censored if the physician previously indicated that they had not used the drug, since physicians often selected the answer "0" in the absence of experience with AADs, leading to a significant underestimation of the values for propafenone and flecainide.

Descriptive statistics were applied to determine the mean and standard deviation, as well as the calculation of kurtosis and skewness for the mean satisfaction scores of class IC AADs. Percentages were used to assess response frequency in the ETERNITY population. Comparisons were made by determining the two-tailed p-value using a two-sample t-test with unequal variances, while percentages were compared using the method of alternative variation. For each question, the actual number of responses was considered in both the general analysis and the comparative analysis, with a p-value of <0.05 considered statistically significant. Calculations were performed using statistical software within Microsoft® Excel® for Microsoft 365 MSO (version 2501, build 16.0.18429.20132).

Results

A total of 104 questionnaires were completed. Three questionnaires were censored because the respondents did not confirm that they were physicians managing patients with rhythm/conduction disorders. One questionnaire was censored because, apart from the first section of questions, the respondent did not provide answers to any questions in Sections II–IV, making it entirely non-informative regarding the subject of the study. Consequently, the final analysis included data from 100 completed questionnaires.

Questions of Section I. Section I focused on the general characteristics of the physicians who participated in the survey. The sample primarily consisted of cardiologists conducting outpatient consultations *(Table 1)*.

Questions of Section II. Section II focused on general questions regarding the prescription of class IC AADs *(Table 2)*. The majority of respondents (54.1 %) reported that they prescribe class IC AADs "quite often". Among these drugs, ethacizine was the most frequently used (56.8 %).

The most common indications for which physicians prescribed class IC AADs included AF and the combination of ventricular and supraventricular rhythm disturbances *(Table 2)*.

Further clarifying questions were asked about the main class IC AADs, allowing for the creation of individual profiles for each drug, facilitating convenient comparison *(Table 3)*. The primary reasons for prescribing ethacizine included personal positive experience (48.8 %), followed by publications, reports, and

Table 1. Section I questions. General information about ETERNITY study respondents

Questions and answers (n)	Abs.	%
1. Please confirm that you are a physician and manage patients with rhythm and conduction disorders (n = 100)		
Yes	100	100
2. Country where you work (n = 100)		
Ukraine	100	100
3. Your specialty (choose one, or add not listed) (n = 100)		
Internal medicine doctor	15	15
General practitioner	23	23
Cardiologist	60	60
Other	2	2
4. Specify the type of facility where you work (n = 100)		
Inpatient	25	25
Outpatient	66	66
Emergency department	3	3
Other	6	6

recommendations from scientists (15.5 %), and its additional cholinolytic effect (14.3 %). For propafenone, the three main reasons for its prescription were positive personal experience (37.1 %), its inclusion in European and national guidelines, and its additional beta-blocking effect. Conversely, flecainide was primarily chosen for its availability in European and national guidelines, positive experiences with its use, its lack of effect on the autonomic nervous system, and its effectiveness in managing life-threatening ventricular rhythm disturbances. In summary, a key factor in selecting both propafenone and flecainide was their endorsement in European and national guidelines.

The primary reasons for not prescribing a specific class IC AAD were more similar *(Table 2)*. Interestingly, among the reasons for non-prescription, the proarrhythmic effect was cited most frequently for flecainide (6.9 %), slightly less for propafenone (6.6 %), and not mentioned at all for ethacizine. Furthermore, the difference between ethacizine and the other two drugs was statistically significant in favour of ethacizine (see *Tables 2*, *3*).

About one in five physicians prescribe class IC AADs in hospitals when possible, occasionally administering them in outpatient settings under ECG monitoring. Moreover, 48.9 % mainly or exclusively prescribe these medications in outpatient settings, while 14.9 % do not initiate therapy themselves but continue treatment already prescribed by another specialist.

The results of the physicians' evaluations of the three class IC AADs indicated that ethacizine received the highest satisfaction score, significantly surpassing that of propafenone (p = 0.014). Although the score for ethacizine was quantitatively higher than that for flecainide, this difference was not statistically significant. Additionally, no significant difference was observed between the scores for propafenone and flecainide (see *Table 3*). When the scores were categorized into the gradations of "Poor" (0–3 points), "Fair" (4–6 points), "Good" (7–8 points), and "Very Good" (9–10 points), all three drugs exhibited statistically similar distributions. Nonetheless, some quantitative trends were noted: flecainide performed slightly better in the "Good" category, while ethacizine excelled in the "Very Good" category.

Further insights emerged from responses regarding the approaches to prescribing AADs and treating rhythm disturbances. Despite a relatively widespread application of patient-oriented management principles among the ETERNITY respondents, it is interesting to note that 20 % of physicians believe their patients fully trust them. This suggests that discussions about treatment strategies may be considered unnecessary. Additionally, 3 % of physicians indicated that patients often make independent decisions regarding adjustments to their AAD doses, similar to the "pill-in-the-pocket" approach *(Table 2)*.

Section III questions. The third section examined the use of ethacizine regimens and consideration of the patient's opinion in its prescription *(Table 4)*.

The most commonly reported daily dose of ethacizine among ETERNITY respondents was 100 mg, with a preferred administration frequency of twice daily. Among the respondents, 39.0 % considered 50 mg to be the maximum single dose of ethacizine, while 92.2 % reported using doses up to 100 mg. Additionally, 7.8 % of respondents have an experience of prescribing single doses exceeding 100 mg.

Section IV questions. Section IV questions examined the use of ethacizine as a pharmacological strategy for cardioversion AF *(Table 5)*.

Among the respondents, 52.23 % reported using ethacizine for this purpose. Furthermore, 54.8 % incorporated ethacizine into a regimen similar to the "pill-in-the-pocket" approach for managing other rhythm disturbances. The vast majority of respondents found the approach similar to the "pill-in-the-pocket", but applied to ethacizine, sufficiently effective (*Fig. 1*).

Table 2. Answers to Section II questions. General questions regarding class IC drugs

Questions and answers (n)	Abs.	%
1. How often do you prescribe class IC AADs to patients with rhythm disturbances? (n = 98)		
Quite often	53	54.1
Sometimes	22	22.4
Rarely	18	18.4
In exceptional cases	5	5.1
2. Which class IC AAD do you personally prescribe most frequently? (n = 95)		
Ethacizine	54	56.8
Propafenone	26	27.4
Flecainide	15	15.8
3. Which class IC drugs have you never prescribed and have no personal experience with? (multiple choice possible) (n = 70)		
Ethacizine	13	18.6
Propafenone	24	34.3
Flecainide	43	61.4
4. What is the most frequent indication for which you prescribe class IC AADs (choose one, most frequent)? (n = 99)		
Atrial fibrillation	43	43.4
Other supraventricular rhythm disturbances	6	6.1
Rhythm disturbances with accessory pathways	3	3.1
Ventricular rhythm disturbances	13	13.1
Combination of ventricular and supraventricular rhythm disturbances	34	34.3
5. What is the most important reason why you choose ethacizine when prescribing class IC AADs (choose one, most important)? (n = 84)		
Additional cholinolytic effect	12	14.3
Positive experience of prescribing	41	48.8
Few side effects	3	3.6
Stable pharmacokinetics not dependent on cytochrome P450 system	5	5.9
Publications, reports, scientists' recommendations	13	15.5
Minimal number of drug interactions among class IC AADs	3	3.6
Availability for patients through reimbursement programs in my country	3	3.6
Lack of effect of other drugs	1	1.1
Other	3	3.6
6. What is the most important reason why you choose propafenone when prescribing class IC AADs (choose one most important)? (n = 70)*		
Additional beta-sectioning effect	17	24.3
Inclusion in European and national guidelines	18	25.7
Positive experience of prescribing	26	37.1
Publications, reports, scientists' recommendations	5	7.1
Availability for patients through reimbursement programs in my country	2	2.9
Lack of effect of other drugs	1	1.4
Other	1	1.4

Cont. of Table 2.

Questions and answers (n)	Abs.	%
7. What is the most important reason why you choose flecainide when prescribing class IC AADs (choose one most important)? (n = 56)		
No effects on sympathetic/parasympathetic nervous system	8	14.3
Long half-life	3	5.3
Patients having life-threatening ventricular arrhythmias	8	14.3
Inclusion in European and national guidelines	17	30.4
Positive experience of prescribing	13	23.2
Publications, reports, scientists' recommendations	6	10.7
Availability for patients through reimbursement programs in my country	0	0
Need to prescribe to children aged 12 years and older	0	0
Other	1	1.8
8. What is the most frequent reason why you do NOT prescribe ethacizine when there are indications for class IC AADs and prefer another drug (choose one most frequent)? (n = 94)		
Absence in European/national guidelines	12	12.8
Absence in reimbursement programme	6	6.4
Patient's alcohol consumption	8	8.5
Too high cost	15	15.9
Presence of contraindications specific to ethacizine not applicable to other class IC drugs	14	14.9
Negative experience with use	2	2.1
Proarrhythmic effect of ethacizine	0	0
Advantages of another drug in a specific clinical situation	37	39.4
9. What is the most frequent reason why you do NOT prescribe propafenone when there are indications for class IC AADs and prefer another drug (choose one most important)? (n = 91)		
Absence in reimbursement programme	4	4.4
Too high cost	2	2.2
Asthma	9	9.9
Concerns regarding erectile function/fertility in men	1	1.1
Other contraindications specific to propafenone not applicable to other drugs	17	18.7
Negative experience with use	1	1.1
Adverse drug interactions	5	5.5
Proarrhythmic effect of propafenone	6	6.6
Advantages of another drug in a specific clinical situation	46	50.5
10. What is the most frequent reason why you do NOT prescribe flecainide when there are indications for class IC AADs and prefer another drug (choose one most important)? (n = 87)		
Absence in reimbursement programme	9	10.3
Too high cost	2	2.4
Other contraindications specific to flecainide not applicable to other drugs	15	17.2
Negative experience with use	1	1.2
Adverse drug interactions, including with psychotropic drugs	5	5.8
Proarrhythmic effect of flecainide	6	6.9

Cont. of Table 2.

Questions and answers (n)	Abs.	%
Advantages of another drug in a specific clinical situation	33	37.9
CAST I study results	4	4.6
Ventricular arrhythmias not considered potentially life-threatening	12	13.7
11. Do you always initiate class IC AAD therapy in hospital under monitoring for possible proarrhythmic effect? (n = 94)*		
Yes, always	13	13.8
If possible, sometimes I initiate therapy in outpatient settings with ECG monitoring	21	22.3
I initiate therapy predominantly in outpatient settings, but with ECG monitoring and management of proarrhythmic effect	30	31.9
I initiate therapy in outpatient settings with small doses, if possible with ECG monitoring	16	17.0
I do not initiate, but continue therapy already prescribed by another specialist	14	14.9
12. How would you rate your own satisfaction (efficacy/safety) with ethacizine on a 10-point scale (0 – extremely dissatisfied, 10 – extremely satisfied)? (n = 84)		
Poor (0–3)	1	1.2
Fair (4–6)	16	19.0
Good (7–8)	37	44.1
Very good (9–10)	30	35.7
Mean score ± standard deviation	7.9 ± 1.8	
13. How would you rate your own satisfaction (efficacy/safety) with propafenone on a 10-point scale (0 – extremely dissatisfied, 10 – extremely satisfied)? (n = 75)		
Poor (0–3)	4	5.3
Fair (4–6)	23	30.7
Good (7–8)	30	40.0
Very good (9–10)	18	24.0
Mean score ± standard deviation	7.2 ± 2.0	
14. How would you rate your own satisfaction (efficacy/safety) with flecainide on a 10-point scale (0 – extremely dissatisfied, 10 – extremely satisfied)? (n = 57)		
Poor (0–3)	0	0
Fair (4–6)	13	22.8
Good (7–8)	31	54.4
Very good (9–10)	13	22.8
Mean score ± standard deviation	7.5 ± 1.4	
15. To what extent do you consider the patient's opinion when prescribing class IC AADs in your clinical practice (multiple answers possible)? (n = 100)		
I necessarily discuss the drug prescription, and for planned therapy, agree on the strategy and treatment plan	60	60.0
I consider the patient's wish to also use the drug for SR restoration in AF as "pill-in-the-pocket"	46	46.0
I consider the patient's concerns, and if necessary change the treatment approach/drug at the patient's request	9	9.0
Most often the patient trusts the physician and there is no need to discuss treatment approaches, drug choice, or regimen	21	21.0
I discuss only the "pill-in-the-pocket" approach and, with consent, suggest checking efficacy and safety in hospital	20	20.0
Often the patient, without consulting the physician, decides to change the dose or use the drug as "pill-in-the-pocket"	3	3.0

***:** For marked questions, the sum of percentages when assessing the frequency of answer options may differ from 100 % by 0.1, which is due to the rounding of the obtained values.

Table 3. Profiles of class IC AADs available in Ukraine, analysed in ETERNITY

Indicators	Ethacizine	Propafenone	Flecainide
Mean satisfaction score ± SD	7.9 ± 1.8	7.2 ± 2.0 p1 = 0.014	7.5 ± 1.4 p1 = 0.159 p2 = 0.222
Poor, %	1.2	5.3	0[#]
Fair, %	19.0	30.7	22.8
Good, %	44.1	40.0	54.4
Very good, %	35.7	24.0	22.8
Class IC AAD most frequently prescribed, %	56.8	27.4	15.8
Class IC AAD never prescribed, %	18.6	34.3	61.4
Top 3 main reasons for prescription	Positive experience 48.8 %, Publications/reports/ recommendations 15.5 % Additional cholinolytic effect 14.3 %	Positive experience 37.1 %, Inclusion in European/national guidelines 25.7 %, Additional beta-sectioning effect	Inclusion in European/national guidelines 30.4 %, Positive experience 23.2 % Absence of effects on autonomic nervous system and presence of life-threatening ventricular arrhythmias (14.3 % each)
Proarrhythmic effect as main reason for non-prescription, %	0	6.6*	6.9*

p-values depended on the number of responses for each question. **p1:** comparison with ethacizine, **p2:** comparison with propafenone; ***:** p compared with ethacizine <0.05; **#:** p compared with propafenone <0.05.

Table 4. Section III: General questions on ethacizine use

Questions and answers (n)	Abs.	%
1. What is the most frequent daily dose of ethacizine you prescribe? (n = 83)		
50 mg	16	19.3
100 mg	45	54.2
150 mg	20	24.1
200 mg	2	2.4
2. What is the most frequent dosing frequency of ethacizine in your practice? (n = 84)		
Once daily	7	8.3
Twice daily	52	61.9
Three times daily	24	28.6
Four times daily	1	1.2
3. What is the highest single dose of ethacizine you have prescribed? (n = 77)		
50 mg	30	39.0
75 mg	4	5.2
100 mg	37	48.0
125 mg	2	2.6
150 mg	4	5.2

Cont. of Table 4.

Questions and answers (n)	Abs.	%
4. To what extent do you take into account the patient's opinion when prescribing ethacizine in your clinical practice (multiple choice possible)? (n = 84)		
I necessarily discuss the drug prescription, and for planned therapy, agree on the strategy and treatment plan	52	61.9
I consider the patient's wish to also use the drug for SR restoration in AF as "pill-in-the-pocket"	24	28.6
I consider the patient's concerns, and if necessary change the treatment approach /drug at the patient's request	14	16.4
Most often the patient trusts the physician and there is no need to discuss treatment approaches, drug choice, or regimen	26	31.0
I discuss only the "pill-in-the-pocket" approach and, with consent, suggest checking efficacy and safety in hospital	7	8.3
Often the patient, without consulting the physician, decides to change the dose or use the drug as "pill-in-the-pocket"	2	2.4

Table 5. Section IV questions: Use of ethacizine for pharmacological cardioversion in AF

Questions and answers (n)	Abs.	%
1. Have you ever prescribed/your patients ever used ethacizine as "pill-in-the-pocket" approach for AF? (n = 92)		
Yes	48	52.2
No	44	47.8
2. Have you ever prescribed/your patients ever used ethacizine in a single high dose (as "pill-in-the-pocket" approach) for the treatment of other rhythm disturbances? (n = 93)		
Yes	51	54.8
No	42	45.2
3. If you answered positively to the previous question, which other rhythm disturbances were treated with a single high (100 mg) dose of ethacizine (multiple answers possible)? (n = 51)		
Supraventricular rhythm disturbances	25	49.0
Ventricular rhythm disturbances	33	64.7
Rhythm disturbances associated with accessory pathways	5	9.8
Rhythm disturbances associated with vagotonia	16	31.4
Rhythm disturbances related to gastrointestinal pathology (e.g., cholecystocardiac syndrome)	7	13.7
4. If you have experience with ethacizine in the "pill-in-the-pocket" regimen, how do you evaluate its efficacy for SR restoration in AF? (n = 45)*		
Very effective	11	24.4
Rather effective	28	62.2
Fair	6	13.3
Rather ineffective	0	0
Ineffective	0	0
5. If you have experience with ethacizine in the "pill-in-the-pocket" regimen, how do you evaluate its efficacy for SR restoration in AF compared with flecainide/propafenone? (n = 43)*		
Better than propafenone/flecainide	8	18.6
Rather better than propafenone/flecainide	17	39.5
On the same level as propafenone/flecainide	12	27.9
Rather worse than propafenone/flecainide	5	11.6
Worse than propafenone/flecainide	1	2.3

Cont. of Table 5.

Questions and answers (n)	Abs.	%
6. If you have experience with ethacizine as the "pill-in-the-pocket" approach, why was it chosen instead of flecainide or propafenone (choose the most important)? (n = 53)		
Because the patient independently decided to use ethacizine in this regimen during paroxysm, as he/she was already receiving it for planned treatment	15	28.3
Because this drug was recommended by another specialist after proving efficacy and safety in this regimen	16	30.2
Because I personally prefer this drug in this regimen and recommended it to the patient	20	37.7
Other	2	3.8
7. What is the usual dose when using ethacizine as "pill-in-the-pocket" in your practice? (n = 57)		
50 mg	19	33.3
75 mg	4	7.0
100 mg	33	57.9
125 mg	0	0
150 mg	1	1.8
8. What is the highest dose of ethacizine in the "pill-in-the-pocket" regimen you have used/observed in your practice? (n = 59)		
50 mg	3	5.1
75 mg	2	3.4
100 mg	38	64.4
125 mg	4	6.8
150 mg	12	20.3
9. What is the lowest dose of ethacizine in the "pill-in-the-pocket" regimen you have used/observed in your practice? (n = 59)		
25 mg	14	23.7
50 mg	45	76.3
75 mg	0	0
Other	0	0
10. Have you ever prescribed/your patients ever used fractional administration of ethacizine for SR restoration in AF (a prolonged regimen of low doses at short intervals)? (n = 91)		
Yes	29	31.9
No	62	68.1
11. What was the reason for fractional administration of ethacizine for SR restoration in AF? (n = 30)		
To increase the probability of SR restoration by increasing the daily dose, i.e., did not consider it as "pill-in-the-pocket"	10	33.3
Side effects of the drug at a 100 mg dose	1	3.3
Attempt to avoid increased risk of proarrhythmic effect	17	56.7
Bradycardia	2	6.7
12. What was the efficacy of fractional administration of ethacizine for SR restoration in AF? (n = 30)		
Ineffective	1	3.3
Weaker efficacy than the standard dose	11	36.7
Effective	16	53.3
As effective as a standard high dose	2	6.7

Cont. of Table 5.

Questions and answers (n)	Abs.	%
13. Which side effects did you most frequently observe with the use of ethacizine as "pill-in-the-pocket" for SR restoration in AF? (n = 48)		
Proarrhythmic effect (appearance of rhythm and conduction disturbances)	4	8.3
Ocular symptoms (accommodation disorders, diplopia)	1	2.1
Neurological symptoms (dizziness, vertigo, balance disorders during abrupt head turns)	9	18.8
Did not observe significant side effects influencing patient management	27	56.2
Prolongation of QRS interval without rhythm disturbances and blocks	7	14.6
14. Did the side effects observed with the use of ethacizine as "pill-in-the-pocket" influence your and the patient's decision regarding continuation of this drug for SR restoration? (n = 47)		
Yes, I revised the therapy and chose another drug/strategy	8	17.0
Yes, I reduced the single dose	6	12.8
Yes, I decided to try fractional administration of smaller doses at short intervals	10	21.3
No, side effects were minor and did not require therapy modification	23	48.9
15. Do you support the feasibility of introducing ethacizine into national guidelines as "pill-in-the-pocket" for SR restoration in AF based on your own experience and studies of such use, including 2024 data obtained in Ukraine (presented at the 25th National Congress of Cardiologists)? (n = 91)*		
Yes, definitely support	35	38.5
Yes, but only in cases of vagus-associated rhythm disturbances	14	15.4
Rather support	18	19.8
Difficult to answer	12	13.2
Rather do not support	3	3.3
Do not support	6	6.6
In our country, this strategy has already been introduced into the national standard for this indication	3	3.3

*: for marked questions, the sum of percentages when assessing the frequency of answer options may differ from 100 % by 0.1, which is due to the rounding of the obtained values.

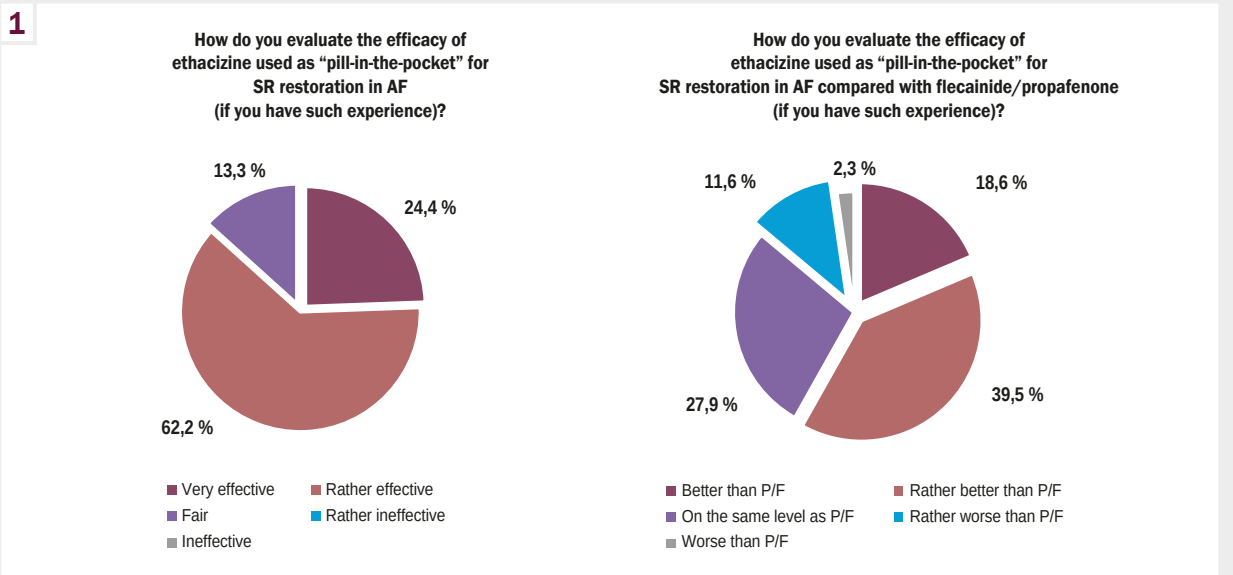

Fig. 1. Answers to questions 4 and 5 of Section IV. P = propafenone; F = flecainide. The sum of percentages when assessing the frequency of answer options may differ from 100 % by 0.1, which is due to the rounding of the obtained values.

Discussion

In this survey, 61.4 % of respondents indicated that they had never prescribed flecainide, and more than one-third had no personal experience with propafenone. This observation aligns with previous data regarding the popularity of class IC AADs in Ukraine [16]. Interestingly, similar trends have been observed in Latvia, where ethacizine is commonly prescribed to maintain SR after cardioversion for paroxysmal AF [16,17,18,19].

Unexpectedly, only 13.8 % of respondents reported that they always initiate therapy with class IC AADs in an inpatient setting, as recommended [3,7,8,9].

Among the main reasons for using ethacizine specifically for pharmacological cardioversion in AF, 28.3 % of respondents indicated patients` decision who were already receiving ethacizine as part of their planned treatment [14]. When considering the maximum dose for this clinical scenario [11,12], most physicians opted for ethacizine 100 mg (64.4 %), while 27.1 % prescribed a maximum dose exceeding 100 mg in their practice.

Interestingly, nearly one-third of respondents employed a discrete (fractional) regimen of ethacizine when restoring SR during AF episodes: a prolonged regimen of low doses at short intervals. Commonly used regimens included:

1. 50 mg at 2-hour intervals three times (totalling 150 mg)
2. 75 mg + 25 mg after 2 hours (totalling 100 mg)
3. 50 mg + 50 mg after 1 hour (totalling 100 mg)

The rationale behind the fractional use of ethacizine during AF episodes was to minimize the risk of a proarrhythmic effect. Furthermore, one-third of respondents increased the daily dose to enhance the likelihood of restoring SR in AF, without considering this strategy a "pill-in-the-pocket" approach. This approach is now also recommended by Ukrainian experts in arrhythmology [11,12].

More than half of the respondents recognized the discrete regimen of ethacizine administration during AF episodes for SR restoration as effective. Additionally, 6.7 % considered it equally effective as a single high dose, following the "pill-in-the-pocket" approach, while 36.7 % deemed this regimen less effective.

When administering high doses of ethacizine for SR restoration in AF, physicians generally did not observe significant side effects that required modifications to therapy (56.2 %). However, 18.8 % of respondents reported neurological symptoms related to ethacizine use, including dizziness, vertigo, and balance disturbances during abrupt head turns. Side effects such as rhythm and conduction disturbances were noted by 8.3 % of respondents, and 16.6 % observed a prolongation of the QRS interval without the development of blocks. Most respondents indicated that side effects occurring during the use of high doses of ethacizine for SR restoration in AF were minor and did not lead to changes in patient management strategies (48.9 %). In case of more prominent side effects, 21.3 % of physicians opted for a discrete regimen of ethacizine administration, 12.8 % reduced the drug dose, and 17 % modified the strategy or switched to a different drug.

Regarding the question, "Do you support the feasibility of introducing ethacizine into national guidelines as 'pill-in-the-pocket' for SR restoration in AF based on your experience and studies of such use?" the most common response was "Yes, definitely support" (38.5 %). Overall, 73.7 % of respondents positively evaluated this offer, while 9.9 % confidently opposed it. Interestingly, 3.3 % indicated that ethacizine has already been included in the national standard for this indication, which is true but new information 2025 [11,12].

Study Limitations

The main limitation of this study is its subjective nature, as respondents may have expressed personal opinions and beliefs that are not objective measures. Some may have avoided answering certain questions or intentionally provided overly positive or negative answers (respondent "pleasers" or "deniers" [20]). The Hawthorne effect may also come into play, causing participants to respond in a manner they believe aligns with the researchers' expectations since they were informed about the survey's focus on ethacizine. To encourage objectivity, participants were asked at the beginning of the survey to respond as honestly as possible. However, misunderstandings did occur when physicians indicated they had never prescribed a drug yet still provided evaluations. Therefore, data censorship was applied to ensure that physicians without experience could not offer assessments. The kurtosis and skewness indicators confirmed the parametric nature of the satisfaction data, thus minimizing significant systematic errors associated with subjective responses.

The regional proportions of the survey respondents were neither established nor analyzed, since such an analysis would not affect the predefined objectives of the study. During the survey, high mobility of doctors remained both within Ukraine and as a result of leaving the country, therefore, for the researchers, the fundamental point was that the respondent doctor still practices in Ukraine.

Conclusions

The ETERNITY survey successfully achieved its objective of identifying actual conditions for the use of class IC AADs, particularly ethacizine, in managing AF patients in Ukraine — both for long-term therapy and acute episodes.

1. The physicians involved in the ETERNITY population most frequently prescribe ethacizine among class IC AADs, while nearly two-thirds of respondents had never prescribed flecainide. The primary reasons for prescribing ethacizine are clinical factors, such as personal experience and its additional cholinolytic effect, whereas for propafenone and flecainide, adherence to European guidelines influenced physician decisions. Ethacizine received a significantly higher satisfaction rating compared to propafenone, with the highest frequency of "very good" evaluations.

2. More than half of the respondents report experience using ethacizine for SR restoration in AF, and 27.1 % sometimes use a single maximum dose greater than 100 mg. Every fourth respondent mentioned that patients already receiving ethacizine sometimes chose regimens similar to the "pill-in-the-pocket" approach during AF onset without the doctor's consent.

3. Almost one-third of the respondents apply a discrete regimen of ethacizine for SR restoration in AF (several doses at short intervals but at lower amounts). Thus, it is more appropriate to use the term "pharmacological cardioversion in a single-dose or discrete regimen" instead of "pill-in-the-pocket," as both approaches are utilized in actual clinical practice.

4. In conclusion, 73.7 % of respondents expressed support for incorporating ethacizine into national guidelines as a treatment for SR restoration in AF.

Prospects for further research. The authors recommend planning a series of high-quality multicentre studies to assess the efficacy of ethacizine, especially in comparison to other class IC AADs for maintaining and restoring SR in patients with paroxysmal or persistent AF. These studies should specifically evaluate the optimal dosing regimens for SR restoration when employing a strategy similar to "pill-in-the-pocket" or using fractional dosing.

Ethical approval
Bioethics Commission of Zaporizhzhia State Medical and Pharmaceutical University (Protocol No. 12 dated October 23, 2025).

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